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META-ANALYSIS

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Patients with Obstructive Sleep Apnea Display Decreased Flow-Mediated Dilatation: Evidence from a Meta-Analysis

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Endothelial dysfunction, which can be measured by flow-mediated dilatation (FMD), is an early clinical marker of atherosclerosis, which is considered to be the main cause of the observed cardiovascular complications in obstructive sleep apnea (OSA) patients. The association between OSA and endothelial dysfunction has been reported in a number of studies; however, the findings are not entirely consistent. Our aim was to meta-analytically synthesize the existing evidence to explore the association between OSA and endothelial dysfunction.

Material/Methods: Data from PubMed, EMBASE, the Cochrane library, and Google Scholar for all trials that investigated the relationship between endothelial dysfunction and OSA were systematically reviewed. The minimum inclusion criteria for the studies were reporting of the Apnea-Hypopnea Index (AHI) and FMD measurements (as an indicator of endothelial dysfunction) for both OSA and control groups. Data from case-control studies that met the inclusion criteria were extracted.

Results: Twenty-eight studies comprising a total of 1496 OSA patients and 1135 controls were included in the meta-analysis. A random-effects model was used. The weighted mean difference in the FMD measurements was –3.07 and the 95% confidence interval was –3.71 to –2.43 ($P<0.01$). Meta-regression analysis showed that age, sex, body mass index (BMI), blood pressure, glucose, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol did not explain the heterogeneity.

Conclusions: This meta-analysis showed that patients with OSA have decreased FMD, which may contribute to the development of atherosclerosis.

MeSH Keywords: Sleep Apnea, Obstructive • Meta-Analysis as Topic • Atherosclerosis

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Background

Obstructive sleep apnea (OSA) is a chronic disorder characterized by repetitive apneas, oxygen desaturation, and disruption during sleep [1–3]. OSA affects 3%-24% of the general population and an even higher percentage (35–45%) of individuals who are obese or are suffering from diabetes mellitus (DM) [4–7]. Recent studies have found that OSA increases the risk of cardiovascular disease (CVD) independent of age, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), or smoking habit [8–10]. Importantly, atherosclerosis is considered to be the main cause of cardiovascular complications in OSA patients [11].

Endothelial dysfunction, as an early marker of atherosclerosis, correlates significantly with OSA [12]. In general, the multiple methods measuring markers of endothelial function were invasive procedures. Recently, flow-mediated dilatation (FMD) [13], a non-invasive method that evaluates nitric oxide (NO)-dependent vasodilatation, has been used to detect atherosclerosis in its subclinical phase. As a safe and convenient procedure, FMD is of interest for large-scale screening for endothelial dysfunction. However, studies examining the relationship between OSA and FMD have reported conflicting results. Therefore, we performed this meta-analysis to assess whether atherosclerosis could be detected based on brachial artery FMD in patients with OSA.

Material and Methods

The meta-analysis was performed in accordance with the recommendations of the Cochrane Collaboration and the Quality of Reporting of Meta-analyses (QUORUM) guidelines.

Data collection

Studies reported in English concerning OSA and endothelial function were identified by searching electronic databases, including PubMed, EMBASE, the Cochrane library, and Google Scholar. The databases were searched from the earliest available dates until May 16, 2016. Only those papers published with full-length text were considered. Unpublished data from scientific meetings were also searched but not included since their abstracts did not provide detailed data. The search terms used were “obstructive sleep apnea” or “sleep apnea” or “OSA” or “sleep-breathing disorders” and “flow-mediated” or “FMD” or “endothelial function” or “endothelial dysfunction” or “endothelium-dependent.” References for all relevant articles, review articles, and relevant non-electronic literature were searched manually to identify additional relevant studies. Two authors (Drs. Wang and Xu) individually searched and scored manuscripts for inclusion. Manuscripts were scored in duplicate, and if their scores differed, a third author (Dr. Guan) participated and inclusion was decided through discussion.

Inclusion and exclusion criteria

FMD was selected as a marker of endothelial function based on a review of the literature. Studies were included if they met the following criteria: (1) they were published in English and performed on adult humans; (2) full-text manuscripts were available; (3) they included at least two separate groups, one diagnosed with OSA and the other made up of control subjects without OSA; (4) OSA was diagnosed by polysomnography (PSG); (5) initial FMD values recorded by ultrasound were available; and (6) the reported values were presented as means and standard deviation or standard error or interquartile range. Studies were excluded from the analysis for the following reasons: (1) FMD was not used to measure endothelial function; (2) the results of comparison were not reported, or the data could not be extracted from the published results; (3) they were non-human studies, letters, reviews, or case reports; (4) the patients had other medical conditions that may have interfered with sleep, such as chronic respiratory disorders, heart failure, or uncontrolled allergies, or they were being treated with continuous positive airway pressure (CPAP); (5) the outcomes of the same patient group were reported in another publication (in that case, the higher-quality article was included); (6) the trials were not published in English. The definition of OSA varied in the different publications, because Apnea-Hypopnea Index (AHI) cutoffs in epidemiological investigations conducted to date have been variable. Thus, our meta-analysis also accepted OSA as defined by the authors and not by the AHI criteria.

Data extraction

Two reviewers (Dr. Wang and Xu) independently assessed the content of all studies to be included, and selected those that met the inclusion criteria while annotating the reasons for study exclusion. Included studies were carefully scanned and the following information was extracted: first author, year of publication, number of participants, subject demographics (age, sex, and BMI), AHI, FMD values, and confounding factors (SBP, DBP, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, and glucose).

For studies in which OSA groups were divided based on severity, all sets of data were combined into one single group. For example, Chami and colleagues [14] divided OSA patients into mild, moderate, and severe groups, and the control group into two groups (AHI 1.5–4.9, AHI <1.5). Therefore, we combined the three OSA groups as well as the two control groups into one OSA and one control group according to the methodology of the Cochrane Handbook (9.2.4 Effect measures for ordinal outcomes and measurement scales). If the study enrolled

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participants with other diseases, then the methodology was processed in the same way.

Statistical analysis

Continuous values such as FMD were analyzed using the weighted mean difference (WMD) and were reported with 95% confidence intervals (CIs). The WMD summarizes the differences between two groups with respect to continuous variables, while accounting for sample size. For studies that presented continuous data as means and SEs, the SDs were calculated using the formula $SD=SE\times\sqrt{n}$. For studies that presented continuous data as means and quartiles, the SDs were calculated using statistical algorithms according to the Cochrane Handbook: $SD=\frac{v73-v23}{1.35}$. We graphically inspected Forest plots and used I^2 statistics to evaluate heterogeneity. An I^2 of 25–49% was considered to represent a low level of heterogeneity, 50–74% a moderate level, and 75–100% a high level. A fixed-effects or random-effects model was used according to the heterogeneity between studies. Meta-regression and subgroup analysis were conducted to reveal potential sources of heterogeneity. The covariates in the regression analyses included age, sex, BMI, blood pressure, glucose, and HDL and LDL cholesterol. Subgroup analysis was used to assess the heterogeneity of race. Egger's test and funnel plots were used to test publication bias. The powers of the included studies were determined using Power and Precision V4 software. All meta-analyses were conducted using the Cochrane Collaboration's Review Manager Software version 5.0 and STATA version 12.0 (StataCorp., College Station, Texas, USA) software packages.

Results

Literature search

We identified 713 titles of potentially relevant articles from the literature search. From these, 622 articles were excluded based on preliminary title and abstract screening (irrelevant=361, case report or review=191, non-adult population=44, non-English=26). The remaining 91 studies were scanned for full-text evaluation, and a further 63 articles were excluded for the following reasons: 31 articles did not use FMD to measure endothelial function, 11 did not contain original data, 16 did not have a control group, 3 included OSA patients under CPAP treatment, and 2 used medians with a range (minimum, maximum) to measure FMD (Figure 1). Thus, 28 articles covering 1496 OSA patients and 1135 controls were finally included in the meta-analysis [11,12,14–39].

Study characteristics

A total of 28 articles providing 28 data sets were pooled for this meta-analysis. In these case-control studies, 11 were from

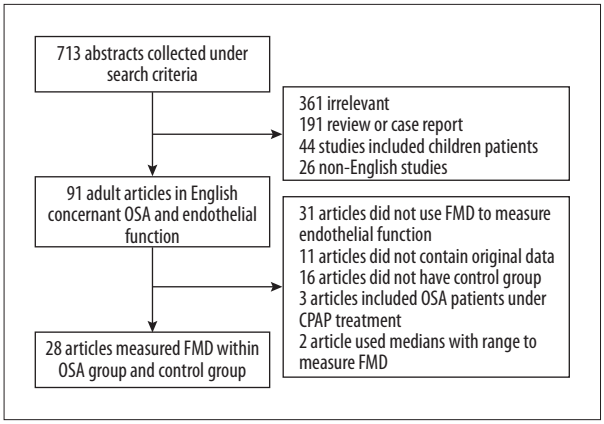

Figure 1. Flow diagram of included and excluded studies.

Asian researchers, 10 from American researchers, and 7 recruited patients from European countries. A total of 24 were clinically based, recruiting patients from hospitals or research centers, while 4 were population-based. Most studies used in-hospital complete PSG. There were no significant differences between the methods to measure FMD. The outcomes of the studies are discussed in Table 1.

Meta analysis of studies on OSA and FMD

The pooled data from the eligible studies suggested that FMD was significantly reduced in OSA patients. For FMD, the WMD was –3.07 and the 95% CI was –3.71 to –2.43 (P<0.00001). We re-performed another meta-analysis of studies using only full PSG to exclude the impact of portable monitoring devices. The relationship between OSA and FMD remained the same (WMD: –3.30, 95% CI: –3.83 to –2.78, P<0.00001). Significant heterogeneity was observed between the studies in both analyses (I^2=90%, I^2=78%). Thus, a random-effects model was applied (Figures 2, 3).

In addition, when studies with an inadequate number of OSA subjects (<20 in each group) [11,12,16,19,25–30,32–34,39] were excluded, according to the guidelines for the measurement of FMD [40], the pooled data also provided a robust result (WMD: –2.42, 95% CI: –3.32. to –1.52, P<0.001) (Supplementary Figure 1).

A power calculation showed that seven studies [14,16,21,23, 24,38,39] lacked sufficient power (<80%) (Table 2). However, their exclusion did not change the pooled result (WMD: –3.50, 95% CI: –4.04. to –2.96, P<0.001) (Supplementary Figure 2).

Meta-regression analysis, subgroup analysis, and publication bias

Multiple meta-regression analyses were performed to evaluate the effect of the covariant variables on FMD when reported.

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Table 1. Characteristics of the included case-control studies on OSAS and FMD.

Study	Study site	Based population	Study population	PSG assessment	FMD assessment	Outcome
Akdag S 2015 [15]	Turkey	Clinic-based	116 OSA 90 control	standard PSG OSA diagnosed with a AHI >5 h-1	20 and 25°C brachial artery inflation for 5 mins measure at 30 s, 60 s after deflation	FMD was significantly decreased in patients with OSA compared to controls
Ali A. El Solh 2007 [16]	USA	Clinic-based	14 OSA 10 control	PSG, device not mentioned OSA diagnosed with a AHI >5 h-1	Performed between 08:30 am and 09:30 am supine position right brachial artery inflation for 5 mins measure at 1 min after deflation	CPAP therapy led to a significant improvement in the decreased brachial artery vascular reactivity
Altintas N 2016 [17]	Turkey	Clinic-based	26 severe OSA 14 moderate OSA 40 control"	standard PSG OSA diagnosed with a AHI ≥5 h-1	Brachial artery inflation for 5 mins measure at 60 s after deflation	The FMD had significant and independent correlation with AHI
B.Jafari 2013 [18]	USA	Clinic-based	27 OSA 36 OSA+HTN 19 control 13 control+HTN	standard PSG OSA diagnosed with a AHI >5 h-1	Brachial artery inflation for 5 mins measure within 5 mins after deflation	There was a modest but significant negative correlation between AHI and FMD showing that the higher the AHI the lower the FMD
Bayram NA 2009 [19]	Sweden	Clinic-based	29 OSA 17 control	standard PSG OSA diagnosed with a AHI ≥5 h-1	Brachial artery 22–25°C inflation for 5 mins measure at 60 s after deflation	Patients with OSA display an impaired endothelium-dependent FMD in OSA, which can be improved after 6 months of CPAP treatment in complaint patients
Bruno RM 2013 [20]	Italy	Clinic-based	20 OSA without CVR 20 OSA with CVR 20 control	Standard PSG OSA diagnosed with a AHI ≥5 h-1	Brachial artery inflation for 5 mins measure within 15 s after deflation	OSAS is characterized by endothelial dysfunction and activation and impaired renal vasodilating capacity even in the absence of traditional cardiovascular risk factors
Chami HA 2009 [14]	USA	Community-based	272 OSA 410 control	In-home portable PSG OSA diagnosed with a AHI ≥5 h-1	Brachial artery inflation for 5 mins measure within 2 mins after deflation	No apparent association was observed between either measure of SDB and%FMD
Chung S 2007 [21]	Korea	Clinic-based	40 severe OSA 28 mild to moderate OSA 22 control	standard PSG OSA diagnosed with a AHI ≥5 h-1	Brachial artery inflation for 5 mins measure 3 times at 40, 60 and 80 s after deflation	FMD was decreased in OSA patients and was found to be correlated with ODI, average O2 saturation, lowest O2 saturation, systolic blood pressure, AHI, and BMI

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Table 1 continued. Characteristics of the included case-control studies on OSAS and FMD.

Study	Study site	Based population	Study population	PSG assessment	FMD assessment	Outcome
Chung S 2010 [22]	Korea	Clinic-based	44 severe OSA 39 mild to moderate OSA 29 control	Standard PSG OSA diagnosed with a AHI ≥5 h-1	Brachial artery inflation for 5 mins measure 3 times at 40,60 and 80s after deflation	FMD was significantly lower in the severe OSAS group than in the normal control group
Del Ben M 2012 [23]	Italy	Clinic-based	30 severe OSA 61 mild-moderate OSA 47 control	in-home portable PSG OSA diagnosed with a AHI ≥5 h-1	Brachial artery supine position inflation for 5 mins	Patients with OSAS and cardio metabolic comorbidities have increased oxidative stress and arterial dysfunction that are partially reversed by CPAP treatment
Faulx MD 2004 [24]	USA	Family-based	42 moderate to severe OSA 46 mild OSA 105 control	Standard PSG OSA diagnosed with a AHI ≥5 h-1	Brachial artery inflation for 5 mins	Women with SDB may be more vulnerable to early SDB-related cardiovascular disease than are men
Grebe M 2006 [25]	Germany	Clinic-based	10 OSA 10 control	OSA patients use standard PSG while controls were excluded with portable device OSA diagnosed with a AHI ≥5 h-1	Brachial artery supine position inflation for 5 mins measure at 60s after deflation	When compared with control subjects, baseline FMD was significantly reduced in the patients with OSA
Ip MS 2004 [11]	Hong Kong	Clinic-based	28 OSA 12 control	Standard PSG OSA diagnosed with a AHI≥15h-1	Brachial artery	Men with moderate/severe OSA have endothelial dysfunction and treatment with CPAP could reverse the dysfunction; the effect was dependent on ongoing use.
Jelic S 2008 [12]	USA	Clinic-based	30 OSA 15 control	Standard PSG OSA diagnosed with a AHI ≥5 h-1	Brachial artery according to the guidelines	OSA affects the vascular endothelium by promoting inflammation and oxidative stress while decreasing NO availability and repair capacity
Jelic S 2009 [26]	USA	Clinic-based	16 OSA 16 control	Standard PSG OSA diagnosed with a AHI ≥5 h-1	Brachial artery according to the guidelines	OSA alone impairs endothelial repair capacity and promotes endothelial apoptosis
Kanbay A 2016 [27]	Turkey	clinic-based	113 OSA 15 control	Standard PSG OSA diagnosed with a AHI ≥5 h-1	Brachial artery	Endocan levels were significantly higher and FMD measurements were lower in patients with OSA compared to healthy controls

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Table 1 continued. Characteristics of the included case-control studies on OSAS and FMD.

Study	Study site	Based population	Study population	PSG assessment	FMD assessment	Outcome
Kohler M 2008 [28]	UK	Clinic-based	64 OSA 15 control	standard PSG OSA diagnosed with a AHI ≥5 h-1	Brachial artery inflation for 5 mins measure at 60s after deflation	In patients with OSA, flow-mediated dilatation was significantly lower than in control subjects
Lederer DJ 2009 [29]	USA	Clinic-based	11 OSA 10 control	Standard PSG OSA diagnosed with a AHI ≥5 h-1	Performed between 09:00 am and 11:00 am	FMD were lower in patients with OSA compared with controls
Lee MY 2009 [30]	Taiwan	Clinic-based	14 OSA(UPPPs) 16 OSA(UPPPf) 15 control	Complete PSG OSA diagnosed with a RDI ≥5 h-1	Brachial artery at the dominant arm inflation for 5 mins measure at 60 s after deflation	Successful treatment of OSAS with UPPP leads to restoration of lower FMD
Namtvedt SK 2012 [31]	Norway	Population-based	37 OSA 34 control	Standard PSG OSA diagnosed with a AHI ≥10 h-1	Brachial artery supine position inflation for 5 mins measure at 2 mins after deflation	Endothelial function was found to be impaired in subjects with OSA
Oflaz H 2006 [32]	Turkey	Clinic-based	23 OSA 15 control	Standard PSG OSA diagnosed with a AHI ≥5 h-1	Brachial artery supine position 20 to 25°C inflation for 5 mins measure at 60s after deflation	We detected a prominent diurnal deterioration in endothelial function in normotensive OSAS patients compared with healthy subjects
Panoutsopoulos A 2012 [33]	Greece	Clinic-based	20 OSA male 18 control	Standard PSG OSA diagnosed with a AHI ≥5 h-1	Brachial artery 22 to 24°C inflation for 5 mins measure at 40–60 s after deflation	OSA group had significantly lower FMD value. There was a significant increase in the FMD values after CPAP treatment
Patt BT 2010 [34]	USA	Clinic-based	7 OSA 7 control	PSG, device not mentioned OSA diagnosed with a AHI ≥15 h-1	Brachial artery performed according to published guidelines	FMD was lower in patients than in control subjects at baseline and increased after treatment
Sert Kuniyoshi FH 2011 [35]	USA	Clinic-based	25 moderate to severe OSA 19 mild OSA 20 control	Standard PSG OSA diagnosed with a AHI ≥5 h-1	Brachial artery performed between 6:30 am and 7:30 am inflation for 5 mins measure at 60–90 s after deflation	FMD is severely impaired in patients with moderate to severe OSA post myocardial infarction
Tanriverdi H 2006 [36]	Turkey	Clinic-based	40 OSA 24 control	Standard PSG OSA diagnosed with a AHI ≥5 h-1	Brachial artery inflation 4–5 mins measure at 45–60 s after deflation	Subjects with OSA demonstrated lower FMD than the controls
YANG HB 2012 [37]	China	Clinic-based	49 OSA 35 control	Standard PSG OSA diagnosed with a AHI ≥5 h-1	Brachial artery 25°C inflation for 5 mins measure at 60–90 s after deflation	FMD was significantly lower in the OSA group than in the control group and was significantly improved 6 months after H-UPPP compared with preoperative FMD

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Table 1 continued. Characteristics of the included case-control studies on OSAS and FMD.

Study	Study site	Based population	Study population	PSG assessment	FMD assessment	Outcome
Yim-Yeh S 2010 [38]	USA	Community-based	38 OSA 34 control	Standard PSG OSA diagnosed with a AHI ≥5 h-1	Brachial artery 24–26°C inflation for 5 mins	In obesity, both OSA and aging impair endothelial function and increase arterial stiffness
Zhang L 2012 [39]	China	Clinic-based	32 OSA 18 control	Standard PSG OSA diagnosed with a AHI ≥5 h-1	Brachial artery according to guidelines	FMD was significantly lower in the OSA group compared with the non-OSAS group

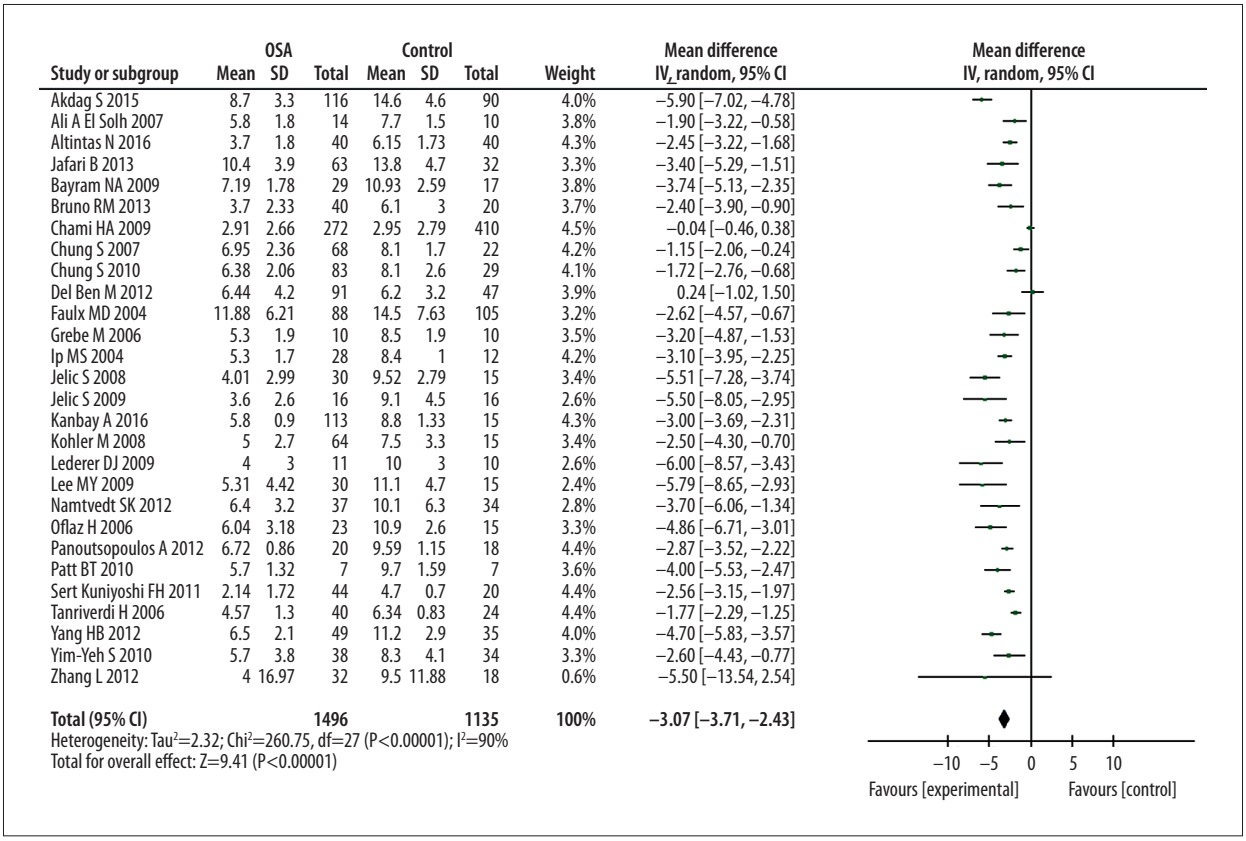

Figure 2. Forest plot summarizing the results of the random-effects meta-analysis of the association between OSA and FMD.

The confounding factors were recruited from the articles in which they were mentioned. Age (slope=0.149, P=0.136), sex (slope=6.970, P=0.095), BMI (slope=–0.014, P=0.817), SBP (slope=0.193, P=0.147), DBP (slope=0.204, P=0.080), glucose (slope=–0.058, P=0.486), triglycerides (slope=0.017, P=0.592), total cholesterol (slope=0.028, P=0.607), HDL cholesterol (slope=0.091, P=0.280) and LDL cholesterol (slope=–0.167, P=0.066) were shown to not have a significant effect as confounding factors (Table 3).

To study the effect of complications, such as hypertension, diabetes, dyslipidemia, and treatment, we conducted a subgroup analysis according to whether the recruited subjects were free of the above disorders. The result showed that there was a significant association between OSA and decreased FMD in subjects with (WMD: –2.83, 95% CI: –3.67 to –1.98, P<0.001) versus those without (WMD: –3.51, 95% CI: –4.41 to –2.60, P<0.001) these disorders (Supplementary Figure 3).

Another subgroup analysis was conducted trying to explain the heterogeneity. The pooled analysis was divided into three

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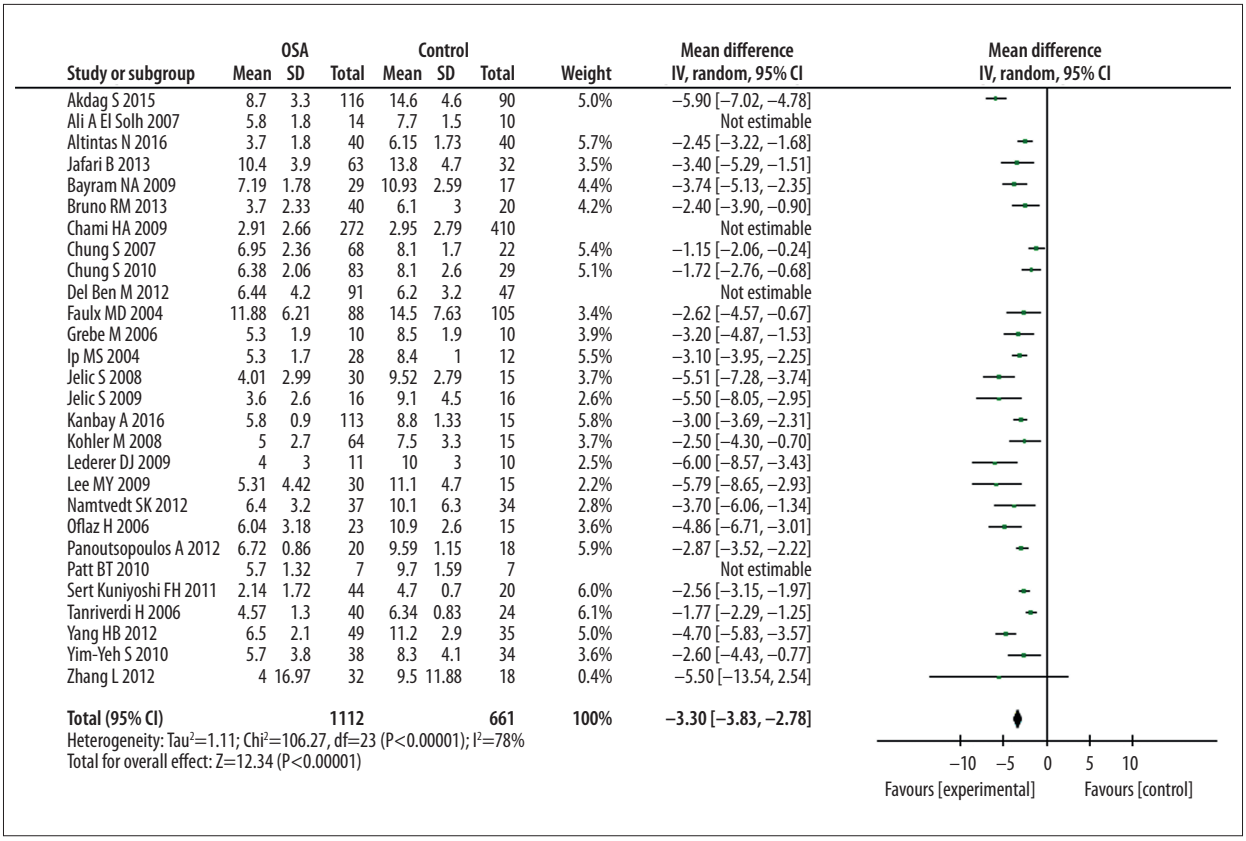

Figure 3. Forest plot summarizing the relationship between OSA and FMD within articles using only full PSG to diagnose OSA.

Table 2. Power calculation of all included articles.

Study	Power
Akdag S 2015 [15]	100%
Ali A El Solh 2007 [16]	74%
Altintas N 2016 [17]	100%
Jafari B 2013 [18]	96%
Bayram NA 2009 [19]	100%
Bruno RM 2013 [20]	92%
Chami HA 2009 [14]	5%
Chung S 2007 [21]	55%
Chung S 2010 [22]	95%
Del Ben M 2012 [23]	6%
Faulx MD 2004 [24]	75%
Grebe M 2006 [25]	95%
Ip MS 2004 [11]	100%
Jelic S 2008 [12]	100%

Study	Power
Jelic S 2009 [26]	98%
Kanbay A 2016 [27]	100%
Kohler M 2008 [28]	86%
Lederer DJ 009 [29]	99%
Lee MY et al. 2009 [30]	98%
Namtvedt SK 2012 [31]	88%
Oflaz H 2006 [32]	100%
Panoutsopoulos A 2012 [33]	100%
Patt BT 2010 [34]	100%
Sert Kuniyoshi FH 2011 [35]	100%
Tanriverdi H 2006 [36]	100%
Yang HB 2012 [37]	100%
Yim-Yeh S 2010 [38]	79%
Zhang L 2012 [39]	22%

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Table 3. Meta-regression of all confounding factors.

Confounding factors	Involved articles	OSA subjects	Control subjects	Slope	P value
Age	28	1496	1135	0.149	0.136
Gender	28	1496	1135	6.970	0.095
BMI	26	1389	1083	–0.014	0.817
SBP	20	1039	865	0.193	0.147
DBP	20	1039	865	0.204	0.080
Glucose	15	714	334	–0.058	0.486
Triglycerides	14	767	413	0.017	0.592
TC	22	942	556	0.028	0.607
HDLc	14	796	500	0.091	0.280
LDLc	10	565	385	–0.167	0.066

BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; TC – total cholesterol; HDLc – high-density lipoprotein cholesterol; LDLc – low-density lipoprotein cholesterol.

subgroups according to continent. Thus, 11 studies were from Asia, 10 were from the USA, and 7 were from Europe. In all of the subgroups, decreased FMD was related to OSA: the WMD (95% CI) values from each subgroup were –2.68 (–2.96 to –2.40), –1.46 (–1.76 to –1.16), and –2.54 (–3.00 to –2.09), respectively. The I^2 values from the three subgroups were 88%, 92%, and 75%, respectively (Asia, America, and Europe). In the European subgroup, the heterogeneity was no longer apparent (I^2=0%) (WMD: –3.03, 95% CI: –3.55. to –2.51) after the two studies that recruited subjects from Italy were excluded (Figures 4, 5).

Egger's test (P=0.249) and funnel plot (Figure 6) showed no evidence of publication bias.

Discussion

To the best of our knowledge, this is the first meta-analysis to pool the available data and provide a summary of the relationship between decreased FMD and OSA patients. Twenty-eight studies, pooling 1496 OSA patients and 1135 controls, were included. FMD was found to be significantly lower in OSA patients than in the controls.

Though many previous studies have assessed the relationship between OSA and endothelial dysfunction, the results are conflicting. The majority of studies reviewed for this analysis reported a decrease in FMD in OSA patients compared with controls. After summarizing all of the data, our results showed a statistically significantly lower FMD in OSA patients than in controls. In addition, the results of several studies support a correlation between OSA and decreased FMD, while also demonstrating that FMD values become even smaller as the severity of OSA increases. In those studies, the subjects were divided into control, mild, moderate, and severe OSA groups [21–24,35], and the results showed that moderate-severe OSA patients suffered more from decreased FMD compared with mild OSA patients. However, it is regrettable that the validity of this relationship remains to be established due to the small number of relevant studies; thus, large-scale studies are required to obtain high-level evidence.

The mechanism underlying OSA impairment of endothelial function is unclear but is likely to involve several pathways. The three acute consequences of OSA, intermittent hypoxia, intrapleural pressure swings, and recurrent arousals, are thought to be the main causes of impaired endothelial function [41–43]. Of these, intermittent hypoxia is considered the most important factor promoting the production of reactive oxygen species (ROS), thereby increasing oxidative stress and decreasing nitric oxide (NO) synthetase activity. This causes an attenuation of NO and an impairment of endothelial function [43,44].

Whether OSA is independently associated with decreased FMD is controversial. Some studies [21,31,33,39] have reported that age, BMI, and SBP were correlated with FMD; in contrast, others [11,19,36] found no significant relationship between FMD and age, BMI, SBP, DBP, lipids, or fasting glucose

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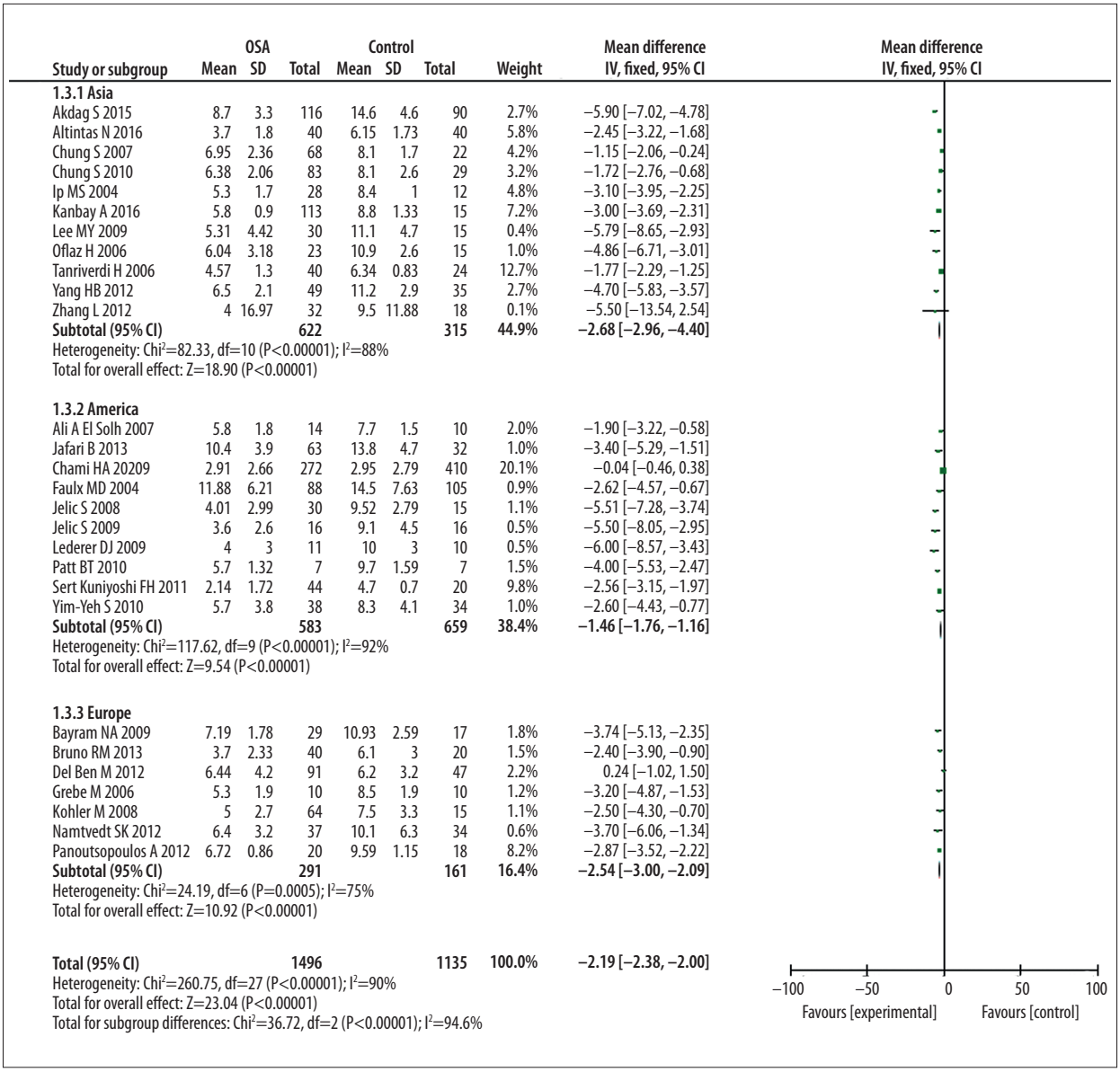

Figure 4. Meta-analysis of the relationship between OSA and FMD according to the geographical location of the patients.

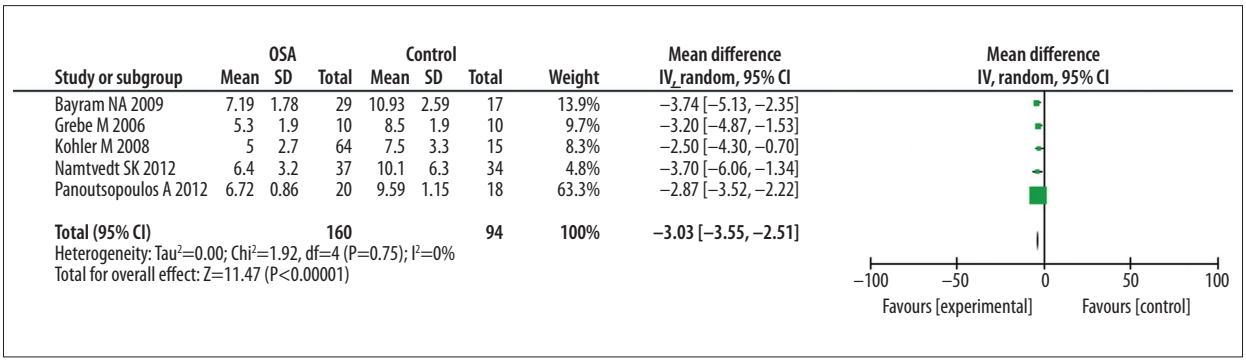

Figure 5. Meta-analysis of the relationship between OSA and FMD in Europe (excluding studies recruiting subjects from Italy).

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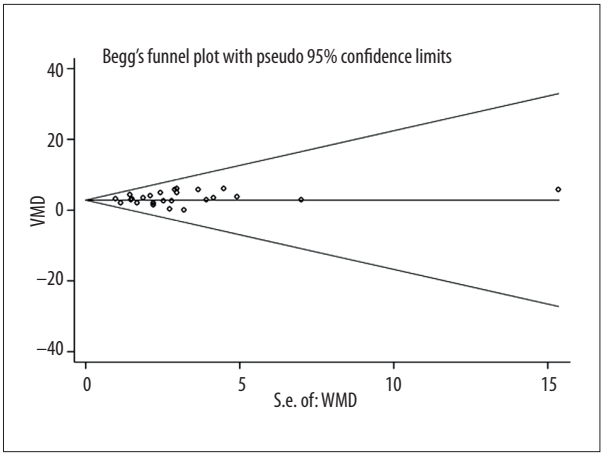

Figure 6. Begg's funnel plot.

levels. Sex may be another confounding factor. Faulx et al. [24] showed an association between moderate OSA and impaired endothelial function in females. Females were also more vulnerable than males to early OSA-related cardiovascular diseases. After adjustment for variables significantly associated with FMD, Namtvedt et al. [31] and Jelic et al. [26] reported an independent association between increasing AHI and a reduction in FMD. According to Chami et al. [14], however, there was no apparent association between OSA and FMD after adjustment for age, sex, race, and all covariates. Since the data in the majority of included studies were not adjusted for covariates, significant findings about the impact of confounding factors cannot be obtained.

Heterogeneity was observed in our meta-analysis; meta-regression and subgroup analysis were conducted to determine the potential sources of the heterogeneity. Meta-regression analysis excluded age, sex, BMI, blood pressure, glucose, HDL cholesterol, and LDL cholesterol as sources of heterogeneity. Subgroup analysis suggested that ethnicity explained at least part of the heterogeneity. The European subgroup exhibited an I^2 of 75%; however, the exclusion of two studies that recruited subjects from Italy lessened the heterogeneity (I^2=0%). We assumed that this was due to ethnic diversity among the subgroups, leading to different physiological responses. Other factors may also have contributed to the heterogeneity. The majority of studies included were clinically rather than community based, which could have introduced referral bias, resulting in heterogeneity. Also, FMD might be affected by environmental effects such as noise, temperature, alcohol, caffeine, or fasting. Although these factors were well controlled in the majority of studies according to the methods described by Celermajer et al. [45], variations among studies are possible.

Multiple limitations in this meta-analysis should be addressed. First, the included studies were limited to publications in English, which may have increased the possibility of publication bias. In addition, it is known that positive results are more likely to be published; since we included data only from published studies, publication bias was likely. Second, no randomized controlled trials and no prospective studies were identified. Third, this meta-analysis was not an overview of all methods of evaluating endothelial dysfunction. Other indicators of endothelial function, such as NO levels, endothelin-1 (ET-1) levels, measurements of circulating endothelial cells (CECs), and peripheral artery tonometry (PAT), were not searched for and evaluated. Also, most included articles did not clearly describe their OSA patients, such as with respect to compliance and complications, both of which may affect the results. Nonetheless, the subgroup analysis showed that decreased FMD was related to OSA in all subgroups. Recently, several articles [31,46] declared that FMD is concomitantly dependent on initial artery diameter, which may itself be higher in OSA patients. Thus, future studies should carefully consider initial artery diameter. Other limitations pertaining to the methods of the individual studies included in this meta-analysis should also be addressed. Finally, some of the included studies lacked enough power to detect an association or were not based on the use of standard PSG to diagnose OSA, but our results were also robust when these inadequate studies were excluded.

Conclusions

OSA significantly decreases FMD in OSA patients compared with controls. Future larger randomized studies of longer duration should focus on the effect of treatment of OSA on endothelial dysfunction.

Disclosure

The investigators have no financial associations with any entity with an interest in the subject of this study. There was no funding from any institution.

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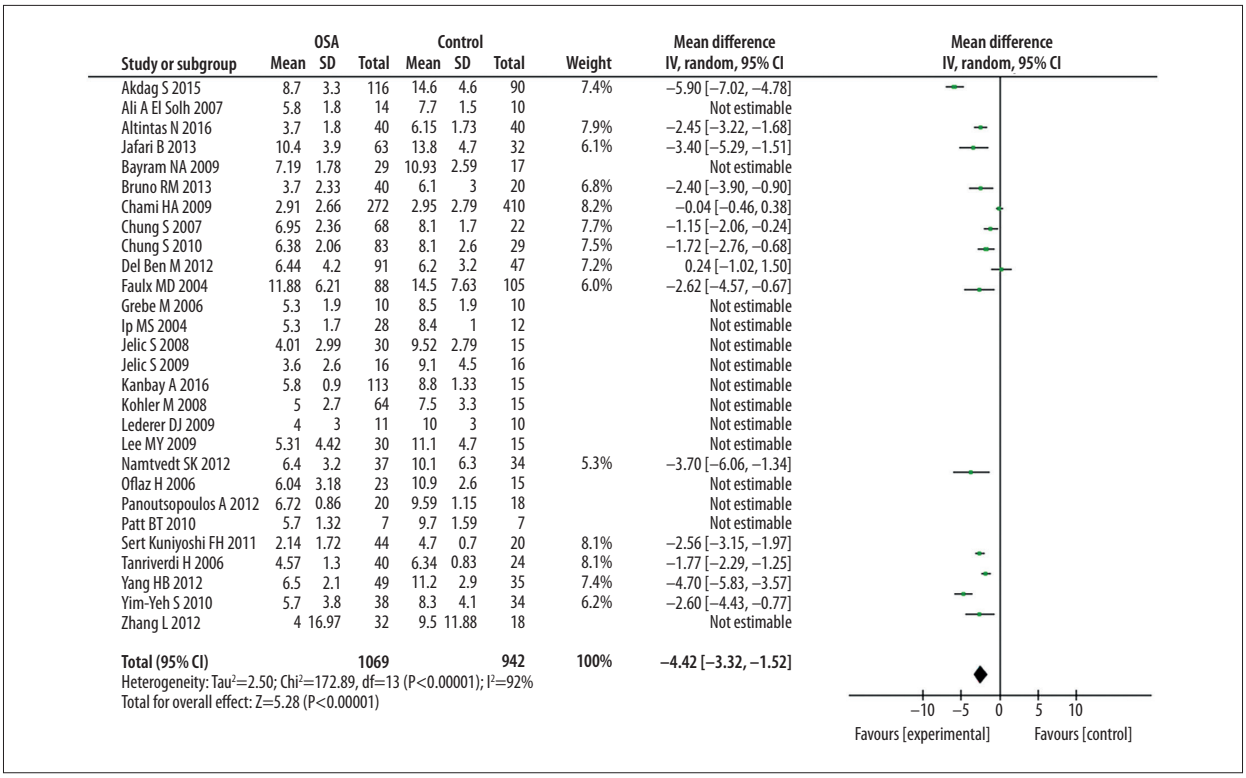
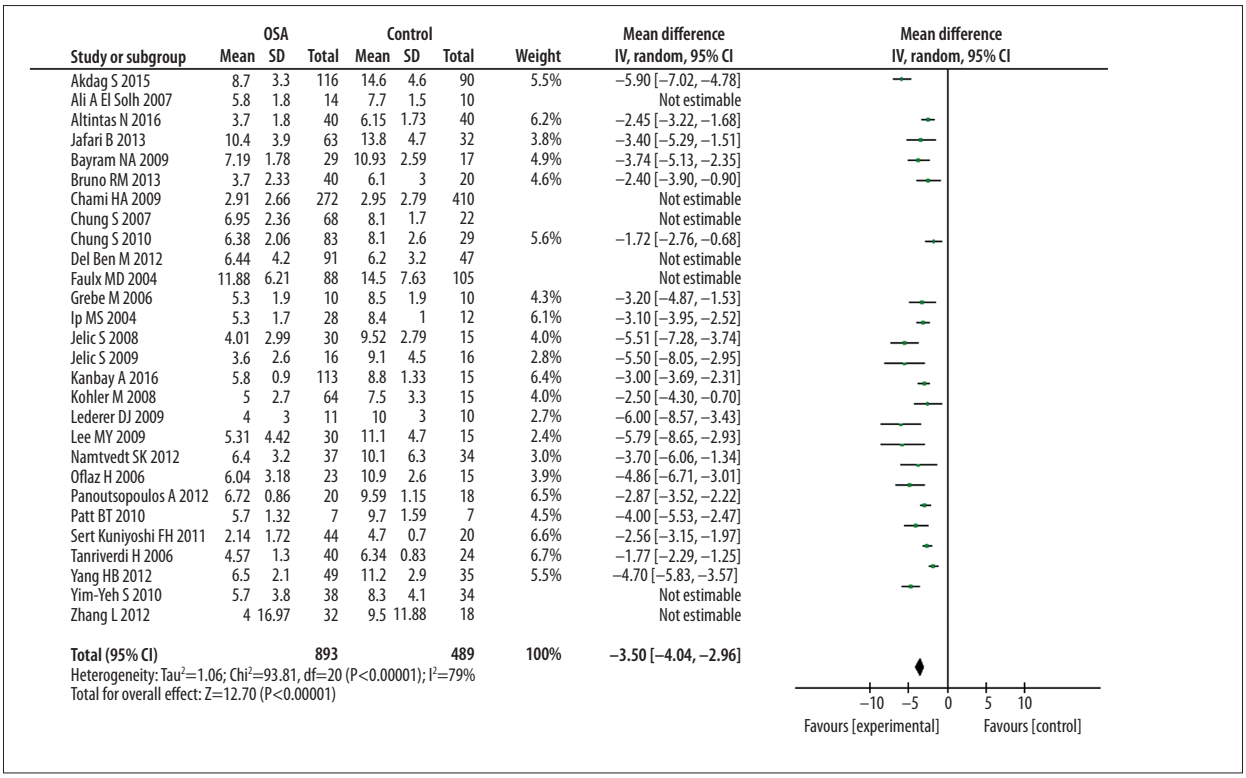
Supplemenatry Figures



Supplementary Figure 1. Forest plot excluding studies with an inadequate number of OSA subjects (<20 in each group).



Supplementary Figure 2. Forest plot excluding studies lacked sufficient power (<80%).

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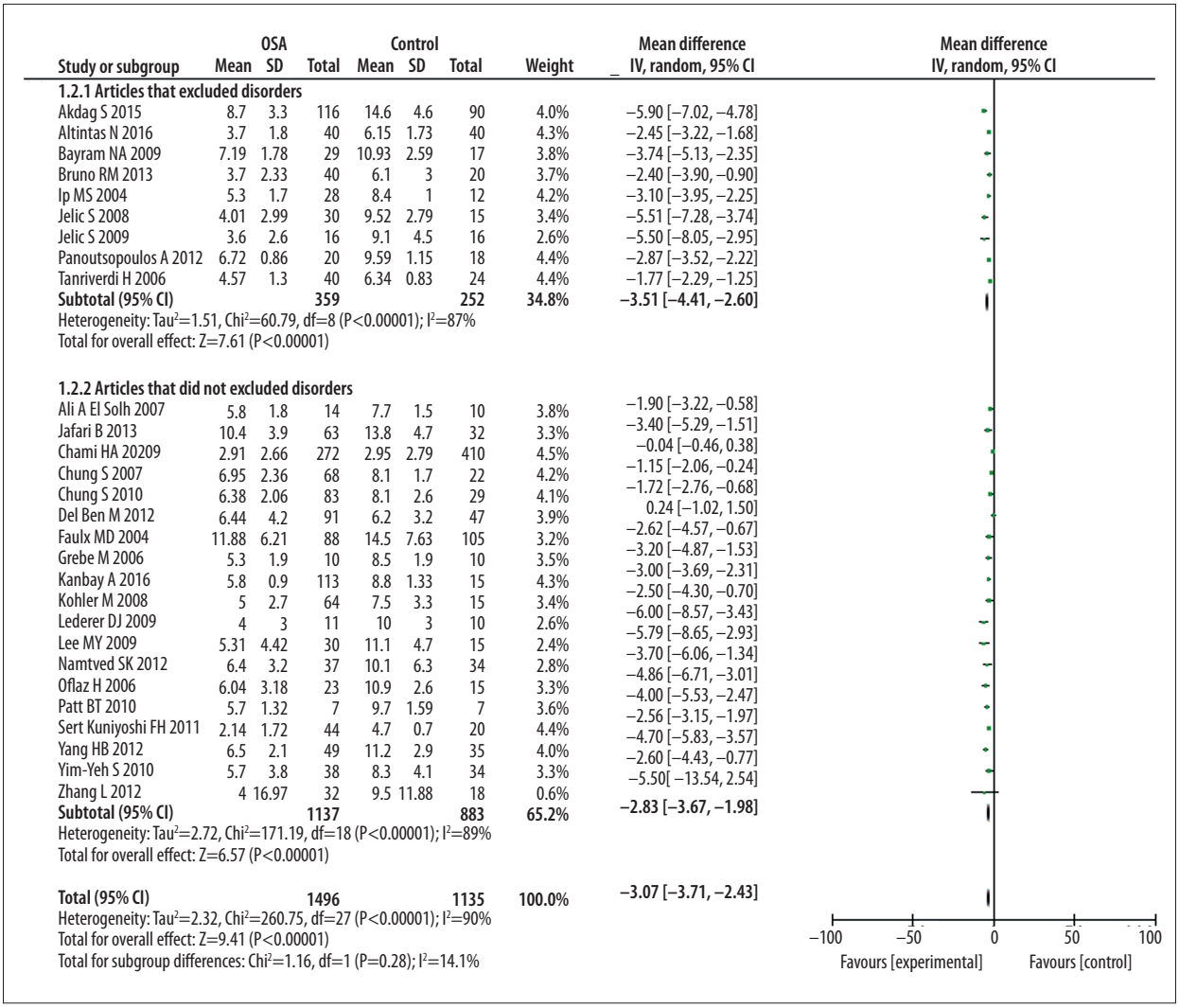

Supplementary Figure 3. Meta-analysis of the relationship between OSA and FMD according to whether other disorders were excluded or not.

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