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ORIGINAL RESEARCH

# Temporal Dynamics of Fractional Exhaled Nitric Oxide (FeNO) During CPAP Therapy in Obstructive Sleep Apnea: A Prospective Follow-Up Study

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**Background:** This study aimed to assess: (i) whether long-term continuous positive airway pressure (CPAP) reduces fractional exhaled nitric oxide (FeNO) in obstructive sleep apnea (OSA), and (ii) how FeNO change relates to baseline OSA severity. Unlike prior cross-sectional work, we performed a prospective longitudinal follow-up with FeNO at baseline, after short-term titration, and at three months. Primary and secondary endpoints were prespecified.

**Methods:** We enrolled 62 patients with moderate-to-severe OSA; 43 completed CPAP titration and three-month follow-up. FeNO was measured preCPAP, after two nights (postCPAP1), and at three months (postCPAP2). Secondary analyses examined correlations between FeNO change and baseline indices—apnea–hypopnea index (AHI), oxygen desaturation index (ODI), percent sleep time with $SpO_2 < 90\%$ (TS90%), and Epworth Sleepiness Scale (ESS)—and the effect of CPAP adherence. Statistics: normality (Shapiro–Wilk); *t*-test or Mann–Whitney U; $\chi^2$/Fisher's exact for categorical data; repeated-measures ANOVA with Huynh–Feldt for longitudinal change; Spearman correlations. Missing data were handled by complete-case analysis with multiple imputation (m = 5) as sensitivity.

**Results:** At baseline, FeNO was higher in OSA than in AHI < 15 reference subjects from our earlier cohort (21.49 ± 5.56 vs 13.28 ± 3.70 ppb, $P < 0.001$). Within the OSA cohort, FeNO rose slightly after titration (22.84 ± 4.58 ppb, $P > 0.05$) but decreased significantly after 3 months of treatment (17.95 ± 3.27 ppb, $P < 0.001$ vs baseline).FeNO reduction correlated with AHI ($r = 0.674$), ODI ($r = 0.617$), TS90% ($r = 0.461$), and ESS ($r = 0.552$; all $P < 0.001$). Greater reductions occurred with adherence ≥ 6 h/night.

**Conclusion:** Sustained CPAP significantly lowers FeNO, reflecting reduced airway inflammation in OSA. FeNO may serve as a promising non-invasive candidate biomarker for monitoring CPAP response, but larger multicenter studies are needed.

**Keywords:** obstructive sleep apnea, fractional exhaled nitric oxide, CPAP, airway inflammation, polysomnography, candidate biomarker

## Introduction

Obstructive Sleep Apnea (OSA) is a common condition marked by repeated blockage of the upper airway during sleep, causing intermittent low oxygen levels, disturbed sleep patterns, and various physiological effects.[1] Emerging evidence highlights airway inflammation as a critical contributor to OSA pathogenesis and progression,[2,3] thus prompting research aimed at identifying reliable, non-invasive biomarkers of inflammation in affected individuals.[4,5]

Fractional exhaled nitric oxide (FeNO) is widely recognized as an indicator of eosinophil-driven inflammation in the airway, particularly in conditions like chronic obstructive pulmonary disease (COPD) and asthma.[6,7] Studies investigating biologic therapies for asthma, however, suggest that FeNO and eosinophil counts may not directly correlate, given their regulation by distinct cytokines and involvement in separate inflammatory pathways.[8] Recently, FeNO has gained

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attention in the context of OSA,[9,10] as intermittent hypoxia and mechanical stress from recurrent airway obstruction may stimulate inflammatory responses in the airway. In our previous study, we identified a cross-sectional relationship between FeNO levels and cognitive performance in OSA patients, highlighting FeNO as a promising biomarker for airway inflammation in this population.[11] Yet, research findings on FeNO in OSA patients remain inconsistent, with some reporting elevated FeNO levels, while others find no significant differences compared to healthy controls.[10,12–14] Recent studies, including meta-analyses and mechanistic investigations, further highlight the role of intermittent hypoxia-induced oxidative stress and inflammatory cytokine release in modulating FeNO expression in OSA.[15–18]

Continuous positive airway pressure (CPAP) therapy remains the primary treatment for managing OSA, effectively reducing apneic episodes and improving oxygen saturation.[19,20] In addition to its mechanical effects on airway patency, CPAP has been reported to modulate inflammatory processes.[21] Several studies have indicated a reduction in FeNO levels following CPAP treatment, suggesting potential anti-inflammatory effects.[22,23] However, unlike our previous study which focused on cross-sectional analysis, comprehensive insights into the temporal dynamics of FeNO changes throughout different stages of CPAP therapy remain limited.

The key knowledge gap is the absence of longitudinal evidence regarding how FeNO levels fluctuate across both short-term and long-term CPAP therapy in OSA patients. We hypothesized that: (i) OSA patients would exhibit higher FeNO levels compared to healthy controls; (ii) FeNO may show a transient fluctuation following short-term CPAP titration; and (iii) sustained CPAP treatment would significantly reduce FeNO levels, with the magnitude of reduction positively associated with baseline OSA severity.

Therefore, this study aims to systematically evaluate FeNO changes in OSA patients at multiple stages, including baseline, after short-term CPAP titration, and following three months of consistent CPAP use. Such an approach could enhance understanding of airway inflammation responses to CPAP therapy. Clarifying FeNO's role as a biomarker of therapeutic efficacy and airway inflammation has significant potential to improve clinical management strategies for OSA patients.

This study builds upon our previous cross-sectional investigation of FeNO and cognitive outcomes in OSA patients,[11] but differs in several important ways. First, it adopts a prospective design with repeated FeNO measurements at baseline, immediately after short-term CPAP titration, and following three months of therapy. Second, it evaluates temporal FeNO dynamics under CPAP treatment rather than single-timepoint associations. Third, it directly links FeNO reduction to both disease severity and CPAP adherence. These aspects highlight the novelty and added value of the present work compared with prior research.

## Materials and Methods

This was a prospective longitudinal follow-up study (non-randomized and non-controlled) focusing exclusively on patients with moderate-to-severe obstructive sleep apnea (OSA; apnea–hypopnea index [AHI] ≥ 15 events·h$^{-1}$). These participants were part of a previously published cross-sectional cohort that included 40 individuals with AHI < 15 and 62 with moderate-to-severe OSA.[11] In the present investigation, we restricted the analysis to the OSA cohort and performed repeated measurements of fractional exhaled nitric oxide (FeNO) at three predefined time points: before CPAP initiation (preCPAP), after two nights of titration (postCPAP1), and after three months of therapy (postCPAP2). Among the 62 eligible patients, 43 completed CPAP titration and the three-month follow-up and were included in the final longitudinal analysis.

Adults aged 18–60 years who presented to the Sleep Medicine Center of Affiliated Nantong Hospital 3 of Nantong University and the Affiliated Hospital of Xuzhou Medical University, a tertiary academic medical institution, between January 2025 and 30 April 2025 were consecutively recruited. Patient referral context. As a tertiary sleep medicine center, referrals included adults with suspected sleep-disordered breathing on clinical grounds (eg, loud snoring, witnessed apneas, non-restorative sleep/insomnia, excessive daytime sleepiness), cardiometabolic comorbidities (eg, resistant hypertension), or pre-operative risk stratification. Referral was therefore independent of the eventual diagnostic AHI. In our previously published cross-sectional cohort, individuals with AHI < 15 were retained as a baseline reference group for cross-sectional comparisons, but no longitudinal follow-up was planned in that cohort for the present study. To maximise external validity, no advertising or financial incentives were offered; all candidates were approached in strict referral order and screened on the day of their outpatient consultation. Participants were thoroughly informed about the study through both verbal discussion and written materials. According to the ethical standards of the Declaration of

Helsinki, formal written consent was gathered. The study protocol was approved by the institutional ethics board (EK2023115; initial approval December 2023; renewed and amended in December 2024 to authorize recruitment and data collection from January to April 2025). Screening and exclusions. Of 159 screened individuals, 57 were excluded based on a pre-specified hierarchy of primary reasons (mutually exclusive): recent active smoking within 3 months (n = 12), recent respiratory infection within 4 weeks (n = 9), physician-diagnosed asthma/COPD (n = 8), systemic or inhaled corticosteroid use within 1 month (n = 6), shift-work status (n = 5), central sleep apnea on diagnostic PSG (n = 4), refusal of FeNO testing (n = 4), incomplete/failed PSG (n = 4), alcohol abuse by prespecified thresholds (n = 3), and pregnancy (n = 2). Reasons for exclusion are summarized in Supplementary Table S6. In total, 159 patients were screened; 57 were excluded and 19 declined participation. A total of 62 participants with moderate-to-severe OSA were enrolled in this follow-up study, of whom 43 completed CPAP titration and the three-month follow-up.

## Study Objectives and Endpoints (Primary and Secondary Outcomes)

The primary objective of this study was to investigate the temporal changes in fractional exhaled nitric oxide (FeNO) in patients with moderate-to-severe OSA undergoing continuous positive airway pressure (CPAP) therapy. The primary endpoint was the within-subject change in FeNO across three predefined time points: before CPAP initiation (preCPAP), after two nights of titration (postCPAP1), and after three months of therapy (postCPAP2). These measurements were performed longitudinally in the same individuals to capture the temporal dynamics of CPAP-induced changes.

The secondary objectives were to assess:

I. the associations between the magnitude of FeNO reduction (ΔFeNO) and baseline OSA severity indices, including AHI, oxygen desaturation index (ODI), percentage of total sleep time with $SpO_2$ < 90% (TS90%), and ESS;
II. the influence of CPAP adherence on FeNO changes; and
III. the distribution patterns of FeNO change across different baseline airway inflammatory states.

## Eligibility Criteria

Inclusion criteria: (i) aged between 18 and 60 years; (ii)referral for suspected sleep-disordered breathing; and (iii) willingness to undergo diagnostic polysomnography (PSG) and FeNO testing. Participants with AHI ≥ 15 were classified as having moderate-to-severe OSA and were included in this follow-up analysis. We excluded shift workers and pregnant women because circadian disruption and hormonal changes can independently alter FeNO. Other exclusion criteria were: smoking within the past 3 months (to avoid smoking-induced NO variability); alcohol abuse (≥14 drinks/week for men, ≥7 for women); uncontrolled comorbidities such as asthma, COPD, or active respiratory infection; central sleep apnoea(CSA); regular use of oral sedatives, opioids, or hypnotics; inability or unwillingness to comply with study visits; respiratory infection within the past four weeks; systemic or inhaled corticosteroid therapy in the preceding month; refusal of FeNO measurement; Non-steroidal anti-inflammatory drugs (NSAIDs) exposure was assessed at each visit via a structured medication questionnaire and reconciliation with the medical record medication list; participants were instructed to avoid any NSAID use for ≥72 hours prior to FeNO measurements.

## Study Flow and Measurements

All eligible participants underwent overnight diagnostic PSG in a room designed to block out sound. A visual summary of participant screening, exclusion, and final allocation is shown in Figure 1. Recordings were scheduled from 21:00 to 06:00 and lasted at least seven hours. Data were acquired with the Nox A1 system (ResMed, Australia). A typical polysomnographic setup was employed, featuring eight EEG channels (F3, F4, C3, C4, O1, O2, M1, M2), bilateral electrooculograms, chin and anterior tibialis EMG recordings, ECG, nasal airflow measured by a pressure transducer, oronasal airflow via thermistor, thoracoabdominal movement assessed with inductance plethysmography belts, a body position sensor, and pulse oximetry on the fingertip. Signal integrity was verified hourly by an onsite technologist, and any electrode detachment or artefact was corrected immediately to minimise data loss.

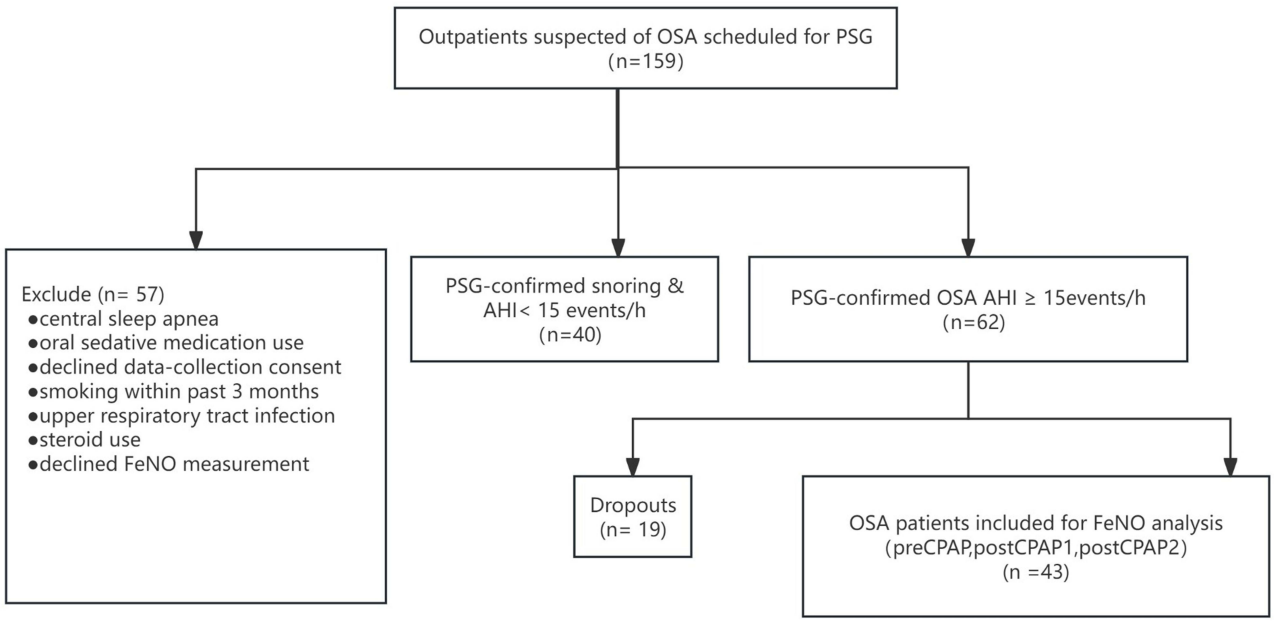


**Figure 1** Flowchart of participant screening, exclusion, and final allocation for FeNO analysis.
**Note**: Primary reasons for screening exclusions are summarized in Supplementary Table S6.

Two experienced technologists, blinded to participants' clinical data and to each other's assessments, independently scored the raw PSG recordings. Sleep architecture and related events were annotated following the criteria established by the American Academy of Sleep Medicine(AASM)[24] criteria, version 2.3. Extracted indices included sleep efficiency (SE), sleep-onset latency, total sleep time (TST), percentages of NREM stages N1, N2, and N3, and REM sleep, AHI, oxygen desaturation index (ODI), cumulative time with $SpO_2 < 90\%$ (TS90%), and lowest peripheral oxygen saturation ($LSpO_2$). Subjective daytime sleepiness was assessed on the evening prior to PSG using the ESS, which scores from 0 to 24, with higher values reflecting increased daytime sleepiness. ESS license for use in this study was obtained from Mapi Research Trust (license ID: 119346). Definitions for subjective symptoms were standardized as follows: fatigue = daytime tiredness on ≥3 days/week; dry mouth = morning oral dryness on ≥3 days/week; memory deterioration = self-reported decline within 1 year.

## CPAP Titration and Treatment

Participants diagnosed with OSA (AHI ≥ 15 events·$h^{-1}$) were invited to undergo auto-titrating CPAP (AirSense 11 AutoSet, ResMed) with heated humidification for two consecutive nights within two weeks of diagnosis. A nasal mask was used as the first-line interface; in cases of nasal obstruction, intolerance, or craniofacial mismatch, an oronasal (full-face) mask was fitted under therapist supervision. Mask fit was reassessed after the first titration night, and humidification was adjusted to optimize comfort and minimize leak. CPAP adherence was quantified from device-downloaded usage logs (AirSense 11 compliance reports), while self-reported hours were recorded but not used in the primary analyses.

## FeNO Assessment

FeNO was measured with a chemiluminescence analyser (Wuxi Shangwo, China) following the protocols outlined by the American and European Thoracic Societies. The analyser was calibrated daily with certified 0 ppb and 200 ppb NO standard gases, and ambient NO levels in the testing room were recorded before each session. All measurements were conducted in the morning between 07:30 and 09:00, prior to breakfast, to minimize circadian variability. Participants were instructed to avoid nitrate-rich foods (eg, green leafy vegetables, processed meats) for at least 3 hours, and to refrain from caffeine, alcohol, smoking, and vigorous physical activity for at least 1 hour before testing. Per structured self-report and medication list reconciliation, no participant reported ongoing or recent (≤72 h) NSAID use during the study

period. The testing was performed in a quiet, temperature-controlled room (22–24 °C) with ambient NO levels < 10 ppb. For quality assurance, two trained technicians independently supervised the measurements, and inter-operator reliability was confirmed in a random subset of 15 subjects, yielding an intraclass correlation coefficient (ICC) of 0.92, indicating excellent agreement. Measurements were scheduled at three identical circadian windows to minimise diurnal variation: (i) within 60 minutes before PSG or the first titration night (preCPAP); (ii) within 60 minutes after completion of the second titration night (postCPAP1); (iii) within 60 minutes after the final follow-up PSG at three months (postCPAP2). Participants abstained from smoking, caffeine, alcohol, and vigorous exercise for at least one hour and avoided nitrate-rich foods for at least three hours prior to testing. Following a deep breath to full lung inflation, exhalation was maintained at a fixed flow rate of 50 mL per second for at least 6 seconds; three technically acceptable manoeuvres (plateau ≥ 3 s, repeatability within 10%) were obtained, and the mean value was used for analysis.

Timing rationale. FeNO was scheduled at three standardized windows to capture distinct phases of CPAP response: (i) preCPAP as the untreated baseline; (ii) postCPAP1 (after two titration nights) to probe acute/early effects; and (iii) postCPAP2 at three months, a period by which device use stabilizes and anti-inflammatory effects are most consistently reported. Intermediate monthly measurements were not implemented to minimize participant burden and align with routine clinical review cycles.

## Sample Size Estimation and Statistical Analysis

Using G*Power 3.1, a pre-study power analysis determined that enrolling 36 OSA patients with complete 3-month follow-up would yield 90% statistical power ($\alpha = 0.05$) to identify a moderate effect size ($f = 0.25$) in FeNO changes over three time points via repeated-measures ANOVA, assuming a correlation of 0.5 among measures and 10% attrition. As the primary objective of this study was to evaluate temporal FeNO changes with CPAP, the sample size calculation was based on this endpoint. The secondary objective was to assess correlations between FeNO reduction and OSA severity indices, which was addressed by post-hoc sensitivity analyses. To compensate for potential loss to follow-up, we aimed to enroll at least 45 patients with moderate-to-severe OSA. Ultimately, 43 patients completed the protocol, thereby fulfilling the predefined power requirement.

The Shapiro–Wilk test was used to evaluate the distribution of continuous variables. Normally distributed variables are expressed as mean ± SD and were compared using the independent-samples *t*-test. Non-normally distributed variables are expressed as median (IQR) and were compared using the Mann–Whitney *U*-test (Z value). Categorical variables are expressed as n (%) and were compared using the $\chi^2$-test or Fisher's exact test, as appropriate. Repeated-measures ANOVA with Huynh–Feldt corrections was applied to assess FeNO changes over time, and mixed-effect models adjusting for Body Mass Index(BMI) and age were used as a robustness check. OSA patients were stratified into high (≥6 h/night) and low (<6 h/night) adherence groups to compare ΔFeNO. Mean nightly CPAP use was added as a covariate in repeated-measures models, and the CPAP effect on FeNO remained significant. Regression coefficients (β) with 95% confidence intervals were reported. Multiplicity of endpoints was controlled using Bonferroni correction. Effect sizes ($\eta^2$p, r) were reported where applicable. A two-tailed $P < 0.05$ was considered statistically significant. Missing data were documented, and analyses were based on complete cases. Sensitivity analyses confirmed that excluding missing cases did not materially change the results. Relationships between FeNO change (preCPAP–postCPAP2) and baseline OSA severity markers were explored with Spearman rank correlations; results were illustrated with scatterplots and 95% confidence bands. Statistical significance was determined by a two-sided *P*-value < 0.05. Missing data handling: primary analyses used complete cases. As a sensitivity analysis, we performed multiple imputation (m=5) under a missing-at-random assumption using predictive mean matching for continuous variables and logistic models for categorical variables; the imputation model included age, sex, BMI, AHI, ODI, TS90%, ESS, and baseline FeNO. Pooled estimates were combined using Rubin's rules. Detailed imputation specifications and sensitivity analyses (worst-/best-case scenarios; pooled estimates) are provided in Supplementary Methods S1 and Supplementary Tables S3–S5.

This study was conducted in accordance with the STROBE reporting guidelines for observational studies. The completed STROBE checklist is provided as Supplementary Material (Supplementary Table S1).

## Results

A total of 62 patients with moderate-to-severe OSA (AHI ≥ 15 events·h$^{-1}$) were initially enrolled based on our previously published cross-sectional study.[11] Of these, 43 completed CPAP titration and three-month follow-up and were included in the final longitudinal analysis. No new control group was enrolled; previously published AHI < 15 data were used solely for baseline reference (Table 1). Flow of participants is shown in Figure 1. The present follow-up investigation therefore focused exclusively on within-subject longitudinal changes in FeNO across three time points (preCPAP, postCPAP1, and postCPAP2), to evaluate the temporal response to CPAP and its association with baseline OSA severity. Reasons for screening exclusions are detailed in Supplementary Table S6.

## Baseline Demographic, Sleep, and Inflammatory Parameters (Reference Comparison)

Baseline demographic, PSG, and inflammatory features of the OSA cohort and the AHI < 15 reference group are presented in Table 1. No significant differences were found between the two groups in terms of age, education level, sex distribution, smoking history, drinking history, history of hypertension or diabetes (all $P > 0.05$).

However, significant differences were observed in several key parameters: BMI, neck circumference(NC), ESS, proportion of NREM1 sleep, TS90%, $LSpO_2$, ODI, ArI, longest apnea duration, and FeNO (median [IQR] was 21.0 [17.3–26.0] ppb in OSA vs 13.6 [11.3–16.0] ppb in the AHI < 15 reference group; all $P < 0.05$; see Table 1).

**Table 1** Baseline Demographic, Polysomnographic, and Inflammatory Parameters of OSA and Reference Groups

| Parameters | Control (n = 40) | OSA (n = 62) | t/z/$\chi^2$ Value | *P*-value | Test |
|---|---|---|---|---|---|
| **Demographics** | | | | | |
| Age, years | 37.4 ± 7.0 | 39.8 ± 7.7 | t =−1.45 | 0.135 | *t*-test |
| Gender, male, n (%) | 33(82.5%) | 52(83.8%) | $\chi^2$ =0.18 | 0.858 | $\chi^2$ test / Fisher |
| Education, years | 15.0(14.0–16.0) | 15.0(14.0–15.0) | z =−1.50 | 0.502 | Mann–Whitney U |
| BMI, kg/m$^2$ | 24.6(22.8–26.3) | 26.9(25.5–29.3) | z =−4.11 | <0.001*** | Mann–Whitney U |
| NC, cm | 36.0 ± 2.0 | 41.1 ± 2.5 | t =−9.35 | <0.001*** | *t*-test |
| Drinking, n (%) | 10(25.0%) | 7(11.3%) | $\chi^2$ =0.32 | 0.358 | $\chi^2$ test / Fisher |
| Smoking, n (%) | 5(12.5%) | 6(10.0%) | $\chi^2$ =0.08 | 0.665 | $\chi^2$ test / Fisher |
| **Common comorbidities** | | | | | |
| Hypertension, n (%) | 10(25.0%) | 17(27.4%) | $\chi^2$ =2.20 | 0.156 | $\chi^2$ test / Fisher |
| Diabetes, n (%) | 2(5.0%) | 5(8.1%) | $\chi^2$ =0.59 | 0.502 | $\chi^2$ test / Fisher |
| **Questionnaires** | | | | | |
| ESS | 7.0(4.0–9.0) | 8.0(6.3–11.8) | z =−3.05 | 0.001** | Mann–Whitney U |
| **Polysomnography** | | | | | |
| TST, min | 399.3±77.9 | 425.0±52.3 | t =−1.29 | 0.199 | *t*-test |
| SE, % | 90.3(82.3–93.9) | 88.6(87.0–93.9) | z =−0.41 | 0.686 | Mann–Whitney U |
| NREM1 (% TST) | 9.4(5.5–17.8) | 15.1(10.0–23.3) | z =−2.84 | 0.004** | Mann–Whitney U |
| NREM2 (% TST) | 48.9±9.9 | 50.8±13.8 | t =−0.54 | 0.589 | *t*-test |
| REM (% TST) | 19.5±6.1 | 19.0±6.1 | t =−0.77 | 0.441 | *t*-test |
| ODI | 2.8(1.2–5.6) | 37.3(18.9–66.3) | z =−7.90 | <0.001*** | Mann–Whitney U |
| TS90%, % | 0.1(0.0–0.4) | 7.7(1.8–29.9) | z =−7.81 | <0.001*** | Mann–Whitney U |
| $LSpO_2$, % | 89.5(87.0–92.0) | 76.0(63.8–82.0) | z =−7.51 | <0.001*** | Mann–Whitney U |
| Longest time of apnea, s | 44.3±18.7 | 69.8±8.3 | t =−4.49 | <0.001*** | *t*-test |
| ArI | 2.9(1.3–4.5) | 13.6(6.7–32.3) | z =−6.56 | <0.001*** | Mann–Whitney U |
| **FeNO, ppb** | 13.6(11.3–16.0) | 21.0(17.3–26.0) | z =−6.73 | <0.001*** | Mann–Whitney U |

**Notes**: Continuous variables are shown as mean ± SD (if approximately normal) or median (IQR) (if non-normal); categorical variables as n (%). Between-group comparisons used independent-samples t-tests or Mann–Whitney *U*-tests for continuous variables and $\chi^2$ or Fisher's exact tests for categorical variables. Effect sizes (eg, partial $\eta^2$, r) are reported where applicable. Two-tailed P < 0.05 was considered statistically significant. FeNO values represent baseline (pre-titration). Reference-group values (AHI < 15) are reproduced from our prior cross-sectional dataset[11] and provided for baseline comparison only (no longitudinal follow-up).

**Abbreviations**: BMI, body mass index; NC, neck circumference; NREM, non-rapid eye movement sleep; REM, rapid eye movement sleep; TST, total sleep time; SE, sleep efficiency; TS90%, proportion of sleep time with $SpO_2$ below 90%; $LSpO_2$, lowest oxygen saturation; ESS, Epworth Sleepiness Scale; ODI, oxygen desaturation index; ArI, arousal index; FeNO, fractional exhaled nitric oxide.

## Characteristics of the 43 OSA Patients Who Completed CPAP Titration and Follow-Up

Among the initial cohort of 62 OSA patients, 43 completed CPAP titration and adhered to three months of regular therapy; their baseline clinical and demographic characteristics are presented in Table 2. Mean nightly CPAP use among these patients was 6.6 ± 1.8 hours. Baseline FeNO levels prior to CPAP titration were significantly elevated in these OSA patients relative to reference values reported for the previously described AHI < 15 cohort ($P < 0.001$, see Table 2).

## Analysis of Participants Lost to Follow-Up and Sensitivity Checks

Of the 62 enrolled OSA participants, 19 did not complete the 3-month follow-up (Figure 1).

Reasons for discontinuation included poor mask tolerance (n = 8), relocation or scheduling conflicts (n = 6), and withdrawal of consent (n = 5).

Baseline demographic and polysomnographic characteristics of completers (n = 43) and dropouts (n = 19) are summarized in Supplementary Table S2.

No significant differences were observed between the two groups in age, sex distribution, BMI, AHI, ODI, or baseline FeNO (all $P > 0.10$).

Sensitivity analyses using complete-case and multiple imputation (m = 5) yielded consistent estimates for all endpoints, indicating that attrition did not materially affect the conclusions; see Supplementary Tables S2–S5 for baseline comparisons and imputation/scenario results.

**Table 2** Baseline Characteristics of OSA Patients Who Completed CPAP Titration and 3-month Follow-up (n=43)

| Parameters | OSA (n=43) |
|---|---|
| Age, years | 39.0 (36.0–43.5) |
| Gender, males, n (%) | 40 (93.0%) |
| BMI ($kg \cdot m^{-2}$) | 27.5 ± 3.1 |
| Education, years | 16 (15–16) |
| Drinking, n (%) | 7 (16.3%) |
| Smoking, n (%) | 6 (14.0%) |
| Fatigue morning, n (%) | 35 (81.4%) |
| Headaches morning, n (%) | 8 (18.6%) |
| ESS | 17.0 (13.0–19.0) |
| ODI | 21.6(16.7–40.3) |
| TS90%, % | 3.3(1.6–9.3) |
| $LSpO_2$, % | 80.0(74.0–84.0) |
| Longest time of apnea, s | 65.5±29.5 |
| ArI | 13.8±10.3 |
| Titration CPAP level, $cmH_2O$ | 14.0±5.0 |
| CPAP nightly usage, h | 6.6±1.8 |
| CPAP treatment duration, weeks | 9.8±2.1 |
| FeNO (pre-CPAP), ppb | 21.5±5.6 |

**Notes**: Data are presented as n (%) for categorical variables and mean ± SD or median (IQR) for continuous variables. Percentages were calculated based on the total number of participants within each group and rounded to one decimal place. *n* = 43 unless otherwise specified.

**Abbreviations**: ESS, Epworth Sleepiness Scale; ODI, oxygen desaturation index; TS90%, proportion of sleep time with $SpO_2$ below 90%; CPAP, continuous positive airway pressure; $LSpO_2$, minimum oxygen saturation; ArI, arousal index.


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## Changes in FeNO Levels at Different Time Points

FeNO measurements at the three predefined time points (preCPAP, postCPAP1, and postCPAP2) are illustrated in Figure 2. The previously described AHI < 15 reference group was not longitudinally followed in the present study and is shown only for baseline comparison. At baseline (preCPAP), FeNO levels were elevated compared with the previously reported AHI < 15 reference group. After two nights of CPAP titration (postCPAP1), FeNO levels showed a non-significant increase. After three months of CPAP therapy (postCPAP2), FeNO decreased significantly compared with both preCPAP and postCPAP1 ($P < 0.001$, Figure 2).

A repeated-measures ANOVA revealed a significant main effect of time on FeNO ($F(2, 84) = 93.538$, $P < 0.001$; generalized $\eta^2$ ($\eta^2G$) = 0.172; partial $\eta^2$($\eta^2p$) = 0.690). A significant between-subjects difference was also observed ($F(1,42) = 979.891$, $P < 0.001$, $\eta^2G = 0.955$,$\eta^2p = 0.959$). Mauchly's test of sphericity was violated ($W = 0.818$, $P = 0.016$), and Huynh–Feldt correction was applied. Post hoc analysis confirmed that FeNO at postCPAP2 (17.95 ± 3.27 ppb) was significantly lower than both preCPAP (21.49 ± 5.56 ppb) and postCPAP1 (22.84 ± 4.58 ppb, all $P < 0.001$, see Figure 2).

## Correlation of FeNO Reduction with Baseline OSA Severity

As shown in Figure 3, significant positive correlations were observed between FeNO reduction (preCPAP–postCPAP2) and baseline OSA severity indices. Reductions in FeNO correlated with baseline AHI ($r = 0.674$, $P < 0.001$), ODI ($r = 0.617$, $P < 0.001$), TS90% ($r = 0.461$, $P = 0.002$), and ESS ($r = 0.552$, $P < 0.001$) (see Figure 3).

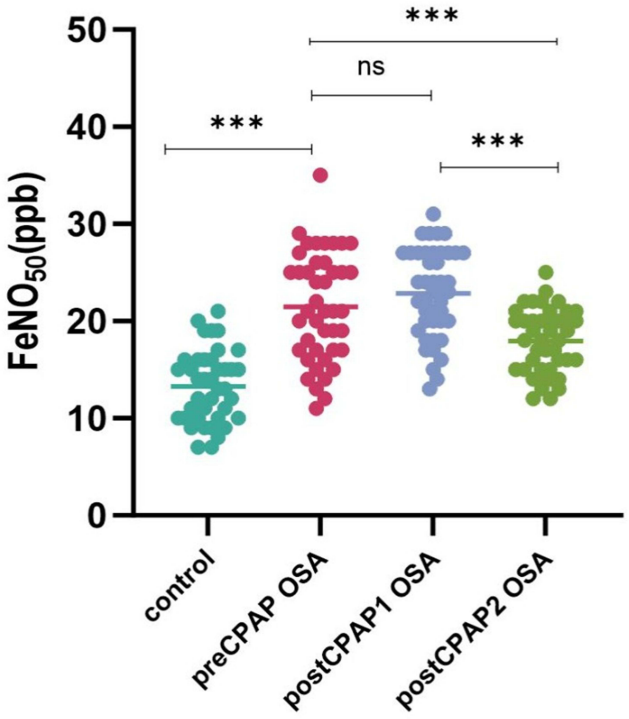


**Figure 2** Longitudinal changes in fractional exhaled nitric oxide (FeNO) across study phases.
**Notes**: Individual data points are shown as dots,and group means ± standard deviation (SD) are indicated by horizontal bars. Compared with the AHI < 15 reference group, patients with OSA exhibited significantly higher baseline FeNO levels (P < 0.001). After two nights of CPAP titration, FeNO showed a non-significant (ns) transient increase. Following three months of CPAP therapy, FeNO levels declined significantly versus baseline and post-titration (both P < 0.001). Symbols: ns = not significant; ***P < 0.001.

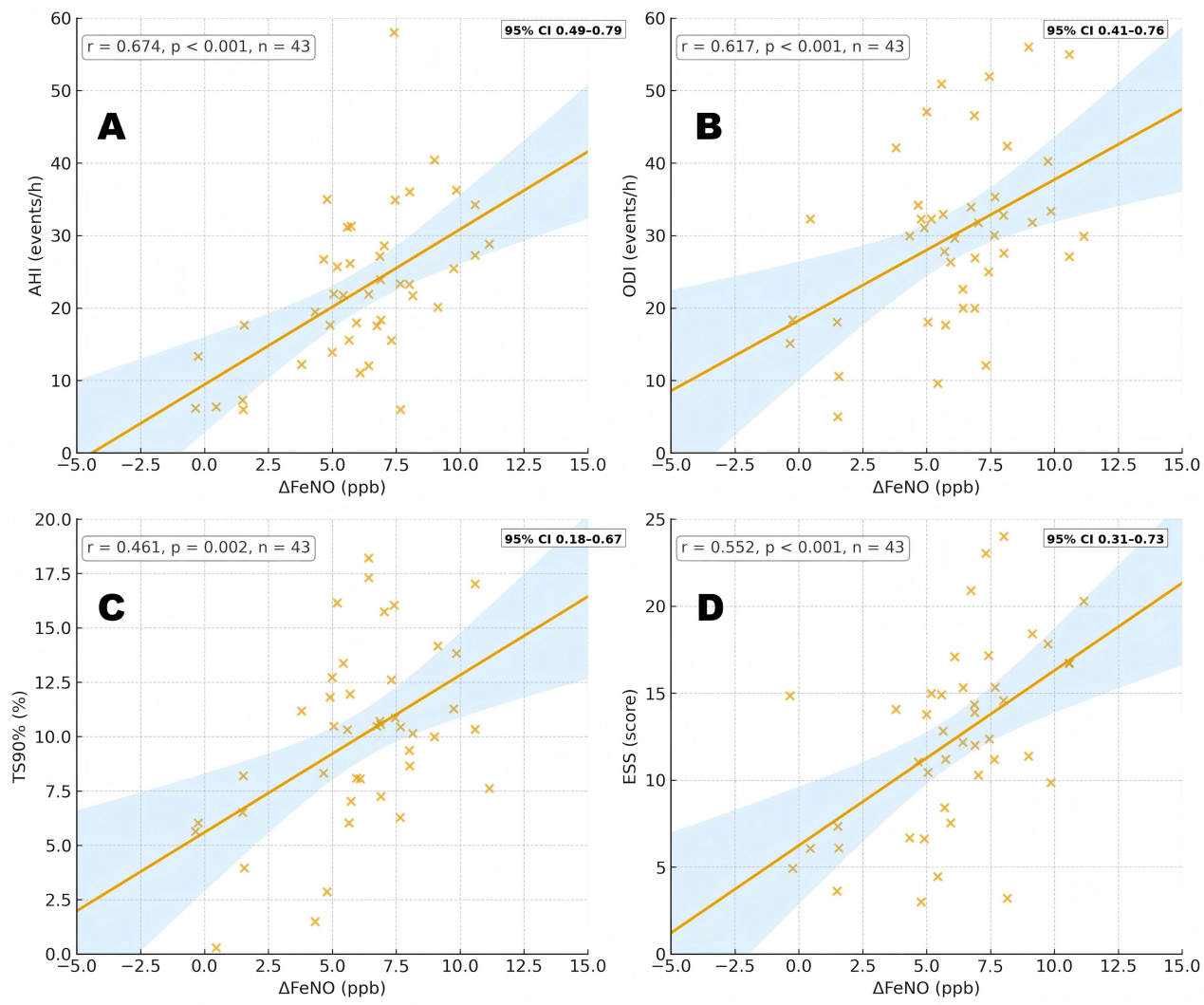


**Figure 3** Correlations between baseline OSA severity indices and changes in fractional exhaled nitric oxide (ΔFeNO = preCPAP – postCPAP2).
**Notes**: (**A**) Correlation between AHI and ΔFeNO (r = 0.674, 95% CI 0.49–0.79, P < 0.001, n = 43). (**B**) Correlation between ODI and ΔFeNO (r = 0.617, 95% CI 0.41–0.76, P < 0.001, n = 43). (**C**) Correlation between TS90% and ΔFeNO (r = 0.461, 95% CI 0.18–0.67, P = 0.002, n = 43). (**D**) Correlation between ESS and ΔFeNO (r = 0.552, 95% CI 0.31–0.73, P < 0.001, n = 43). Each data point represents an individual patient (n = 43). Spearman correlation coefficients (r), 95% confidence intervals (CI), and P-values are shown. Significant positive correlations indicate that patients with more severe OSA at baseline exhibited greater FeNO reductions following CPAP therapy.

## Discussion

The present investigation revealed that individuals with OSA exhibited markedly higher FeNO concentrations than an AHI < 15 reference group reported previously, indicating elevated airway inflammation consistent with recent findings in snoring populations.[9] After two nights of CPAP titration, FeNO showed a slight, non-significant increase, in contrast with the significant FeNO reductions observed after prolonged CPAP therapy.[25] Importantly, after three months of treatment, FeNO decreased significantly compared with baseline, and the magnitude of this reduction correlated with baseline disease burden as indexed by AHI, ODI, and ESS. Taken together, these findings suggest that long-term CPAP therapy not only alleviates airway inflammation-as reflected by FeNO-but that the degree of improvement is proportional to initial OSA severity at baseline.

Our observations align with the broader literature examining FeNO in OSA and the therapeutic effects of CPAP.[25] A meta-analysis of 16 trials reported that OSA patients exhibit higher FeNO than controls and that FeNO falls significantly with extended CPAP treatment.[12] In the context of our results, this synthesis helps reconcile why a substantial decline became evident after sustained CPAP use, whereas no significant FeNO change was detectable


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after just two titration nights. Even so, some studies indicate that short-term CPAP—occasionally as brief as two nights—can reduce FeNO among patients with severe OSA,[26] suggesting that disease severity and phenotypic heterogeneity may influence early trajectories. Complementing these physiologic readouts, tissue biopsy findings further indicate that prolonged CPAP use can mitigate inflammation-related cellular infiltration in the upper airway,[27] lending histological weight to the anti-inflammatory interpretation of our FeNO data.

At the same time, not all studies show FeNO reductions with CPAP. Several have reported null effects, a pattern plausibly attributable to short treatment duration, suboptimal adherence, and population heterogeneity.[28] Notably, some investigations observed significantly elevated alveolar nitric oxide concentration (CaNO) in OSA and a robust drop in CaNO after two nights of CPAP, whereas FeNO remained unchanged.[12] Other reports describe only transient or inconsistent FeNO responses to CPAP, underscoring that the inflammatory phenotype and adherence patterns likely shape NO-based readouts.[29] Methodological features also matter: variation in FeNO measurement (eg, flow rates, device calibration, ambient NO control), timing of sampling, and environmental standardization can introduce additional noise. Across studies, differences in titration strategies, follow-up period, and inclusion criteria (eg, proportion of mild OSA; prevalence of asthma, allergic rhinitis, or smoking) further complicate comparisons. In this context, our cohort's average nightly CPAP use (6.6 ± 1.8 h over nearly 10 weeks) likely contributed to the consistent FeNO reduction we observed and may partially explain disparities with studies reporting weaker effects.

Mechanistically, elevated FeNO in OSA likely reflects airway inflammation triggered by repetitive upper-airway collapse, intermittent hypoxia, and subsequent reoxygenation during apneic events.[30,31] The hypoxia–reoxygenation cycle promotes oxidative stress, perturbs endothelial function, and elevates reactive oxygen species (ROS) levels, thereby amplifying inflammatory signaling and facilitating nitric oxide synthesis.[32] In parallel, hypoxia-induced inflammatory cytokines and oxidative injury can upregulate inducible nitric oxide synthase (iNOS) in airway epithelial cells, increasing exhaled NO output.[33] CPAP addresses several elements of this cascade by maintaining airway patency and stabilizing oxygenation.[22,34] Beyond mechanical splinting, CPAP may reduce airway resistance and improve mucociliary function, thereby dampening local inflammatory activity. Sustained CPAP therapy has been associated with reductions in airway and systemic inflammatory mediators (eg, IL-6, TNF-α, CRP) in meta-analyses,[21,35] with additional support from observational/interventional evidence[36,37] and a systematic review.[38]

A notable feature of our data is the transient, non-significant FeNO rise after two nights of titration. Several non-mutually exclusive mechanisms may explain this pattern. First, positive pressure can impose acute mechanical stretch on airway epithelium, activating mechanotransduction pathways and epithelial stress responses that transiently upregulate iNOS and raise FeNO.[39] Acute epithelial stretch can transiently upregulate iNOS and NO output via mechanotransduction pathways, providing a plausible basis for the early FeNO rise.[33,39] Related reviews also link epithelial iNOS activation to enhanced NO output.[33] Second, an early phase of airway hyperresponsiveness in susceptible OSA patients cannot be excluded.[40] Third, circadian variability is a credible contributor given our early-morning sampling schedule; domiciliary monitoring has described higher morning than evening FeNO values with meaningful diurnal fluctuation, and healthy-volunteer data likewise show greater morning variability.[35] Consistent with these mechanisms, a synthesis of prior work indicates that FeNO can rise overnight in OSA, that one to two nights of CPAP do not reliably lower FeNO, and that sustained therapy over weeks to months is the setting in which FeNO reductions are most robustly observed.[25,41] In this light, the early FeNO increase in our cohort may represent a reactive phase that is subsequently outweighed by longer-term anti-inflammatory effects during continued CPAP use. Because we did not measure cellular or cytokine markers in parallel with FeNO, however, this interpretation remains provisional and warrants mechanistic confirmation.

Adherence emerged as a key determinant of effect size in our analyses. Nightly CPAP use was derived primarily from device-recorded usage data; patients with higher nightly CPAP use (≥ 6 h/night) demonstrated larger FeNO reductions than those with lower adherence, consistent with a dose–response relationship. Across the cohort, nightly hours of CPAP use correlated positively with the magnitude of FeNO decline ($r = 0.36$, $P < 0.05$). Importantly, in models that included mean nightly usage as a covariate, the overall CPAP effect on FeNO remained significant, underscoring the robustness of our primary finding even after accounting for adherence. While self-reported hours were also recorded, device-downloaded data provide more accurate exposure ascertainment and minimize misclassification; therefore, adherence analyses prioritized objective logs. If any reliance on self-reported data occurred, some nondifferential misclassification

may persist. Together, these findings reinforce the clinical message that adherence counselling and device optimization are central to realizing CPAP's anti-inflammatory benefits; objective device-downloaded data should be prioritized to enhance dose–response inference and reduce recall bias.

The positive association between baseline OSA severity and FeNO reduction suggests that patients with more severe disease may experience greater inflammation relief under CPAP. Clinically, this insight could inform prioritization for CPAP initiation and the intensity of follow-up. It may also help flag patients at higher risk for systemic inflammation and cardiometabolic comorbidity, facilitating tailored management strategies. At the same time, caution is warranted: regression-to-the-mean and ceiling effects may contribute to the appearance of larger absolute declines among those starting at higher FeNO levels, and our observational design precludes causal inference. From a mechanistic perspective, more severe OSA entails more frequent and profound hypoxia–reoxygenation cycles that can amplify oxidative stress and nuclear factor kappa-B (NF-κB) activation, thereby upregulating iNOS and elevating FeNO.[30] Intermittent hypoxia has been shown to activate NF-κB signaling and induce iNOS expression in cellular and animal models relevant to OSA.[30–34] Prior biomarker work also supports that CPAP can counter these pathways by stabilizing oxygenation, reducing ROS, and dampening pro-inflammatory cytokines such as IL-6 and TNF-α.[42] Definitive clarification, however, will require larger studies that integrate FeNO with molecular biomarkers of epithelial injury and inflammation.

Beyond statistical significance, clinical interpretability hinges on whether observed changes meet accepted response thresholds. In our cohort, the mean FeNO reduction after three months (≈3–4 ppb; ≈ 16–17% relative) was statistically robust but modest, falling just short of commonly cited ATS/ERS minimal clinically important difference (MCID) criteria: a ≥ 20% relative decline for baseline FeNO > 50 ppb, or an absolute decrease ≥ 10 ppb when baseline FeNO < 50 ppb.[43] External validations linking FeNO deltas to clinical outcomes also converge on ~ 20% as a practical benchmark, albeit with modest sensitivity and specificity.[43] Accordingly, FeNO should at present be regarded as a promising candidate biomarker for monitoring airway inflammation and CPAP response in OSA. Its non-invasive nature, reproducibility, and point-of-care availability make it attractive for routine practice, but broader validation is needed before it can be recommended as a standalone decision guide.[44]

Several features strengthen our inferences. The prospective design with three standardized time points (baseline, post-titration, and three-month follow-up) allowed us to map short-and intermediate-term dynamics rather than relying on cross-sectional contrasts alone. Use of previously published AHI < 15 baseline data as a reference improved interpretability by anchoring baseline differences. Statistical rigor-normality testing, appropriate parametric and non-parametric comparisons, and repeated-measures modeling with prespecified covariates-provided convergent evidence for our primary conclusion.

Nevertheless, limitations should temper interpretation. First, a key limitation of this study is the absence of a parallel longitudinal control group. Although baseline comparisons with individuals with AHI < 15 were reported in our previous cross-sectional study,[11] the present follow-up exclusively examined patients with moderate-to-severe OSA undergoing CPAP across three standardized time points. Consequently, while our within-subject design strengthens internal validity, it limits external comparability and precludes definitive attribution of FeNO reduction solely to CPAP rather than to spontaneous temporal variation. Second, while a priori power analysis was satisfied by 43 OSA completers, the sample size remains modest, particularly for subgroup analyses, and the single-center setting with exclusions (eg, smokers; comorbid asthma/COPD) restricts generalizability to broader OSA populations. Third, although FeNO measurements were standardized, small variations in measurement conditions, device calibration, and inter-operator procedures can introduce error. Fourth, verification of NSAID exposure relied on self-report and medication reconciliation; although long-term or regular NSAID users were excluded, residual confounding from intermittent use cannot be entirely excluded. Fifth, despite documenting missingness and conducting complete-case analyses with sensitivity checks, attrition (19/62 OSA participants) could still bias estimates if unmeasured factors influenced dropout; residual confounding related to adherence or clinical heterogeneity cannot be fully excluded.[45,46] Finally, we did not collect additional inflammatory or oxidative stress biomarkers alongside FeNO, and the follow-up period was limited to three months, precluding assessment of longer-term trajectories and downstream clinical outcomes.

In addition, FeNO was sampled at baseline, immediately after titration, and at three months; intermediate time points were not collected. While this schedule reflects common clinical review intervals, denser sampling (eg, 2–4 weekly) could better delineate the onset and trajectory of CPAP-related FeNO changes and should be explored in future work.[12,36]

Future work should therefore prioritize well-powered, multicenter clinical trials to confirm FeNO's diagnostic and prognostic roles in OSA. Studies that incorporate objective adherence metrics, broader inflammatory biomarker panels, and longer follow-up will better delineate CPAP's anti-inflammatory effects and clarify whether FeNO trajectories predict symptom improvement, cardiometabolic risk modification, or adherence behavior. Mechanistic investigations that pair FeNO with epithelial injury markers and cytokine/ROS indices will be essential to validate the hypothesized pathways linking hypoxia–reoxygenation stress, iNOS activation, and NO output. Ultimately, these efforts may establish whether FeNO can support personalized CPAP management-by identifying patients most likely to benefit, flagging insufficient response early, and guiding adjunctive anti-inflammatory strategies-in routine clinical practice. Future trials should standardize objective adherence capture from device downloads, which improves accuracy over self-report and reduces misclassification of exposure.

## Conclusion

Our results demonstrate that FeNO is elevated in OSA patients, indicating enhanced airway inflammation. Three months of CPAP therapy significantly reduced FeNO, with reductions correlating with baseline disease severity. These findings support FeNO as a promising, non-invasive candidate biomarker for monitoring airway inflammation and treatment response in OSA. However, its clinical application remains preliminary, and further validation in larger, multicenter studies is warranted before routine use.

## Data Sharing Statement

To access the data that back up this study's findings, one must make a reasonable request to Qilin Zhu and obtain permission from the Affiliated Nantong Hospital 3 of Nantong University, Jiangsu, China.

## Ethics Approval and Consent to Participate

The research followed the Declaration of Helsinki guidelines and received approval from the Ethics Committee at Affiliated Nantong Hospital 3 of Nantong University (protocol EK2023115; initial approval December 2023; renewal/amendment December 2024 covering January-April 2025). All participants in the study provided informed consent.

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## Author Contributions

Qilin Zhu (QZ): Conceptualization; Study design; Data curation; Formal analysis; Writing–original draft.
Donghua Niu (DN): Methodology; Investigation; Data collection; Writing–review & editing.
Qingqing Ma (QM): Formal analysis; Visualization; Writing–review & editing.
Rong Chen (RC): Data curation; Investigation, Writing–review & editing.
Haiyan Shi (HS): Data curation; Writing–review & editing.
Yunfeng Zhang (YZ): Data curation; Investigation; Writing–review & editing.
Yihua Wang (YW): Supervision; Formal analysis; Writing–review & editing.
Lei Ji (LJ): Funding acquisition; Project administration; Supervision; Writing–review & editing.

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work.

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## Disclosure

It is declared by the authors that there are no conflicts of interest.

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