

U-Shaped Relationship Between MSpO₂ Levels and the Incidence of Frailty in Elderly OSA Patients: Findings from a Multicenter Cohort Study

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Background: Previous studies have demonstrated a significant correlation between obstructive sleep apnea (OSA) and frailty. However, the association of mean pulse oxygen saturation (MSpO₂) with frailty among OSA patients remains unconfirmed. This study aimed to explore this potential association using data from a multicenter, prospective cohort.

Methods: A total of 1006 elderly patients diagnosed with OSA through polysomnography (PSG) from January 2015 to October 2017 were enrolled. Patients were stratified into four groups according to their MSpO₂ levels to assess differences in frailty onset. Multivariate Cox regression analysis, Kaplan-Meier curves, restricted cubic splines, and subgroup analyses were employed to evaluate variations in frailty onset across different MSpO₂ levels.

Results: Over a median follow-up period of 52 months, 275 patients developed frailty. Analysis using restricted cubic splines revealed a U-shaped trend between MSpO₂ and frailty risk (non-linear p -value = 0.028). Patients in the lowest quartile (MSpO₂ < 91.6%) exhibited a higher risk of frailty (hazard ratio [HR] = 1.43, 95% confidence interval [CI] 1.03–1.97, P = 0.029) compared to those in the third quartile (MSpO₂ 93–95%). Subgroup and sensitivity analyses confirmed the robustness of the U-shaped relationship.

Conclusion: There is a U-shaped association between MSpO₂ and frailty among patients with OSA. Enhancing MSpO₂ levels may mitigate the risk of frailty and improve prognosis in this population.

Keywords: obstructive sleep apnea, frailty, mean pulse oxygen saturation, elderly

Introduction

Obstructive sleep apnea (OSA) poses significant health risks, particularly within the aging population.¹ This condition induces acute physiological disturbances including intermittent hypoxia (IH) and sleep fragmentation (SF).² Although severe IH is linked to various pathological conditions, moderate IH may enhance neuronal functions,³ cardiovascular parameters,^{4–6} exercise tolerance,⁷ and immune function.⁸ Mild to moderate IH poses a lower risk of cardiovascular disease incidence in older OSA patients compared to younger patients; this is attributed to reduced ventilatory output and metabolic demand in older individuals.^{9,10} However, it is noteworthy that hypoxia parameters, such as mean oxygen saturation, were significantly higher in elderly patients than in younger ones. This finding emphasizes the pathophysiological relationship between intermittent hypoxia and age, which appears to be separate from the severity of OSA and its associated cardiovascular risks.¹¹

Frailty represents an emerging public health concern with profound implications for clinical practice.¹² As the demographic of older individuals expands, the incidence of frailty is expected to increase.¹³ Research indicates that chronic low-grade inflammation and oxidative stress are pivotal factors.¹⁴ Geriatricians characterize frailty as a biological syndrome marked by diminished reserve and reduced resilience to stressors, arising from progressive declines in multiple physiological systems and leading to susceptibility to adverse outcomes. Individuals exhibiting frailty are at heightened risk for negative events such as falls, hospital admissions, and mortality.^{15–17}

While numerous studies have identified an increased prevalence of frailty among those with OSA,^{18–20} the influence of IH on the development of frailty remains unexplored. Our research aims to elucidate the relationship between oxygen desaturation levels and frailty in patients with OSA, to develop tailored interventions that mitigate frailty, decrease the risk of adverse outcomes, and enhance quality of life.

Methods

Study Design and Participants

This study employed a multicenter cohort design to enroll 1290 elderly patients aged 60 years and older with a confirmed diagnosis of OSA, as determined by polysomnography (PSG). Recruitment occurred across several institutions: PLA General Hospital, the Affiliated Hospital of Gansu University of Traditional Chinese Medicine, Peking University People's Hospital, Peking University International Hospital, Beijing Chaoyang Hospital, and the 960th Hospital of PLA, during the period from January 2015 to October 2017. The exclusion criteria included: 1) a diagnosis of frailty based on one or more criteria from the FRAIL scale, or by receiving interventions that impact frailty; 2) presence of Parkinson's disease, stroke, or mental disorders that could interfere with the assessment of frailty; 3) loss to follow-up or death; 4) patients who had maintained regular continuous positive airway pressure (CPAP) therapy for three months during the follow-up period or who remained on CPAP until the end of follow-up; and 5) patients with chronic lung, chest or neuromuscular disease that could lead to chronic overnight hypoxaemia causing pulse oxygen saturation (SpO₂) to fall below 90% at rest. Ultimately, 1006 elderly patients with OSA aged 60 years and older were included in the analysis. Based on the MSpO₂ quartiles, the participants were stratified into four groups. This observational study did not interfere with standard care; all participants continued their prescribed treatments throughout the study. This study adheres to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines and was conducted in accordance with the Declaration of Helsinki. The Ethics Committee of the General Hospital of the People's Liberation Army of China (S2022-366-01) approved the study protocol. All participants provided written informed consent. The study design is illustrated in [Figure 1](#).

Diagnosis of OSA

Portable laboratory-based PSG is recognized as the gold standard for diagnosing OSA. In the present study, participants underwent comprehensive PSG evaluations in the sleep laboratories of affiliated hospitals. The initial scoring of OSA and sleep studies adhered to the 2012 Guidelines of the American Academy of Sleep Medicine.²¹ Data were collected using the Compumedics system, developed in Melbourne, Australia, and encompassed a comprehensive suite of sleep metrics such as electroencephalography, electrooculography, electrocardiography, nasal-oral airflow, thoracic and abdominal movements, oxygen saturation (SpO₂), and body orientation. Analysis involved automated computer processing supplemented by manual verification by two sleep technologists and a senior physician. OSA was defined by an apnea-hypopnea index (AHI) of ≥ 5 events per hour. The AHI was computed as the total number of apnea and hypopnea events divided by the sleep duration in hours.²¹

Diagnosis of Frailty

Frailty was assessed using the FRAIL scale, which includes five criteria: (1) fatigue, assessed by querying participants on the frequency of fatigue experienced over the past four weeks; (2) resistance, indicated by difficulties in ascending a 10-step staircase; (3) ambulation, reflected by the inability to walk one block; (4) comorbidities, defined as the presence of five or more conditions from a list including hypertension, diabetes, cancer (excluding minor skin cancers), chronic lung disease, myocardial infarction, congestive heart failure, angina, asthma, arthritis, stroke, and kidney disease; and (5)

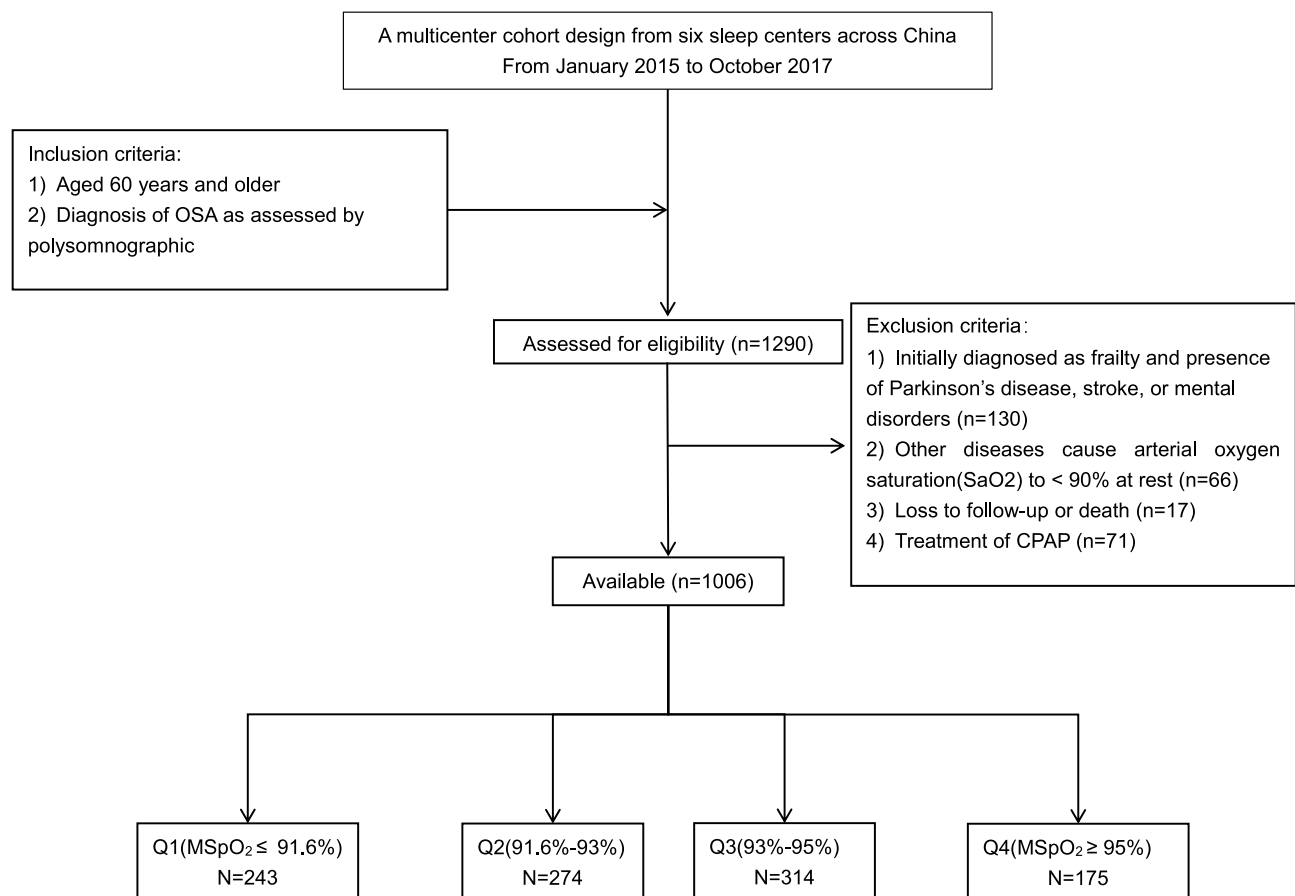


Figure 1 Study flow chart.

Abbreviations: OSA, obstructive sleep apnea; CPAP, continuous positive airway pressure.

weight loss, characterized by an unintentional decrease of more than 5.0% in body weight over the past year. Participants were categorized as frail if they met three or more of these criteria, pre-frail if they met fewer than three, and non-frail if they met none. For the purposes of this study, those meeting three or more criteria were categorized as frail, while those meeting 0–2 criteria were considered non-frail.²²

Covariates and Definitions

We collected demographic and relevant clinical data for all patients, including sex, age, height, weight, body mass index (BMI; calculated as weight divided by height squared, kg/m²), history of smoking (defined as smoking at least 1 cigarette per day or having smoked for more than 6 months), and history of alcohol consumption (defined as consuming alcohol at least once a week for 6 months or longer). Sleep parameters recorded included the AHI, oxygen desaturation index (ODI), mean apnea time (MAT), mean pulse oxygen saturation (MSpO₂), and lowest pulse oxygen saturation (LSpO₂), and the duration of time with SaO₂ <90% (TSA90). Medical conditions were confirmed using the hospital management database, which included diabetes, chronic kidney disease (CKD), cardiac dysfunction, atrial fibrillation (AF), dyslipidemia, hypertension, and chronic obstructive pulmonary disease (COPD).

Sample Size

According to previous meta-analyses, the prevalence of frailty in the elderly population is 13.6%.²³ We conducted sample size calculations using PASS software, setting the significance level at 0.05 and the desired power at 0.8. The calculations indicated that a minimum of 642 participants would be required to achieve adequate statistical power. Our study population included 1006 participants, meeting the sample size requirements.

Follow-Up

The follow-up commenced subsequent to the verification of all data. The inception of the follow-up was marked by the diagnosis of OSA via PSG, and the endpoint identified was the onset of frailty. We assessed patients' frailty employing various communication methods, including telephone and WeChat, based on the frailty questionnaire proposed by Morley et al, which is endorsed by Chinese experts.¹⁸ Evaluations were conducted at 1, 3, 6, and 12 months, and subsequently every 6 months thereafter, ranging from a minimum of 3 months to a maximum of 1 year, with an average follow-up duration of 52 months. Patients who were unable to provide information during follow-up were considered lost to follow-up. The follow-up period concluded in December 2022.

Statistical Analysis

Initially, we performed tests for normality and homogeneity of variance. Data that followed a normal distribution are presented as means \pm standard deviations, and were analyzed using the *t*-test. Data not normally distributed are expressed as quartiles [median (P25, P75)]. Discrete variables are reported as proportions and assessed using the chi-square test. We investigated the association between sleep parameters and frailty using multivariate Cox regression analysis. The relationship between MSpO₂ and time-to-event endpoints was delineated through the Kaplan-Meier method, with curve comparisons conducted via the Log rank test. Additionally, we employed restricted cubic spline analysis to elucidate the dose-response relationship between MSpO₂ and the risk of frailty, positioning four knots at the 25th, 50th, 75th, and 95th percentiles.

Subgroup analyses were stratified by age (<70 years vs \geq 70 years), gender (male vs female), BMI (<28 kg/m² vs \geq 28 kg/m²), and AHI (5.0–14.9 events/hour vs \geq 15 events/hour). Sensitivity analyses excluded participants diagnosed with frailty within the first year or those diagnosed with chronic obstructive pulmonary disease or heart failure to verify the robustness of our findings. Model 1 was unadjusted, whereas Model 2 adjusted for potential risk factors including age, sex, BMI, smoking status, alcohol consumption, systolic and diastolic blood pressure, diabetes, CKD, cardiac dysfunction, AF, dyslipidemia, hypertension, and COPD. All statistical analyses were performed using SPSS 25.0 (SPSS Inc., Chicago, Illinois, USA) and R statistical software (version 4.4.1). A two-sided *p*-value of less than 0.05 was considered to indicate statistical significance.

Results

Baseline Characteristics

Table 1 shows the characteristics of participants according to MSpO₂ quartiles. A total of 1006 subjects (mean age = 71.8 years, 39.2% females) were included in the analysis. The age, smoking, as well as the levels of BMI, AHI, ODI, MAT, TSA90 and the prevalence of hypertension and COPD exhibited a decreasing trend with the elevated MSpO₂, except for the levels of LSpO₂ and the prevalence of dyslipidemia, which showed an increasing trend (all *P* < 0.005).

Association Between Various Sleep Parameters and the Risk of Frailty in Patients with OSA

Multivariate Cox regression analysis indicated that MSpO₂ (HR = 0.941, 95% CI: 0.903–0.981, *P* = 0.005) and TSA90 (HR = 1.002, 95% CI: 1.001–1.004, *P* < 0.001) serves as an independent protective factor against frailty in elderly patients with OSA. However, no significant associations were observed between other sleep parameters and frailty (all *P* > 0.05, Table 2).

Association Between MSpO₂ and the Risk of Frailty in Patients with OSA

Patients with OSA and an MSpO₂ level below 91.6% exhibited a higher risk of frailty compared with those whose MSpO₂ level ranged from 93% to 95%, serving as a reference group (Q3 vs Q1, HR = 1.43, 95% CI 1.03–1.97, *P* = 0.029). No significant differences were observed in the other groups (Table 3). Kaplan-Meier curves indicate that an MSpO₂ level below 91.6% significantly increases the risk of frailty (Log rank test, *P* < 0.001; Figure 2). To further investigate the pattern of this association, restricted cubic splines demonstrated an increasing trend for MSpO₂ and frailty risk (*P* for nonlinearity = 0.028).

Table 1 Characteristics of Subjects by MSpO₂ Quartiles

	Total N=1006	Q1 (≤ 91.6%) N=243	Q2 (91.6–93%) N=274	Q3 (93–95%) N=314	Q4 (≥ 95%) N=175	P for trend
Demographics						
BMI (kg/m ²)	26.70±4.31	27.96±5.18	26.96±3.86	26.18±3.85	25.49±3.98	< 0.001
Age (year)	71.88(66.00, 76.00)	73.42(67.00, 78.00)	76.00(70.00, 82.00)	71.72(66.00, 76.00)	69.91(65.00, 73.00)	< 0.001
SBP (mmHg)	135.44(123.00, 143.00)	136.33(123.00, 149.00)	134.86(124.00, 140.00)	135.94(124.00, 142.25)	134.22(120.00, 145.00)	0.347
DBP (mmHg)	76.19(70.00, 81.00)	76.41(70.00, 82.00)	76.09(70.00, 81.00)	75.87(70.00, 80.00)	76.60(70.00, 83.00)	0.905
Female, n (%)	395(39.26)	99(40.74)	112(40.87)	112(35.66)	72(41.14)	0.479
Smoking, n (%)	237(23.55)	79(32.51)	70(25.54)	61(19.42)	27(15.42)	< 0.001
Drinking, n (%)	117(11.63)	39(16.04)	30(10.94)	29(9.23)	19(10.85)	0.086
Sleep parameters						
AHI (events/h)	30.66(14.50, 44.32)	37.74(14.90, 57.00)	31.79(17.90, 44.30)	27.81(14.45, 38.45)	24.17(11.10, 32.80)	< 0.001
ODI (events/h)	26.66(10.30, 40.00)	38.59(19.50, 56.20)	28.01(13.50, 42.27)	22.15(8.50, 32.50)	16.10(6.40, 21.80)	< 0.001
MAT (s)	23.25(19.55, 25.30)	24.46(19.57, 27.75)	22.91(18.33, 26.00)	23.17(19.69, 25.14)	22.25(20.20, 23.71)	0.002
LSpO ₂ (%)	77.28(72.00, 85.00)	69.96(62.00, 80.00)	76.61(72.00, 83.00)	79.97(77.00, 86.00)	83.68(82.00, 89.00)	< 0.001
TSA90, min	13.43(2.20, 59.32)	150.00(60.14, 246.03)	25.00(10.35, 53.85)	6.60(1.60, 14.95)	1.30(0.00, 4.20)	< 0.001
Medical condition						
Diabetes, n (%)	238(23.65)	52(21.39)	62(22.62)	83(26.43)	41(23.42)	0.543
CKD, n (%)	35(3.47)	7(2.88)	7(2.55)	15(4.77)	6(3.42)	0.470
Cardiac dysfunction, n (%)	62(6.16)	21(8.64)	12(4.37)	21(6.68)	8(4.57)	0.172
AF, n (%)	92(9.14)	28(11.52)	21(7.66)	31(9.87)	12(6.85)	0.299
Hypertension, n (%)	645(64.11)	174(71.60)	168(61.31)	196(62.42)	107(59.42)	0.048
COPD, n (%)	63(6.26)	28(11.52)	19(6.93)	14(4.45)	2(1.14)	< 0.001

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; AHI, the apnea-hypopnea index; ODI, the oxygen desaturation index; MAT, the mean apnea time; LSpO₂, the lowest pulse oxygen saturation; TSA90, the duration of time with SaO₂ <90%; CKD, chronic kidney disease; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease.

Table 2 Results of Cox Regression Analysis

	Model 1		Model 2	
	HR (95% CI)	P-value	HR (95% CI)	P-value
AHI	0.991(0.980 ~ 1.003)	0.134	0.997(0.985 ~ 1.010)	0.675
ODI	1.005(0.993 ~ 1.017)	0.435	1.005(0.992 ~ 1.018)	0.435
MAT	0.995(0.977 ~ 1.013)	0.598	0.992(0.972 ~ 1.012)	0.405
LSpO ₂	0.795(0.986 ~ 1.011)	0.795	1.002(0.989 ~ 1.015)	0.791
MSpO ₂	0.927(0.892 ~ 0.964)	< 0.001	0.941(0.903 ~ 0.981)	0.005
TSA90	1.002(1.001 ~ 1.003)	< 0.001	1.002(1.001 ~ 1.004)	< 0.001

Notes: Model 1 was unadjusted, whereas Model 2 adjusted for potential risk factors including age, sex, BMI, smoking status, alcohol consumption, systolic and diastolic blood pressure, diabetes, CKD, cardiac dysfunction, AF, dyslipidemia, hypertension, and COPD.

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CKD, chronic kidney disease; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease.

Table 3 Association of MSpO₂ with the Risk of Frailty

	Model 1		Model 2	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Q1 (≤ 91.6%)	1.652(1.221 ~ 2.236)	0.001	1.430(1.037 ~ 1.971)	0.029
Q2 (91.6–93%)	0.892(0.643 ~ 1.238)	0.495	1.157(0.822 ~ 1.627)	0.403
Q3 (93–95%)	Reference	Reference	Reference	Reference
Q4 (≥ 95%)	1.024(0.677 ~ 1.549)	0.910	0.955(0.622 ~ 1.466)	0.832

Notes: Model 1 was unadjusted, whereas Model 2 adjusted for potential risk factors including age, sex, BMI, smoking status, alcohol consumption, systolic and diastolic blood pressure, diabetes, CKD, cardiac dysfunction, AF, dyslipidemia, hypertension, and COPD.

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CKD, chronic kidney disease; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease.

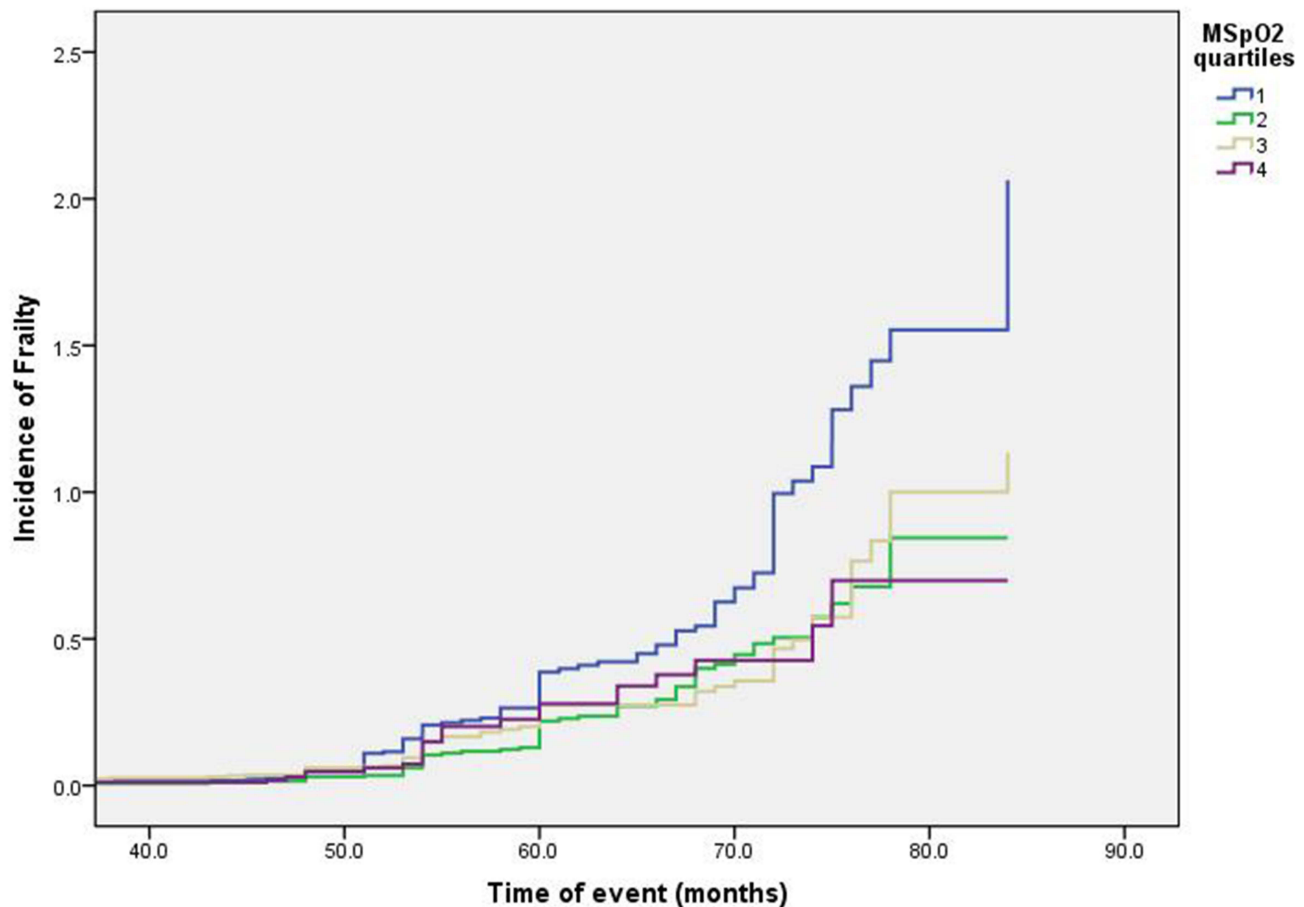


Figure 2 Kaplan-Meier curve of MSpO₂ levels and frailty risk. This figure presents the Kaplan-Meier curve of MSpO₂ quartiles in relation to the risk of frailty, utilizing Model I. The Kaplan-Meier curve corresponds to the general population of patients with OSA included in this study. Quartile 1: MSpO₂ ≤ 91.6%, Quartile 2: 91.6% to 93%, Quartile 3: 93% to 95%, Quartile 4: MSpO₂ ≥ 95%. The Log rank *P*-value is less than 0.001.

There was a gradual decrease in the risk of frailty until MSpO₂ levels reached 93% and then began to increase substantially thereafter (Figure 3).

Sensitivity and Subgroup Analysis

In the subgroup analysis, a U-shaped relationship was observed consistently across multiple subgroups, including by gender (Figure 4A), and in individuals classified as either obese (BMI < 28) or non-obese (BMI ≥ 28) (Figure 4B), as well as in those with mild OSA (AHI 5.0–14.9) and moderate-to-severe OSA (AHI ≥ 15) (Figure 4C), and age categories of less than 70 years and 70 years or older (Figure 4D). The sensitivity analysis, which excluded participants with COPD or heart failure (*n* = 106) and those diagnosed with frailty within the first year (*n* = 30), yielded results consistent with the primary findings after adjustment for known risk factors (Table 4).

Discussion

To the best of our knowledge, this article represents the first investigation into the relationship between varying levels of IH and the occurrence of frailty in elderly patients with OSA. Based on a 52-month average follow-up period, our primary findings highlight two critical points: (i) MSpO₂ is significantly associated with frailty compared to other sleep parameters; (ii) MSpO₂ exhibits a U-shaped relationship with frailty among patients with OSA, suggesting that mild to moderate IH may reduce the incidence of frailty.

Frailty is an age-related syndrome characterized by diminished biological reserves, potentially leading to adverse outcomes such as disability, institutionalization, hospitalization, and mortality.²⁴ Our research primarily explores the

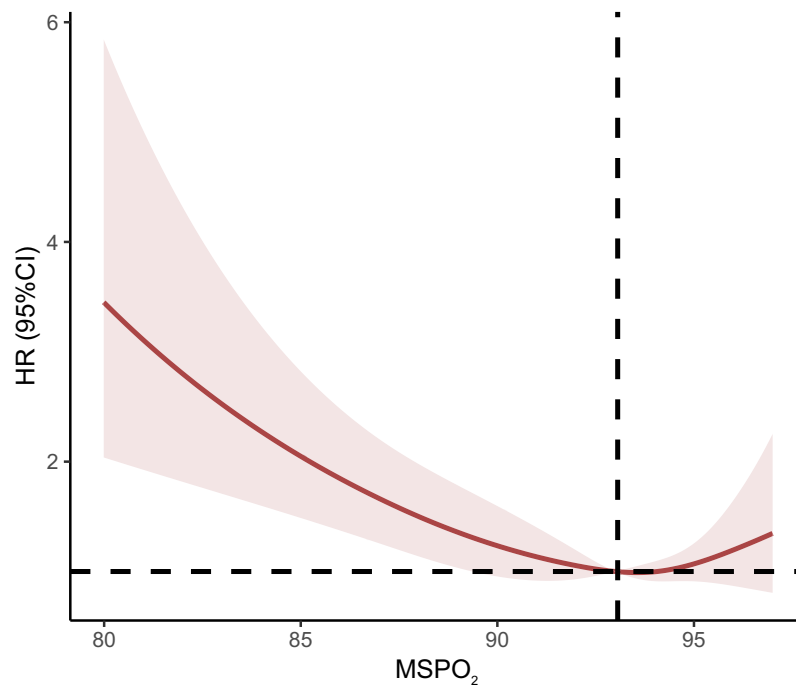


Figure 3 Title: Association of MSpO₂ levels and frailty risk. This figure illustrates penalized cubic spline curves derived from a binary Cox regression model, adjusted for age, sex, body mass index (BMI), smoking status, alcohol consumption, systolic blood pressure (SBP), diastolic blood pressure (DBP), diabetes, chronic kidney disease (CKD), cardiac dysfunction, atrial fibrillation (AF), dyslipidemia, hypertension, and chronic obstructive pulmonary disease (COPD). The non-linear *P*-value is 0.02.

correlation between IH and frailty. IH, a fundamental pathology of OSA, subjects cells to repeated cycles of hypoxia/normoxia, thereby inducing oxidative stress and systemic inflammation.²⁵ In our analysis, after adjusting for other variables that might influence oxygen saturation, elderly OSA patients with an MSpO₂ level below 91.6% experience an earlier onset of frailty. This observation aligns with numerous studies. Previous research indicates that CPAP therapy significantly reduces the onset of frailty in elderly individuals diagnosed with OSA.²⁶ IH notably enhances frailty risk in this demographic. First, the absolute dependence of the mammalian brain on oxygen for ATP production makes it acutely susceptible to hypoxic conditions. Hypoxia plays a critical role in the pathogenesis of several neurological disorders, including Alzheimer's and Parkinson's diseases, as well as other age-related neurodegenerative conditions.³ Second, IH specifically impacts left ventricular remodeling, diastolic dysfunction,²⁷ and pulmonary circulation,²⁸ which significantly limits functional capacity and may reduce survival. Third, IH is hypothesized to serve as a crucial mechanistic trigger for potential systemic effects on organs or tissues in individuals with OSA.²⁹ Over time, IH may lead to chronic conditions that contribute to the development of frailty.

Severe IH has been extensively studied as a causative mechanism for frailty. However, our findings suggest that mild IH could potentially mitigate the risk of frailty in the elderly. Emerging evidence supports the notion that “low dose” IH—characterized by modest levels of hypoxia over few episodes—may represent a straightforward, safe, and efficacious treatment with significant therapeutic potential for various clinical conditions.^{8,30} Our results delineate a U-shaped association between the risk of frailty and MSpO₂, indicating that mild IH significantly lowers the incidence of frailty compared to severe IH or the absence of IH. Modest hypoxia might decelerate the progression of diverse age-related disorders and enhance anti-inflammatory responses, oxidative stress management, mitochondrial functionality, and cellular survival. Regarding disease management, accumulated data from animal models and human studies indicate that moderate IH conditioning could serve as a preventive and therapeutic approach for chronic obstructive pulmonary disease,³¹ hypertension,³² myocardial infarction,³³ stroke,³⁴ and depression.³⁵ In terms of physical strength, numerous investigations have documented the positive effects of mild IH on the exercise capacity of elderly individuals. Earlier research has demonstrated improvements in physical fitness (chair sit-to-stand) and pulmonary function in older men following a combined regimen of aerobic and elastic resistance exercise conducted for 12 weeks at 3000-m normobaric

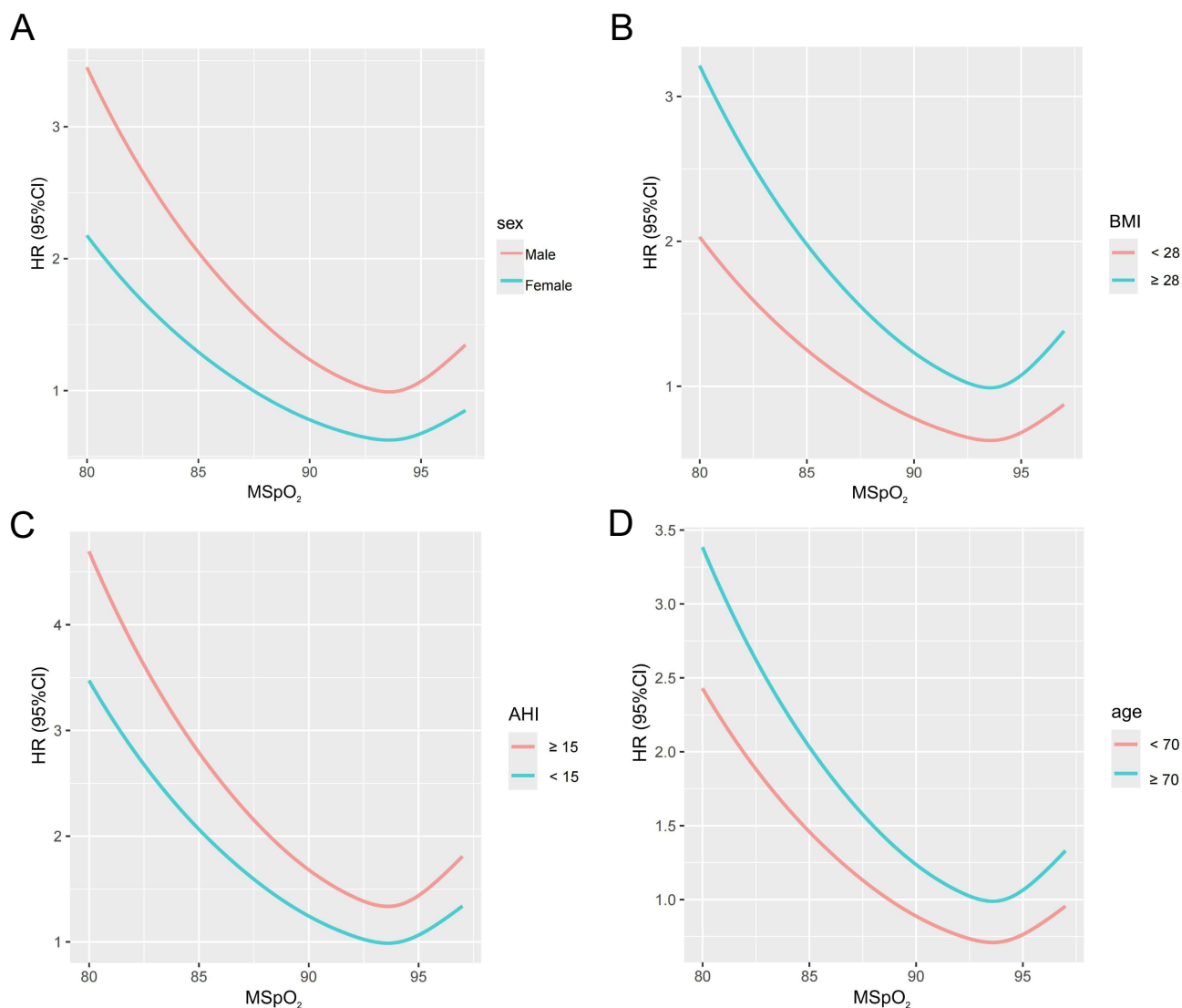


Figure 4 Title: Subgroup analysis. Penalized cubic spline curves derived from the binary Cox regression model—including variables such as age, sex, BMI, smoking status, alcohol consumption, SBP, DBP, diabetes, CKD, cardiac dysfunction, AF, dyslipidemia, hypertension, and COPD—were stratified by gender (A), obesity status (BMI <28 and BMI ≥28) (B), severity of OSA (mild OSA with AHI 5.0–14.9 and moderate-severe OSA with AHI ≥15) (C), and age categories (<70 and ≥70 years) (D). All non-linear associations were statistically significant with *P* < 0.05.

hypoxia.³⁶ Furthermore, a cohort of individuals over 65 years exhibited enhanced peak aerobic power and extended time to exhaustion following a regimen that integrated aerobic training with passive hypoxic exposures for 90 minutes three times per week.³⁷ These enhancements in physical performance³⁷ could be attributed to specific muscular adaptations to

Table 4 Sensitivity Analysis for the Association Between MSpO₂ Levels and Frailty Risk

	Model 1		Model 2	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Excluding participants with medical conditions (COPD or heart failure) that could affect MSpO₂ (n = 106)				
Q1 (≤ 91.6%)	1.502(1.079 ~ 2.090)	0.016	1.354(0.959 ~ 1.912)	0.045
Q2 (91.6–93%)	0.830(0.585 ~ 1.177)	0.295	0.883(0.621 ~ 1.256)	0.490
Q3 (93–95%)	Reference	Reference	Reference	Reference
Q4 (≥ 95%)	1.164(0.741 ~ 1.830)	0.510	1.071(0.675 ~ 1.700)	0.770

(Continued)

Table 4 (Continued).

	Model 1		Model 2	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Excluding participants diagnosed with frailty in the first year during the follow-up period (n = 30)				
Q1 (\leq 91.6%)	1.740(1.274 ~ 2.378)	0.001	1.457(1.064 ~ 2.044)	0.020
Q2 (91.6–93%)	0.949(0.678 ~ 1.328)	0.758	1.005(0.717 ~ 1.410)	0.975
Q3 (93–95%)	Reference	Reference	Reference	Reference
Q4 (\geq 95%)	0.984(0.641 ~ 1.511)	0.942	0.842(0.543 ~ 1.306)	0.443

Notes: Model 1 was unadjusted, whereas Model 2 adjusted for potential risk factors including age, sex, BMI, smoking status, alcohol consumption, systolic and diastolic blood pressure, diabetes, CKD, cardiac dysfunction, AF, dyslipidemia, hypertension, and COPD.

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CKD, chronic kidney disease; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease.

moderate hypoxic conditioning, including increased muscle fiber recruitment, stimulated muscle protein synthesis, regulated inflammatory responses, optimized metabolic oxidation, and improved mitochondrial efficiency.^{38,39}

Interestingly, our study found no correlation between four additional nocturnal hypoxemia parameters related to OSA—AHI, ODI, MAT, and LSpO₂—and frailty. It appears that different attributes of hypoxic exposure, such as severity, duration, and frequency, determine whether hypoxic stimuli have beneficial or detrimental health effects.⁸ Although these parameters are valuable for assessing the severity of OSA, they do not accurately reflect nocturnal blood oxygen levels and IH.

This represents the first study to identify a U-shaped association between MSpO₂ levels and frailty. Significant strengths of our study include its multicenter cohort design and extended follow-up period, which confer enhanced rigor and reliability to our findings. Additionally, we conducted subgroup and sensitivity analyses to bolster the credibility and validity of our results. Nonetheless, the study is subject to several limitations. First, the cohort primarily consisted of Asian patients, which may limit the generalizability of our findings to non-Asian populations. Additionally, it is important to note that the generalizability of oximetry-dependent data may be affected by variations in skin pigmentation. Second, patient sleep data were collected only at baseline, which does not account for the potential variability in sleep parameters over time, especially given that the severity of OSA may fluctuate throughout the follow-up period. Third, we utilized the FRAIL scale to assess frailty, rather than the Fried frailty phenotype, potentially introducing inaccuracies into our results. Fourth, this study did not include therapeutic interventions, such as CPAP or supplemental oxygen. The lack of these interventions limits our ability to draw definitive conclusions regarding causality. Future research incorporating these treatments is warranted to elucidate this relationship further.

Conclusion

In this multicenter cohort study conducted among an Asian demographic, we observed that lower MSpO₂ levels are independently associated with an increased risk of developing frailty in elderly patients with OSA, while mild intermittent hypoxia may mitigate the risk of frailty. This finding emphasizes the importance of considering MSpO₂ levels in this population, suggesting that while chronic exposure to low oxygen levels is harmful, mild IH might offer a protective benefit against frailty. Future research should explore the mechanisms underlying this phenomenon and the potential therapeutic implications for managing frailty in geriatric OSA patients.

Data Sharing Statement

Our research is conducted collaboratively, with a focus on teamwork. In the event that all team members are in agreement to share the data, the corresponding author can be contacted to request access to the information.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Ethics Committee of the PLA General Hospital (S2022-366-01), and informed consent was obtained from all participants prior to study commencement.

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Author Contributions

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.

Disclosure

There were no potential conflicts of interest in the study, according to the authors.

References

1. Johnson KG, Johnson DC. When will it be time? Evaluation of OSA in stroke and TIA patients. *Sleep Med.* 2019;59:94–95. doi:10.1016/j.sleep.2018.10.016
2. Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. *Lancet.* 2014;383(9918):736–47. doi:10.1016/s0140-6736(13)60734-5
3. Burtscher J, Mallet RT, Burtscher M, Millet GP. Hypoxia and brain aging: neurodegeneration or neuroprotection? *Ageing Res Rev.* 2021;68:101343. doi:10.1016/j.arr.2021.101343
4. Burtscher M, Pachinger O, Ehrenbourg I, et al. Intermittent hypoxia increases exercise tolerance in elderly men with and without coronary artery disease. *Int J Cardiol.* 2004;96(2):247–254. doi:10.1016/j.ijcard.2003.07.021
5. Dudnik E, Zagaynaya E, Glazachev OS, Susta D. Intermittent hypoxia-hyperoxia conditioning improves cardiorespiratory fitness in older comorbid cardiac outpatients without hematological changes: a randomized controlled trial. *High Alt Med Biol.* 2018;19(4):339–343. doi:10.1089/ham.2018.0014
6. Bikov A, Frent S, Deleanu O, et al. Time spent with Saturation below 80% versus 90% in patients with obstructive sleep apnoea. *J Clin Med.* 2023;12(13):4205. doi:10.3390/jcm12134205
7. Viscor G, Torrella JR, Corral L, et al. Physiological and biological responses to short-term intermittent hypobaric hypoxia exposure: from sports and mountain medicine to new biomedical applications. *Front Physiol.* 2018;9:814. doi:10.3389/fphys.2018.00814
8. Raberin A, Burtscher J, Burtscher M, Millet GP. Hypoxia and the aging cardiovascular system. *Ageing and Disease.* 2023;14(6):2051–2070. doi:10.14336/ad.2023.0424
9. Liu X, Chen X, Kline G, et al. Reduced cerebrovascular and cardioventilatory responses to intermittent hypoxia in elderly. *Respir Physiol Neurobiol.* 2020;271:103306. doi:10.1016/j.resp.2019.103306
10. Vgontzas AN, He F, Fernandez-Mendoza J, et al. Age-related differences in the association of mild-to-moderate sleep apnea with incident cardiovascular and cerebrovascular diseases. *Sleep Med.* 2024;113:306–312. doi:10.1016/j.sleep.2023.11.1133
11. Bostanci A, Bozkurt S, Turhan M. Impact of age on intermittent hypoxia in obstructive sleep apnea: a propensity-matched analysis. *Sleep Breath.* 2018;22(2):317–322. doi:10.1007/s11325-017-1560-z
12. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci.* 2001;56(3):M146–56. doi:10.1093/gerona/56.3.m146
13. Wu C, Smit E, Xue QL, Odden MC. Prevalence and correlates of frailty among community-dwelling Chinese older adults: the china health and retirement longitudinal study. *J Gerontol A Biol Sci Med Sci.* 2017;73(1):102–108. doi:10.1093/gerona/glx098
14. Pansarasa O, Mimmi MC, Davin A, Giannini M, Guaita A, Cereda C. Inflammation and cell-to-cell communication, two related aspects in frailty. *Immunity Ageing.* 2022;19(1):49. doi:10.1186/s12979-022-00306-8
15. Hoogendijk EO, Afilalo J, Ensrud KE, Kowal P, Onder G, Fried LP. Frailty: implications for clinical practice and public health. *Lancet.* 2019;394(10206):1365–1375. doi:10.1016/s0140-6736(19)31786-6
16. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci.* 2004;59(3):255–263. doi:10.1093/gerona/59.3.m255
17. Chow WB, Rosenthal RA, Merkow RP, Ko CY, Esnaola NF. Optimal preoperative assessment of the geriatric surgical patient: a best practices guideline from the American college of surgeons national surgical quality improvement program and the American geriatrics society. *J Am Coll Surg.* 2012;215(4):453–466. doi:10.1016/j.jamcollsurg.2012.06.017
18. Mehawej J, Saczynski JS, Kiefe CI, et al. Association between risk of obstructive sleep apnea and cognitive performance, frailty, and quality of life among older adults with atrial fibrillation. *J Clin Sleep Med.* 2022;18(2):469–475. doi:10.5664/jcsm.9622
19. Piovezan RD, Abucham J, Dos Santos RV, Mello MT, Tufik S, Poyares D. The impact of sleep on age-related sarcopenia: possible connections and clinical implications. *Ageing Res Rev.* 2015;23(Pt B):210–220. doi:10.1016/j.arr.2015.07.003
20. Moreno-Tamayo K, Manrique-Espinoza B, Guerrero-Zúñiga S, Ramírez-García E, Sánchez-García S. Sex differences in the association between risk of obstructive sleep apnea, insomnia, and frailty in older adults. *Nat Sci Sleep.* 2021;13:1461–1472. doi:10.2147/nss.S320192
21. 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
22. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. *J Nutr Health Aging.* 2012;16(7):601–608. doi:10.1007/s12603-012-0084-2
23. Ofori-Asenso R, Chin KL, Mazidi M, et al. Global incidence of frailty and prefrailty among community-dwelling older adults: a systematic review and meta-analysis. *JAMA Network Open.* 2019;2(8):e198398. doi:10.1001/jamanetworkopen.2019.8398

24. Dent E, Martin FC, Bergman H, Woo J, Romero-Ortuno R, Walston JD. Management of frailty: opportunities, challenges, and future directions. *Lancet*. 2019;394(10206):1376–1386. doi:10.1016/s0140-6736(19)31785-4
25. Shobatake R, Ota H, Takahashi N, Ueno S, Sugie K, Takasawa S. The impact of intermittent hypoxia on metabolism and cognition. *Int J Mol Sci*. 2022;23(21):12957. doi:10.3390/ijms232112957
26. Xue X, Zhao LB, Zhao Z, et al. Effect of continuous positive airway pressure on incident frailty in elderly patients with obstructive sleep apnea: a study based on propensity score matching. *Clin Interventions Aging*. 2024;19:255–263. doi:10.2147/cia.S446129
27. Maiolino G, Bisogni V, Maggi M, et al. Nocturnal hypoxia indexes are associated with left ventricular remodeling and diastolic dysfunction in obstructive sleep apnea patients. *Sleep Med*. 2023;103:180–186. doi:10.1016/j.sleep.2023.02.004
28. Ismail K, Roberts K, Manning P, Manley C, Hill NS. OSA and pulmonary hypertension: time for a new look. *Chest*. 2015;147(3):847–861. doi:10.1378/chest.14-0614
29. Ji Y, Liang Y, Mak JCW, Ip MSM. Obstructive sleep apnea, intermittent hypoxia and non-alcoholic fatty liver disease. *Sleep Med*. 2022;95:16–28. doi:10.1016/j.sleep.2022.04.006
30. Navarrete-Opazo A, Mitchell GS. Therapeutic potential of intermittent hypoxia: a matter of dose. *Am J Physiol Regulatory Integr Comp Physiol*. 2014;307(10):R1181–97. doi:10.1152/ajpregu.00208.2014
31. Serebrovskaya TV, Swanson RJ, Kolesnikova EE. Intermittent hypoxia: mechanisms of action and some applications to bronchial asthma treatment. *J Physiol Pharmacol*. 2003;54(Suppl 1):35–41.
32. Serebrovskaya TV, Manukhina EB, Smith ML, Downey HF, Mallet RT. Intermittent hypoxia: cause of or therapy for systemic hypertension? *Exp Biol Med*. 2008;233(6):627–650. doi:10.3181/0710-mr-267
33. Xu WQ, Yu Z, Xie Y, et al. Therapeutic effect of intermittent hypobaric hypoxia on myocardial infarction in rats. *Basic Res Cardiol*. 2011;106(3):329–342. doi:10.1007/s00395-011-0159-y
34. Dirnagl U, Becker K, Meisel A. Preconditioning and tolerance against cerebral ischaemia: from experimental strategies to clinical use. *Lancet Neurol*. 2009;8(4):398–412. doi:10.1016/s1474-4422(09)70054-7
35. Basovich SN. The role of hypoxia in mental development and in the treatment of mental disorders: a review. *Biosci Trends*. 2010;4(6):288–296.
36. Park HY, Jung WS, Kim J, Lim K. Twelve weeks of exercise modality in hypoxia enhances health-related function in obese older Korean men: a randomized controlled trial. *Geriatrics Gerontol Int*. 2019;19(4):311–316. doi:10.1111/ggi.13625
37. Schega L, Peter B, Brigadski T, et al. Effect of intermittent normobaric hypoxia on aerobic capacity and cognitive function in older people. *J Sci Med Sport*. 2016;19(11):941–945. doi:10.1016/j.jsams.2016.02.012
38. Dempsey JA, Morgan BJ. Humans in hypoxia: a conspiracy of maladaptation?! *Physiology*. 2015;30(4):304–316. doi:10.1152/physiol.00007.2015
39. Gangwar A, Paul S, Ahmad Y, Bhargava K. Intermittent hypoxia modulates redox homeostasis, lipid metabolism associated inflammatory processes and redox post-translational modifications: benefits at high altitude. *Sci Rep*. 2020;10(1):7899. doi:10.1038/s41598-020-64848-x

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