Sleep and Breathing (2019) 23:1115–1122
https://doi.org/10.1007/s11325-019-01795-6

SLEEP BREATHING PHYSIOLOGY AND DISORDERS • ORIGINAL ARTICLE

Association of continuous positive airway pressure with F2-isoprostanes in adults with obstructive sleep apnea: a meta-analysis

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Received: 13 November 2018 / Revised: 21 January 2019 / Accepted: 26 January 2019 / Published online: 7 February 2019

Abstract

Purpose Obstructive sleep apnea (OSA) is associated with increased F2-isoprostanes, a reliable standard biomarker of oxidative stress. Treatment with continuous positive airway pressure (CPAP) is effective for all degrees of OSA. However, it remains unknown whether treatment with CPAP will decrease F2-isoprostanes. A meta-analysis was conducted to determine the effect of CPAP treatment on F2-isoprostanes among patients with OSA.

Methods The PubMed, Embase, Web of Science, and Cochrane library were searched before September, 2018. Eight articles assessing indices of F2-isoprostanes from various body fluids were identified. Pooled standardized mean difference (SMD) and weighted mean difference (WMD) were appropriately calculated through fixed or random effects models after assessing between-study heterogeneity.

Results A total of 4 studies with 108 patients were pooled for exhaled breath condensate (EBC) F2-isoprostanes; 3 studies with 93 patients were pooled for serum or plasma F2-isoprostanes; and 3 studies with 102 patients were pooled for urinary F2-isoprostanes. A significant decrease of EBC F2-isoprostanes was observed after CPAP treatment (WMD = 2.652, 95% CI = 0.168 to 5.136, $z = 2.09$, $p = 0.036$), as well as serum or plasma F2-isoprostanes and urinary F2-isoprostanes (SMD = 1.072, 95% CI = 0.276 to 1.868, $z = 2.64$, $p = 0.008$ and WMD = 85.907, 95% CI = 50.443 to 121.372, $z = 4.75$, $p = 0.000$, respectively).

Conclusions This meta-analysis suggested that CPAP therapy was associated with a significant decrease in F2-isoprostanes in patients with OSA.

Keywords Obstructive sleep apnea · Continuous positive airway pressure · Oxidative stress · F2-isoprostanes · Meta-analysis

Zhi-Wei Huang, Wu Ouyang and Liang-Ji Zhang contributed equally to this work.

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Introduction

Obstructive sleep apnea (OSA) is a sleep disorder characterized by multiple-level narrowing of the upper airway, which causes recurrent partial or complete obstruction of the upper airway during sleep. It is a highly prevalent disease affecting 2–4% of the adult population and 35–45% of obese individuals [1, 2]. There is clear evidence that untreated OSA is an independent risk factor for cardiovascular and cerebrovascular morbidity and mortality [3–5]. The association of increased cardiovascular risk and OSA is believed to be mediated by several intermediary mechanisms such as sympathetic activation and oxidative stress [6].

Oxidative stress describes a condition occurring when the physiological balance between oxidants and antioxidants is disrupted in favor of the former with potential damage for the organism. Various oxidants, particularly reactive oxygen species (ROS), can be generated endogenously or derived from

exogenous sources such as radiation, tobacco smoke, and drugs. Excessive accumulation of ROS can cause damage to biomolecules, including lipids, proteins, and nucleic acids. The repeated episodes of hypoxia and reoxygenation that cause ischemia–reperfusion events are currently believed to result in the generation of ROS and oxidative stress [7]. Oxidative stress may lead to endothelial dysfunction, vascular inflammation, and atherosclerosis, playing a major role in the initiation and progression of cardiovascular disease in OSA [3].

The increase of oxidative stress in OSA patients has been demonstrated using various biomarkers, among which a widely studied biomarker is F2-isoprostanes [8, 9]. F2-isoprostanes are prostaglandin-like compounds formed from free fatty acids. F2-isoprostanes are considered to be a reliable standard biomarker of oxidative stress in vivo, due to their high sensitivity and specificity, stability, and detectability in a variety of body fluids including exhaled breath condensate (EBC), plasma, and urine [10, 11].

Continuous positive airway pressure (CPAP), which keeps the airway open during sleep, is the most common and effective nonsurgical treatment for OSA patients. Whether F2-isoprostanes in various body fluids may be influenced or not by CPAP treatment in patients with OSA is unclear. The purpose of the present meta-analysis was to quantitatively evaluate the efficacy of CPAP treatment on F2-isoprostanes, an established stable marker of oxidative stress, in OSA patients.

Methods

This meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Statement for the conduct of meta-analyses of intervention studies [12].

Search strategy

We searched for publications in Embase, Web of Science, PubMed, and Cochrane Library database up to September 9, 2018. Searches combined free-text and MeSH terms. The search comprised the following terms: “continuous positive airway pressure or (CPAP)” and “sleep apnea or sleep apnoea or (OSA)” combined with “isoprostane.” Additionally, reference lists from the retrieved articles were reviewed for identifying any additional articles.

Study selection

Studies had to meet the following criteria to be included in the meta-analysis: (1) the study populations were limited to adult patients with newly diagnosed OSA, (2) the intervention was an application of CPAP therapy and the period of follow-up was ≥ 4 weeks, (3) the studies included F2-isoprostanes measurements before and after CPAP treatment, (4) the study provided sufficient data that allowed for a meta-analysis.

Studies that did not satisfy the inclusion criteria were excluded. Other exclusion criteria were as follows: (1) abstracts, expert opinions, case reports, letters, editorials, reviews without original data, and animal studies; (2) non-English article. If any of the required data could not be found in the published report, the corresponding author was contacted to provide the missing data of interest.

Two researchers independently assessed the titles and abstracts that were identified by the searches. Conflicting decisions were resolved through a consensus with a third researcher. Full articles were obtained when they appeared to meet the inclusion criteria, or there were insufficient data in the title and abstract to make a clear decision for their inclusion. The decision for the inclusion was made after reviewing the full articles.

Data extraction

Data were extracted from each study by a single researcher and then reviewed by a second researcher to ensure that no errors were made. These data were the first author, year of publication, the country in which the work was performed, number of subjects, patient inclusion criteria, mean daily CPAP usage time, duration of CPAP intervention, F2-isoprostanes measurement, study design, sample source, participant characteristics, and F2-isoprostanes before and after CPAP treatment.

Statistical analysis

In both EBC sample and urine sample group, the pooled estimate of the weighted mean difference (WMD) and 95% confidence interval (CI) were calculated, as the outcome measurements were the same for each analysis. In the blood sample group, the standardized mean difference (SMD) and 95 CI% were used as a summary effect size estimator, as the absolute value of outcome between included studies varied greatly. Q test and I^2 tests were used to assess between-study heterogeneity. If a p value was < 0.10, the existence of statistical heterogeneity was suggested and the data were analyzed using a random effects model. Otherwise, the data were considered to be homogeneous and a fixed model was employed. Publication bias was statistically evaluated with Egger’s and Begg’s tests. A two-sided p value of less than 0.05 was considered as significant. All calculations were performed with Stata statistical software (version 12.0, Stata Corporation).

Results

Searching results

A total of 77 studies were initially identified by electronic and manual searching. After reviewing the titles and abstracts, 11 studies were considered to be potentially relevant. Of these, 3 studies were excluded for the following reasons: therapy duration of 2 studies was less than 4 weeks [13, 14], one was a pediatric study [15]. The detailed steps of the literature search were presented in Fig. 1.

Characteristics of the studies

Eight studies meeting the inclusion criteria were included in the meta-analysis: 4 studies assessed EBC F2-isoprostanes [16–19], 3 studies assessed serum or plasma F2-isoprostanes [18–20], 3 studies assessed urinary F2-isoprostanes [21–23]. Two studies were randomized controlled trials (RCTs) [20, 23], while others were observational studies. The characteristics of included studies for assessing F2-isoprostanes from different sample sources are summarized in Tables 1, 2, and 3, respectively.

Results for EBC F2-isoprostanes

Four studies comprising 108 patients assessed the influence of CPAP treatment on EBC F2-isoprostanes in OSA patients. The results showed that CPAP treatment had a favorable effect on the reduction of EBC F2-isoprostanes in these OSA subjects (WMD = 2.652, 95% CI = 0.168 to 5.136, $z = 2.09$, $p = 0.036$) with evidence of significant heterogeneity (chi-squared = 21.87, $p = 0.000$; I^2 = 86.3%) (Fig. 2a). A random effects model was used for the pooled analysis. Egger's tests ($p = 0.991$) and Begg's tests ($p = 1.000$) did not find significant publication bias (Fig. 2b). We excluded data from the report by Li et al. [18], and the I^2 index changed to 0.00(chi-squared = 1.29, $p = 0.526$). After excluding this study, the results remained significant (WMD = 1.571, 95% CI = 0.665 to 2.477, $z = 3.40$, $p = 0.001$).

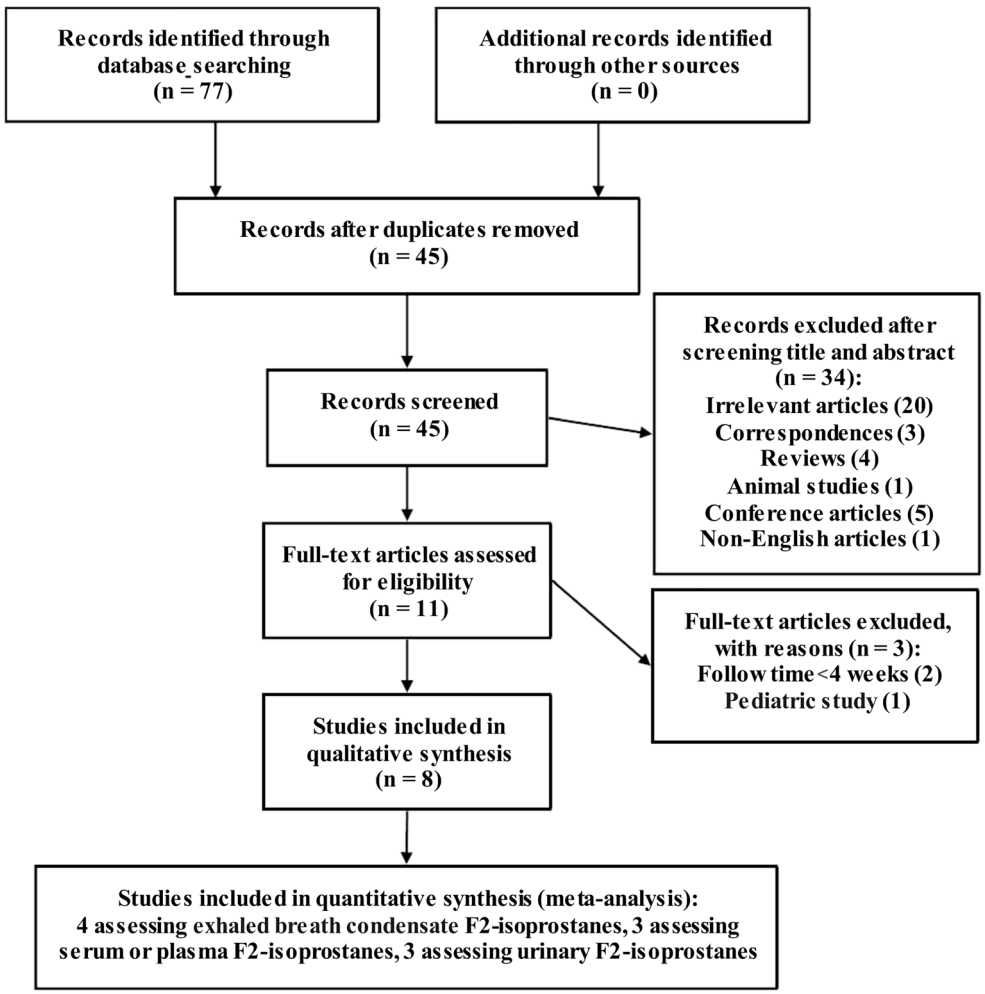

Fig. 1 Flow diagram of study selection

Table 1 Characteristics of included studies for assessing exhaled breath condensate F2-isoprostanes

Study	Year	Nation	Sample size/male	Inclusion criteria	Ventilation duration/night (h)	Therapy duration (M)	Measurement	Study design	Age	BMI	AHI	$LowSO_2$	Pre-CPAP F2-isoprostanes	Post-CPAP F 2 - isoprostanes
Petrosyan	2008	Greece	20/NR	AHI > 20	4.3 ± 1.7	1	EIA	OS	55.4 ± 14.1 (n = 26)	37.5 ± 10.0 (n = 26)	63.7 ± 29.5 (n = 26)	NR	11.6 ± 5.7 pg/ml	11.8 ± 8.7 pg/ml
Li	2008	China	33/NR	AHI ≥ 5	5.7 ± 1.9	2	EIA	OS	NR	NR	45.7 ± 24.9	61.9 ± 14.8	20.1 ± 3.0 pg/ml	14.8 ± 2.5 pg/ml
Karamanli	2014	Turkey	35/21	AHI ≥ 15	5.8 (4.2–7.7)*	3	EIA	OS	52.5 ± 10.3	NR	45.6 ± 22.1	72.1 ± 13	5.7 ± 7.9 pg/ml	3.0 ± 1.6 pg/ml
Fernandez Alvarez	2016	Spain	20/10	AHI ≥ 5	> 4	4	EIA	OS	53 ± 12	35 ± 6	42 ± 18	77 ± 8	6.8 ± 1.9 pg/ml	5.3 ± 1.2 pg/ml

NR not reported, *AHI* apnea-hypopnea index, *h* hour, *M* month, *EIA* enzyme immunoassay kit, *OS* observational study, *BMI* body mass index, *$LowSO_2$* lowest O_2 saturation, *CPAP* continuous positive airway pressure

*Mean (range)

Table 2 Characteristics of include studies for assessing serum or plasma F2-isoprostanes

Study	Year	Nation	Sample size/male	Inclusion criteria	Ventilation duration/night (h)	Therapy duration (M)	Measurement	Study design	Age	BMI	AHI	$LowSO_2$	Pre-CPAP F2-isoprostanes	Post-CPAP F2-isoprostanes
Li	2008	China	33/NR	AHI ≥ 5	5.7 ± 1.9	2	EIA	OS	NR	NR	45.7 ± 24.9	61.9 ± 14.8	29.8 ± 5.7 pg/ml	20.6 ± 3.7 pg/ml
Alonso-Fernandez	2009	Spain	25/25	AHI ≥ 10	6.2 ± 1.1	3	EIA	RCT	52 ± 13 (n = 31)	30.5 ± 4.0 (n = 31)	43.8 ± 27.0 (n = 31)	72 ± 15 (n = 31)	40.6 ± 27.1 pg/ml	24.8 ± 15.0 pg/ml
Karamanli	2014	Turkey	35/21	AHI ≥ 15	5.8 (4.2–7.7)*	3	EIA	OS	52.5 ± 10.3	NR	45.6 ± 22.1	72.1 ± 13	103.4 ± 162.8 pg/ml	32.3 ± 24.1 pg/ml

R not reported, *AHI* apnea-hypopnea index, *h* hour, *M* month, *EIA* enzyme immunoassay kit, *OS* observational study, *RCT* randomized controlled trial, *BMI* body mass index, *$LowSO_2$* lowest O_2 saturation, *CPAP* continuous positive airway pressure

*Mean (range)

Table 3 Characteristics of include studies for assessing urinary F2-isoprostanes

Study	Year	Nation	Sample size/male	Inclusion criteria	Ventilation duration/night (h)	Therapy duration (M)	Measurement	Study design	Age	BMI	AHI	$LowSO_2$	Pre-CPAP F2-isoprostanes	Post-CPAP F2-isoprostanes
Minoguchi	2006	Japan	20/20	AHI ≥ 15	4.8 ± 1.3	3	EIA	OS	49.3 ± 15.7	28.9 ± 2.7	46.5 ± 43.8	70.9 ± 35.3	412.6 ± 225.8 pg/ml Cr	246.2 ± 53.2 pg/ml Cr
Del Ben	2012	Italy	10/10	AHI ≥ 30	≥ 4	6	EIA	OS	NR	35.3 ± 5.4	43.4 ± 12.6	NR	350.5 ± 43.3 pg/mg Cr	269.6 ± 48.4 pg/mg Cr
Mar	2016	USA	72/NR	AHI ≥ 15	4.5 (2.6–5.7)*	2	EIA	RCT	50.3 ± 11.7 (*n* = 75)	37.3 ± 8.1 (*n* = 75)	19.1 (12.5–35.1) *(*n* = 75)	NR	502 ± 375 pg/mg Cr	474 ± 310 pg/mg Cr

NR not reported, *AHI* apnea-hypopnea index, *h* hour, *M* month, *EIA* enzyme immunoassay kit, *OS* observational study, *RCT* randomized controlled trial, *BMI* body mass index, $LowSO_2$ lowest O_2 saturation, *CPAP* continuous positive airway pressure, *Cr* creatinine

*Median (interquartile range)

Results for serum or plasma F2-isoprostanes

Three studies including 93 patients assessed the effect of CPAP treatment on serum or plasma F2-isoprostanes in patients with OSA. The heterogeneity test showed that there were significant differences across individual studies (chi-squared = 12.80, $p = 0.002$; $I^2 = 84.4\%$). A random effects model was used for the pooled analysis. Pooling the data showed that CPAP was associated with a statistically significant decrease in serum or plasma F2-isoprostanes among OSA patients (SMD = 1.072, 95% CI = 0.276 to 1.868, $z = 2.64$, $p = 0.008$) (Fig. 3a). There was no statistical significance of publication bias in the present meta-analysis (Egger's test, $p = 0.526$; Begg's test, $p = 0.296$) (Fig. 3b). We excluded data from the report by Li et al. [18], and the I^2 index changed to 0.00 (chi-squared = 0.08, $p = 0.772$). After excluding this study, the results remained significant (SMD = 0.656, 95% CI = 0.289 to 1.024, $z = 3.50$, $p = 0.000$).

Results for urinary F2-isoprostanes

With respect to urinary F2-isoprostanes, a total of 3 studies with 102 patients were included. No significant heterogeneity was detected among the studies (chi-squared = 3.51, $p = 0.173$; $I^2 = 43.1\%$). A fixed effects model was used for the pooled analysis. The results showed that CPAP produced statistically significant reductions in the urinary F2-isoprostanes of study participants (WMD = 85.907, 95% CI = 50.443 to 121.372, $z = 4.75$, $p = 0.000$) (Fig. 4a). The publication bias was not considered significant. Neither the Egger's test ($p = 0.874$) nor the Begg's test ($p = 1.000$) showed publication bias (Fig. 4b).

Discussion

This study aimed to clarify the effects of CPAP on a reliable biomarker of oxidative stress, namely, F2-isoprostanes, in patients suffering from OSA through the meta-analysis. The results demonstrated that CPAP therapy significantly lowered EBC, serum or plasma, and urinary F2-isoprostanes levels.

This meta-analysis had several strengths that increase confidence to our findings. First, to the best of our knowledge, this was the first meta-analysis to determine the impact of OSA treatment with CPAP on F2-isoprostanes in subjects with OSA. Second, pooling of information from all eligible yielded more precise and reliable results than data from individual studies. Third, the analysis showed that there was no evidence to support publication bias in our study. Finally, the results of EBC, blood, and urine group were consistent, supporting a favorable effect of CPAP treatment on decreasing oxidative stress among patients with OSA.

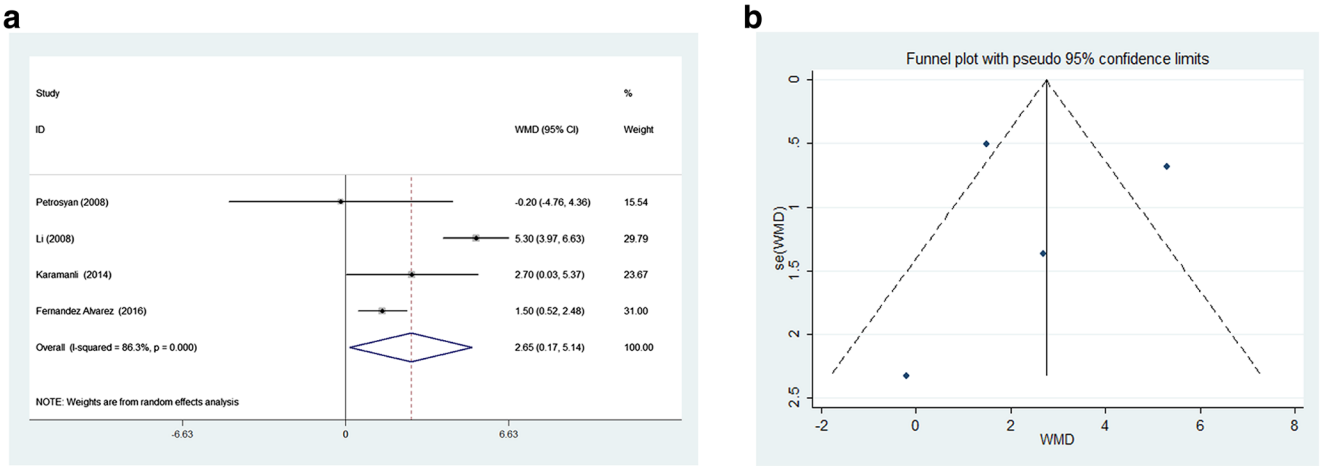

Fig. 2 Forest plot of the effect of CPAP treatment on exhaled breath condensate F2-isoprostanes in OSA patients and funnel plots for assessing publication bias of studies included. **a** Forest plot of the effect of CPAP treatment on exhaled breath condensate F2-isoprostanes in OSA patients. **b** Funnel plots for assessing publication bias of studies included. CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea; WMD, weighted mean difference; SE, standard error

Research has focused on the association between OSA and oxidative stress, and there is growing evidence to support an independent adverse effect of OSA on local as well as systemic oxidative stress status [7, 14, 24]. Carpagnano and coworkers [9] studied 18 OSA patients, 10 obese subjects, and 15 healthy age-matched controls. EBC 8-isoprostane (a prostaglandin F2–like compound belonging to the F2-isoprostane class) levels were found to be higher in OSA patients than in obese subjects and healthy subjects. Minoguchi et al. [22] demonstrated that overnight urinary excretion of 8-isoprostane was significantly higher in patients with moderate-to-severe OSA compared with patients with mild OSA and obese or lean subjects without OSA. The severity of OSA was an independent factor predicting the urinary excretion of 8-isoprostane. Very recently, a study focusing OSA children showed that OSA patients yielded higher 8-isoprostane levels in EBC than primary snoring patients and control subjects. Further analysis demonstrated that EBC 8-isoprostane, but not exhaled nitric oxide, can distinguish children with OSA from those with primary snoring or healthy [25]. Row et al. [26] reported that intermittent hypoxia (IH) induced lipid peroxidation and increased isoprostane concentrations in the cortical tissue concentrations in an IH mouse model.

The mainstay of OSA treatment is the application of CPAP therapy, which can reverse OSA-associated IH and disrupted sleep architecture. Given that oxidative stress is caused by ischemia–reperfusion events that induced by IH [7], it is therefore not unexpected that CPAP therapy could decrease F2-isoprostanes in OSA patients. Our meta-analysis showed that the F2-isoprostanes were consistently reduced in the sample from EBC, blood, and urine after CPAP therapy among OSA

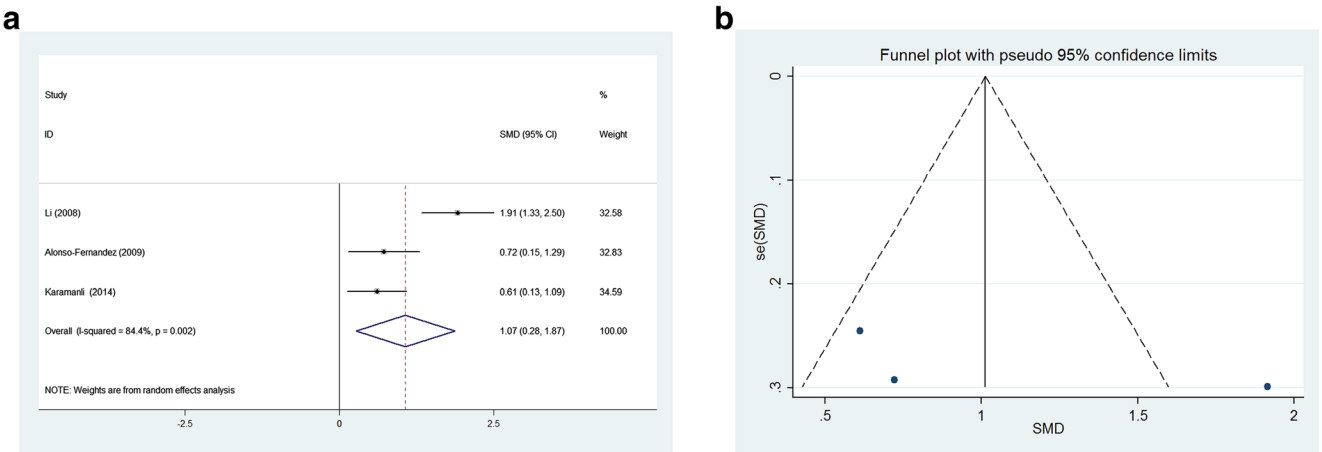

Fig. 3 Forest plot of the effect of CPAP treatment on serum or plasma F2-isoprostanes in OSA patients and funnel plots for assessing publication bias of studies included. **a** Forest plot of the effect of CPAP treatment on serum or plasma F2-isoprostanes in OSA patients. **b** Funnel plots for assessing publication bias of studies included. CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea; SMD, standardized mean difference; SE, standard error

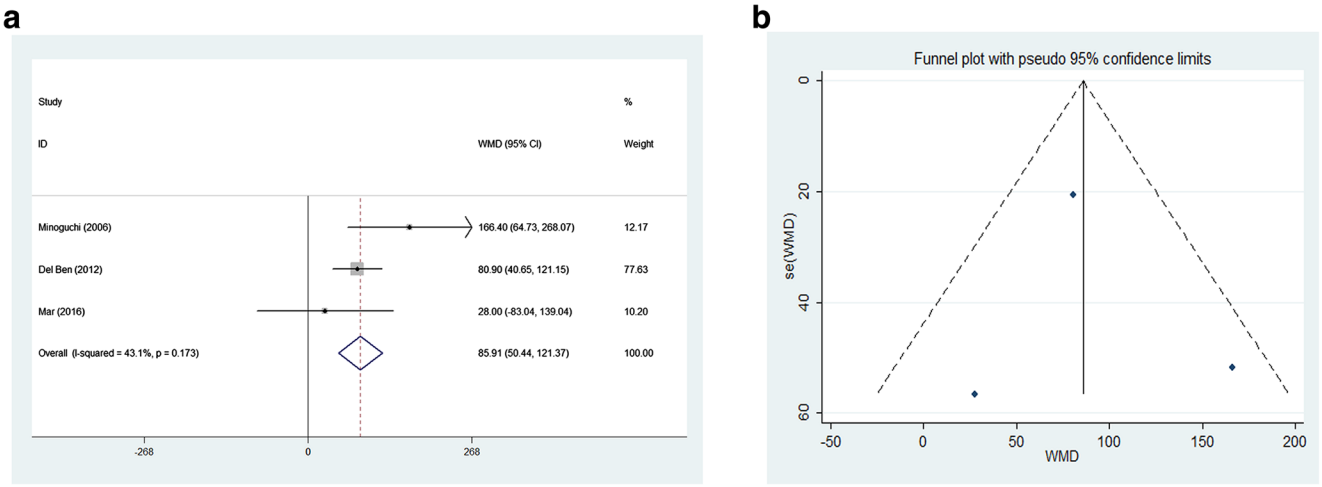

Fig. 4 Forest plot of the effect of CPAP treatment on urinary F2-isoprostanes in OSA patients and funnel plots for assessing publication bias of studies included. **a** Forest plot of the effect of CPAP treatment on urinary F2-isoprostanes in OSA patients. **b** Funnel plots for assessing publication bias of studies included. CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea; WMD, weighted mean difference; SE, standard error

adults. The results suggested that CPAP treatment could reduce not only local oxidative stress but also systemic oxidative stress. There is a strong correlation between oxidative stress and cardiovascular diseases such as atherosclerosis, hypertension, and endothelial dysfunction [27]. Given that increased oxidative stress is a potential mechanism of cardiovascular diseases in OSA [28], our evidence of a link between CPAP and reduced F2-isoprostanes may have clinical implications.

Only two RCTs accessed the effect of CPAP treatment on F2-isoprostanes in OSA patients. Consistent with our results, Alonso-Fernandez et al. [20] found that 12 weeks CPAP significantly decreased the plasma concentration of F2-isoprostanes when compared with sham CPAP. While Paz and colleague [23] failed to find a significant change in urinary F2-isoprostanes after 2-month CPAP treatment as compared with sham CPAP. The conflicting outcomes may be explained by several potential reasons. First, compared with 3 months of CPAP therapy in the study by Alonso-Fernandez et al. [20], the duration of OSA treatment (2 months) in the study by Paz et al. [23] was relatively shorter. Second, the overall degree of OSA (mean apnea-hypopnea index = 20) and hypoxia (average 2% sleep time < 90% oxygen saturation) in the study of Paz et al. [23] was less severe than that (mean apnea-hypopnea index = 43, average 6% sleep time < 90% oxygen saturation) in the study of Alonso-Fernandez et al. [20]. Third, it is plausible that at lesser degrees of hypoxia, counter-regulatory anti-oxidant mechanisms are at play, and greater hypoxia burden may be overcome by pro-oxidant stress at which point treatment amenability is realized.

The present meta-analysis had several limitations that must be taken into account. First, the heterogeneity was a major concern because obvious heterogeneity was detected in the analyses of the EBC and blood sample group. Second, most of the included studies were observational rather than RCTs. Third, data from observational studies and experimental arm of RCTs were pooled in this study. This might have potential for bias. Fourth, the total sample size in this meta-analysis was relatively small. Fifth, only papers published in English were enrolled, it might raise the possibility of publication bias. Finally, the mean and standard deviation were extracted by calculating results from median and interquartile range in a study according to the method as described previously for suitable use in meta-analysis [29, 30].

In conclusion, this meta-analysis suggested that in OSA patients, CPAP therapy for at least 1 month was associated with a decrease of F2-isoprostanes in various body fluids. As F2-isoprostanes is a well-established indicator of oxidative stress, it might be considered that CPAP treatment could improve local and systemic oxidative stress status in OSA patients. However, the body of evidence supporting this conclusion was weak, and further research and well-designed RCTs are needed.

Funding information This work was supported by grant 2015-1-98 for Youth Research Fund from Fujian Provincial Health Bureau and grant 2017XQ1117 for Startup Fund for Scientific Research from Fujian Medical University. The funders had no role in study design, data collection, and analysis, decision to publish, or preparation of the manuscript.

Compliance with ethical standards

This article does not contain any studies with human participants performed by any of the authors.

Conflict of interest The authors declare that they have no conflict of interest.

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