REVIEW ARTICLES

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Effect of Oral Appliances on Blood Pressure in Obstructive Sleep Apnea: A Systematic Review and Meta-analysis

Imran H. Iftikhar, M.D.[1]; Erin Rikard Hays, M.D.[1]; Michelle-Anne Iverson, D.O.[1]; Ulysses J. Magalang, M.D.[3]; Andrea Kay Maas, M.D.[2]

[1]University of South Carolina, School of Medicine, Columbia, SC; [2]The William Jennings Bryan Dorn Veterans Affairs Hospital and University of South Carolina, School of Medicine, Columbia, SC; [3]The Ohio State University, Columbus, OH

Background: Obstructive sleep apnea (OSA) is an independent risk factor for the development of hypertension. However the effect of continuous positive airway pressure (CPAP) on lowering systemic blood pressure (BP) in OSA patients has been conflicting. Oral appliance (OA) therapy is an important alternative therapy to CPAP for patients with mild to moderate OSA.

Objective: To conduct a meta-analysis of studies which have evaluated the effect of OAs on BP in patients with OSA.

Data Sources: Studies were retrieved by searching PubMed (all studies that were published until December 15, 2011)

Study Selection: Three independent reviewers screened citations to identify trials of the effect of OA on BP.

Data Extraction: Data from observational and randomized controlled trial (RCT) studies was extracted for pre- and post-treatment systolic, diastolic, and mean arterial blood pressure (SBP, DBP, and MAP).

Data Synthesis: A total of 7 studies that enrolled 399 participants met the inclusion criteria. The pooled estimate of mean changes and the corresponding 95% CIs for SBP, DBP, and MAP from each trial are -2.7 mm Hg (95% CI: -0.8 to -4.6), p-value 0.04; -2.7 mm Hg (95% CI: -0.9 to -4.6), p-value 0.004; and -2.40 mm Hg (95% CI: -4.01 to -0.80), p-value 0.003 (Figures 2-4). The pooled estimate of mean changes and the corresponding 95% CIs for nocturnal SBP, DBP, and MAP from each trial are -2.0 mm Hg (95% CI: 1.1 to -5.3), p-value 0.212; -1.7 mm Hg (95% CI: -0.1 to -3.2), p-value 0.03; and -1.9 mm Hg (95% CI: 1.3 to -5.1), p-value 0.255 (Figures 5-7) respectively.

Conclusions: The pooled estimate shows a favorable effect of OAs on SBP, MAP, and DBP. Most of the studies were observational. Therefore, more RCTs are warranted involving a larger number of patients and longer treatment periods to confirm the effects of OA on BP.

Keywords: Oral appliances, obstructive sleep apnea, blood pressure, meta-analysis

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Obstructive sleep apnea (OSA) is a highly prevalent condition characterized by repetitive upper airway obstruction resulting in cyclic intermittent hypoxia during sleep in affected individuals.[1,2] Longitudinal studies have shown that OSA is an independent risk factor for the development of hypertension.[3,4] Different treatment options for OSA have been studied. These include behavioral modification, such as weight loss programs,[5-8] positional modification,[9] upper airway surgical procedures,[10,11] pharmacological treatments,[12,13] and continuous positive airway pressure (CPAP).[14] Since there is the strongest data for the effectiveness of CPAP in treatment of OSA, it has been the modality of choice for OSA treatment.[15] A meta-analysis of several randomized controlled trials (RCTs) has shown that CPAP reduces blood pressure (BP) in patients with OSA.[16] The efficacy of CPAP largely depends upon the patient compliance. Poor tolerance with CPAP combined with its complex and ever evolving designs potentially outweighs perceived treatment benefit.[17-21] Most patients and physicians consider oral appliances (OA) to be less cumbersome than CPAP.[22]

The American Academy of Sleep Medicine recommends OA therapy for patients with mild to moderate OSA and for patients with severe OSA if they fail CPAP treatment.[23] There are limited data on the effect of OAs on BP. We sought to conduct a meta-analysis of the available studies to study the effect of OAs on BP.

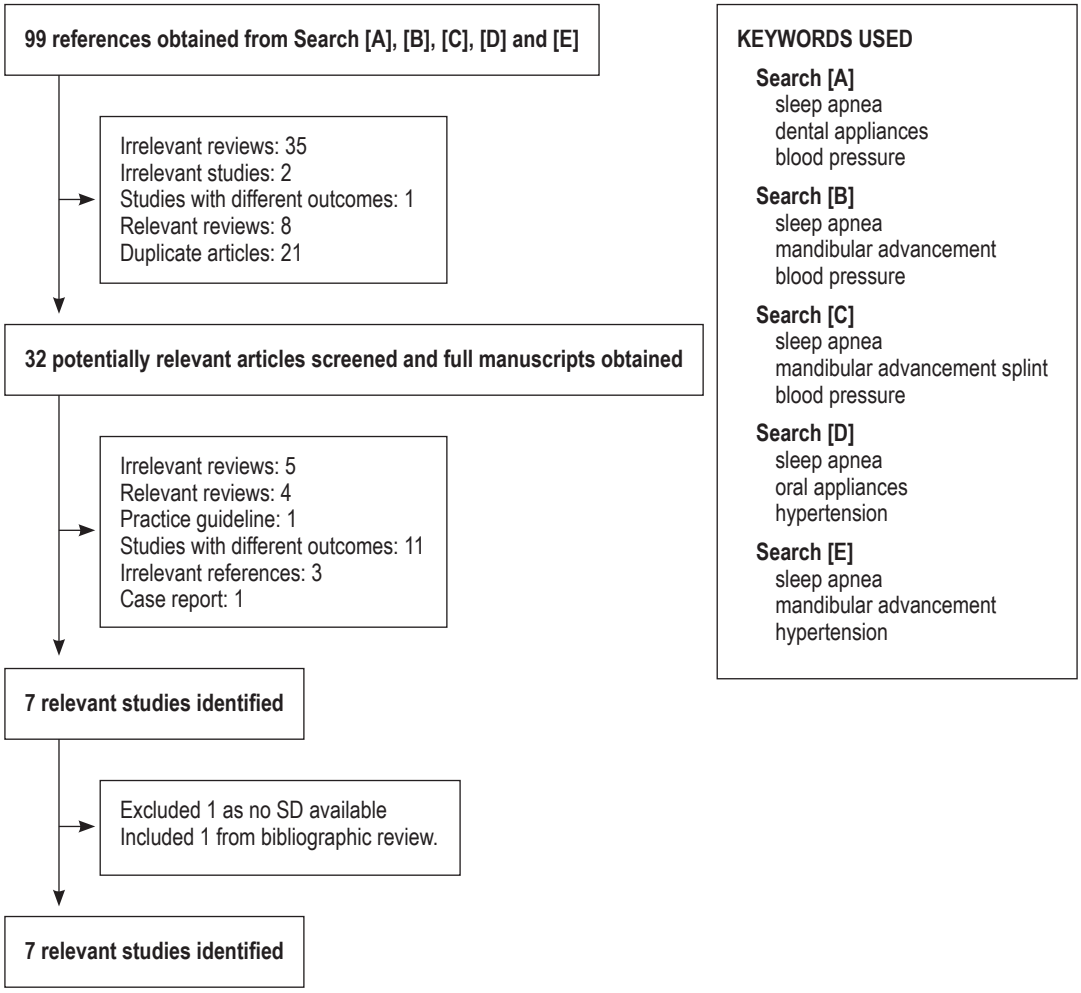
METHODS

We followed the MOOSE (Meta-analysis Of Observational Studies in Epidemiology) guidelines during all stages of the design, implementation, and reporting of this meta-analysis since most of the published papers are observational studies.[24]

Search Strategy and Selection Criteria

We searched PubMed for RCTs and observational studies that studied the effects of OAs on systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial blood pressure (MAP). All relevant studies that were ever published in PubMed until December 15, 2011, were included. **Figure 1** explains our search strategy in detail. In our initial search, no efforts were made to contact the authors of the references that were unavailable (such as those published in a non-English language or abstracts published in the supplement journals). This is because this initial search did not identify any relevant references that were pertinent to our meta-analysis. Once we had shortlisted the 32 references, full manuscripts of these references were obtained. A total of 7 studies were finally included in our meta-analysis.[25-31] There was one disagreement on including the study by Lam et al.,[32]

Figure 1—Flow diagram of articles identified and evaluated during the study selection process



as no standard deviation (SD) for individual outcomes were reported. The disagreement was resolved through mutual discussion and we decided not to include this study. We used the following inclusion criteria:

1. The study had to include only adult human participants (age ≥ 18 years).
2. All studies that investigated the pre-treatment and post-treatment effect of OA on SBP, DBP, and MAP were included.
3. All relevant studies were included if the study population comprised patients with OSA.

The exclusion criteria consisted of the following:

1. If multiple publications of the same trial were identified, only the most recent publication was included.
2. All case reports, case series, and review articles were excluded. Studies that did not include standard deviation data were excluded.

Three investigators (I.I., E.H., and M.I.) performed the final screening, and all investigators had to agree that an article met the inclusion and exclusion criteria. In the instance of the disagreement (as cited above) between the investigators, a fourth investigator (A.M.) reviewed the article, and disagreement was resolved through discussion.

Data Abstraction

For studies that met the inclusion criteria (**Figure 1**), data was extracted by a reviewer onto a standardized data collection worksheet. Extracted data included first author's name, year of publication, number of participants, pre- and post-treatment SBP, DBP, and MAP measurements with standard deviations, control and intervention SBP, DBP, and MAP from the RCTs, country of origin, source of publication, study design, and the method of outcome measurement (ambulatory BP monitoring or clinical BP). Ambulatory blood pressure monitoring (ABPM) obtains automated BP measurements at fixed time intervals in a 24-h period during the patient's usual daily activities and during sleep. ABPM data was used, when available, because several studies have shown that ABPM is superior in predicting target organ damage and cardiovascular events compared to office BP. For ABPM, the 24-h BP measurements as well as nocturnal BP measurements were recorded. However, we did separately perform a meta-analysis of the nocturnal BP measurements. We have also reported the morning and evening figures of BP from studies where these data were available (**Table 1**). For the studies where standard errors of mean (SEM) were reported,[26-28] we calculated the SDs based on the number of participants in the study and the reported SEM. All data were entered in mm Hg.

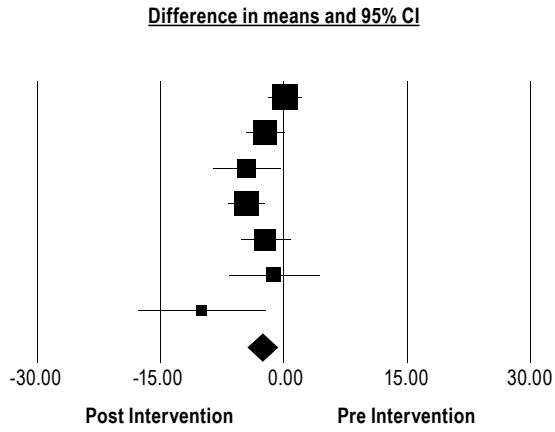
Table 1—Effect of oral appliances on morning and evening BP

	Pre Treatment				Post Treatment			
Study	Morning SBP	Nighttime SBP	Morning DBP	Nighttime DBP	Morning SBP	Nighttime SBP	Morning DBP	Nighttime DBP
Otsuka et al.	136.5 ± 8.2	118.4 ± 10.0	87.5 ± 6.8	71.6 ± 8.0	130.1 ± 6.2	113.7 ± 9.1	82.6 ± 5.7	67.2 ± 7.9
Zhang et al.	133.6 ± 8.1	125.3 ± 9.3	85.7 ± 6.3	78.8 ± 6.8	131.6 ± 6.8	121.3 ± 7.0	85.1 ± 5.9	76.1 ± 6.1
Lam et al.	127.1 ± 12.2	131.9 ± 18.0	76.2 ± 12.2	77.8 ± 12.8	125.9 ± 19.2	129.8 ± 21.5	73.4 ± 11.6	75.9 ± 11.6

All values mean ± SD. SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Figure 2—Forest plot for mean change in systolic blood pressure and corresponding 95% CIs

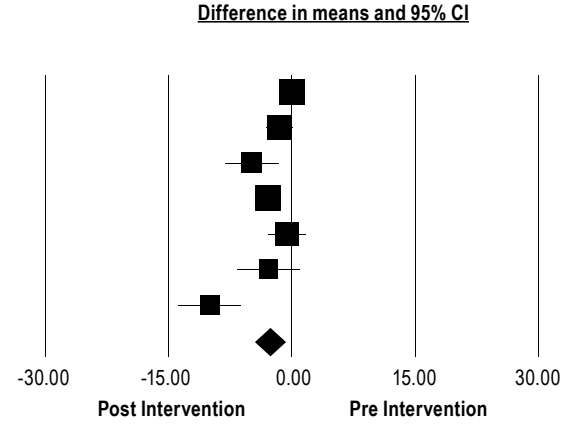
Study name	Statistics for each study						
	Difference in means	SE	Variance	LL	UL	Z	p
Barnes (2004)	0.200	1.112	1.237	-1.980	2.380	0.180	0.857
Gostopoulos (2004)	-2.300	1.300	1.689	-4.847	0.247	-1.770	0.077
Otsuka (2006)	-4.500	2.182	4.763	-8.777	-0.223	-2.062	0.039
Yoshida (2006)	-4.500	1.228	1.508	-6.906	-2.094	-3.665	0.000
Zhang (2009)	-2.200	1.645	2.708	-5.425	1.025	-1.337	0.181
Lam (2007)	-1.200	2.886	8.331	-6.857	4.457	-0.416	0.678
Andren (2009)	-10.000	4.050	16.400	-17.937	-2.063	-2.469	0.014
Pooled Mean Change	-2.725	0.959	0.919	-4.604	-0.845	-2.842	0.004



SE, standard error; LL, lower limit; UL; upper limit; Z, Z-value; p, p-value.

Figure 3—Forest plot for mean change in diastolic blood pressure and corresponding 95% CIs

Study name	Statistics for each study						
	Difference in means	SE	Variance	LL	UL	Z	p
Barnes (2004)	0.000	0.753	0.568	-1.477	1.477	0.000	1.000
Gostopoulos (2004)	-1.500	0.899	0.808	-3.262	0.262	-1.669	0.095
Otsuka (2006)	-4.900	1.739	3.023	-8.308	-1.492	-2.818	0.005
Yoshida (2006)	-2.900	0.813	0.661	-4.493	-1.307	-3.568	0.000
Zhang (2009)	-0.600	1.240	1.539	-3.031	1.831	-0.484	0.629
Lam (2007)	-2.800	2.043	4.173	-6.804	1.204	-1.371	0.170
Andren (2009)	-10.000	2.037	4.151	-13.993	-6.007	-4.908	0.000
Pooled Mean Change	-2.785	0.966	0.932	-4.678	-0.893	-2.884	0.004



SE, standard error; LL, lower limit; UL; upper limit; Z, Z-value; p, p-value.

All included studies were peer reviewed and were assumed to represent valid information regarding the effect of OAs. Characteristics of the study participants in each study at baseline were recorded. This includes the age and sex distribution, baseline BP, baseline body mass index (BMI), and the severity of OSA by apnea-hypopnea index (AHI).

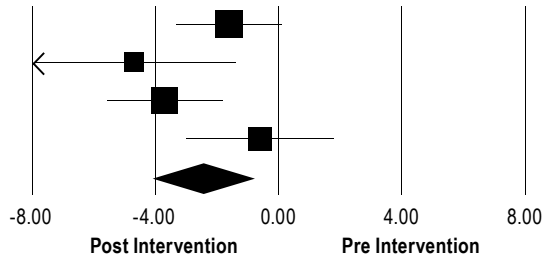
Quantitative Data Synthesis

The absolute effectiveness of OA was quantified by estimating the mean difference of outcomes (mean SBP, mean DBP, and MAP) before and after intervention in the observational studies and RCTs. We also separately analyzed the 2 RCTs for the data on SBP, DBP, and nocturnal DBP. This was done by estimating and comparing the mean and SDs of the BP variables between control and intervention groups. The mean change in AHI of the available studies was also analyzed. Effect sizes and 95% confidence intervals (CIs) were estimated by pooling available data using the Comprehensive Meta-Analysis V2 software. A meta-analysis of correlation and sample size for the change in BP with corresponding change in AHI was also performed.

Random effects methods were used to account for variance between the studies as well as within the studies. Fixed effects methods were used to account for variance within the studies. Results from the random effects models have been reported in this meta-analysis, as the included studies used different methods of measurements and involved different study participants and duration of studies. Results are displayed in the form of forest plots (**Figures 2-12**).

Figure 4—Forest plot for mean change in mean arterial pressure and corresponding 95% CIs

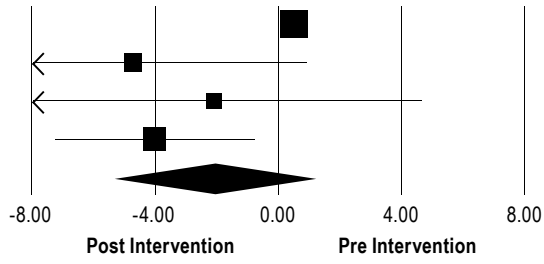
Study name	Difference in means	SE	Variance	LL	UL	Z	p
Gostopoulos (2004)	-1.600	0.899	0.808	-3.362	0.162	-1.780	0.075
Otsuka (2006)	-4.700	1.709	2.919	-8.049	-1.351	-2.751	0.006
Yoshida (2006)	-3.700	0.983	0.967	-5.627	-1.773	-3.764	0.000
Zhang (2009)	-0.600	1.240	1.539	-3.031	1.831	-0.484	0.629
Pooled Mean Change	-2.478	0.847	0.718	-4.139	-0.817	-2.925	0.003



SE, standard error; LL, lower limit; UL; upper limit; Z, Z-value; p, p-value.

Figure 5—Forest plot for the mean change in nocturnal systolic blood pressure

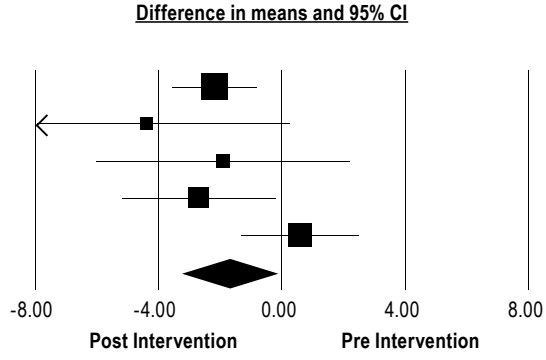
Study name	Difference in means	SE	Variance	LL	UL	Z	p
Gostopoulos (2004)	0.500	0.186	0.035	0.135	0.865	2.688	0.007
Otsuka (2006)	-4.700	2.889	8.346	-10.362	0.962	-1.627	0.104
Lam (2007)	-2.100	3.473	12.065	-8.908	4.708	-0.605	0.545
Zhang (2009)	-4.000	1.678	2.816	-7.289	-0.711	-2.384	0.017
Pooled Mean Change	-2.086	1.670	2.788	-5.359	1.186	-1.249	0.212



SE, standard error; LL, lower limit; UL; upper limit; Z, Z-value; p, p-value.

Figure 6—Forest plot for the mean change in nocturnal diastolic blood pressure

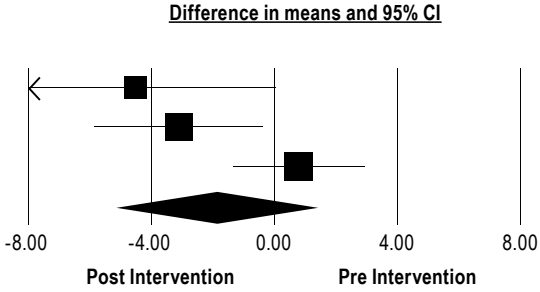
Study name	Difference in means	SE	Variance	LL	UL	Z	p
Barnes (2004)	-2.200	0.721	0.520	-3.614	-0.786	-3.050	0.002
Otsuka (2006)	-4.400	2.397	5.746	-9.098	0.298	-1.836	0.066
Lam (2007)	-1.900	2.128	4.527	-6.070	2.270	-0.893	0.372
Zhang (2009)	-2.700	1.296	1.679	-5.239	-0.161	-2.084	0.037
Gostopoulos (2004)	0.600	0.999	0.997	-1.357	2.557	0.601	0.548
Pooled Mean Change	-1.724	0.798	0.636	-3.287	-0.160	-2.161	0.031



SE, standard error; LL, lower limit; UL; upper limit; Z, Z-value; p, p-value.

Figure 7—Forest plot for the mean change in nocturnal mean arterial pressure

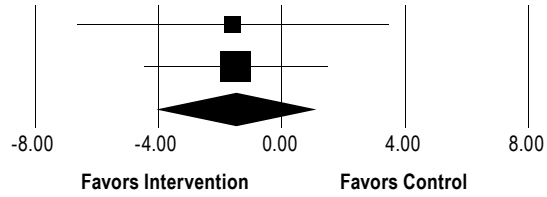
Study name	Difference in means	SE	Variance	LL	UL	Z	p
Otsuka (2006)	-4.500	2.340	5.477	-9.087	0.087	-1.923	0.055
Zhang (2009)	-3.100	1.415	2.003	-5.874	-0.326	-2.190	0.029
Gostopoulos (2004)	0.800	1.113	1.240	-1.382	2.982	0.719	0.472
Pooled Mean Change	-1.903	1.671	2.794	-5.179	1.373	-1.139	0.255



SE, standard error; LL, lower limit; UL; upper limit; Z, Z-value; p, p-value.

Figure 8—Forest plot for the mean change in systolic blood pressure from randomized controlled trials

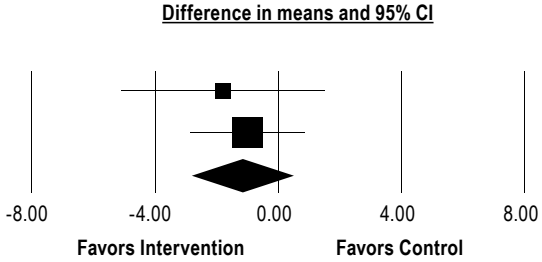
Study name	Difference in means	SE	Variance	LL	UL	Z	p
Gostopoulos (2004)	-1.600	2.602	6.772	-6.700	3.500	-0.615	0.539
Barnes (2004)	-1.500	1.542	2.379	-4.523	1.523	-0.972	0.331
Pooled Mean Change	-1.526	1.327	1.761	-4.127	1.075	-1.150	0.250



SE, standard error; LL, lower limit; UL; upper limit; Z, Z-value; p, p-value.

Figure 9—Forest plot for the mean change in diastolic blood pressure from the randomized controlled trials

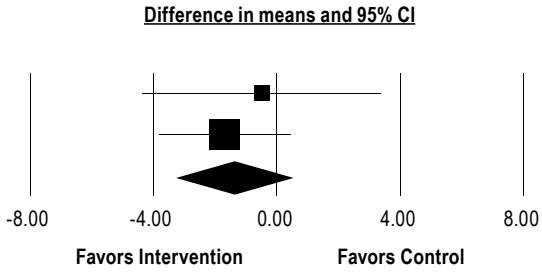
Study name	Difference in means	SE	Variance	LL	UL	Z	p
Gostopoulos (2004)	-1.800	1.709	2.921	-5.150	1.550	-1.053	0.292
Barnes (2004)	-1.000	0.974	0.949	-2.909	0.909	-1.027	0.305
Pooled Mean Change	-1.196	0.846	0.716	-2.855	0.462	-1.413	0.158



SE, standard error; LL, lower limit; UL; upper limit; Z, Z-value; p, p-value.

Figure 10—Forest plot for the mean change in nocturnal diastolic blood pressure from the randomized controlled trials

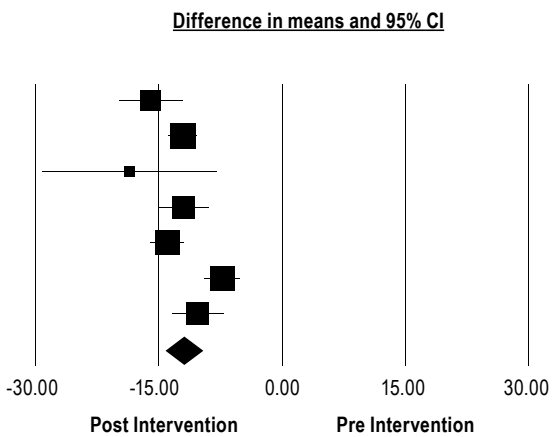
Study name	Difference in means	SE	Variance	LL	UL	Z	p
Gostopoulos (2004)	-0.500	2.002	4.009	-4.425	3.425	-0.250	0.803
Barnes (2004)	-1.700	1.113	1.239	-3.882	0.482	-1.527	0.127
Pooled Mean Change	-1.417	0.973	0.947	-3.324	0.490	-1.456	0.145



SE, standard error; LL, lower limit; UL; upper limit; Z, Z-value; p, p-value.

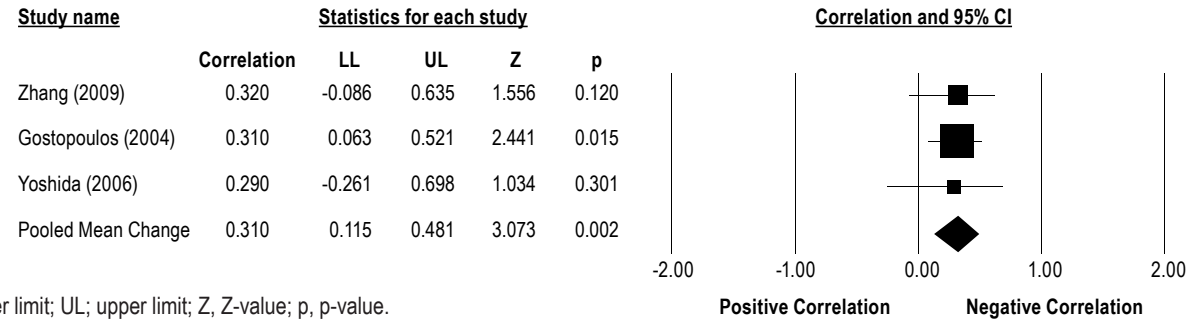
Figure 11—Forest plot for the mean change in AHI with oral appliances

Study name	Difference in means	SE	Variance	LL	UL	Z	p
Gostopoulos (2004)	-16.000	2.061	4.246	-20.039	-11.961	-7.765	0.000
Yoshida (2006)	-12.100	0.967	0.934	-13.995	-10.205	-12.518	0.000
Otsuka (2006)	-18.600	5.509	30.346	-29.397	-7.803	-3.376	0.001
Andren (2009)	-12.000	1.670	2.787	-15.272	-8.728	-7.188	0.000
Zhang (2009)	-14.000	1.131	1.280	-16.217	-11.783	-12.376	0.000
Barnes (2004)	-7.300	1.212	1.468	-9.675	-4.925	-6.025	0.000
Lam (2007)	-10.300	1.700	2.888	-13.631	-6.969	-6.060	0.000
Pooled Mean Change	-12.071	1.176	1.384	-14.377	-9.765	-10.260	0.000



SE, standard error; LL, lower limit; UL; upper limit; Z, Z-value; p, p-value.

Figure 12—Forest plot for the correlation of change in AHI reduction and magnitude of change in BP



LL, lower limit; UL; upper limit; Z, Z-value; p, p-value.

Table 2—Characteristics of studies

Study	Year	Type of study	N	Comorbid conditions	Age (SD)	Sex (%Male) (frequency)	BMI (SD)	Duration of intervention (used in this meta-analysis)	Method of BP measurement
Gotsopoulos et al.[27]	2004	RCT	61	Hypertension	48 ± 11	79.1% (53)[c]	28.4 ± 5.2	4 weeks	ABPM
Yoshida et al.[30]	2006	Observational	161	Hypertension	54.3 ± 13.7	75.1% (121)	24.9 ± 4.2	15 weeks	Clinical[b]
Otsuka et al.[29]	2006	Observational	11	Hypertension	52.2 ± 7.2 Range: 43-58	72.7% (8)	28.6 ± 4.0 Range: 22.9-35.8	32 weeks	ABPM[e]
Andren et al.[25]	2009	Observational	29	Hypertension	57 Range: 34-71	62% (18)	28.7 ± 3.9 Range: 22-37	12 weeks	Clinical[a]
Zhang et al.[31]	2009	Non RCT	25	Hypertension	36 to 67	84% (21)	29.7 ± 3.8	12 weeks	ABPM
Barnes et al.[26]	2004	RCT	85	Hypertension	46.4 (1.1 SEM)	78.8% (67)[d]	31.0 (0.6 SEM)	12 weeks	ABPM
Lam et al.[28]	2007	RnCT[f]	34[g]	Hypertension[g]	45 (2 SEM)	76% (26)[a]	27.3 (0.6 SEM)[g]	10 weeks[g]	Clinical[g]

[a]BP was measured twice at each visit using an electronic BP monitor. The second measurement was used. [b]The average of 2 to 4 BP measurements in the mornings was used. [c]53 males from the initial randomization of 67 participants. Six participants did not complete the study and the gender of these was not specified. [d]78.8% males of the total number of participants who completed the study in the entire cohort. [e]24-h ambulatory blood pressure monitoring. [f]Randomized non-controlled trial. [g]Data reflect only the participants in the OA group. Of these, only 4 were hypertensive and taking antihypertensive treatment. RCT, randomized control trial; N, number of participants; SEM, standard error of mean; SD, standard deviation; BMI, body mass index.

Heterogeneity was assessed with I^2 index and the tau-squared test. To assess the risk of publication bias, funnel plots (see **Appendix**; only funnel plots for SBP, DBP, MAP, and nocturnal SBP, DBP, and MAP are shown) of standard error and difference in means were constructed.

RESULTS

A total of 7 studies that enrolled 399 participants met the inclusion criteria. The SBP, DBP, and MAP data were available for 399 participants. Characteristics of study population in each trial are outlined in **Table 2**. Study participants in all of the studies were ≥ 36 years and had a mean BMI ≥ 24 kg/m^2. The duration of OA treatment ranged from 4-32 weeks. There was one nonrandomized controlled trial,[31] one uncontrolled cross-sectional study,[30] two observational studies that followed study participants longitudinally,[25,29] one randomized controlled trial,[26] and one randomized, controlled, crossover trial.[27] Four studies used the ABPM and also reported the nocturnal BPs.[26,27,29,31] Two studies reported the BP recorded in the office.[25,30] Two of the studies were conducted in Australia,[26,27] one in Sweden,[25] one in Japan,[30] one in China,[31] one in Canada,[29] and one in Hong Kong.[28]

In the study by Andren et al.,[25] OSA patients (diagnosed by somnographic evaluation with an AHI > 10/h) received OA treatment. They were followed for 3 months and after 3 years of treatment. All treatments and measurements were performed by the same dentist. BP was measured twice at each visit using an electronic BP monitor. The somnographic evaluations were made with a portable digital recording unit. At baseline, all but 3 participants had hypertension, and 7 of these were on antihypertensive drugs. At the 3-year evaluation, another 2 started to medicate for hypertension.

In the study by Otsuka et al.,[29] the selected OSA study participants were referred to an orthodontic practice for OA treatment. Two of the 11 participants were on antihypertensive drugs. The OA was inserted between day 1 and week 2 after pretreatment BP measurement. An acclimatization period of 1 to 3 weeks was used. The OA was titrated to therapeutic position over 2 to 8 months. BP measurement pretreatment and posttreatment was

Table 3—Effect of oral appliances on AHI/RDI

Study	Pre Treatment AHI/RDI (mean ± SD)	Post Treatment AHI/RDI (mean ± SD)	MD (SE)	p-value
Gotsopoulos et al.[27]	28 ± 17 (AHI)	12 ± 2 (AHI)	-16.0 (2.0)	0.00
Yoshida et al.[30]	17.9 ± 14.1 (AHI)	5.8 ± 5.9 (AHI)	-12.1 (0.9)	0.00
Otsuka et al.[29]	24.7 ± 20.1 (RDI)	6.1 ± 4.5 (RDI)	-18.6 (5.5)	0.00
Andren et al.[25]	16.1 ± 8.8 (AHI)	4.1 ± 2.6 (AHI)	-12.0 (1.6)	0.00
Zhang et al.[31]	21.0 ± 6.5 (AHI)	7.0 ± 3.8 (AHI)	-14.0 (1.1)	0.00
Barnes et al.[26]	21.3 ± 11.98 (AHI)	14.0 ± 10.13 (AHI)	-7.3 (1.2)	0.00
Lam et al.[28]	20.9 ± 9.91 (AHI)	10.6 ± 9.91 (AHI)	-12.0 (1.17)	0.00

AHI, apnea-hypopnea index; RDI, respiratory disturbance index; SD, standard deviation; MD, mean difference; SE, standard error.

done by ABPM. Post-titration sleep monitoring was performed within 2 weeks, using either a home sleep study or an attended sleep study in the hospital.

In the study by Yoshida et al.,[30] participants were fitted with individual customized appliances. Mandibular advancement was 60% to 80% for each patient's maximum protrusive distance. Sleep study post-titration was done in the hospital. BP was measured using an automatic blood measure monitor. The measurements were taken between 09:00 and 11:00. The investigators repeated the measurements at least twice on the same day and used the average values. Eighty-one of 161 participants had hypertension, and 51 of them were on antihypertensive drugs.

Gostopoulos et al.[27] used an RCT protocol. Their OSA study participants received a mandibular advancement splint (MAS) which was custom-made. For baseline assessment, these participants were studied with an overnight polysomnography (PSG) and ABPM. This was followed by an acclimatization period to MAS, a 1-week washout period, randomization to control and treatment groups, and finally post-titration assessment with PSG and ABPM. Thirty-nine percent of the participants were on antihypertensive drugs.

Zhang et al.[31] in a non-randomized controlled trial performed baseline PSG and ABPM in the OA treatment group (OA group) and in the non-tolerated OA treatment group (N-OA group). PSG and ABPM were repeated in the OA treatment group after a completion of 12 weeks of treatment and in the N-OA group after a cessation of treatment for 12 weeks. Fifteen of the 25 participants were on antihypertensives and continued to take the same kind and same dose of antihypertensive drugs during the study.

Barnes et al.[26] utilized a randomized, 3-way crossover trial in 2 Australian centers. Responses to 3 months of treatment with nasal CPAP, a mandibular advancement splint, and a placebo tablet were compared allowing a 2-week washout between the treatment periods. They performed an overnight PSG, comprehensive neurobehavioral testing, ABPM, and echocardiography in all participants at the beginning of the trial and at the end of the 3-month treatment period. Sixteen of the participants were hypertensive, and 44 were non-dippers. The authors did not report if their study participants were on any antihypertensive drugs.

In the study by Lam et al.,[28] 101 participants were randomized into 3 treatment groups. The OA group, CPAP group, and the group with "conservative measures" treatment had 34, 34, and 33 participants, respectively. Study participants underwent overnight PSG before and after the intervention that lasted for 10 weeks in each group. BP was measured clinically in the evening before a sleep study and in the morning after a sleep study. At baseline, 19 study participants were hypertensive and on antihypertensive drugs (7 in CPAP group, 4 in the OA group, and 8 in the control group).

The pooled estimate of mean changes and the corresponding 95% CIs for SBP, DBP, and MAP from each trial were -2.7 mm Hg (95% CI: -0.8 to -4.6), p-value 0.04; -2.7 mm Hg (95% CI: -0.9 to -4.6), p-value 0.004; and -2.40 mm Hg (95% CI: -4.01 to -0.80), p-value 0.003 (**Figures 2**, **3**, and **4**), respectively. The pooled estimate of mean changes and the corresponding 95% CIs for nocturnal SBP, DBP, and MAP from each trial were -2.0 mm Hg (95% CI: 1.1 to -5.3), p-value 0.212; -1.7 mm Hg (95% CI: -0.1 to -3.2), p-value 0.03; and -1.9 mm Hg (95% CI: 1.3 to -5.1), p-value 0.255 (**Figures 5**, **6**, and **7**), respectively.

The data from the 2 RCTs were also meta-analyzed. The pooled estimate of mean changes and the corresponding 95% CIs for 24-h average of SBP and DBP were -1.5 mm Hg (95% CI: 4.1 to -1.0), p-value 0.25; and -1.1 mm Hg (95% CI: 2.8 to -0.46), p-value 0.15 (**Figures 8** and **9**), respectively. The pooled estimate of mean changes and the corresponding 95% CIs for the nocturnal DBP was -1.4 mm Hg (95% CI: 3.3 to -0.4), p-value 0.14 (**Figure 10**).

The pooled estimate of mean changes and the corresponding 95% CIs for AHI reduction of the studies included in this meta-analysis was -12.07 (% CI: -9.7 to -14.3), p-value 0.00 (**Figure 11, Table 3**).

We performed a meta-analysis of correlation and sample size for the change in BP with corresponding change in AHI. Such data was available for MAP in the studies by Zhang et al. and Yoshida et al. and for DBP in the study by Gostopoulos et al. The correlation was 0.31 with a p-value of 0.002 (**Figure 12**).

I^2 index was used to account for variability in effect size estimates across the studies.

The I^2 indices for SBP, DBP, and MAP were 53.9, 78.6, and 14.5, respectively. The I^2 indices for nocturnal SBP, DBP, and MAP were 72.1, 47.6, and 71.4, respectively. These data suggest moderate to severe heterogeneity.

The I^2 indices for the 24-h average of SBP and DBP from the RCTs were 0.00 and 0.00, respectively. The I^2 index for the nocturnal DBP from the 2 RCTs was 0.00. These data suggest no heterogeneity.

Table 4—Description of the types of oral appliances used

Study	Description of OA used	Titratable vs Non titratable
Gotsopoulos et al.	Custom made MAS, consisting of upper and lower removable oral appliances	Titratable
Yoshida et al.	Custom-made with copolyester foil (Erkudor, Erkodent) and autopolymerizing resin (Quick Resin, Shofu)	Titratable
Otsuka et al.	The Klearway OA	Titratable
Andren et al.	Custom-made OA of a monoblock design	Titratable
Zhang et al.	—	Titratable
Barnes et al.	Custom-made MAS	Titratable
Lam et al.	Tailor made nonadjustable OA –Harvold type [dental acrylic modified]	Non titratable

OA, oral appliance; MAS, mandibular advancement splint.

To assess for the potential for publication bias, we constructed funnel plots (see **Appendix**) of standard error and difference in means. We also used the Begg and Mazumdar Rank correlation test to check for publication bias (see **Appendix**).

DISCUSSION

Our meta-analysis shows that OA treatment for mild to moderate sleep apnea improves BP control. Reductions in both SBP and DBP, as well as in nocturnal SBP were seen with OA treatment. Although the reductions in BP with OA were modest, these effects were comparable to those reported with CPAP treatment.[16,33-35]

Seven studies were identified with designs to evaluate this theorized effect of adequate OA therapy on BP measurements in patients diagnosed with OSA by previous PSGs. Across the board, it appears that effective OA therapy, as evidenced by decreased apneas/hypopneas, leads to a decrease in SBP, DBP, and MAP. Previous studies have shown that even a modest reduction in BP may reduce the risk of coronary artery disease and stroke.[36,37] MacMahon et al. reported that a change in DBP of 5 mm Hg across a population of 420,000 individuals was associated with ≥ 34% less stroke and 21% less coronary heart disease (CHD).[36] Based on the overviews of observational studies and RCTs, Cook et al. suggested that a decrease in 2 mm Hg DBP would result in a decrease in the prevalence of hypertension by 17%, in the risk of CHD by 6%, and in risk of stroke and TIAs by 15%.[37]

Thus, it is possible that the BP reduction seen in the studies included in this meta-analysis may portend significant risk reduction for these prevalent comorbidities by the adequate treatment of mild to moderate OSA with OA therapy alone. Further research is warranted in this area.

This meta-analysis is one of the first to systematically review and analyze the studies that focused on the effect of OAs on BP in patients with OSA. The pooled mean change in the SBP, DBP and the MAP in our study were -2.7 mm Hg, -2.7 mm Hg, and -2.40 mm Hg, respectively. A previous meta-analysis by Bazzano et al. that analyzed the effects of CPAP on BP in OSA patients reported a mean net change in the SBP, DBP, and MAP as -2.46 mm Hg (95% CI: -4.31 to -0.62), -1.83 mm Hg (95% CI: -3.05 to -0.61), and -2.22 mm Hg (95% CI: -4.38 to -0.05), respectively.[16] The results of our meta-analysis show a similar effect size of the OAs, in reducing BP levels in OSA patients. However, it must be taken into account that there were significant differences in the patient population included in the Bazzano meta-analysis as compared to our meta-analysis. This is because there were 818 participants from a total of 16 trials in the Bazzano meta-analysis that had mostly moderate to severe OSA. On the other hand, our meta-analysis had only 399 participants from a total of 7 studies that had predominantly mild to moderate disease.

Our meta-analysis had enough power to detect a BP lowering effect of OAs in the included studies. Given a total of 399 participants, we estimate that our meta-analysis has a power of 0.97 to detect a change in BP of 2 mm Hg assuming a standard deviation of 10 mm Hg. In our sensitivity analyses, we found that the study by Andren et al.[25] did influence the overall results. This is because, the authors state that 2 of the 15 patients without antihypertensive drugs at baseline had started taking medication at the 3-year evaluation. The authors also mention that seven patients were taking medication at the start of the study and cite this as a confounding factor. However, the significant results seen by Andren et al. may also be due to the fact that the participants were studied for a significantly longer time (3 years) than other studies.

There are limitations to our study. Most of the studies included in this meta-analysis are observational and not RCTs. As a result, in our main analysis we had to compare the pre-treatment and post-treatment effects of OAs on BP including the two RCTs. Hence, potential confounding factors aside from OA treatment could have affected our findings. The difference in BP observed in the studies could have been confounded by age, sex, BMI, and concurrent treatment with antihypertensives, and also because none of the studies reported adjusted mean differences. Most of the studies had a small sample size and included mostly overweight male participants in middle age. Therefore, the results may not be generalizable to populations of different demographics. Most of the studies included in our meta-analysis were carried over a short length of time, ranging from 4-32 weeks, though this was comparable to the duration of studies included in the Bazzano et al. meta-analysis,[16] which ranged from 2-24 weeks. Only four of the six studies used the ABPM for BP measurement. Finally, although not reported in all of the studies, different types of OAs may have been used (**Table 4**). However, the AHI was significantly reduced in all seven of these studies (**Figure 11**). Despite these limitations, we believe that the results of our meta-analysis remain valuable in that it

supports the performance of more expensive large scale RCTs to determine the effects of OA treatment on BP in OSA patients.

A growing body of evidence suggests that untreated sleep disordered breathing is associated with many significant cardiovascular health outcomes such as hypertension,[3] stroke, congestive heart failure, atrial fibrillation,[21] increased risk of motor vehicle accidents,[38] excessive daytime sleepiness, and impaired quality of life and social life.[20] As mentioned above, OAs are a favorable option for the treatment of sleep disordered breathing. OAs tend to increase the oropharyngeal and hypopharyngeal airway space.[39] This is achieved by mandibular protrusion and also by triggering the stretch receptors that activate the airway support muscles.[40] MADs (mandibular advancement devices) are the most commonly prescribed and most efficacious OAs in the treatment of OSA.[41] It is important to bear in mind that the design features of the various appliances may have an impact on the overall treatment efficacy.[42] For example, Lawton et al. showed that compared to the Herbst device, the Twin block MAD actually worsened the AHI in a study patient.[43] Similar observed discrepancy in terms of reduction of AHI was also found in two other studies that compared two different MADs (the two-piece Silencer MAD and one-piece Karwetzky MAD).[44,45] Additionally, upon review of the Littieri et al. study,[46] it was apparent that a greater reduction in AHI was noted with adjustable devices than those that were non-adjustable. However, the one study by Lam et al. included in our meta-analysis that used a non-adjustable device showed a statistically significant reduction in AHI (p value 0.00) and a BP reduction of the same magnitude as noted in other comparable studies. Most of the other studies in our meta-analysis used a titratable and custom-made appliance. Therefore, it would be hard to speculate whether a particular OA type was associated with the change in BP.

Although it is unclear at this point which OA would work the best in terms of getting the desired therapeutic effect on AHI reduction, it can be safely concluded that OAs in general are associated with a significant, albeit modest BP reduction in OSA patients. In conclusion, the pooled estimate from our meta-analysis of all these studies demonstrates a favorable effect of OAs on BP in patients with OSA. While the OAs may widely differ in their design features, fabrication, and the maximum desirable mandibular protrusion, we believe that this meta-analysis adds to the therapeutic profile of OAs in OSA patients. Further research and randomized controlled trials are warranted involving a larger number of patients and longer treatment periods to determine if the beneficial effects of OAs on BP can be sustained over prolonged periods of time.

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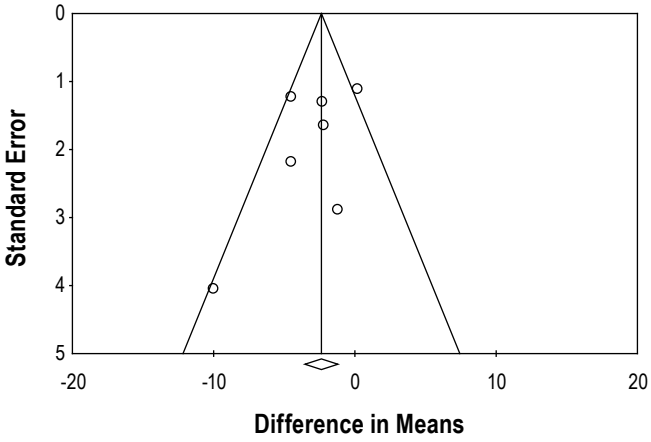
Address correspondence to: Imran Iftikhar, M.D., One Richland Medical Park, Suite 300, Columbia, South Carolina 29203; Tel: (803) 873-3193; E-mail: Imran.Iftikhar@uscmed.sc.edu

DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.

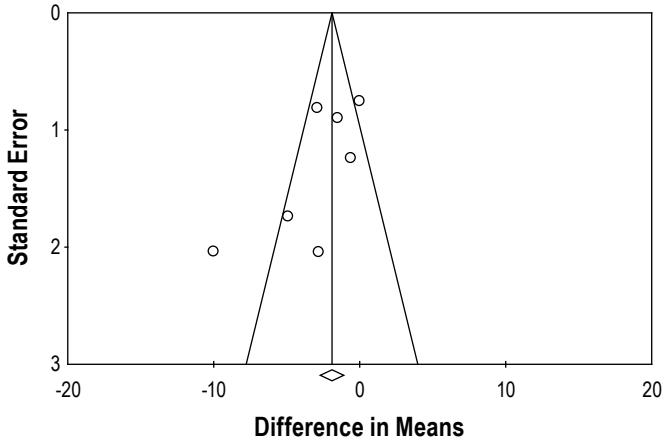
SUPPLEMENTAL MATERIAL

Figure S1—Funnel plot for the data on systolic blood pressure



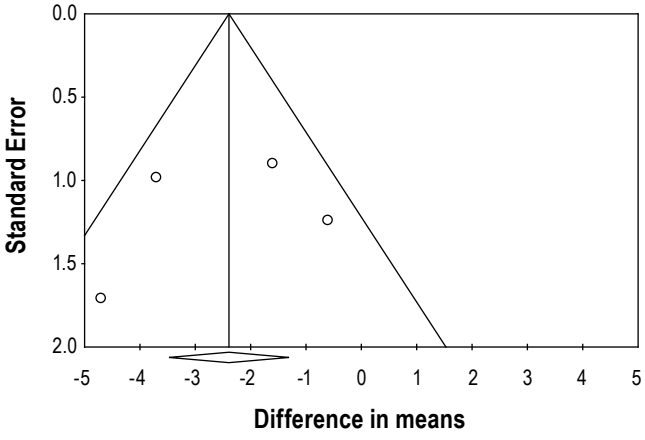
The Kendall's tau b (corrected for ties, if any) is -0.09524, with a 1-tailed p-value (recommended) of 0.3819.

Figure S2—Funnel plot for the data on diastolic blood pressure



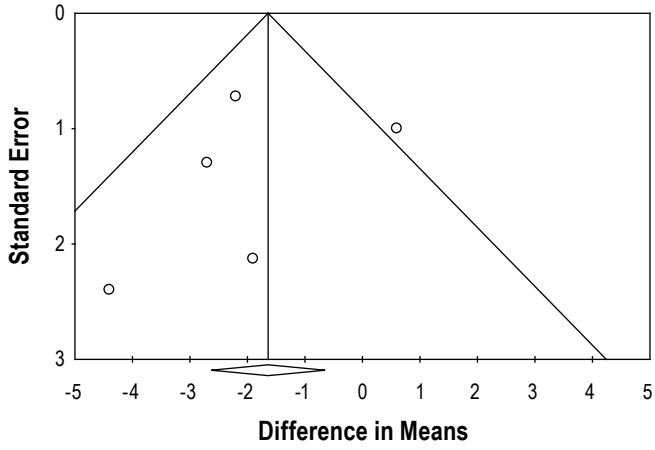
The Kendall's tau b (corrected for ties, if any) is -0.53333, with a 1-tailed p-value (recommended) of 0.06643.

Figure S3—Funnel plot for the data on mean arterial pressure



The Kendall's tau b (corrected for ties, if any) is 0.00000, with a 1-tailed p-value (recommended) of 0.50000

Figure S4—Funnel plot for the data on nocturnal diastolic blood pressure



The Kendall's tau b (corrected for ties, if any) is -0.10000, with a 1-tailed p-value (recommended) of 0.40325.