Systematic Review and Meta-Analysis

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Measurement of exhaled nitric oxide concentration in patients with obstructive sleep apnea

A meta-analysis

Dongmei Zhang, MD, Jinmei Luo, MD, Yixian Qiao, MD, Yi Xiao, MD*, Rong Huang, MD, Xu Zhong, MD

Abstract

Background: Exhaled nitric oxide (eNO) has been proposed as a noninvasive measure of airway inflammation. However, its value in patients with obstructive sleep apnea (OSA) is still controversial. The authors aim to assess the difference in eNO levels between patients with OSA and controls by a meta-analysis.

Methods: A systematic search was performed in the PubMed, EMBASE, the Cochrane Library, and MEDLINE databases to collect relevant studies published from 1996 to 2016. Eligible studies that reported eNO levels in patients with OSA were included. STATA (version 12.0) was used for data analysis.

Results: Two hundred eighty-four studies were reviewed for inclusion, with 16 studies pooled for analysis (16 studies for fractional exhaled nitric oxide [FENO], 5 for alveolar nitric oxide [CANO], and 4 for the maximum airway wall flux of nitric oxide [J'awNO]). The FENO levels were significantly higher in patients with OSA compared with that in the control groups (6.32 ppb, 95% confidence interval [CI] 4.46–8.33, $P < 0.001$). Furthermore, FENO was significantly increased (4.00 ppb, 95% CI 1.74–6.27, $P = 0.001$) after overnight sleep in patients with OSA, but not in healthy controls. Additionally, long-term continuous positive airway pressure (CPAP) therapy reduced FENO levels (−5.82 ppb, 95% CI −9.6 to −2.01, $P < 0.001$). However, the CANO (−0.01 ppb, 95% CI −1.66 to 1.64, $P = 0.989$) and J'awNO levels (220.32 pl/s, 95% CI −49.31 to 489.94, $P = 0.109$) were not significantly different between the OSA groups and non-OSA groups.

Conclusion: The results of the meta-analysis suggest that OSA is significantly associated with airway inflammation and elevated FENO levels can be modified by long-term CPAP therapy. J'awNO and CANO levels were not significantly different between the OSA groups and control groups.

Abbreviations: AHI = apnea–hypopnea index, BMI = body mass index, CANO = concentration of alveolar nitric oxide, CI = confidence interval, CPAP = continuous positive airway pressure, CST = cross-sectional trail, eNO = exhaled nitric oxide, eNOS = endothelial nitric oxide synthase, FENO = fractional exhaled nitric oxide, iNOS = inducible nitric oxide synthase, J'awNO = the maximum airway wall flux of nitric oxide, nNOS = neuronal nitric oxide synthase, NO = nitric oxide, NOS = nitric oxide synthase, OSA = obstructive sleep apnea, PSG = polysomnography, SpO_2 = pulse oxygen saturation, WMD = weighted mean difference.

Keywords: airway inflammation, continuous positive airway pressure, exhaled nitric oxide, obstructive sleep apnea

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Since it was a meta-analysis, it did not require ethical approval or patient consent.

Conceived and designed the experiments: YX, DZ, and JL; Performed the studies search and data integrity: DZ, YQ, and RH. Analyzed the data: JL, YX, RH, and XZ. Contributed reagents/materials/analysis tools: all authors. Wrote the paper: all authors.

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Department of Respiratory Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Dongcheng District, Beijing, China.

** Correspondence: Yi Xiao, Department of Respiratory Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 1 Shuaifuyuan Street, Dongcheng District, Beijing 100730, China (e-mail: pumch_yixiao@sina.com).*

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1. Introduction

Obstructive sleep apnea (OSA) is a common sleep disorder characterized by repetitive episodes of upper airway obstruction during sleep leading to significant hypoxemia and frequent arousals. With a high prevalence, ranging from 9% to 38% in the overall population,[1] OSA is increasingly regarded as a public health concern because it is closely associated with cardiovascular disorders.[2] Because an altered upper airway structure and function is 1 etiology of OSA,[3,4] local pathophysiological processes such as upper airway inflammation could amplify these abnormalities and may further compromise upper airway patency during sleep. A large body of experimental evidence indicates that patients with OSA present with airway inflammation[5,6] mainly because of the mechanical trauma of recurrent snoring and oxidative stress. Furthermore, it has been reported that the repetitive hypoxia/reoxygenation phenomenon increases the levels of reactive oxygen species, which aggravate vascular endothelium injury in patients with OSA.[7] Therefore, an assessment of respiratory inflammation might be a predictor of OSA and its complications.[8]

Exhaled nitric oxide (eNO) levels have been suggested as a simple, noninvasive, and reproducible marker of respiratory inflammation.[9] Nitric oxide (NO) is a molecule synthesized by NO synthase (NOS). eNO derived from the central airway and alveolus can be separately assessed by obtaining measurements at different flow rates.[10] Fractional exhaled nitric oxide (FENO) reflects bronchial NO production and diffusion, the maximum airway wall flux of NO (J′awNO) represents NO from the airway tree, and alveolar NO (CANO) represents the steady-state alveolar NO concentration.[11] In the lungs, NO regulates pulmonary vascular tone and reduced NO levels may be associated with the development of pulmonary hypertension by contributing to pulmonary vascular smooth muscle proliferation and remodeling.[12] Hypoxia may impair NO release by reducing substrate availability or by inhibiting NOS. Increased levels of eNO are indicative of lung inflammation by overexpression of the inducible NOS, as observed in asthma,[13] while reduced eNO levels can be found in cardiovascular disorders such as pulmonary hypertension,[14] due to decreased NOS expression and activity caused by endothelial dysfunction. In patients with OSA, both principal pathological processes, hypoxia and endothelial dysfunction, coexist and may change eNO concentrations.

In the last 20 years, several studies measuring eNO levels in patients with OSA have been reported, but the results are controversial. Different studies have found increased eNO levels,[15–26] no significant difference,[27–30] or decreased eNO levels[31] in patients with OSA compared with healthy controls. Therefore, the aim of this meta-analysis was to evaluate the potential association between OSA and eNO levels. Our secondary purpose was to review the potential influence of OSA on the severity of airway inflammation to address the question of whether eNO can be a predictor of the diagnosis of OSA or a marker of treatment efficacy.

2. Materials and methods

2.1. Data sources and study selection

We searched for relevant articles in the following databases: PubMed, MEDLINE, EMBASE, and the Cochrane Library. Even though MEDLINE is a component of PubMed, they differ in update frequency and retrieval mechanism; we thus treated them as separate databases to avoid miss any eligible studies. The details of the search strategy are included in the supplementary material (Supplementary Digital Content 1, http://links.lww.com/MD/B613). Briefly, we searched for the terms ("obstructive sleep apnea" or "apnea" or "hypopnea" or "OSA") and ("FENO" or "exhaled nitric oxide" or "fractional exhaled nitric oxide" or "CANO" or "alveolar NO" or "J'awNO") and in articles published from 1996 to 2016. Moreover, the references of the retrieved articles were checked, and the PubMed function "related articles" was used to identify additional papers. Two authors reviewed all abstracts independently to determine the eligibility criteria or establish the appropriateness of the research issue. Any disagreements were resolved by discussion with a third reviewer. All levels of evidence were considered, but because of a lack of higher levels of evidence, only controlled trials were included. Studies were included if they met the following criteria: All patients with OSA were newly diagnosed by polysomnography (PSG); patients with OSA and eligible controls had no history of asthma, rhinitis, or sinusitis, and none of them had an allergic disease or were receiving anti-inflammatory medications at the time of the study. All subjects were over 16 years old. Studies were excluded if they were case reports, editorials, reviews, or abstracts. Details of the exclusion criteria can be seen in Fig. 1.

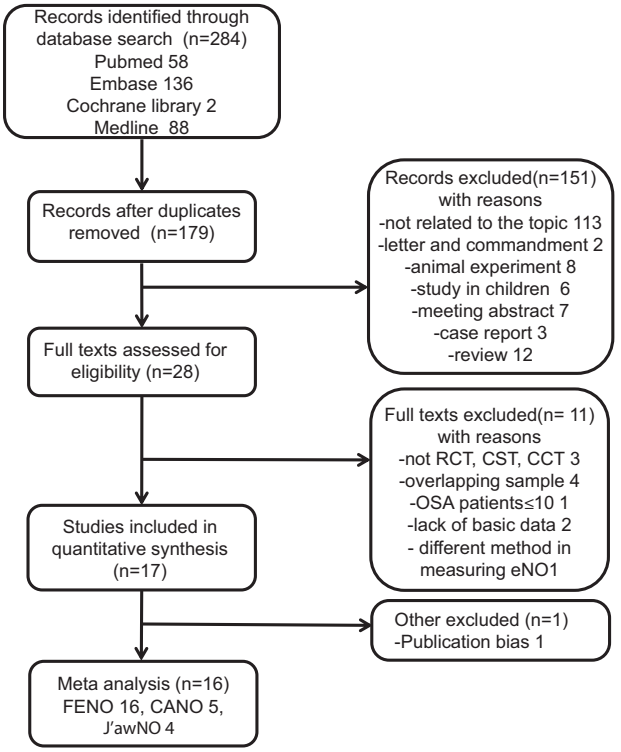

Figure 1. Flow diagram of the literature search.

2.2. Data extraction and analysis

The following information was extracted from the included studies: name of first author, year of publication, country, sample size, age, gender, diagnostic standard for OSA, type of study, and eNO measurement (method, parameters, and expiratory flow

rates). When pertinent data were not included in a published article, the corresponding author was contacted to seek clarification. If the data could not be acquired, the article was excluded. The data were extracted by 2 authors independently. All data were expressed as mean ± standard deviation. For studies with data reported in median and range, or median and interquartile range, the mean and standard error were calculated utilizing the methods outlined by Hozo et al.[32]

For studies in which patients with OSA were compared with more than 1 group of control patients (e.g., obese and nonobese controls), only the one that was a better match for the patients with OSA in the study was included in the meta-analysis. For example, Petrosyan et al[33] compared FENO levels in obese patients with OSA with 2 control groups, obese controls and nonobese controls; we only extracted the data of the obese controls because the mean body mass index (BMI) in this group was not significantly different to that in the OSA group. Similarly, Foresi et al[31] compared patients with OSA with 2 control groups, but the hypertension group did not undergo PSG, so we included only the data of the healthy controls. For studies measuring eNO at different times, we used the parameters measured in the morning for our analysis. If eNO was measured at multiple flow rates, we extracted the data for an approximately 50-mL/s flow rate.

Heterogeneity was assessed by calculating the I^2 statistics. An I^2 of 25% to 49% was considered to represent a low level of heterogeneity, 50% to 74% a moderate level, and 75% to 100% a high level. Due to the high level of heterogeneity presented, a random-effects model was employed to combine the effect size. All statistical analysis was performed using STATA version 12.0 (Stata Statistical Software, College Station, TX). A meta-regression analysis was also performed to assess the influence of study-related factors on the outcomes and analysis of heterogeneity. Publication bias was checked by funnel plots, Begg test, and Egger test. A 2-sided P value ≤ 0.05 was considered statistically significant.

3. Results

3.1. Search results and study characteristics

The search identified 284 potential studies, 267 of which were excluded as described in Fig. 1. Seventeen studies were included in the analysis, but 1 study[34] had obvious publication bias and was excluded from the final meta-analysis. The remaining 16 studies differed in their study design: 5 were cross-sectional trials (CSTs) and 11 were case–control trials (Table 1). The number of patients included in the studies ranged from 13 to 97 in the OSA groups (total 688) and from 7 to 53 in the control groups (total 366). Among the studies, the mean age of participants ranged from 37 to 66 years in both the groups, and generally, more than half of them were male (Table 1). Among the included studies, 7 also analyzed the effects of continuous positive airway pressure (CPAP) treatment on airway inflammation: 2[24,31] evaluated the effects of short-term (2 nights) CPAP therapy while the other 5[21,22,26,30,33] followed CPAP treatment for more than 1 month. A total of 5 studies[21,24,25,29,31] including 359 subjects were pooled for CANO analysis, and 4 studies[21,24,25,29] with 296 subjects were pooled for J'awNO analysis.

All the studies scored well in terms of adequate descriptions of selection criteria and reference tests, and the availability of clinical data. All included studies clearly described the data source, and patient inclusion and exclusion criteria, and presented measurements for the primary study end points.

3.2. FENO

Because there was heterogeneity in this endpoint ($I^2 = 82.8\%$), the random-effects model was used to combine the effect size. The pooled mean difference was 6.39, which indicates that FENO levels in the OSA group were 6.39 ppb (95% confidence interval [CI] 4.46–8.33, $P < 0.001$) higher than that in the control group (Fig. 2).

Subgroup analyses were conducted based on BMI, age, apnea–hypopnea index (AHI), smoking status, and expiratory flow rate. In all subgroups, FENO levels were higher in the patients with OSA than they were in the controls, with a weighted mean difference (WMD) ranging from 3.49 ppb to 8.27 ppb (Supplemental Fig. 1A–C, Supplemental digital Content 2, http://links.lww.com/MD/B613, which shows the results of the subgroup analyses). However, significant heterogeneities still existed in these subgroups (I^2 41.7–92.0%).

In 5 studies,[16,22,25,28,29] exhaled NO was measured separately before and after overnight PSG to evaluate the variation of FENO levels in the morning and in the evening. For these studies, 2 analyses were performed. The first analysis was performed with the baseline parameters of morning and evening FENO levels in the patients with OSA and controls. The pooled WMD was 4.00 ppb (95% CI 1.74–6.27, $P = 0.001$) in the OSA groups compared with 0.29 ppb (95% CI −1.84 to 2.42, $P = 0.791$) in the control groups (Fig. 3). The second analysis included the changes after PSG (FENO levels in the morning minus FENO levels in the evening) in the OSA groups and controls, and the WMD was calculated to be 3.91 ppb (95% CI 0.55–7.28, $P = 0.022$), which indicated that in patients with OSA, the overnight increase of FENO levels was larger than that in non-OSA controls. There was medium heterogeneity in this endpoint ($I^2 = 65.3\%$) (Fig. 3).

The random-effects analysis revealed that long-term CPAP therapy promoted a significant decrease in FENO levels (−5.82 ppb, 95% CI −9.64 to −2.01, $P < 0.001$; Fig. 4). However, short-term CPAP could not reduce FENO (−3.99 ppb, 95% CI −19.56 to 11.59, $P = 0.616$; Fig. 4). There was significant heterogeneity due to the limited number of trials, with an I^2 of 81.6% and 94.2%, respectively.

3.3. CANO and J'awNO

For CANO, a random-effects analysis was applied since there was evidence of heterogeneity among the 5 studies ($I^2 = 96.1\%$, $P < 0.001$). The calculated WMD (−0.01 ppb, 95% CI −1.66 to 1.64, $P = 0.989$; Fig. 5) indicated that there was no statistical difference in the CANO levels between the OSA groups and control groups.

For J'awNO, the pooled WMD was 220.32 pl/s (95% CI −49.31 to 489.94, $P = 0.109$). There was heterogeneity in this analysis ($I^2 = 74.2\%$, $P = 0.009$; Fig. 6).

3.4. Publication bias

The funnel plot was almost perfectly symmetrical (Fig. 7) after excluding the study by Devouassoux et al,[34] suggesting that this study might have publication bias. The bias might have been caused by the inclusion of subjects with allergies. Subsequently, Begg tests ($P = 0.822$) and Egger tests ($P = 0.463$) were performed and found no evidence of publication bias in the remaining 16

Table 1

Characteristics of included studies.

First author and publication year	Country	Design	LOE	Male/all subjects	Age	BMI, kg/m^2	AHI	FENO, ppb	NO parameters	Method	Expiratory flow rates, mL/s
Hamada, 2016[30]	Japan	CCT	3b	22/34	57±11	26.8±4.9	31.5±26.4	25.4±13.2	FENO, nasal NO	Online	NA
				8/17	48±16	23.6±5.0	6.6±2.9	28.4±34.4			
Tichanon, 2016[26]	Thailand	CCT	3b	10/13	53±12	28.4±3.5	15.9±6.6	25.9±5.0	FENO	Online	50
				10/13	53±12	23.3±1.5	NA	17.5±5.9			
Duong-Quy, 2016[25]	Vietnam	CCT	3b	28/52	54±13	23.9±3.4	25.6±15.9	22.1±16.8	FENO, CANO, J'awNO	2CM model	50, 100, 150, 300
				15/30	54±14	21.6±3.0	3.0±1.4	12.0±5.9			
Liu, 2016[24]	China	CCT	3b	23/32	51±11	28.2±3.5	30.5±21.3	19.99±7.0	FENO, CANO, J'awNO	2CM model	50, 100, 120, 180, 250
				15/27	49±11	23.5±2.9	NA	9.45±4.5			
Hua-Huy, 2015[29]	France	CST	2b	46/71	58±10	29.9±6.5	26.4±17.4	17.2±11.5	FENO, CANO, J'awNO	Trumpet model	NA
				11/24	53±15	27.4±5.7	2.5±1.5	16.7±14.2			
JalilMirmohammadi, 2014[28]	Iran	CST	2b	NA/47	50±13	32.7±5.1	39.7±15.7	20.0±10.0	FENO	Online	50
				NA/7	45±7	26.1±4.4	3.0±0.88	11.8±7.3			
Cowan, 2014[23]	UK	CST	2b	67/97	51±11	33±81	≥5	18±10.4	FENO	Online	NA
				15/32	44±12	31±5.9	<5	15±9.6			
Chua, 2013[22]	USA	CST	2b	43/75	46±14	37±10.3	40±33	19.0±7.7	FENO	Online	50
				14/29	35±14	31.7±9.3	2±1	6.9±3.7			
Fortuna, 2011[21]	Spain	CCT	3b	22/30	54±10	31.2±3.3	46.7±18.0	27.2±18	FENO, CANO, J'awNO, D'awNO	2CM model	10, 30, 100, 200
				14/30	41±10	24.8±2.8	2.4±1.7	16.7±8			
Culla, 2010[20]	USA	CCT	3b	22/39	66±11	30.7±6.0	≥10	23.1±13.1	FENO, oral NO	Online	50
				NA/24	NA	NA	NA	11.0±7.2			
Carpagnano, 2008[18]	Italy	CCT	3b	14/30	39±8	33.2±1.1	59.1±4.1	31.6±1.6	FENO	Online	45
				12/20	45±8	33.8±1.7	5.7±0.8	27.1±1.8			
Petrosyan, 2008[33]	Greece	CCT	3b	NA/26	55±14	37.5±10	63.7±29.5	7.1±4.6	FENO, nasal NO	Online	250
				NA/9	52±7	33.3±2.5	2.7±1.7	5.0±1.1			
Depalo, 2008[17]	Italy	CCT	3b	10/18	48±8	34.2±1.8	59.1±4.1	23.1±2.1	FENO	Online	45
				8/15	53±11	33.6±2.7	3.8±1.1	17.9±2.1			
Foresi, 2007[31]	Italy	CCT	3b	27/34	57±8	31.6±5.5	31.3±17.4	21.8±11.1	FENO, CANO	2CM model	50, 120, 190, 250, 300
				22/29	47±15	25.3±4.2	1.4±0.3	25.1±17.8			
Przybyłowski, 2006[16]	Poland	CST	2b	55/66	54±13	31.0±5.3	40.3±24.9	22.4±13.2	FENO	Online	45–55
				44/53	50±11	28.5±3.7	3.7±2.8	15.3±8.1			
Agustí,1999[27]	Spain	CCT	3b	24/24	48±7	33.2±4.4	55±19.6	22.2±14.7	FENO	Online	NA
				7/7	37±6	23.8±1.6	NA	19.7±8.5			

Every study the upper line listed the data of obstructive sleep apnea group and the second line was the data of controls.

2CM model = 2-compartment model, AHI = apnea–hypopnea index, BMI = body mass index, CANO = concentration of alveolar nitric oxide, CCT = case–control trail, CST = cross-sectional trail, D'awNO = airway diffusion of NO, FENO = fractional exhaled nitric oxide, J'awNO = maximum total airway NO flow, LOE = level of evidence, NA = not available.

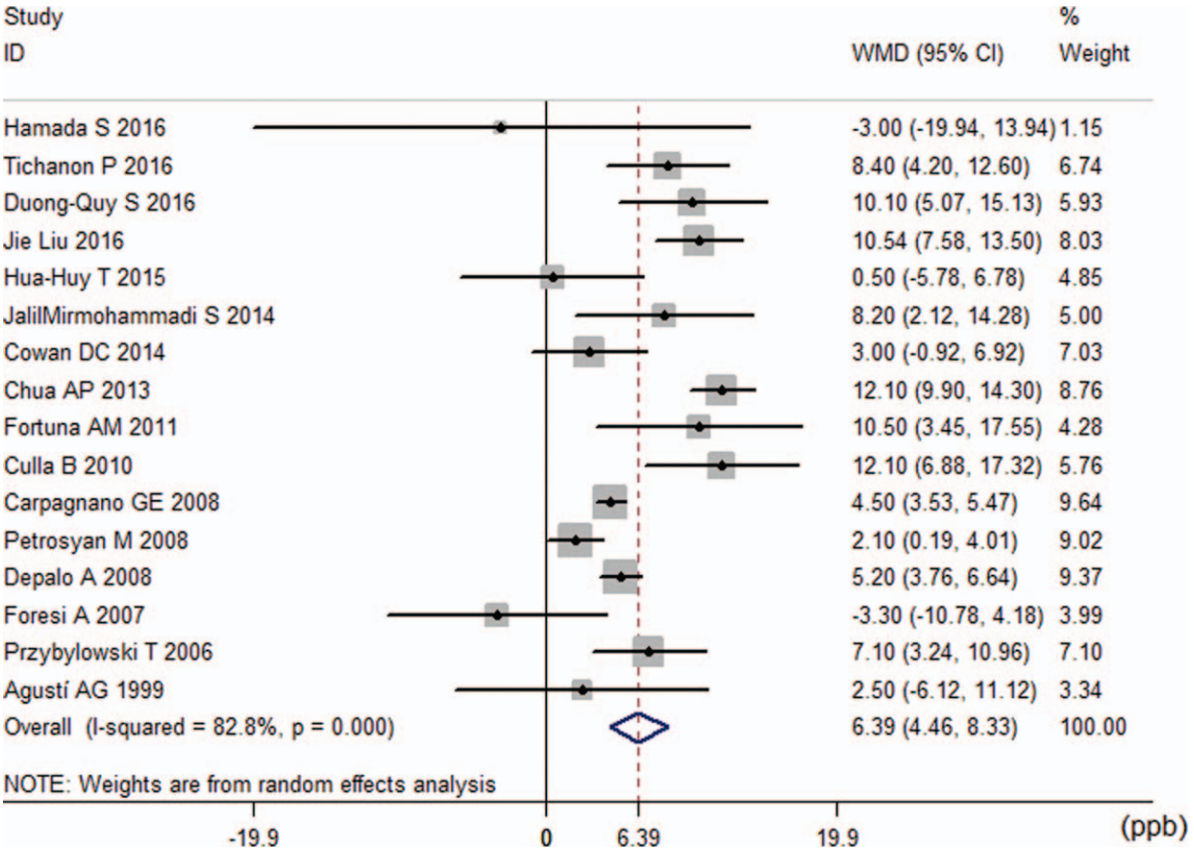

Figure 2. Comparison of fractional exhaled nitric oxide levels between obstructive sleep apnea groups and control groups in the 16 included studies.

studies. For the analysis of CANO levels and J'awNO levels, the Begg tests ($P=0.806$ and $P=0.734$, respectively) and Egger tests ($P=0.391$ and $P=0.862$, respectively) also found no evidence of bias.

3.5. Sensitivity analysis

No single trial, when removed, significantly affected the overall estimate of the effects of the 3 eNO measures (Supplemental Fig. 2A–C, Supplemental digital Content 3, http://links.lww.com/MD/B613, which shows the results of the sensitivity analyses). The pooled analysis using the random-effects model showed that FENO levels were increased significantly (WMD 6.39, 95% CI 4.46–8.33, $P<0.001$). The fixed-effects model found a similar result (WMD 5.56, 95% CI 4.93–6.20, $P<0.001$). After including the previously excluded study, the pooled analysis result was 7.25 (95% CI 3.49–11.00, $P<0.001$) using the random-effects model.

3.6. Meta-regression analysis

Meta-regression analyses were performed to evaluate the effect of age, BMI, AHI, and minimum pulse oxygen saturation (SpO_2) on the levels of FENO. The FENO levels were not significantly correlated with the age of the patients with OSA ($P=0.980$) and BMI ($P=0.438$), the age ($P=0.353$) and BMI of normal participants ($P=0.362$), or the AHI ($P=0.399$) and minimum SpO_2 ($P=0.964$). The analyses of CANO levels and J'awNO levels described above were not reanalyzed by meta-regression because of the limited number of studies included.

4. Discussion

NO is a reactive molecule produced by nitric oxide synthase (NOS) in a reaction that converts L-arginine and oxygen to citrulline and NO. Three distinct forms of NOS have been identified: endothelial NOS (eNOS), neuronal NOS (nNOS), and inducible NOS (iNOS).[35] Among them, only iNOS can produce a large amount of NO for longer periods of time after activation by stimuli; it plays a role in pathophysiological processes such as inflammation. Exhaled NO levels are elevated in conditions associated with airway inflammation, for example, asthma, and are used as simple, noninvasive markers of airway inflammation.

To our knowledge, this is the first meta-analysis addressing the exhaled NO levels in patients with OSA. We found that there was an increase in FENO levels in subjects with OSA; however, CANO and J'awNO were not significantly different between the patients with OSA and the controls. Moreover, FENO levels were significantly increased on waking up in patients with OSA, but not in non-OSA groups, and long-term CPAP was able to modify FENO in OSA groups.

Our results showed that FENO was significantly increased in subjects with OSA, and that this might be linked to the over-expression of iNOS,[15,17,36] which was partially reversible after long-term CPAP treatment. In our pooled analysis, the level of FENO on waking up was significantly increased in subjects with OSA (Fig. 3) but not in healthy controls. Mechanical stress on the mucosa caused by intermittent airway closure and reopening as well as ischemia-reperfusion injury from intermittent nocturnal hypoxemia produces oxygen free radicals, which can lead to increased upper airway inflammation. The nasal, tonsillar, and

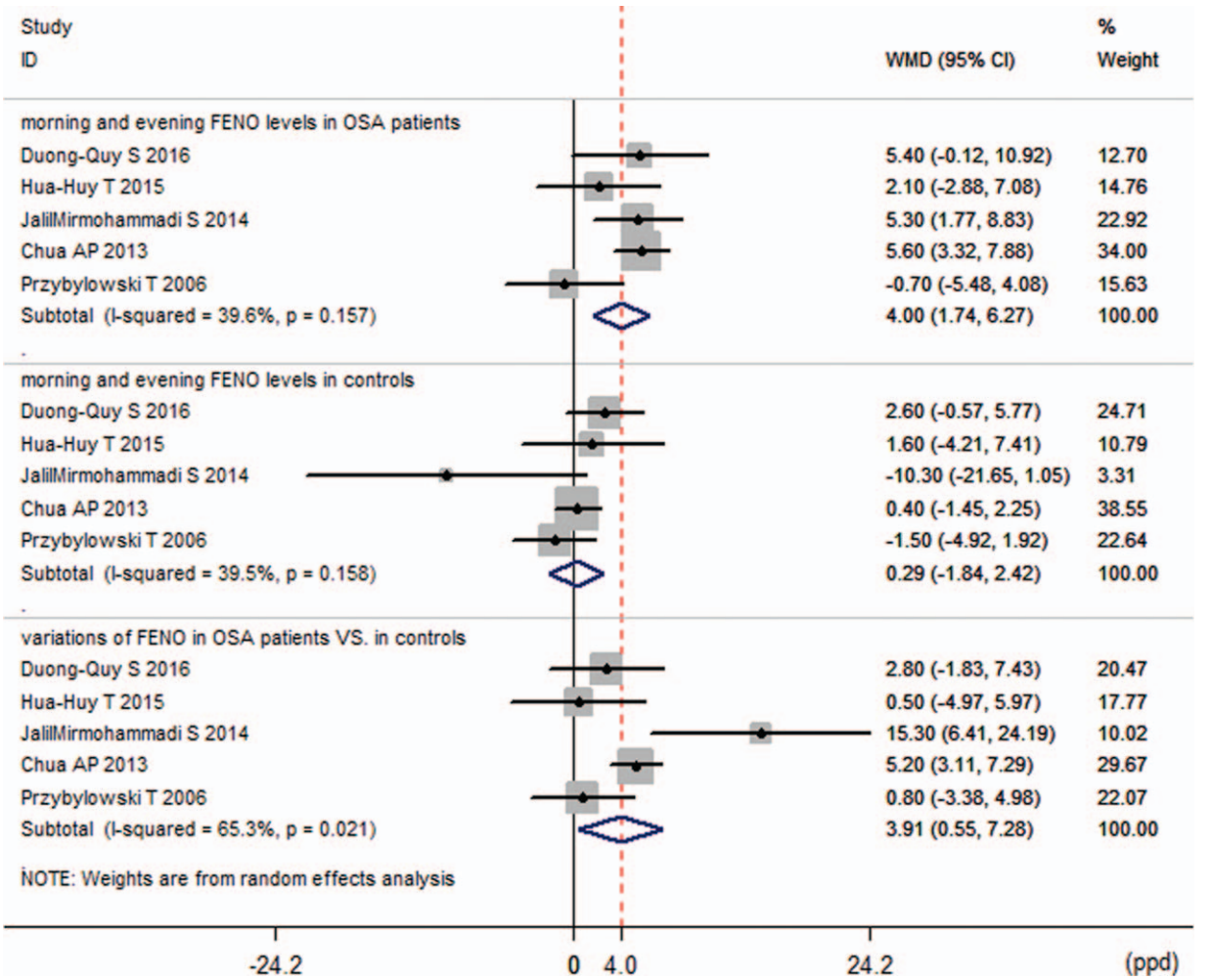

Figure 3. Variation of fractional exhaled nitric oxide (FENO) levels.

oropharyngeal tissues are potential inflammatory sites in patients with OSA,[37–40] and plasma cell infiltration and interstitial edema have been documented in tissue biopsies.[40] Local upper-airway inflammation promotes oropharyngeal inspiratory muscle dysfunction and the formation of progressive local neurogenic lesions, thus amplifying the upper airway narrowing and collapsibility.[41] Additionally, tissue biopsies confirmed the significant effect of long-term CPAP treatment on reducing inflammation-related infiltration in upper airways.[38] Thus, FENO can be used as a simple, noninvasive marker of upper airway inflammation in patients with OSA, allowing a more accurate prediction of response to treatment.

Experimental studies have found that other exhaled markers of airway inflammation and oxidative stress such as interleukin 6, interleukin 10, and 8-isopentane were also raised in the breath condensate of adults with OSA,[42,43] and that there was a significantly higher percentage of neutrophils in the induced sputum of patients with OSA than in healthy volunteers.[6,18,34] These findings may suggest lower airway inflammation in patients with OSA. However, our results indicate that J'awNO is not a marker of lower airway inflammation in patients with OSA.

The CANO levels reflect the balance between the local production of NO from distal parts of the lung and diffusion across the alveolar capillary wall. Increased CANO has been found in patients with asthma,[44] alveolitis,[10] and chronic obstructive pulmonary disease,[45] mainly due to the increased NO production by inflammatory cells, epithelium, or endothelial cells. Although OSA is associated with systemic inflammation, increased oxidative stress, and endothelial dysfunction, we speculate that the extent of these processes was not enough to alter the concentration of CANO, as demonstrated by the lack of a significant difference in CANO levels between the OSA and control subjects. An alternative explanation might be the presence of endothelial dysfunction in patients with OSA; unfortunately, none of the included studies investigated this issue. The CANO levels in patients with OSA should be further investigated and characterized.

In the meta-regression, both the characteristics (age and BMI) and OSA severity (AHI and minimum SpO_2) had no correlation with the increased FENO levels. In another experiment by Verhulst et al[46] involving the pediatric population, habitual snoring and age were the only variables associated with raised FENO levels in the morning and afternoon, leading them to conclude that snoring is more important than the actual obstructive respiratory events for increased upper airway inflammation. They proposed that snoring induced vibration of the soft tissues, which caused damage to these tissues contributing to the pathogenesis of OSA. In our analysis, only FENO was significantly different between the OSA and control

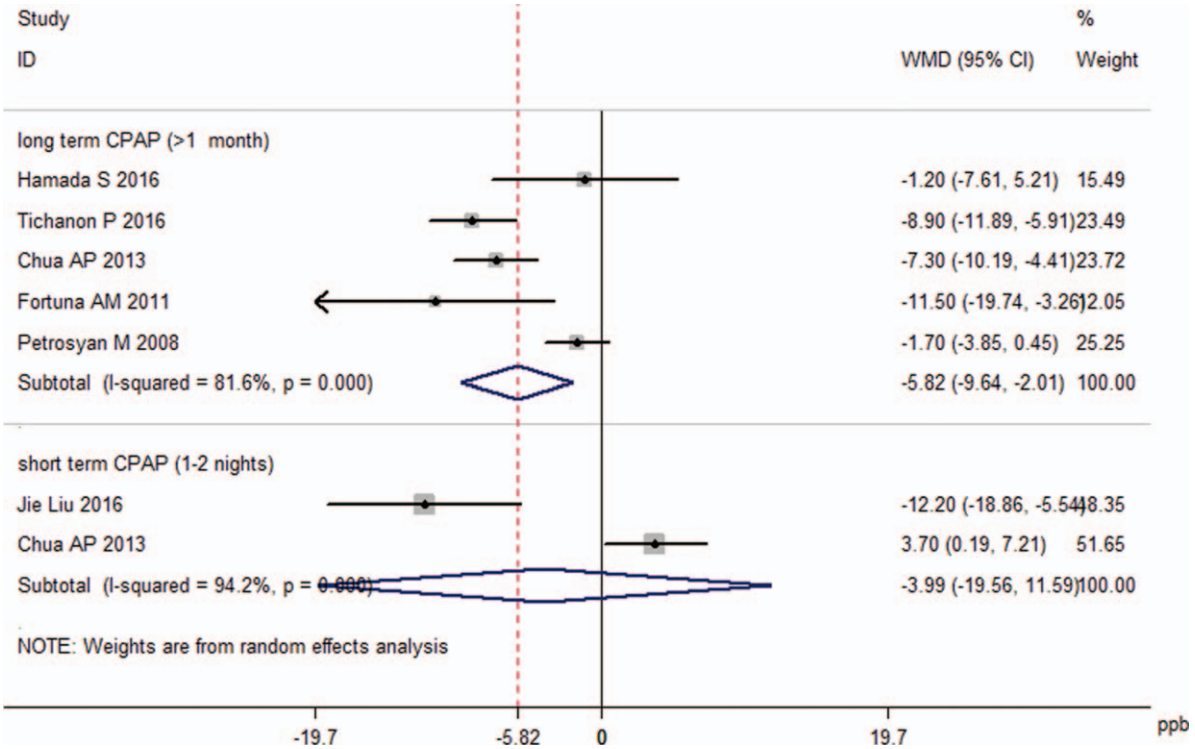

Figure 4. Effect of continuous positive airway pressure (CPAP) treatment on fractional exhaled nitric oxide levels.

subjects, implying that mechanical damage may play a more important role in the upper airway inflammation than that of hypoxemia. This hypothesis needs to be confirmed in further studies. Notably, even though FENO levels increased after sleep in patients with OSA, their FENO levels were still around the upper limit of the normal range (25 ppb). Therefore, FENO might not be an effective predictor of diagnosis of OSA, especially for distinguishing suspected OSA and the pure snorers.

The observed heterogeneity might be explained by the differences in patient inclusion criteria and the time of exhaled NO measurement. Further, only some of the studies included smokers. In the study by Fortuna et al,[21] currently smoking

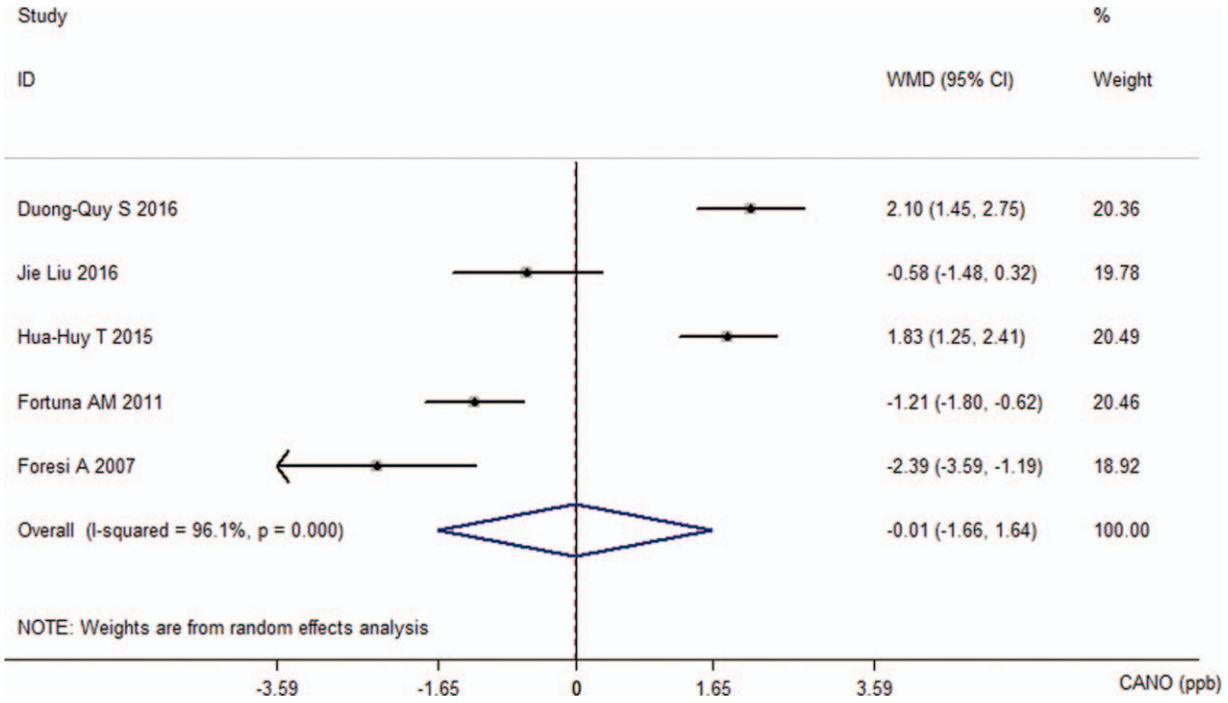

Figure 5. Comparison of concentration of alveolar nitric oxide between the obstructive sleep apnea groups and control groups in the 5 included studies.

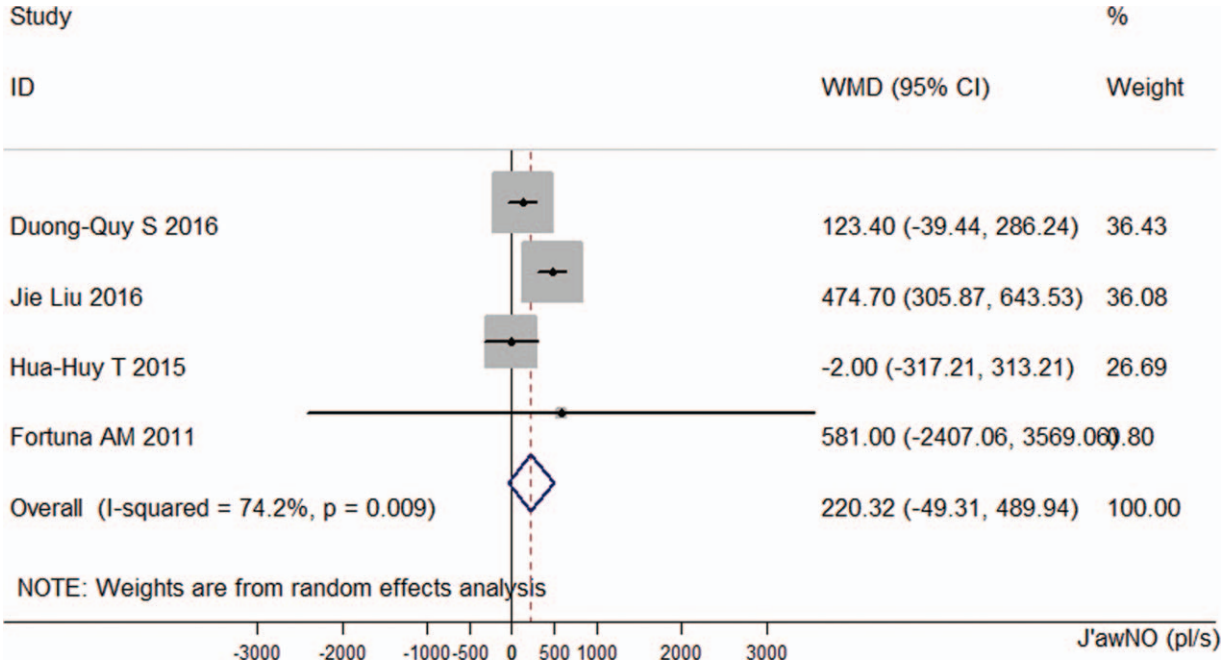

Figure 6. Comparison of the maximum airway wall flux of nitric oxide between the obstructive sleep apnea groups and control groups in the 4 included studies.

patients had lower FENO and CANO levels than ex-smokers and nonsmokers, possibly because cigarettes contain a large number of free radicals and pro-oxidant substances, which cause lower NO bioactivity, and the fact that smokers have a tetrahydrobiopterin deficit, which reduces the generation of NO.[47] However, in Liu et al's study,[24] FENO and CANO were not significantly different between the smokers and nonsmokers in both the OSA group and the healthy controls. Most studies measured the eNO from 6 AM to 10 AM and between 8 PM to 11 PM, a few studies did not report the measurement time,[17] and 1 study only evaluated the eNO from 11 AM to 1 PM.[33] Dias et al confirmed that patients with OSA and healthy subjects showed a circadian pattern of FENO with a decrease of values across the day,[19] suggesting that the time of measurement may be a confounder in this analysis. Finally, some baseline data, such as age, BMI, and AHI, were significantly different between groups.

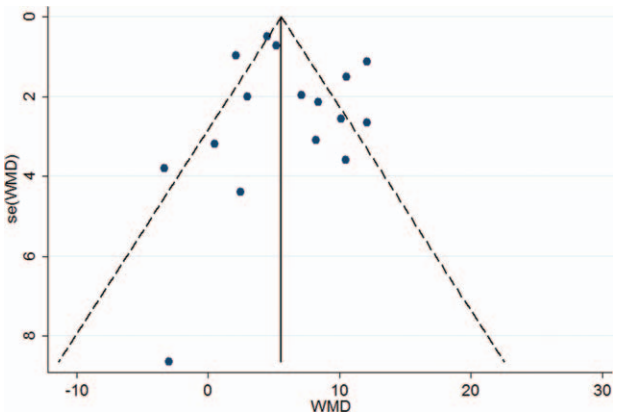

Figure 7. Funnel plot of fractional exhaled nitric oxide.

5. Limitations

Despite these meaningful findings, several limitations of this meta-analysis still need to be emphasized. Firstly, the available literature is largely low-level evidence; either case–control or CSTs of a relatively small size. Secondly, different techniques and instruments were used for the measurement of exhaled NO, which could be another source of study heterogeneity. Thirdly, there was also heterogeneity across the sample populations. We could not perform meta-regression for other confounding factors —snoring[25] or time of measurement[19]—since we did not have enough data on these variables. These factors have previously been found to be associated with eNO levels.

6. Conclusion

Our findings suggest that OSA was significantly associated with elevated FENO levels, especially after waking up, and long-term CPAP therapy can reduce FENO levels. Accordingly, FENO levels might be a noninvasive marker of upper airway inflammation in patients with OSA. However, J'awNO and CANO are not useful markers of airway inflammation for patients with OSA.

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