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SLEEP BREATHING PHYSIOLOGY AND DISORDERS • ORIGINAL ARTICLE

The effect of continuous positive airway pressure on circulating malondialdehyde among obstructive sleep apnea patients: a meta-analysis

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Abstract

Background Obstructive sleep apnea (OSA) has been demonstrated to be associated with an increase of oxidative stress. However, whether circulating malondialdehyde (MDA), a widely used biomarker of oxidative stress, could be reduced by the treatment of OSA by continuous positive airway pressure (CPAP) is debated. The present meta-analysis was performed to determine the effect of CPAP treatment on circulating MDA among patients with OSA.

Methods A systematic search of PubMed, Embase, and Web of Science was performed for literature covering the period between 1967 and August 2019. Standardized mean difference (SMD) was calculated to estimate the treatment effects of pre- and post-CPAP therapy.

Results A total of 10 studies with 220 patients were included in this meta-analysis. A significant decrease in circulating MDA was observed after CPAP treatment (SMD = 1.164, 95% CI = 0.443 to 1.885, $z = 3.16$, $p = 0.002$) in OSA patients. Subgroup analyses revealed that CPAP therapy was associated with a significant decrease of circulating MDA in elder (SMD = 1.629, 95% CI = 0.265 to 2.994, $z = 2.34$, $p = 0.019$), more obese patients (SMD = 0.954, 95% CI = 0.435 to 1.473, $z = 3.61$, $p = 0.000$), more severe OSA patients (SMD = 0.879, 95% CI = 0.421 to 1.336, $z = 3.76$, $p = 0.000$), patients with therapeutic duration ≥ 3 months (SMD = 1.867, 95% CI = 0.563 to 3.172, $z = 2.80$, $p = 0.005$), and patients with good compliance (SMD = 1.004, 95% CI = 0.703 to 1.305, $z = 6.54$, $p = 0.000$).

Conclusions This meta-analysis suggested that CPAP therapy exerted significant lowering effects on circulating MDA, especially in elder, more obese, and more severe OSA patients and patients with good compliance as well as longer duration of CPAP application.

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

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Introduction

Obstructive sleep apnea (OSA) is the most common form of breathing-related sleep disorder, which is characterized by recurrent episodes of partial or complete upper airway obstruction during sleep leading to chronic intermittent hypoxia (CIH). Accumulating evidence reveals that OSA is a significant risk factor for adverse health outcomes including hypertension, cardiovascular disease, metabolic disorders, cognitive impairment, and reduced quality of life. It is suggested that these comorbidities associated with OSA are largely mediated through oxidative stress [1].

It is well documented that OSA-related multiple cycles of hypoxia/reoxygenation result in the formation of reactive oxygen species and induce oxidative stress, which is known to be mechanistic facilitators of cardiovascular diseases and other disorders [2]. Lipid peroxidation represents a direct consequence of oxidative stress and the main cause of oxidative damage [3]. Among the aldehydes produced by lipid peroxidation, malondialdehyde (MDA) and 4-hydroxynonenal (HNE) have received the most attention. MDA is formed by the polyunsaturated fatty acids in the biofilm, which initiate lipid peroxidation after being attacked by oxygen free radicals. It has been demonstrated that MDA is the most abundant aldehyde generated during lipid peroxidation, where 4-HNE generation only amounts to 10% that of MDA [4]. Since MDA is produced at high levels during lipid peroxidation, it is commonly used as a measure of oxidative stress [5]. MDA has been extensively studied in biological and medical sciences due to its reactivity with biological molecules and connection to various diseases [6]. Previous studies have investigated the systemic oxidative stress status in OSA patients by the use of circulating MDA [7, 8].

Continuous positive airway pressure (CPAP), as the golden standard in current management of OSA patients, has been demonstrated to result in significant clinical benefits [9]. However, the impact of CPAP therapy on oxidative stress biomarker, namely MDA, remains unclear. To our knowledge, no meta-analysis has determined the effect of CPAP treatment on serum/plasma MDA levels among OSA patients. Therefore, in the present meta-analysis, we quantitatively evaluated the effect of CPAP therapy on circulating MDA among OSA patients.

Material and 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 [10].

Search strategy

A computerized search was carried out on the following databases covering the period between 1967 and August 2019: Web of Science, PubMed, and Embase. We used the following search terms; "sleep disordered breathing or sleep apnea" and "CPAP or continuous positive airway pressure", in combination with "malondialdehyde or MDA". Furthermore, we searched the reference lists of review articles and selected articles.

Study selection

Studies were considered eligible for inclusion if they fulfilled the predetermined criteria: (1) subjects were adults (age ≥ 18 years) with newly diagnosed OSA; (2) the intervention was an application of CPAP; (3) the value of serum or plasma MDA needed to be reported pre- and post-CPAP therapy; (4) the study provided sufficient data for analysis including continuous data reported as means with standard deviations/standard errors, or median and interquartile range and sample size. Two investigators identified eligible studies independently. If there was any disagreement, it was resolved by consensus with a third investigator.

Editorials, letters, case reports, reviews, and abstracts without original data were excluded. Animal studies were also excluded. Studies were deemed ineligible if it(1) is a non-English article and (2) has assessment of MDA in low-density lipoprotein (LDL) or erythrocytes. The study with the largest population was included if multiple studies reported outcomes on the same patient group.

Data extraction

Two of the authors extracted data from eligible studies using a standardized form independently. The following information was extracted from each paper: first author, publication year, place of the study, total sample size, sex distribution, inclusion criteria, therapy duration, mean daily CPAP usage time, CPAP average weekly use, patients' characteristics, study design, pre-CPAP MDA concentrations, and post-CPAP MDA concentrations.

Statistical analysis

We performed statistical analyses with Stata software (v12.0; Stata Corp, College Station, TX, USA). Medians and interquartile ranges were converted to means and standard deviations according to Wan et al. [11]. Standardized mean difference (SMD) was used to generate forest plots of continuous data and to evaluate differences in MDA levels before and after CPAP therapy. The statistical significance of SMD was analyzed by the z test, and $p < 0.05$ was deemed statistically

significant. Q statistic was used to test the heterogeneity of SMD across studies (significance level at $p < 0.10$). The I^2 statistic was also calculated to measure inconsistency across studies quantitatively. Statistical heterogeneity was defined as an I^2 statistic value $\geq 50\%$. If significant heterogeneity was observed, we used a random effect model, otherwise we used a fixed-effect model. We conducted sensitive and subgroup analyses to explore the possible sources of heterogeneity in treatment effect. Begg's correlation and Egger's regression were used for assessing publication bias. All statistical tests were two-sided.

Results

Literature search

A total of 38 initially identified studies were excluded after the first screening because of duplicates. The majority of the remaining studies were also excluded, mainly because they were either in abstract or letter format, review, irrelevant, not in English, or animal studies. A flow chart showing the study selection was showed in Fig. 1.

Characteristics of the studies

A total of 10 studies (11 cohorts) were found eligible for inclusion for meta-analysis based on the set criteria. These studies involved 220 subjects. Of them, 2 were randomized clinical trials (RCTs) [12, 13] and 8 were observational studies [14–21]. One study reported results separately for good (≥ 4 h/night) compliance group and poor (< 4 h/night) compliance group [14]. Table 1 summarized the characteristics of the 10 included studies and the patients' characteristics.

Pool analysis

Substantial heterogeneity between studies was detected ($I^2 = 91.0\%$, $p = 0.000$). Thus, a random effect model was used for the pooled analysis. Overall, pooled results showed that a significant decrease in serum or plasma MDA was observed after CPAP treatment (SMD = 1.164, 95% CI = 0.443 to 1.885, $z = 3.16$, $p = 0.002$). The forest plot for MDA concentrations in OSA patients between pre-CPAP treatment and post-CPAP treatment was shown in Fig. 2.

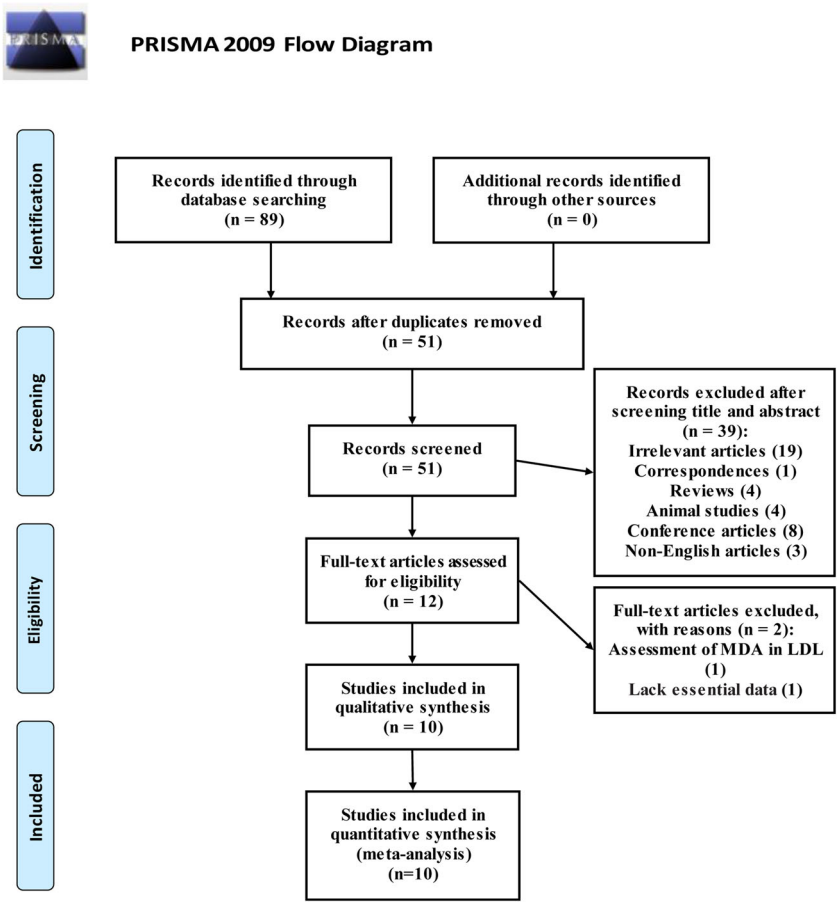

Fig. 1 Flow diagram of study selection. MDA, malondialdehyde; LDL, low-density lipoprotein

Table 1 Characteristics of included studies for assessing circulating MDA

Study	Year	Nation	Sample size/male	Inclusion criteria	Ventilation duration/night (h)	CPAP average weekly use (d)	Therapy duration	Measurement	Study design	Age
Lavie [21]	2004	Israel	5/5	RDI > 10	NR	NR	9.3 ± 3.9 M	TBARS	OS	51.2 ± 5.2
Dorkova (good compliance group) [14]	2008	Slovakia	16/15	AHI ≥ 30	5.07 ± 1.22	NR	2 M	Fluorometric assay	OS	51.3 ± 9.5
Dorkova (poor compliance group) [14]	2008	Slovakia	15/10	AHI ≥ 30	1.92 ± 1.14	NR	2 M	Fluorometric assay	OS	56.1 ± 9.5
Ye [15]	2010	China	10/NR	moderate and severe OSA	NR	NR	6 M	TBARS	OS	NR
Jurado-Gamez [16]	2011	Spain	25/NR	AHI ≥ 15	> 5	NR	3 M	Colorimetric assay	OS	44.52 ± 5.35 ($n = 46$)
Alzoghaibi [17]	2012	Saudi Arabia	34/28	AHI > 30	6	2	2 d	TBARS	OS	45.09 ± 11.77
Yagihara [18]	2012	Brazil	30/30	AHI ≥ 20	NR	NR	6 M	TBARS	OS	66.4 ± 3.8
Dal-Fabbro [12]	2014	Brazil	29/24	AHI ≥ 20	NR	NR	1 M	TBARS	RCT	47.0 ± 8.9
Tichanon [19]	2016	Thailand	13/10	AHI ≥ 5	6.4 ± 0.9	5.4 ± 0.4	3 M	TBARS	OS	53.1 ± 12.4
Wu [13]	2016	China	11/11	AHI ≥ 15	Good compliance	> 4.9	1.5 M	TBARS	RCT	44.45 ± 9.85 ($n = 20$)
Wang [20]	2019	China	32/NR	AHI ≥ 5	≥ 4	NR	3 M	NR	OS	51.59 ± 9.51

Study	BMI	Pre-CPAP AHI/RDI	Post-CPAP AHI/RDI	Pre-CPAP LowSO_2(%)	Post-CPAP LowSO_2(%)	Pre-CPAP T90%	Post-CPAP T90%	Pre-CPAP MDA	Post-CPAP MDA
Lavie [21]	31.8 ± 4.7	55.4 ± 22.5	12.8 ± 0.6	79.0 ± 9.5	88.2 ± 3.0	10.7 ± 11.9%	0.55 ± 0.6%	17.00 ± 6.10 nmol/ml	9.60 ± 2.70 nmol/ml
Dorkova (good compliance group) [14]	32.8 ± 4.4	64.7 ± 23.3	NR	66.5 ± 15.6	NR	NR	NR	1.73 ± 0.26 nmol/ml	1.49 ± 0.22 nmol/ml
Dorkova (poor compliance group) [14]	37.3 ± 6.9	63.2 ± 18. 8	NR	56.8 ± 22.2	NR	NR	NR	1.76 ± 0.44 nmol/ml	1.77 ± 0.34 nmol/ml
Ye [15]	NR	NR	NR	NR	NR	NR	NR	8.11 ± 3.15 nmol/ml	5.55 ± 2.10 nmol/ml
Jurado-Gamez [16]	33 ± 4.72	69.21 ± 25.94	2 ± 1.6	72 ± 15.72	90 ± 4.7	22.4 ± 27.5%	0.6 ± 1.1%	3.31 ± 1.34 μM	1.9 ± 0.47 μM
Alzoghaibi [17]	37.4 ± 8.43	79.17 ± 31.35	NR	71.82 ± 12.94	NR	NR	NR	2.81 ± 0.27 μmol/ml	2.47 ± 0.35 μmol/ml
Yagihara [18]	27.9 ± 3.8	36.6 ± 18.6	4.0 ± 4.9	76.9 ± 17.0	88.7 ± 2.7	20.9 ± 47.1 (min)	0.8 ± 2.2 (min)	2.7 ± 2.9 nmol /ml	1.3 ± 1.7 nmol /ml
Dal-Fabbro [12]	28.4 ± 3.6	42.3 ± 24.2	3.2 ± 2.2	81.2 ± 5.9	90.4 ± 2.7	7.9 ± 12.9 (min)	0.1 ± 0.5 (min)	1.1 ± 1.1 nmol/ml	1.4 ± 0.5 nmol/ml
Tichanon [19]	28.4 ± 3.5	15.9 ± 6.6	4.1 ± 2.1	64.9 ± 11.4	NR	NR	NR	14.6 ± 7.8 mol/l	10.0 ± 6.4 mol/l
Wu [13]	27.35 ± 2.16 (n = 20)	54.44 ± 21.52	42.17 ± 19.53	67.36 ± 14.53	73.55 ± 9.70	20.1 ± 26.8%	9.6 ± 10.3%	5.54 ± 3.55 mmol/ml	4.14 ± 2.42 mmol/ml
Wang [20]	29.67 ± 4.08	42.05 ± 22.70	3.19 ± 1.73	71.56 ± 12.28	94.00 ± 2.75	NR	NR	13.49 ± 0.81 nmol/ml	8.39 ± 0.78 nmol/ml

NR, not reported; *AHI*, apnea-hypopnea index; *RDI*, respiratory disorder index; *min*, minute; *h*, hour; *d*, day; *M*, month; *OS*, observational study; *RCT*, randomized clinical trial; *BMI*, body mass index; *LowSO_2*, lowest O_2 saturation; *CPAP*, continuous positive airway pressure; *MDA*, malondialdehyde; *TBARS*, thiobarbituric acid reactive substances, *T90%*, sleep time spent with $SaO_2 < 90\%$

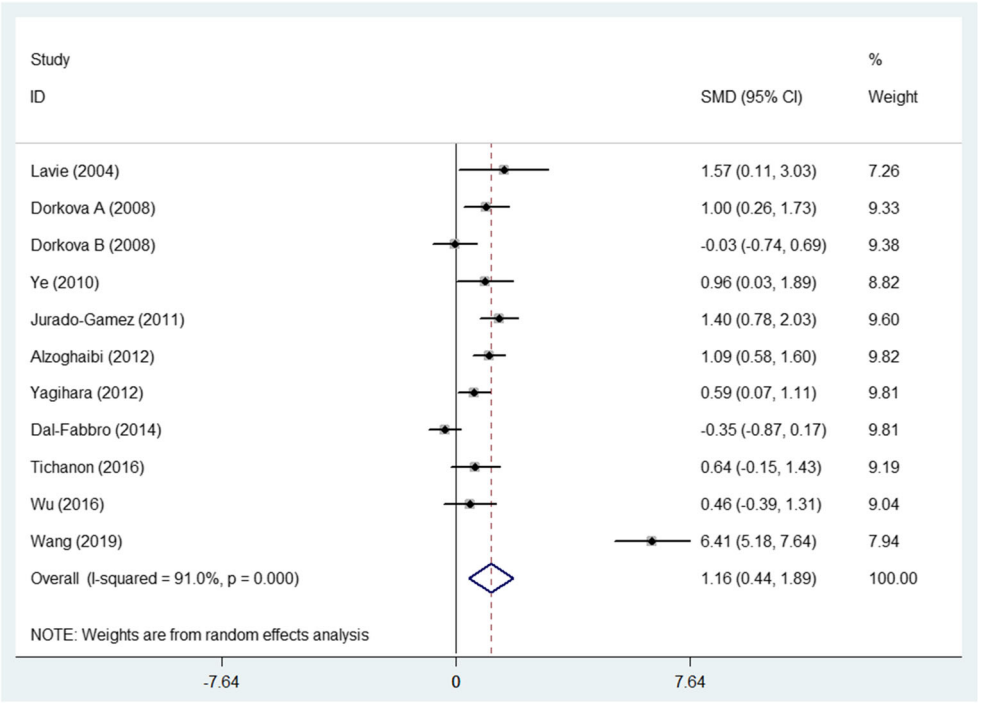

Fig. 2 Forest plot for the change in circulating MDA before and after CPAP treatment. MDA, malondialdehyde; CPAP, continuous positive airway pressure; SMD, standardized mean difference; CI, confidence interval

Sensitivity and subgroup analyses

Sensitivity analyses were performed in order to explore the possible sources of heterogeneity. The results showed that no individual studies significantly affected the pooled results, indicating a statistically robust result (Fig. 3). Subgroup analyses revealed that CPAP therapy resulted in a significant decrease of circulating MDA in elder (≥ 50 years) (SMD = 1.629, 95% CI = 0.265 to 2.994, $z = 2.34$, $p = 0.019$), more obese patients(BMI ≥ 30)(SMD = 0.954, 95% CI = 0.435 to 1.473, $z = 3.61$, $p = 0.000$), more severe OSA patients (AHI ≥ 50 events/h) (SMD = 0.879, 95% CI = 0.421 to 1.336, $z = 3.76$, $p = 0.000$), patients with therapeutic duration ≥ 3 months (SMD = 1.867, 95% CI = 0.563 to 3.172, $z = 2.80$, $p = 0.005$), and patients with good compliance (≥ 4 h/night) (SMD = 1.004, 95% CI = 0.703 to 1.305, $z = 6.54$, $p = 0.000$). However, CPAP has no effect on circulating MDA in OSA patients with age < 50 years, BMI < 30, AHI < 50, follow time < 3 months, and poor compliance(< 4 h/night). The differences in sample size and racial differences did not influence CPAP efficacy. Table 2 showed the detailed results of the subgroup analyses.

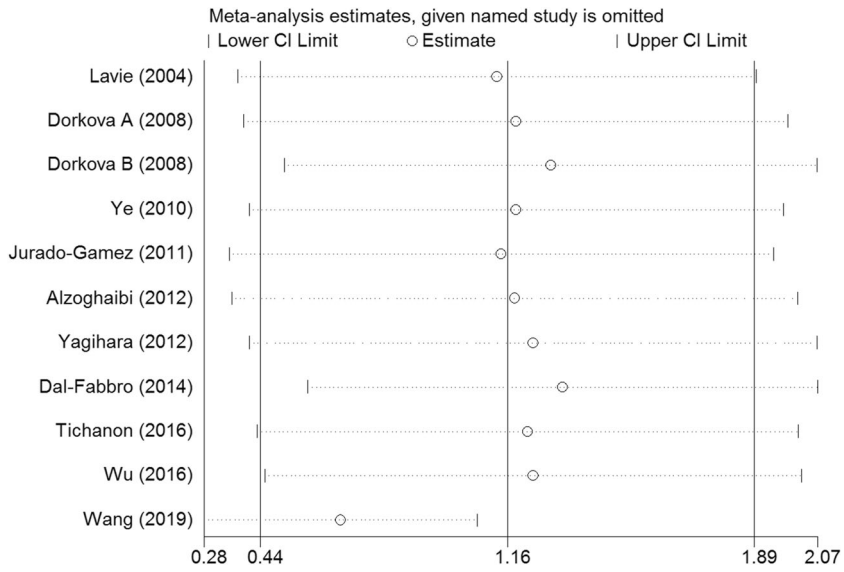

Fig. 3 Sensitivity analysis of the included studies. CI, confidence interval

Table 2 The results of subgroup analyses

Subgroup	Number of studies/patients	Heterogeneity			SMD			
		X^2	p	I^2 (%)	SMD	95%CI	z	p
Age								
< 50	4/99	22.94	0.000	86.9	0.650	−0.186to 1.486	1.52	0.128
≥ 50	6/111	85.99	0.000	94.2	1.629	0.265 to 2.994	2.34	0.019
BMI								
< 30	5/115	98.76	0.000	95.9	1.470	−0.097 to 3.037	1.84	0.066
≥ 30	5/95	10.16	0.038	60.6	0.954	0.435to 1.473	3.61	0.000
AHI (events/h)								
< 50	4/104	98.62	0.000	97.0	1.740	−0.213to 3.693	1.75	0.081
≥ 50	6/106	11.37	0.044	56.0	0.879	0.421to 1.336	3.76	0.000
Follow time (M)								
< 3	5/105	18.91	0.001	78.8	0.429	−0.199 to 1.057	1.34	0.181
≥ 3	6/115	76.95	0.000	93.5	1.867	0.563 to 3.172	2.80	0.005
Average use/night (h)								
< 4	1/15	0.00	–	–	−0.025	−0.741 to 0.690	0.07	0.944
≥ 4	5/99	4.07	0.397	1.7	1.004	0.703 to 1.305	6.54	0.000
Race								
Asian	5/100	73.93	0.000	94.6	1.850	0.299 to 3.401	2.34	0.019
Caucasian	6/120	24.46	0.000	79.6	0.617	0.002–1.232	1.96	0.049
Sample size								
< 20	6/70	6.39	0.270	21.7	0.648	0.253–1.044	3.21	0.001
≥ 20	5/150	103.89	0.000	96.1	1.718	0.340–3.096	2.44	0.015

SMD, standardized mean difference; *CI*, confidence interval; *AHI*, apnea-hypopnea index; *BMI*, body mass index; *M*, month; *h*, hour

Publication bias

No statistical significance of publication bias was indicated by the results of Begg's tests ($z = 0.93$, $p = 0.350$) and Egger's tests ($t = 1.88$, $p = 0.093$) in the present meta-analysis (Fig. 4). Furthermore, trim-and-fill method suggested that no study needed to be statistically corrected for funnel plot asymmetry.

Discussion

The present meta-analysis aimed to assess the effects of CPAP therapy on circulating MDA among OSA patients. We chose this marker because it is a widely studied oxidative stress biomarker and may closely link OSA with various complications. The findings of the study demonstrated that CPAP treatment might be effective in decreasing circulating MDA in patients with OSA. Furthermore, subgroup analyses revealed that CPAP was more effective in decreasing circulating MDA in OSA patients in elder, more obese, and more severe OSA patients, and patients with good compliance as well as therapeutic period ≥ 3 months.

MDA, an important endogenous product of lipid peroxidation, was shown to be elevated in OSA patients in previous studies. Jordan et al. [7] reported that the plasma MDA was positively associated with the duration of sleeping time less than 85% and 90% O_2 saturations. Another study found that MDA levels were higher in the moderate and severe OSA group than the healthy subjects after comparing 25 OSA patients with 24 healthy male subjects [8]. A recent study also found that the mean MDA concentrations in patients with higher AHI values were also higher than those in patients with lower AHI. Higher predominance of apnea in patients with similar AHI values, longer mean apnea durations, O_2 saturation dips to < 90%, and higher ODI values predicted higher plasma MDA concentrations [22]. This has been further supported by animal experiments. An animal study showed that mice were subjected to CIH or intermittent air (IA) for 12 h a day and fed either a high-fat (HF) or a control diet (CD) for 6 weeks. MDA levels were significantly higher in the CDIH group than that in the CDIA group; the increase in MDA levels was more pronounced in the HFIH group [23]. Oxidative stress and systemic inflammation are found to be fundamental mechanisms in the

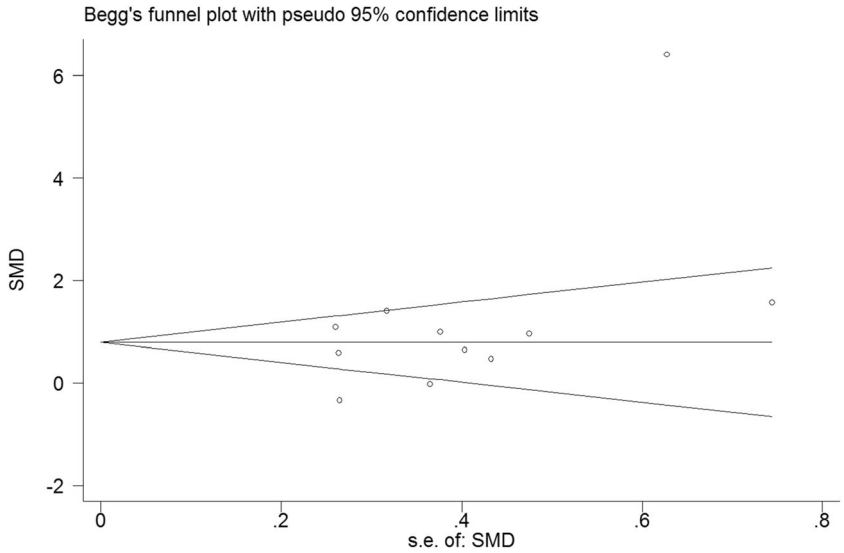

Fig. 4 Funnel plots for assessing publication bias of studies included. SE, standard error; SMD = standardized mean difference

pathophysiology of atherosclerosis and cardiovascular morbidity and other disorders in OSA. Moreover, higher MDA levels in ischemic stroke patients were suggested to be associated with poor functional outcome and early mortality [24, 25]. However, the effect of CPAP on circulating MDA among OSA patients remains unclear.

It is widely accepted that CPAP therapy could eliminate respiratory disturbances, reduce the AHI, and reverse IH. The formation of reactive oxygen species and oxidative stress is caused by OSA-related multiple cycles of hypoxia/reoxygenation. Thus, it is reasonable to speculate that CPAP therapy could decrease circulating MDA in OSA patients. This was further confirmed by the results of the present meta-analysis. Further subgroup analyses suggested that CPAP was more effective in elder, more severe OSA, more obese patients, patients with therapeutic period ≥3 months, and patients with good compliance. While this positive result was not observed in patients with age < 50 years, BMI < 30, AHI < 50, follow time < 3 months, or poor compliance. The results indicated that the efficacy of CPAP therapy was influenced by the baseline condition of patients, CPAP therapy duration, and therapy compliance. Our previous studies also supported this conclusion [26, 27]. This result allows us to predict responses to CPAP treatments and choose the patients with specific OSA phenotypes who can benefit more from CPAP therapy to initiate CPAP therapy. It is valuable to perform precision treatment on patients with OSA, and more research and data are needed to deepen our understandings of the disease and possible new methods of precision treatment.

In the present meta-analysis, the cutoff value for AHI in the subgroup analysis was set as 50. The mean AHI value of most included studies was higher than 30, so it is unsuitable to choose 30, a cutoff value currently used to define severe OSA. The evidence from previous meta-analysis demonstrated that the effect of CPAP therapy was influenced by baseline severity of OSA grouped by AHI ≤ 50 and > 50 [28]. Based on the above two reasons, we set the cutoff value for AHI in the subgroup analysis as 50. Some studies used 35 as the cutoff value for BMI in the subgroup analysis when evaluating the effect of CPAP therapy [29], while several studies used 30 as the cutoff value [28]. Considering the majority of population in our study was Asian, who seemed to be less obese, hence, we chose 30 as the cutoff value for BMI in subgroup analysis.

To the best of our knowledge, this was the first meta-analysis to access the impact of OSA treatment with CPAP therapy on circulating MDA among OSA patients. However, a few caveats are needed to be noted when interpreting the findings from present meta-analysis. First, significant heterogeneity was observed in our meta-analysis, but no consistent determinant was identified. Second, the sample size of the included study was relatively small. Third, the proportion of male patients of the present meta-analysis was significantly high; therefore, it should be cautious to interpret the results when it is generalizable to female patients. Fourth, most of the included studies were observational rather than RCTs. Fifth, most of the studies used TBARS (thiobarbituric acid reactive substances) to measure MDA; however, HPLC, LC-MS/MS, and GC-MS methods have been shown to be specific and more sensitive than the batch TBARS assays. In addition, AASM criteria for apnea and/or hypopnea have changed during the last two decades. The included studies using different published standard definitions led to differences in AHI. This may have implications for disease identification, severity grading. Finally, only English language studies

were included, which may cause some publication biases.

Conclusions

This meta-analysis suggested that in OSA patients, CPAP therapy exerted significant lowering effects on circulating MDA, especially in elder, more obese, and more severe OSA patients, patients with good compliance as well as longer duration of CPAP application. Thus, it could be speculated that CPAP treatment could improve systemic oxidative stress status in OSA patients, which may be one mechanism by which CPAP treatment exerts significant clinical benefits. Furthermore, the circulating MDA might be considered a useful tool in assessing the efficacy of CPAP treatment in reducing OSA-related complication risk in patients.

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Compliance with ethical standards

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

Ethics approval and consent to participate All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

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