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ORIGINAL RESEARCH

Association Between Fractional Exhaled Nitric Oxide (FeNO) and Cognitive Function in Patients with Obstructive Sleep Apnea

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Purpose: Obstructive sleep apnea (OSA) is characterised by intermittent hypoxia and sleep fragmentation, both of which can impair cognition. This study aimed to investigate the association between fractional exhaled nitric oxide (FeNO), a non-invasive marker of airway inflammation, and memory performance in patients with OSA.

Methods: A total of 102 participants were enrolled: 62 with moderate or severe OSA (apnea-hypopnea index, AHI≥15) and 40 with snoring or mild OSA (AHI <15). Memory was assessed with the Rey-Osterrieth Complex Figure Test (RCFT), Digit Ordering Test (DOT), and Logical Memory Test (LMT). FeNO was measured at 50mL/s ($FeNO_{50}$) and 200mL/s ($FeNO_{200}$); alveolar NO (CaNO) was calculated. Group comparisions used *t*-tests and chi-square tests, cognitive scores employed mixed-design ANOVA, and associations were examined with Spearman correlation plus hierarchical regression.

Results: Compared with the snoring or mild OSA group, participants with moderate or severe OSA had larger neck circumference, higher body-mass index, greater daytime sleepiness, and elevated $FeNO_{50}$ and $FeNO_{200}$ ($P < 0.05$). They also showed poorer immediate and delayed visual memory (both $P< 0.05$), which correlated negatively with AHI ($r = -0.088/-0.103$, $P < 0.05$) and $FeNO_{50}$ ($r = -0.286/-0.302$, $P < 0.05$). RCFT scores fell over time ($F = 271.171$, $P < 0.05$), with a significant group × time interaction ($F = 3.065$, $P < 0.05$). $FeNO_{50}$ independently predicted poorer immediate recall ($\beta = -0.28$, $P = 0.018$), whereas $FeNO_{200}$ was not significant.

Conclusion: Moderate or severe OSA is associated with impaired immediate and delayed visual memory. Higher $FeNO_{50}$ correlates with memory decline, supporting a link between airway inflammation and cognitive dysfunction in OSA.

Plain language summary: OSA is a common sleep disorder in which breathing repeatedly stops and restarts during the night. This disrupted sleep can lead to persistent tiredness, poor concentration, and memory problems. In our study, we explored whether a quick, non-invasive breath test called FeNO could flag early memory decline in people with OSA. We found that individuals with more severe OSA had higher FeNO readings and poorer memory scores. These findings suggest that FeNO reflects airway inflammation that may also affect the brain. Our study provides early evidence that this simple breath test could help clinicians identify memory issues in OSA patients sooner and more effectively.

Keywords: obstructive sleep apnea, polysomnography, fractional exhaled nitric oxide, cognitive function

Introduction

Obstructive sleep apnea (OSA) is a widespread sleep disorder that involves repeated partial or complete blockage of the upper airway during sleep, causing intermittent oxygen deprivation and sleep disruption.[1] The prevalence of OSA is particularly on the rise in developed nations.[2] OSA is associated with numerous neurological cognitive deficits, such as

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deficits in memory, executive function and concentration,[3,4] which can significantly enhance the probability neurodegenerative diseases.[5,6]

Although the exact mechanisms of cognitive dysfunction in OSA remain unclear, chronic intermittent hypoxia, oxidative stress, and systemic inflammation are thought to play critical roles.[7] Airway inflammation in OSA may result from mechanical trauma due to recurrent upper airway obstruction, as well as the impact of intermittent hypoxia.[8] Additionally, there is evidence of systemic inflammation in OSA.[9] Persistent airway inflammation in OSA might be involved in the disorder's complex pathophysiology, indicating the necessity for a comprehensive examination of this relationship.

Fractional exhaled nitric oxide (FeNO) provides a rapid and non-invasive method for evaluating airway inflammation,[10–12]which has been extensively studied in asthma, chronic obstructive pulmonary disease, OSA, and COVID-19.[13–15] NO is produced by endothelial and epithelial cells, as well as macrophages, providing insights into respiratory tract inflammation.[16] FeNO has been recognized as a noninvasive biomarker of airway inflammation.[17]

Increased levels of exhaled NO may predict moderate-to-severe OSA.[18] Transcriptomic analysis revealed that peripheral inflammation triggers neuroinflammation within the central nervous system, leading to cognitive decline.[19] However, the mechanisms linking exhaled NO to cognition in OSA remain to be elucidated.

Therefore, the primary aim of this research is to explore the characteristics of exhaled NO in individuals with OSA and to examine its association with cognitive function.

Methods

Participants

This prospective study was conducted at the Affiliated Nantong Hospital 3 of Nantong University from December 2023 to December 2024. Initially, individuals who underwent polysomnography (PSG) for snoring were recruited for the study.

According to the clinical practice guideline for diagnostic testing of adult OSA,[20] the apnea-hypopnea index (AHI) was used as the diagnostic indicator. Ultimately, 102 individuals were included. Participants with AHI≥15/h were classified as moderate/severe OSA (n = 62); while those with AHI<15/h were classified as snoring/mild OSA (n = 40)[4,21] (Figure 1).

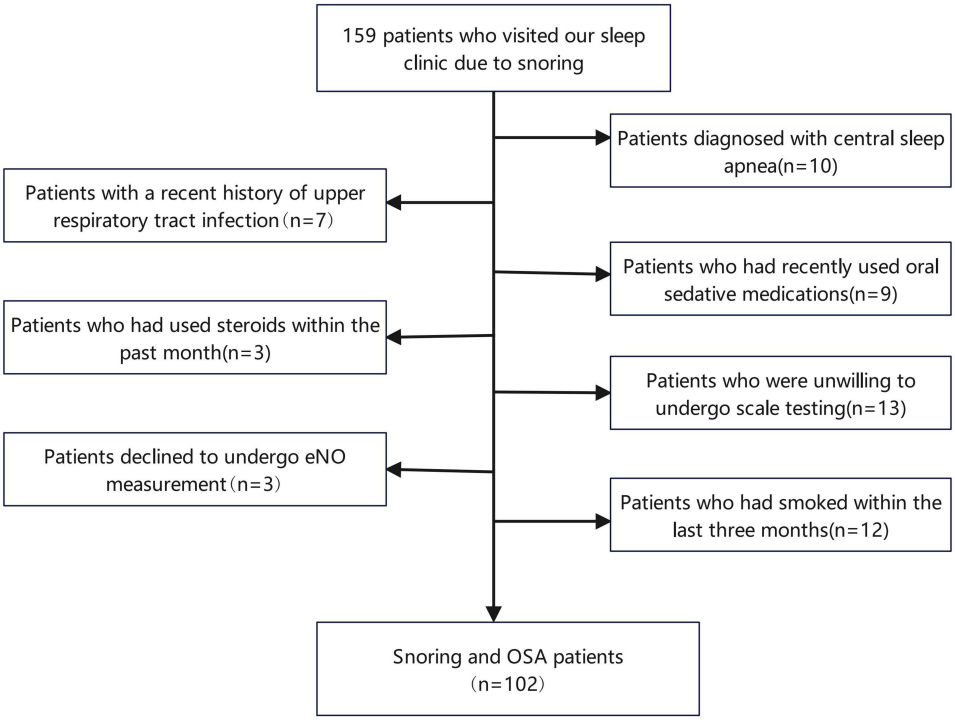

Figure 1 Flow chart illustrating the process of selecting patients for this study.

Inclusion criteria: (1) participants must be aged between 18 and 65 years; (2) participants with at least 9 years of education; (3) participants who have not received OSA treatment. Exclusion criteria: (1) participants with asthma, chronic obstructive pulmonary disease, cancer, cardiopulmonary failure, stroke, hepatic dysfunction, renal dysfunction, anxiety, Parkinson's disease, or Alzheimer's disease; (2) sleep disorders such as insomnia or central sleep apnea; (3) current use of psychotropic medications and corticosteroids; (4) total sleep duration< 5 hours during PSG; (5) smoking in the past three months or active upper airway infection.

The research was performed in compliance with the Declaration of Helsinki, and all procedures were conducted after obtaining written informed consent from the participants. Ethical approval for the study was granted by the Ethics Committee of the Affiliated Nantong Hospital 3 of Nantong University (EK2023115).

Measurement

Fundamental Information

Comprehensive demographic and previous health history information were gathered from all patients. This included age, sex, educational level, body mass index (BMI), neck circumference (NC), history of alcohol consumption and smoking habits, history of hypertension and diabetes, and the presence of symptoms such as nocturnal snoring, nocturnal awakenings, excessive daytime sleepiness, dreaming, memory impairment, morning tiredness, headaches, and dry mouth.

Epworth Sleepiness Scale (ESS)

We utilized the validated Chinese version of the ESS.[22,23] Scores range between 0 and 24, a score of 10 or higher indicating significant sleepiness. The ESS assessments for the patients were administered by experts at the sleep center.

The validated Chinese version of the ESS was used in this study with proper authorization from the Mapi Research Trust (license ID: 116777).

Cognitive Function Assessment

Cognitive assessments were performed 1 hour before PSG to avoid the influence of sleep deprivation on performance. Tests included the Digit Ordering Test (DOT) for working memory, the Logical Memory Test (LMT) for logical memory, and the Rey-Osterrieth Complex Figure Test (RCFT) for visual memory.[24,25] The RCFT involved three phases:Firstly, participants were asked to copy the geometric shape to assess their copying ability (P1). Secondly, without prior notice, participants were asked to immediately redraw the figure from memory on a blank sheet, assessing their immediate visual memory (P2). Thirdly, participants were required to redraw the figure again after 30 minutes to evaluate their delayed visual memory (P3).[26,27] All cognitive tests were conducted approximately one hour before PSG to avoid fatigue or confounding effects from sleep monitoring. Assessors were blinded to participants'PSG and FeNO results to reduce bias.

Polysomnography

Overnight PSG recordings were conducted in a sound-insulated room. Recording began at 9:00 pm and ended at 6:00 am, ensuring at least 7 hours of data. Signals were acquired by the Nox A1 system (ResMed, Australia). The PSG data included eight electroencephalogram channels (F3, F4, C3, C4, O1, O2, M1, M2), electrocardiogram, electromyograms of both anterior tibialis muscles, bilateral electrooculograms, finger pulse oximetry for oxygen saturation, a nasal pressure monitor, a thermistor for airflow, and thoracic/abdominal movements via inductance plethysmography. All data were scored according to the American Academy of Sleep Medicine.[28] Recorded parameters included sleep stages (N1, N2, N3, REM), AHI, oxygen desaturation index (ODI), total sleep time (TST), sleep efficiency (SE), lowest arterial oxygen saturation ($LSpO_2$), percentage of sleep time with arterial oxygen saturation below 90% (TS90%), and sleep latency.

FeNO Measurements

FeNO measurements adhered to the American Thoracic Society's guidelines[29] and were consistently performed immediately after PSG by a skilled technician. The measurements were taken using a nitric oxide analyzer (Wuxi Shangwo, China) and results were recorded in parts per billion (ppb). FeNO levels were assessed at two flow rates: 50 mL/s ($FeNO_{50}$) and 200 mL/s ($FeNO_{200}$), with measurement errors below 10%. Participants refrained from smoking, eating,

vigorous exercise, and pulmonary function testing for at least 1 hour, and avoided consuming nitrogen-rich food for at least 3 hours before the test. Participants took a deep breath, then exhaled steadily at 50 mL/s for at least 6 seconds or at 200 mL/s for at least 4 seconds. Each flow rate was measured 2–3 times, and the mean value of each was recorded. The alveolar NO concentration (CaNO) was estimated using a two-flow rate linear regression model based on FeNO measurements at 50 and 200 mL/s.[30] $FeNO_{50}$ reflects NO from the central airways, $FeNO_{200}$ from the distal airways, and JawNO from the nasal cavity. These measures represented different airway regions and provided complementary information.

Although FeNO was measured post-PSG while cognition was assessed pre-PSG, this design reflects standard clinical practice and minimizes sleep deprivation's potential effects on cognition. The temporal gap was less than 12 hours.

Statistical Analysis

Statistical analyses were conducted with SPSS (version 25.0; SPSS Inc, Chicago, IL, USA), GraphPad Prism (version 9.0; GraphPad Software, San Diego, CA, USA) and the beanplot package (version 1.2).[31] Continuous variables were presented as mean ± standard deviation (M ± SD), and group differences were evaluated using the independent samples *t*-test. Categorical variables were analyzed using the chi-square (χ^2) test. Spearman's rank correlation analysis was used to assess the relationship between cognitive function and clinical or FeNO-related variables. A mixed-design repeated measures ANOVA was used to evaluate cognitive function over time. Group (moderate/severe OSA vs snoring/mild OSA) served as the between-subjects factor, and cognitive domains (copying, immediate, and delayed visual memory) as the within-subjects factor. The Greenhouse-Geisser correction was applied when necessary, and multiple comparisons were adjusted using the Bonferroni correction. Hierarchical regression analysis further explored the relationship between cognitive function and exhaled NO levels. Hierarchical regression analysis was conducted to explore the relationship between cognitive function and exhaled NO levels. Potential confounders—including age, sex, educational level, BMI, and ESS score—were selected based on prior literature and clinical relevance, and were included in the regression models to minimize bias and enhance interpretability. Although no formal a priori power analysis was conducted, the sample size was comparable to previous studies in this field. $P < 0.05$ was considered statistically significant.

Results

Demographic, Clinical, and Sleep Characteristics of All Patients Stratified by AHI

In Table 1, the demographic, clinical, and sleep characteristics are outlined. There were no notable differences between the moderate/severe OSA group and the snoring/mild OSA group in terms of age, gender, years of education, smoking history, drinking history, history of hypertension or diabetes, dreaming, morning fatigue, morning headache, TST, SE, proportion of non-rapid eye movement (NREM) 2 sleep, or proportion of REM sleep ($P > 0.05$). However, BMI, NC, witnessed apnea, drowsiness, dry mouth, memory deterioration, ESS score, proportion of NREM1 sleep, ODI, TS90%, longest apnea duration, and arousal index (ArI), and $LSpO_2$ were significantly higher in the moderate/severe OSA group than in the snoring/mild OSA group ($P < 0.05$).

The Cognitive Function and Exhaled NO Parameters in OSA Patients

The results of the cognitive function and exhaled NO parameters between the snoring/mild OSA group and the moderate/severe OSA group are presented in Table 2. There were no notable differences between the two groups regarding DOT, LMT delay, copying ability scores (P1), or CaNO (all $P > 0.05$). However, the LMT immediate, immediate visual memory (P2) and delayed visual memory (P3) were significantly higher in the snoring/mild OSA group compared to the moderate/severe OSA group ($P < 0.05$). Additionally, $FeNO_{50}$ and $FeNO_{200}$ were significantly higher in the moderate/severe group than in the snoring/mild OSA group ($P < 0.05$). Additionally, FeNO50 and $FeNO_{200}$ were significantly higher in the moderate/severe group than in the snoring/mild OSA group ($P < 0.001$). $FeNO_{200}$ was included to assist in CaNO estimation, not as a standalone marker. While CaNO levels slightly exceeded normal values (6 ppb), no significant group difference was observed.(Table 2 and Figure 2).

Table 1 Comparison of Demographic and Clinical Traits Between the Snoring/Mild and Moderate/Severe OSA Group

Parameters	Snoring or Mild OSA (n = 40)	Moderate or Severe OSA (n = 62)	t/χ2 Value	*P*-value
Demographics				
Age, years	37.42(6.97)	39.76(7.69)	−1.453	0.135
Gender, males	33.00(82.50%)	52.00(83.80%)	0.180	0.858
Education, year	15(14,16)	15(14,15)	−1.502	0.502
BMI, kg/m^2	24.55(22.80,26.30)	26.90(25.50,29.30)	−4.113	<0.001***
NC, cm	36.00(0.52)	41.10(0.80)	−3.026	0.028*
Drinking	10.00(16.6)	7.00(12.50)	0.321	0.358
Smoking	5.00(8.80)	6.00(9.70)	0.083	0.665
Witnessed apnea	23.00(45.60)	41.00(63.20)	6.302	0.011*
Dreaming	32.00(53.80)	32.00(53.00)	0.020	0.952
Fatigue morning	25.00(41.20)	34.00(56.00)	2.256	0.201
Headaches morning	5.00(8.60)	8.00(12.90)	0.720	0.388
Dry mouth	23.00(40.20)	42.00(66.90)	8.037	0.036*
Drowsiness	23.00(38.80)	40.00(66.70)	9.131	0.002**
Memory deterioration	17.00(50.50)	35.00(57.10)	9.436	0.019*
Common comorbidities				
Hypertension	10.00(15.90)	17.00(28.80)	2.235	0.156
Diabetes	2.00(3.50)	5.00(8.50)	0.590	0.502
Questionnaires				
ESS	7.00(4.00,9.00)	8.00(6.25,11.80)	−3.052	0.001**
Polysomnography				
TST, min	399.26(77.94)	424.98(52.26)	−1.285	0.199
SE,%	90.25(82.28,93.85)	88.64(6.81)	−0.405	0.686
NREM1 (% TST)	9.40(5.45,17.83)	15.05(9.98,23.33)	−2.844	0.004**
NREM2(% TST)	48.90(9.87)	50.80(13.81)	−0.540	0.589
REM(% TST)	19.52(6.09)	18.98(6.09)	−0.771	0.441
ODI	2.80(1.20,5.60)	37.30(18.85,66.30)	−7.902	<0.001***
TS90%,%	0.10(0.00,0.40)	7.65(1.80,29.85)	−7.808	<0.001***
$LSpO_2$, %	89.50(87.00,92.00)	76.000(63.750,82.00)	−7.509	<0.001***
Longest time of apnea, s	44.29(18.73)	69.75(8.28)	−4.490	<0.001***
ArI	2.92(2.80)	13.56(6.68,32.33)	−6.557	<0.001***

Notes: *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Abbreviations: BMI, body mass index; NC, neck circumference; NREM, non-rapid eye movement sleep; ESS, Epworth Sleepiness Scale; TST, total sleep time; SE, sleep efficiency; TS90%, Percentage of total sleep time with oxygen saturation <90%; REM, rapid eye movement sleep; $LSpO_2$, lowest oxygen saturation; ODI, oxygen desaturation index; ArI, arousal-index.

Table 2 Cognitive Function and Exhaled NO Parameters for the Snoring/Mild OSA and Moderate/Severe OSA

Parameters	Snoring or Mild OSA (n = 40)	Moderate or Severe OSA (n = 62)	t/Z Value	*P*-value
DOT	8.85(2.30)	8.17(2.32)	−1.273	0.203
LMT				
LMT immediate	5.00(4.00,7.00)	5.00(4.00,7.00)	−2.032	0.013*
LMT delay	5.00(3.00,6.00)	4.00(3.00,6.00)	−0.778	0.436
RCFT				
P1	34.24(2.12)	33.61(1.60)	−2.647	0.082
P2	26.14(6.04)	23.04(5.76)	−1.738	0.032*
P3	25.28(6.28)	22.56(5.59)	−2,178	0.019*

(*Continued*)

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Table 2 (Continued).

Parameters	Snoring or Mild OSA (n = 40)	Moderate or Severe OSA (n = 62)	t/Z Value	*P*-value
$FeNO_{50}$	13.57(3.41)	21.00(17.25,26.00)	−6.728	<0.001***
$FeNO_{200}$	8.67(2.88)	11.00(9.00,13.75)	−3.995	<0.001***
CaNO	6.23(3.08)	6.00(3.20,8.40)	−0.014	0.989

Notes: *$P < 0.05$; ***$P < 0.001$.
Abbreviations: DOT, digit ordering test; LMT, logical memory test; RCFT, rey-osterrieth complex figure test; FeNO, fractional exhaled nitric oxide; CaNO, concentration of alveolar nitric oxide.

Correlation of Exhaled NO with Cognitive Function

Firstly, results showed a significant negative correlation between immediate visual memory and $FeNO_{50}$ ($r = -0.286$, $P = 0.039$), AHI ($r = -0.088$, $P = 0.036$), and witnessed apnea ($r = -0.211$, $P = 0.034$). Furthermore, delayed visual memory (P3) showed a negative relationship with $FeNO_{50}$ ($r = -0.302$, $P = 0.037$) and AHI ($r = -0.103$, $P = 0.031$) (Figure 3). $FeNO_{200}$ and CaNO were not significantly correlated with cognitive test scores ($P > 0.05$).

Secondly, The RCFT scores at three different time points (P1, P2, P3) for patients in both the snoring/mild OSA group and the moderate/severe OSA group followed a normal distribution. In the moderate/severe OSA group, P2 and P3 were significantly lower than those in the snoring/mild group ($P < 0.05$), indicating statistically significant differences. A one-way repeated measures ANOVA revealed that the immediate visual memory and delayed visual memory in the moderate/severe OSA group differed significantly from those in snoring/mild group ($P < 0.05$). Moreover, multiple comparisons using the LSD method demonstrated significant differences in RCFT scores across all time points.

The main effect of time was significant, $F = 271.171$, $P < 0.001$, indicating that P1, P2, and P3 scores changed significantly over time. Furthermore, the group-by-time interaction was significant, with $F = 3.065$, $P < 0.05$, suggesting that the RCFT scores in the moderate/severe OSA group decreased more rapidly over time. The between-subjects main effect revealed a significant difference, $F = 6.041$, $P < 0.05$, indicating that the reduction in P1, P2, and P3 scores differed significantly between the two groups according to Table 3.

Impact of Exhaled Nitric Oxide on Cognitive Function

To investigate the effect of FeNO on cognitive function, a hierarchical regression analysis was conducted with immediate memory as the dependent variable. We employed a two-step modeling approach. Model 1: We first included the following covariates: age, gender, longest apnea duration, ArI, witnessed apnea, BMI, ODI, TS90%, $LSpO_2$, and AHI, constituting Model 1. The results indicated that ArI and AHI were positively associated with immediate visual memory ($P < 0.05$). Model 2: Building upon Model 1, $FeNO_{50}$ and $FeNO_{200}$ were added as predictors. The findings showed that $FeNO_{50}$ had a significant negative impact on immediate visual memory ($P < 0.05$), while $FeNO_{200}$ did not show a significant association ($P > 0.05$) (Table 4).

We also included delayed visual memory as a dependent variable in the hierarchical regression analysis; however, no significant effect of exhaled NO on delayed visual memory was observed. These findings suggest that higher $FeNO_{50}$ are associated with poorer immediate visual memory in OSA, independent of other factors.

Discussion

Earlier research, including our own, has demonstrated that cognitive function is impaired in patients with OSA.[4,32] In this study, we quantified proximal and distal airway inflammation by chemiluminescence analysis and assessed dynamic cognitive trajectories via multi-phase RCFT. Our findings revealed that elevated $FeNO_{50}$ independently predicted impaired visual memory. Furthermore, a significant group × time interaction indicated that RCFT scores declined more rapidly over time in the moderate/severe OSA patients than those in the snoring/mild OSA group. These results underscore the specificity of airway inflammation in driving OSA-related cognitive impairment.

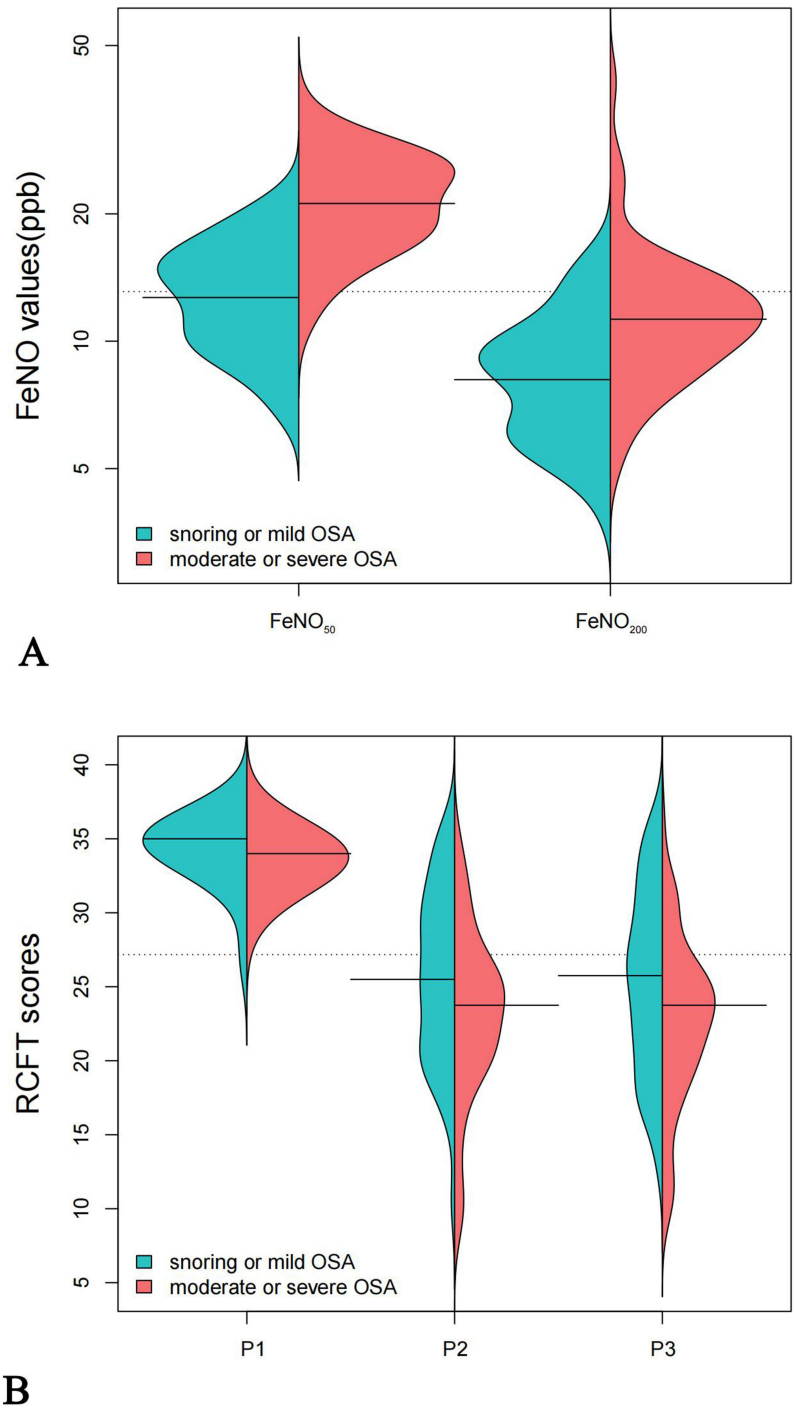

Figure 2 The Cognitive Function and Exhaled NO Parameters in OSA patients. (**A**) Bean plot for the comparison of fractional exhaled NO values between the snoring/mild OSA group and the moderate/severe OSA group. (**B**) Bean plot for the comparison of RCFT scores (P1, P2, P3) between the snoring/mild OSA group and the moderate/severe OSA group. The green distributions present results for the snoring or mild OSA group, and the Orange distributions present results for the moderate or severe OSA group. Horizontal black lines denote the averages of each experiment-specific distribution, while dashed lines indicate the overall averages.

This study provides significant insights into the relationship between FeNO and cognitive function in OSA patients. Notably, we are the first to report that $FeNO_{50}$, a marker of proximal airway inflammation, independently predicts immediate visual memory deficits in OSA. In contrast, $FeNO_{200}$, reflecting distal airway inflammation, showed no significant correlation with cognition. This distinction highlights that proximal airway inflammation may have a more direct cognitive impact than distal inflammation.

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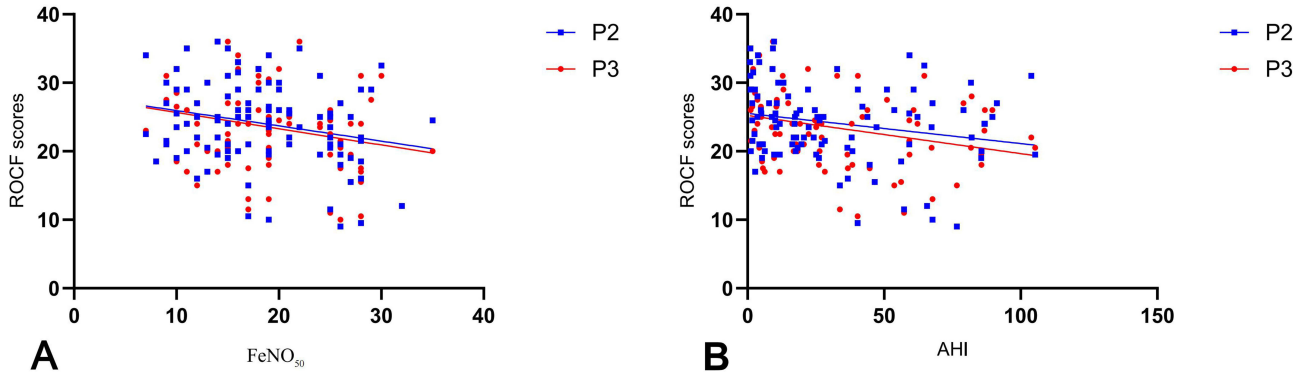

Figure 3 Correlation of Exhaled NO with Cognitive Function. (**A**) Correlation between RCFT scores at various time points and $FeNO_{50}$. (**B**) Correlation between RCFT scores at various time points and AHI.

Furthermore, our findings reveal that individuals suffering from moderate/severe OSA exhibit a more rapid decline in RCFT scores over time. The significant group-by-time interaction highlights the progressive nature of cognitive decline in OSA, which is often overlooked in traditional single time point studies. Through multi-time point assessments, we

Table 3 RCFT Scores Comparison Between the Moderate/Severe OSA and Snoring/Mild OSA Group at Different Time Points

	Snoring or Mild OSA (n = 40)	**Moderate or Severe OSA (n = 62)**	**t Value**	***P*-value**
Copy ability	34.237(2.118)	33.605(1.597)	−2.647	0.082
Immediate visual memory	25.628(6.039)	23.040(5.763)	−1.738	0.032*
Delayed visual memory	25.382(6.282)	22.556(5.591)	−2,178	0.019*
F value	93.421	205.465		
P value	<0.001***	<0.001***		
Between-group effects		*F*=6.041, *P*=0.016*		
Within-group effects		*F*=271.171, *P*<0.001***		
Interaction effects		*F*=3.065, *P*=0.038*		

Notes:The dependent variable is the immediate visual memory. *$P < 0.05$; ***$P < 0.001$.

Table 4 Hierarchical Regression Analysis of Exhaled Nitric Oxide Levels on Cognitive Function

Variable	**Model 1**					**Model 2**				
	B	**SE**	**t**	***P***	***β***	**B**	**SE**	**t**	***P***	***β***
Age	-0.020	0.107	-0.189	0.851	-0.024	-0.009	0.103	-0.084	0.934	-0.010
Gender	-0.902	0.116	-0.266	0.320	-0.252	-0.787	0.112	-0.182	0.402	-0.103
Longest time of apnea	0.027	0.033	0.816	0.418	0.134	0.039	0.032	1.202	0.234	0.192
Arl	0.216	0.078	2.786	0.007**	0.755	0.240	0.080	3.005	0.004**	0.836
Witnessed apnea	-2.863	2.070	-1.383	0.172	-0.167	-3.536	1.979	-1.787	0.079	-0.207
BMI	0.332	0.242	1.368	0.176	0.208	0.211	0.235	0.896	0.374	0.132
ODI	-0.208	0.150	-1.392	0.169	-0.980	-0.136	0.145	-0.934	0.354	-0.637
TS90%	-0.065	0.080	-0.819	0.416	-0.210	-0.112	0.077	-1.453	0.152	-0.362
LSpO2	-0.029	0.128	-0.228	0.821	-0.061	-0.059	0.122	-0.479	0.634	-0.123
AHI	0.110	0.165	0.663	0.031*	0.490	0.082	0.157	0.521	0.042*	0.366
$FeNO_{50}$						-1.373	0.443	-3.103	0.003**	-1.429
$FeNO_{200}$						3.853	1.360	2.834	0.120	3.365
F value	*F* (17,61)=1.362,*P*=0.046*					*F* (20,58) = 1.888, *P*=0.031*				
R^2	0.275					0.394				

Notes: The dependent variable is the immediate visual memory. *$P < 0.05$; **$P < 0.01$.

delineated the dynamic trajectory of cognitive deterioration, offering a comprehensive understanding of cognitive impairment in OSA.

Studies have focused on the link between exhaled NO and cognitive function. The RCFT is widely used to assess visual memory, including both copying and recall tasks,[25,33] and is applied to evaluate cognitive function in OSA patients. Ribeiro[34] demonstrated that in OSA patients following weight loss treatment, the RCFT effectively captures changes in cognitive function, particularly improvements in executive function, memory, and information processing speed. Our study extends these findings by using the RCFT to assess dynamic cognitive trajectories. We observed that immediate and delayed visual memory were negatively correlated with AHI and $FeNO_{50}$, suggesting that $FeNO_{50}$ may be associated with cognitive impairment in OSA.

A meta-analysis found elevated post-sleep FeNO levels in OSA, a pattern absent in controls. Furthermore, long-term continuous positive airway pressure (CPAP) therapy markedly reduces FeNO.[17] In obese OSA patients, this post-sleep FeNO increase is particularly pronounced, likely due to obesity-related oxidative stress and comorbidities.[17] Elevated NO has been recognized as a risk factor for Alzheimer's disease.[35] These findings support FeNO as a marker related to cognitive deficits in OSA. Accordingly, we hypothesized that elevated $FeNO_{50}$ indicates inflammation in OSA patients, contributing to cognitive decline.

Despite progress, inconsistencies remain regarding the relationship between FeNO and cognitive function. Some studies have reported higher bronchial NO and lower alveolar NO in OSA, with CPAP enhancing alveolar NO.[36] Conversely, others have found elevated alveolar NO without bronchial NO level differences,[37] likely due to variations in study design and sample size. Furthermore, a study on vehicle pollution found cognitive impairment in the high-pollution group despite no difference in FeNO.[38] Our analysis of $FeNO_{50}$, $FeNO_{200}$, and CaNO, clarifies their distinct roles.

The negative correlation between $FeNO_{50}$ and immediate visual memory can be explained by proximal airway inflammation triggering systemic inflammation. Gramiccioni[39] reported that exhaled NO increases with age and correlates with systemic oxidative stress and neurocognitive dysfunction, supporting eNO as a biomarker for cognitive impairment in OSA. In contrast, the absence of an association between $FeNO_{200}$ and cognitive function suggests that distal airway inflammation has a limited systemic impact and fewer neurotoxic effects.

FeNO and CaNO primarily reflect inducible nitric oxide synthase (iNOS) activity in the airway, indicating inflammation. In contrast, neuronal nitric oxide synthase (nNOS), expressed in the brain, regulates synaptic plasticity and memory. Dysregulated nNOS impair cognition through disrupted neurotransmission and neurotoxicity. Although FeNO50 is a peripheral marker, it may reflect systemic inflammation that affects central nNOS activity. This suggests interaction between iNOS and nNOS, warranting further investigation, ideally combining FeNO with neuroimaging or cerebrospinal fluid biomarkers.

NO is essential for vascular regulation and neurotransmission.[40] However, in inflammation, excessive NO can worsen neurodegeneration by promoting neuronal apoptosis and oxidative stress.[41,42] Elevated NO levels have been linked to cognitive decline,[35] and patients with OSA are prone to repeated hypoxia-reoxygenation cycles, which trigger oxidative stress and systemic inflammation, further impacting neurocognitive function.[43] $FeNO_{50}$, a marker of proximal airway inflammation, may exacerbate this process by increasing oxidative stress, impairing neuronal integrity and synaptic plasticity, particularly in memory-related regions like the hippocampus.[44]

The observed interaction between OSA severity and cognitive trajectory supports this hypothesis. Studies indicate that high concentrations of NO can lead to the formation of reactive nitrogen species.[45] This aligns with neuroimaging studies demonstrating that severe OSA is associated with structural brain changes, including reduced gray matter volume in the prefrontal cortex and hippocampus, regions critical for memory and executive function.[46] Our findings linking $FeNO_{50}$ to impaired memory reinforce the notion that airway inflammation contributes to neurocognitive dysfunction. Studies on RCFT indicate that memory is closely tied to hippocampal integrity, whereas familiarity-based recognition is associated with the medial temporal cortex.[47,48]

Although cognitive tests were conducted before PSG and FeNO was measured after PSG, this sequence was chosen to minimize fatigue-related interference with cognitive assessments. Since FeNO may reflect acute airway inflammation influenced by nocturnal hypoxia and arousals, post-PSG measurement helps capture relevant physiological changes. We acknowledge this time gap as a methodological limitation.

This study has several limitations. First, its cross-sectional design restricts causal inferences between FeNO and cognitive decline. Second, although the sample size was acceptable for exploratory analysis, it was relatively small, which may limit the generalizability of the findings. Although our regression models adjusted for key covariates including age, sex, education, BMI, and ESS score, we acknowledge that not all significantly different clinical or sleep-related variables (eg, ODI, TS90%) were included. This decision was made to avoid overfitting and maintain model stability given the sample size. Future studies with larger cohorts may incorporate a broader range of variables to further clarify the independent contribution of FeNO to cognitive impairment in OSA. Third, while we measured FeNO, we did not assess other inflammatory markers, which could offer a more comprehensive understanding of the inflammatory processes underlying cognitive decline in OSA. Finally, investigating the effects of OSA treatment on exhaled NO and cognitive function could provide further insights into the reversibility of cognitive impairment in OSA.

Conclusions

This study enhances understanding of the association between exhaled NO and cognitive impairment in patients with OSA. Our results indicate that $FeNO_{50}$, a marker of proximal airway inflammation, is independently associated with poorer immediate visual memory. Additionally, patients with moderate to severe OSA exhibited a faster decline in cognitive function over time. These findings suggest that FeNO50 may serve as a potential non-invasive indicator of cognitive dysfunction in OSA; however, as a cross-sectional study, causality cannot be inferred. The time gap between cognitive testing (pre-PSG) and FeNO measurement (post-PSG) may affect the temporal interpretation of this association. In addition, although key covariates were adjusted for, the possibility of residual confounding remains. Further studies are needed to confirm its diagnostic and prognostic value of FeNO in this population.

Data Sharing Statement

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

Ethics Approval and Consent to Participate

This study adhered to the guidelines set by the Declaration of Helsinki, and approved by the Ethics Committee of the Third Hospital of Nantong University (protocol code K2023115). Informed consent was obtained from all subjects involved in the study.

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Author Contributions

Qilin Zhu (QZ): Conceptualization; Data curation; Formal analysis; Writing–original draft. Lili Huang (LH): Methodology; Investigation; Writing–review & editing. Licheng Zhu (LZ): Formal analysis; Visualization. Xiaobai Zhang (XZ): Investigation; Resources. Honghua Ji (HJ): Data curation. Donghua Niu (DN): Data curation. Wangfei Ji (WJ): Data curation. Qingqing Ma (QM): Data curation. Rong Chen (RC): Data curation. Haiyan Shi (HS): Data curation. Yihua Wang (YW): Supervision; Writing–review & editing. Lina Xu (LX): Funding acquisition; Project administration; Supervision.

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interests.

References

1. Bucks RS, Olaithe M, Rosenzweig I, et al. Reviewing the relationship between OSA and cognition: w here do we go from here? *Respirology*. 2017;22(7):1253–1261. doi:10.1111/resp.13140
2. Benjafield AV, Ayas NT, Eastwood PR, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med*. 2019;7(8):687–698. doi:10.1016/S2213-2600(19)30198-5
3. Kilpinen R, Saunamäki T, Jehkonen M. Information processing speed in obstructive sleep apnea syndrome: a review. *Acta Neurol Scand*. 2014;129 (4):209–218. doi:10.1111/ane.12211
4. Zhu Q, Han F, Wang J, et al. Sleep spindle characteristics and relationship with memory ability in patients with obstructive sleep apnea-hypopnea syndrome. *J Clin Med*. 2023;12(2):634. doi:10.3390/jcm12020634
5. Vanek J, Prasko J, Genzor S, et al. Obstructive sleep apnea, depression and cognitive impairment. *Sleep Med*. 2020;72:50–58. doi:10.1016/j.sleep.2020.03.017
6. Stranks EK, Crowe SF. The cognitive effects of obstructive sleep apnea: an updated meta-analysis. *Arch Clin Neuropsychol*. 2016;31(2):186–193. doi:10.1093/arclin/acv087
7. Orrù G, Storari M, Scano A, et al. Obstructive sleep apnea, oxidative stress, inflammation and endothelial dysfunction-an overview of predictive laboratory biomarkers. *Eur Rev Med Pharmacol Sci*. 2020;24(12):6939–6948. doi:10.26355/eurrev_202006_21685
8. Bikov A, Hull JH, Kunos L. Exhaled breath analysis, a simple tool to study the pathophysiology of obstructive sleep apnoea. *Sleep Med Rev*. 2016;27:1–8. doi:10.1016/j.smrv.2015.07.005
9. Imani MM, Sadeghi M, Farokhzadeh F, et al. Evaluation of blood levels of C-reactive protein marker in obstructive sleep apnea: a systematic review, meta-analysis and meta-regression. *Life*. 2021;11(4):362. doi:10.3390/life11040362
10. Choi J, Sim JK, Oh JY, et al. Relationship between particulate matter (PM_{10}) and airway inflammation measured with exhaled nitric oxide test in Seoul, Korea. *Can Respir J*. 2020;2020:1823405. doi:10.1155/2020/1823405
11. Lluncor M, Barranco P, Amaya ED, et al. Relationship between upper airway diseases, exhaled nitric oxide, and bronchial hyperresponsiveness to methacholine. *J Asthma*. 2019;56(1):53–60. doi:10.1080/02770903.2018.1429465
12. Miranda L, Guerrero J. Fracción de óxido nítrico exhalado: una herramienta clínica para las enfermedades pulmonares [Measurement of exhaled nitric oxide fraction in lung diseases]. *Rev Med Chil*. 2021;149(8):1173–1181. doi:10.4067/s0034-98872021000801173
13. Karrasch S, Linde K, Rücker G, et al. Accuracy of FENO for diagnosing asthma: a systematic review. *Thorax*. 2017;72(2):109–116. doi:10.1136/thoraxjnl-2016-208704
14. Gao J, Zhang M, Zhou L, et al. Correlation between fractional exhaled nitric oxide and sputum eosinophilia in exacerbations of COPD. *Int J Chron Obstruct Pulmon Dis*. 2017;12:1287–1293. doi:10.2147/COPD.S134998
15. Lior Y, Yatzkan N, Brami I, et al. Fractional exhaled Nitric Oxide (FeNO) level as a predictor of COVID-19 disease severity. *Nitric Oxide*. 2022;124:68–73. doi:10.1016/j.niox.2022.05.002
16. Munakata M. Exhaled nitric oxide (FeNO) as a non-invasive marker of airway inflammation. *Allergol Int*. 2012;61(3):365–372. doi:10.2332/allergolint.12-RAI-0461
17. Zhang D, Luo J, Qiao Y, et al. Measurement of exhaled nitric oxide concentration in patients with obstructive sleep apnea: a meta-analysis. *Medicine*. 2017;96(12):e6429. doi:10.1097/MD.0000000000006429
18. Kiaer E, Ravn A, Jennum P, et al. Fractional exhaled nitric oxide-a possible biomarker for risk of obstructive sleep apnea in snorers. *J Clin Sleep Med*. 2024;20(1):85–92. doi:10.5664/jcsm.10802
19. Liu Q, Ou Y, Liu T, et al. Preliminary evidence of immune infiltration and neutrophil degranulation in peripheral blood of non-obese OSA patients related to cognitive decline. *Sci Rep*. 2025;15(1):3481. doi:10.1038/s41598-025-88034-z
20. Kapur VK, Auckley DH, Chowdhuri S, et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an American Academy of sleep medicine clinical practice guideline. *J Clin Sleep Med*. 2017;13(3):479–504. doi:10.5664/jcsm.6506
21. Cai S, Li Z, Wang J, et al. Excessive daytime sleepiness in young and middle-aged Chinese adults with obstructive sleep apnea: implications for cognitive dysfunction. *Sleep Breath*. 2024;28(1):113–121. doi:10.1007/s11325-023-02854-9
22. Peng LL, Li JR, Sun JJ, et al. Reliability and validity of the simplified Chinese version of Epworth sleepiness scale. *Chinese J Otorhinolaryngol Head Neck Surg*. 2011;46(1):44–49.
23. Feng X, Shi Y, Zhang Y, et al. Test-retest reliability of Epworth sleepiness scale score in patients with untreated obstructive sleep apnea. *Nat Sci Sleep*. 2024;16:2299–2309. doi:10.2147/NSS.S490960
24. Langer N, Weber M, Hebling Vieira B, et al. A deep learning approach for automated scoring of the Rey-Osterrieth complex figure. *Elife*. 2024;13:RP96017.
25. Zhang X, Lv L, Min G, et al. Overview of the complex figure test and its clinical application in neuropsychiatric disorders, including copying and recall. *Front Neurol*. 2021;12:680474. doi:10.3389/fneur.2021.680474
26. Collins A, Saling MM, Wilson SJ, et al. The spatial learning task of Lhermitte and Signoret (1972): normative data in adults aged 18-45. *Front Psychol*. 2022;13:860982. doi:10.3389/fpsyg.2022.860982
27. Shin MS, Park SY, Park SR, et al. Clinical and empirical applications of the Rey-Osterrieth complex figure test. *Nat Protoc*. 2006;1(2):892–899. doi:10.1038/nprot.2006.115
28. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. deliberations of the sleep apnea definitions task force of the American Academy of sleep medicine. *J Clin Sleep Med*. 2012;8 (5):597–619. doi:10.5664/jcsm.2172
29. Dweik RA, Boggs PB, Erzurum SC, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med*. 2011;184(5):602–615. doi:10.1164/rccm.9120-11ST

30. Bai H, Shi C, Yu S, et al. A comparative study on the value of lower airway exhaled nitric oxide combined with small airway parameters for diagnosing cough-variant asthma. *Ther Adv Respir Dis*. 2023;17:17534666231181259. doi:10.1177/17534666231181259
31. Yletyinen J, Perry GLW, Stahlmann-Brown P, et al. Multiple social network influences can generate unexpected environmental outcomes. *Sci Rep*. 2021;11(1):9768. doi:10.1038/s41598-021-89143-1
32. Liu X, Ma Y, Ouyang R, et al. The relationship between inflammation and neurocognitive dysfunction in obstructive sleep apnea syndrome. *J Neuroinflammation*. 2020;17(1):229. doi:10.1186/s12974-020-01905-2
33. Toloraia K, Gschwandtner U, Fuhr P. High-frequency multimodal training with a focus on Tai Chi in people with Parkinson's disease: a pilot study. *Front Aging Neurosci*. 2024;16:1335951. doi:10.3389/fnagi.2024.1335951
34. Ribeiro OR, Costa P, Do Carmo I, et al. Cognition, emotion, and obstructive sleep apnoea syndrome before and after severe weight loss treatment. *Sleep Sci*. 2022;15(Spec 2):339–346. doi:10.5935/1984-0063.20210009
35. Picón-Pagès P, Garcia-Buendia J, Muñoz FJ. Functions and dysfunctions of nitric oxide in brain. *Biochim Biophys Acta Mol Basis Dis*. 2019;1865 (8):1949–1967. doi:10.1016/j.bbadis.2018.11.007
36. Fortuna AM, Miralda R, Calaf N, et al. Airway and alveolar nitric oxide measurements in obstructive sleep apnea syndrome. *Respir Med*. 2011;105 (4):630–636. doi:10.1016/j.rmed.2010.12.004
37. Hua-Huy T, Le-Dong NN, Duong-Quy S, et al. Increased alveolar nitric oxide concentration is related to nocturnal oxygen desaturation in obstructive sleep apnoea. *Nitric Oxide*. 2015;45:27–34. doi:10.1016/j.niox.2015.01.008
38. Meo SA, Aldeghaither M, Alnaeem KA, et al. Effect of motor vehicle pollution on lung function, fractional exhaled nitric oxide and cognitive function among school adolescents. *Eur Rev Med Pharmacol Sci*. 2019;23(19):8678–8686. doi:10.26355/eurrev_201910_19185
39. Gramiccioni C, Carpagnano GE, Spanevello A, et al. Airways oxidative stress, lung function and cognitive impairment in aging. *Monaldi Arch Chest Dis*. 2010;73(1):5–11. doi:10.4081/monaldi.2010.307
40. Andrabi SM, Sharma NS, Karan A, et al. Nitric oxide: physiological functions, delivery, and biomedical applications. *Adv Sci*. 2023;10(30): e2303259. doi:10.1002/advs.202303259
41. Liu C, Liang MC, Soong TW. Nitric oxide, iron and neurodegeneration. *Front Neurosci*. 2019;13:114. doi:10.3389/fnins.2019.00114
42. Isik S, Yeman Kiyak B, Akbayir R, et al. Microglia mediated neuroinflammation in Parkinson's disease. *Cells*. 2023;12(7):1012. doi:10.3390/cells12071012
43. She N, Shi Y, Feng Y, et al. NLRP3 inflammasome regulates astrocyte transformation in brain injury induced by chronic intermittent hypoxia. *BMC Neurosci*. 2022;23(1):70. doi:10.1186/s12868-022-00756-2
44. Alomri RM, Kennedy GA, Wali SO, et al. Differential associations of hypoxia, sleep fragmentation, and depressive symptoms with cognitive dysfunction in obstructive sleep apnea. *Sleep*. 2021;44(4):zsaa213. doi:10.1093/sleep/zsaa213
45. Calabrese V, Mancuso C, Calvani M, et al. Nitric oxide in the central nervous system: neuroprotection versus neurotoxicity. *Nat Rev Neurosci*. 2007;8(10):766–775. doi:10.1038/nrn2214
46. Wang J, Li Y, Ji L, et al. The complex interplay of hypoxia and sleep disturbance in gray matter structure alterations in obstructive sleep apnea patients. *Front Aging Neurosci*. 2023;15:1090547. doi:10.3389/fnagi.2023.1090547
47. Kang SH, Park YH, Lee D, et al. The cortical neuroanatomy related to specific neuropsychological deficits in Alzheimer's continuum. *Dement Neurocogn Disord*. 2019;18(3):77–95. doi:10.12779/dnd.2019.18.3.77
48. Gyllenhammar M, Rennie A, Padilla DF, et al. The association between temporal atrophy and episodic memory is moderated by education in a multi-center memory clinic sample. *J Alzheimers Dis*. 2023;92(2):605–614. doi:10.3233/JAD-220741