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ORIGINAL RESEARCH

Dynamic Risk Status of OSA and Its Association with COPD Incidence and Progression to Oxygen Therapy: Insights from a US National Cohort

Yuxin Wang, Jinmei Luo, Rong Huang, Yi Xiao

Department of Pulmonary and Critical Care Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, People's Republic of China

Correspondence: Yi Xiao, Department of Pulmonary and Critical Care Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 1 Shuaifuyuan, Dongcheng District, Beijing, 100730, People's Republic of China, Email xiaoyipumch@sina.com

Video abstract

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Purpose: Obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD) are prevalent respiratory disorders with significant health implications. This study investigates the relationship between OSA risk and the incidence and progression of COPD.

Patients and Methods: We analyzed data from the Health and Retirement Study (HRS) cohort. Participants' OSA risk was assessed using the STOP-Bang questionnaire. Changes in OSA risk were evaluated by comparing baseline and follow-up assessments. COPD incidence and progression were determined through self-reported physician diagnoses and the use of oxygen therapy. After adjusting for covariates, hazard ratios (HR) and 95% confidence intervals (95% CI) were calculated using Cox proportional hazards models.

Results: The analysis included 14398 participants for baseline OSA risk and 11177 for OSA risk changes. Participants with high baseline OSA risk had a significantly higher risk of developing COPD (adjusted HR: 1.255, 95% CI: 1.054–1.496) compared to those with low risk, although no significant relationship was found with progression to oxygen therapy. Participants whose OSA risk decreased showed a lower risk of developing COPD (Baseline low-risk group: adjusted HR: 0.603, 95% CI: 0.418–0.871; Baseline high-risk group: adjusted HR: 0.586, 95% CI: 0.396–0.869). This relationship was significant in women but not in men. Changes in OSA risk were not significantly related to COPD progression to oxygen therapy.

Conclusion: OSA risk and its changes are associated with varying risks of COPD. Progression in OSA risk increases the risk of COPD, while improvement in OSA risk reduces it.

Keywords: obstructive sleep apnea, chronic obstructive pulmonary disease, STOP-Bang, epidemiology, dynamic nature

Introduction

Obstructive sleep apnea (OSA) is a prevalent sleep disorder, affecting over 900 million adults aged 30 to 69 worldwide.[1] It is characterized by recurrent upper airway obstructions during sleep, leading to serious health issues such as hypertension, atrial fibrillation, diabetes, and stroke, all of which contribute to its significant socioeconomic impact.[2,3] Chronic obstructive pulmonary disease (COPD), a leading cause of global morbidity and mortality, causes persistent and progressive airflow obstruction, leading to symptoms like dyspnea, cough, and sputum production.[4,5] COPD imposes a significant economic and social burden as well. COPD has an estimated prevalence of 11.8% in men and 8.5% in women over the age of 40, leading to approximately 3 million deaths annually.[6,7] Severe cases of COPD, especially those with hypoxemia, may require home oxygen therapy for support.[8] The comprehensive management of COPD is crucial for global health. According to the global initiative for chronic obstructive lung disease (GOLD) 2024 guidelines, OSA is a significant comorbidity in patients with COPD.[8] The coexistence of these two diseases, known as overlap syndrome (OS), has been acknowledged for decades.[9] The prevalence of OS is estimated to range from 1% to 3.6%.[10] Among patients with COPD, 56.45% to 78% also have OSA, whereas COPD is present in 11.9% to 23.2% of individuals with

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OSA.[11] This variability likely reflects differences in study populations. Research suggests that OS is associated with poorer clinical outcomes.[12]

The relationship between COPD and OSA is complex. For instance, hyperinflation in COPD may provide some protection against OSA, while fluid retention can worsen the condition. This complex interaction underscores the heterogeneity between these two diseases.[13] Most studies have focused on how OSA affects COPD outcomes, showing that COPD patients with a high risk of OSA or those diagnosed via polysomnography (PSG) experience increased mortality and more frequent exacerbations.[14,15] However, research on whether OSA influences the onset of COPD, particularly in the general population, remains limited.

To further investigate the clinical impact of OSA on the development and progression of COPD, large-scale prospective cohort studies that simultaneously evaluate both conditions are essential. We utilized data from the Health and Retirement Study (HRS), a nationally representative longitudinal survey of over 37000 United States residents. Since 1992, the HRS has conducted biennial surveys to track health changes at individual level.[16] Starting in 2016, the HRS introduced sleep-related questions, enabling researchers to assess OSA risk using the validated STOP-Bang questionnaire.[17] The STOP-Bang questionnaire is a validated screening tool comprising eight questions that evaluate factors known to increase the risk of OSA. The acronym "STOP-Bang" represents snoring, tiredness, observed apnea, high blood pressure, body mass index (BMI), age, neck circumference, and sex.[18,19] Its effectiveness has been widely confirmed across large populations.[19–21] In addition, the biennial follow-up surveys in the HRS allow us to track changes in OSA risk over time.

In this study, we used the HRS cohort to prospectively analyze the impact of baseline OSA risk and changes in OSA risk on the incidence of COPD and its progression defined by the need for oxygen therapy. Our aim was to deepen the understanding of the relationship between OSA and COPD and to provide new evidence to inform comprehensive management strategies aimed at preventing COPD and controlling its progression.

Materials and Methods

Study Design and Population

The HRS is a large, nationwide prospective cohort study conducted in the United States.[16] The study received approval from the Ethics Review Committees of the University of Michigan, and informed consent was obtained from all participants. Starting with the core dataset from the 2016 wave, the HRS included detailed questions related to sleep and OSA.[17] For our research, we used the 2016 wave as the baseline survey and the 2020 wave as the second survey to assess OSA risk and its changes using the STOP-Bang questionnaire. The 2020 wave was selected due to minimal missing data and the availability of subsequent health outcomes. Follow-up continued until the 2022 wave.

Our study focused on participants aged 50 years and older at baseline. We excluded individuals with missing STOP-Bang questionnaire data or missing COPD diagnosis information at baseline. The specific selection process is detailed in Figure 1.

Assessment of OSA Risk

Since the 2016 wave, the HRS has included questions that allow for the calculation of STOP-Bang scores, with the methodology detailed in previously published studies, which have demonstrated its reliability.[17,20,22] The survey covers 7 of the 8 items in the STOP-Bang questionnaire, excluding neck circumference (as shown in Table 1). In our study, participants were categorized into high or low OSA risk groups based on their STOP-Bang scores. High OSA risk was defined by the following criteria: (1) a STOP-Bang score of ≥3, with at least two positive responses from the "STOP" section, accompanied by either male sex or a BMI > 35 kg/m²; or (2) a total STOP-Bang score of ≥4, regardless of the combination of responses.[17] Participants who did not meet these criteria were categorized as low OSA risk. The changes of OSA risk were assessed by comparing the results from the 2020 survey with those from the baseline survey in 2016.

Assessment of Outcomes and Follow-up Duration

The primary outcomes of this study include the incidence of COPD and its progression, defined by the need for oxygen therapy. COPD was identified through the question, "Has a doctor ever told you that you have chronic lung disease, such as chronic bronchitis or emphysema?" Progression was determined by the question, "Are you receiving oxygen for your lung

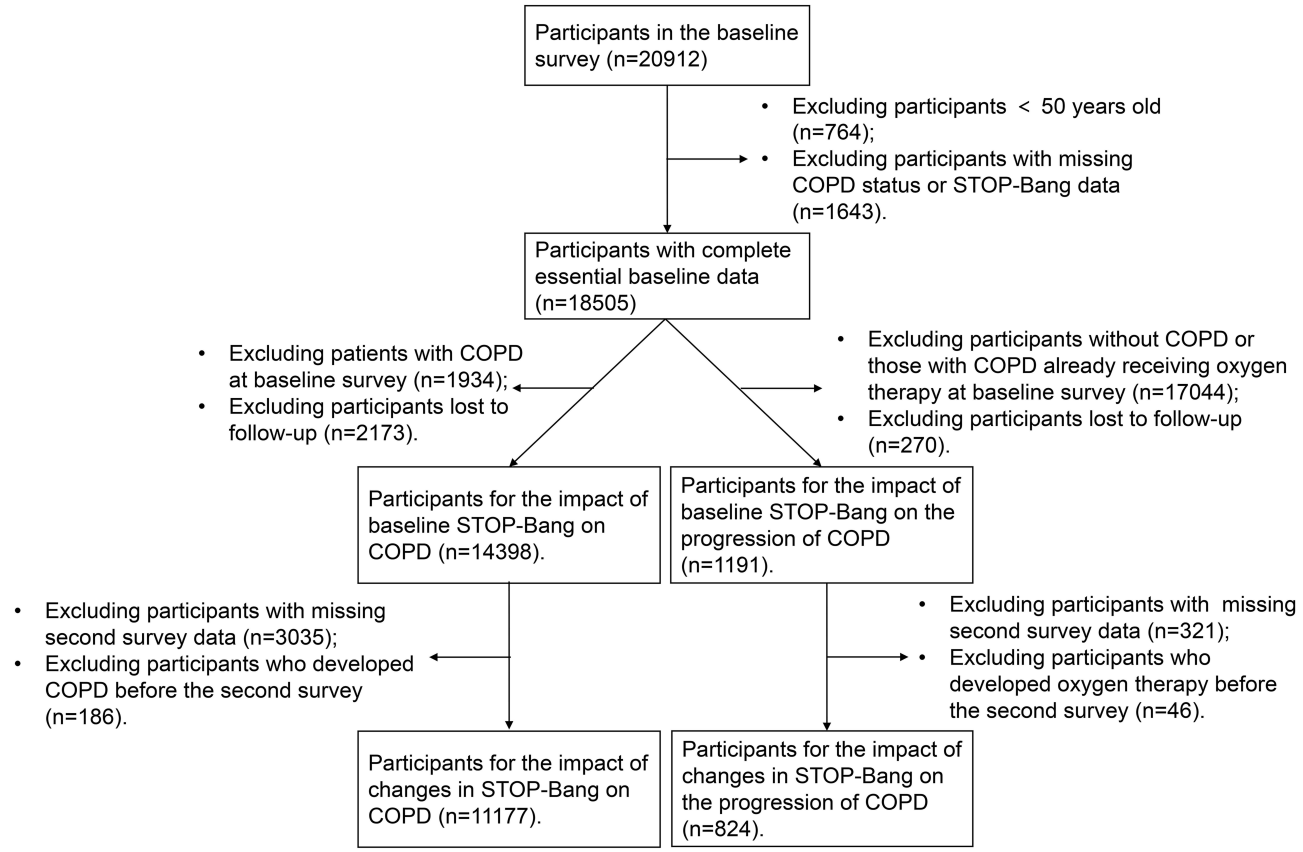

Figure 1 Selection flowchart of the study population.
Abbreviation: COPD, chronic obstructive pulmonary disease.

condition?" Only participants who confirmed having COPD were asked about oxygen therapy. Follow-up for baseline OSA risk began in 2016, and for changes in OSA risk, it started in 2020. The two endpoints for follow-up in this study were: for COPD incidence, the first diagnosis of COPD, death, or the end of the survey period, whichever occurred first; and for COPD

Table 1 Correspondence Between HRS Survey Questions and the STOP-Bang Items

STOP-Bang Items	Corresponding Information from HRS	Standards for Interpreting HRS Questions as a Positive Results
(S): Do you snore loudly?	"In the past 12 months, how often did you snore while you were sleeping?"	Responses equivalent to "≥3 nights/week"
(T): Do you often feel tired, fatigued, or sleepy during the daytime?	"Have you had any of the following persistent or troublesome problems? Severe fatigue or exhaustion".	"Yes"
(O): Has anyone observed you stop breathing during sleep?	"In the past 12 months, how often did you snort, gasp, or stop breathing while you were sleeping?"	"Rarely", "occasionally", or "frequently"
(P): Do you have (or are you being treated for) high blood pressure?	"Has a doctor ever told you that you have high blood pressure or hypertension?" or "Prev wave has high blood pressure?"	Responses equivalent to "yes"
(B): BMI	Calculated based on the "About how much do you weigh (lbs)?" and "How tall are you (feet, inches)?"	> 35 kg/m^2
(a): Age	Calculated based on the "year born"	>50 years old
(n): Neck circumference	NA	NA
(g): Sex	Sex	Male

Note: We acknowledge Dr. Frances Chung and the University Health Network (UHN) as the owners of the STOP-Bang tool, which was used in this study. Detailed information about the tool is available at www.stopbang.ca.
Abbreviations: BMI, body mass index; HRS, Health and Retirement Study; NA, not applicable.

progression, the initial report of needing oxygen therapy, death, or the end of the survey period, whichever came first. The end date of the survey was defined as the last participation date for each individual.

Covariates

The covariates in this study included age, sex, race, education level, marital status, alcohol consumption, smoking status, physical activity score, BMI, sleep quality score, and comorbidities such as hypertension, diabetes, cancer, heart disease, stroke, and nervous and psychiatric problems. Race was categorized as white/Caucasian, black/African American, or other, while education was classified into below high school, high school graduate, and college or above. Marital status was grouped into married/partnered or other, and smoking status was categorized into never, ever, or current smokers. The physical activity score was calculated based on the frequency of light, moderate, and vigorous physical activities. Responses to the "How often mild activity" question were scored as follows: "Hardly ever or never" = 0, "One to three times a month" = 1, "Once a week" = 2, and "More than once a week" = 3. The responses to "How often moderate activity" were scored as 0, 2, 4, and 6, respectively. The responses to "How often vigorous activity" were scored as 0, 3, 6, and 9, respectively. The sum of these three scores constituted the physical activity score.[23] Sleep quality was measured using a modified Jenkins Sleep Scale,[24] which included four questions: (1) "Trouble falling asleep"; (2) "Trouble waking up during the night"; (3) "Trouble waking up too early"; and (4) "Feeling rested in the morning". Responses were scored as "Most of the time" = 2, "Sometimes" = 1, and "Rarely or never" = 0, with the fourth question reverse-coded. The total score from these four questions represented the sleep quality score, where a higher score indicated poorer sleep quality.[25]

Statistical Analyses

For descriptive statistics, continuous variables were assessed for normality and, since they were not normally distributed, were summarized as medians with interquartile ranges (IQR). Categorical variables were presented as counts and percentages. Group comparisons were conducted using the Mann–Whitney *U*-test for continuous variables and the Chi-square test for categorical variables. To explore the relationship between baseline OSA risk and COPD incidence and progression, we used Cox proportional hazards regression to calculate hazard ratios (HRs) with 95% confidence intervals (CIs). We developed three models: an unadjusted model, model 1 adjusted for demographic factors (age, race, education, marital status, smoking status, drinking status, physical activity score, and BMI), and model 2, which further adjusted for comorbidities (hypertension, diabetes, cancer, heart disease, stroke, nervous and psychiatric conditions, and sleep quality). Participants with missing covariate data were excluded from the regression analyses. Sex and hypertension were not included as covariates since they are binary components of the STOP-Bang questionnaire.[17] We performed subgroup analyses based on sex. Besides, we evaluated potential interactions between each covariate and OSA risk, but no significant interactions were found. Using the methods described above, we also analyzed the impact of changes in OSA risk status. Given that baseline OSA risk influenced COPD, we conducted stratified analyses based on baseline OSA risk. The proportional hazards assumption was tested and confirmed via time-interaction terms. Cumulative risk curves were used to visualize COPD incidence and progression. To address missing data, we employed multiple imputation by chained equations (MICE) and reran the Cox regressions for sensitivity analysis. The imputation model included the following variables, namely age, sex, race, education, physical activity score, alcohol consumption, smoking status, BMI, sleep quality score, marital status, hypertension, diabetes, cancer, heart disease, stroke, and psychiatric conditions. We generated five imputed datasets and combined the effect estimates following Rubin's rules.[26] Multiple imputation was conducted using the "mice" package in R. The statistical analyses were performed using R software (version 4.3.3), with two-sided p-values of less than 0.05 considered statistically significant.

Results

Baseline Characteristics of the Study Population

Figure 1 illustrates the selection process for this study. Of the 20912 individuals surveyed in the 2016 hRS cohort, 18505 were aged 50 years or older and had complete data on COPD and the STOP-Bang questionnaire. The baseline cohort had a median age of 64.0 years (IQR: 57.0–75.0), with 43.0% being male. Among these participants, 16571 had no prior

COPD diagnosis, while 1934 had been diagnosed with COPD. Patients with COPD exhibited higher STOP-Bang scores and a greater proportion at high risk for OSA. Additionally, among the 1807 patients with COPD who provided information on oxygen therapy, 346 were receiving home oxygen therapy. These patients also had higher STOP-Bang scores and a greater risk for OSA compared to those not on oxygen therapy (Supplementary Table S1).

Of the 16571 participants without COPD at baseline, 14398 were followed up. For those diagnosed with COPD but not receiving oxygen therapy at baseline, 1191 patients were followed up. These groups formed the baseline cohorts for our prospective study assessing the impact of OSA risk on COPD incidence and progression, with their baseline characteristics shown in Table 2.

The median follow-up for COPD incidence was 5.7 years (IQR: 4.0–6.1 years), during which 612 participants were diagnosed with COPD. Those diagnosed were more likely to have a high OSA risk, were older, had a higher smoking rate, more comorbidities, and poorer sleep quality, although there were no significant differences in sex, BMI, or alcohol use compared to those without COPD.

In the study on COPD progression to oxygen therapy, 162 patients with COPD progressed to requiring oxygen. Compared to those who did not, these patients were older, had a higher proportion of males, a higher prevalence of smoking, and were less physically active. There were no significant differences in comorbidities, except for heart disease. Although their sleep quality was slightly worse, there were no significant differences in STOP-Bang scores or high OSA risk between the two groups.

Association of Baseline OSA Risk with COPD Incidence and Progression

The cumulative risk of COPD incidence is illustrated in Figure 2A and Table 2 shows the relationship between OSA risk and COPD incidence. Cox regression analysis indicated that individuals with a high OSA risk had a significantly increased risk of developing COPD compared to those with a low OSA risk (HR: 1.396, 95% CI: 1.190–1.637, $p<0.001$). This association remained robust even after adjusting for baseline demographic factors and comorbidities (HR: 1.390, 95% CI: 1.171–1.651, $p<0.001$; HR: 1.255, 95% CI: 1.054–1.496, $p=0.011$). When STOP-Bang scores were treated as continuous variables, higher scores were also associated with an increased COPD risk (HR: 1.177, 95% CI: 1.107–1.251, $p<0.001$), with the relationship remaining significant after adjustment for covariates. Additionally, interaction analysis showed no significant interaction between OSA risk and the confounding variables (data not shown with all $p > 0.05$).

We conducted a stratified analysis by sex (Table 3). Among male participants, the association between high OSA risk and increased COPD risk remained strong and statistically significant both before and after adjusting for covariates. In female participants, this relationship persisted after adjusting for baseline demographic factors, but after further adjusting for baseline comorbidities, the association between high OSA risk and COPD risk, whether categorized or treated as a continuous variable, was no longer statistically significant.

The impact of OSA risk on COPD progression to oxygen therapy is detailed in Supplementary Table S2. The cumulative risk of COPD progression to oxygen therapy is shown in Figure 2B. The results indicate that OSA risk level did not significantly affect COPD progression, neither in the overall population nor when stratified by sex.

Association of Changes in OSA Risk with COPD Incidence and Progression

To evaluate whether changes in OSA risk affect COPD incidence, we analyzed participants who had a second STOP-Bang assessment in the prospective cohort study. A total of 11177 participants met the criteria. Of the 7005 participants with low baseline OSA risk, 1167 (16.7%) progressed to high OSA risk, while 5838 (83.3%) remained stable Among the 4172 participants with high baseline OSA risk, 2866 (68.7%) remained at high risk, while 1306 (31.3%) shifted to low risk at the second survey.

Figure 3A illustrates the cumulative COPD risk across different OSA risk change groups. Given the impact of baseline OSA risk on COPD incidence, we conducted a Cox regression analysis stratified by baseline OSA risk (Table 4). In the low baseline OSA risk group, participants with stable OSA risk had a significantly lower incidence of COPD compared to those whose OSA risk increased (HR: 0.542, 95% CI: 0.382–0.769, $p=0.001$). After adjusting for covariates, this reduction in COPD risk remained significant (HR: 0.558, 95% CI: 0.388–0.802, $p=0.002$; HR: 0.603, 95% CI: 0.418–0.871, $p=0.007$). In the high baseline OSA risk group, those whose OSA risk decreased had a significantly lower risk of developing COPD compared to those whose OSA risk remained high (HR: 0.624, 95% CI: 0.428–0.909, $p=0.014$), and this relationship remained significant after adjusting for covariates.

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Table 2 Baseline Characteristics of Participants for Prospective Cohort Analyses

	Impact on COPD Development					Impact on the COPD Progression				
	Total (n=14398)	**Percentage of Missing**	**Non COPD (n=13786)**	**COPD (n=612)**	**p value**	**Total (n=1191)**	**Percentage of Missing**	**Non oxygen Therapy (n=1029)**	**Oxygen Therapy (n=162)**	**p Value**
Age, years	63.0 (57.0, 74.0)		63.0 (57.0, 73.0)	66.0 (58.0, 76.0)	<0.001	67.0 (45.5, 73.0)		64.0 (57.0, 75.0)	67.0 (58.0, 78.0)	0.039
Male, n (%)	6201 (43.1%)		5953 (43.2%)	248 (40.5%)	0.194	439 (36.9%)		368 (35.8%)	71 (43.8%)	0.048
Race, n (%)		0.4%			0.009		0.1%			0.303
White/Caucasian	9482 (66.1%)		9079 (66.1%)	403 (66.1%)		806 (67.7%)		701 (68.2%)	105 (64.8%)	
Black/African American	3182 (22.2%)		3026 (22.0%)	156 (25.6%)		277 (23.3%)		232 (22.6%)	45 (27.8%)	
Other	1682 (11.7%)		1631 (11.9%)	51 (8.4%)		107 (9.0%)		95 (9.2%)	12 (7.4%)	
Education, n (%)		0.0%			<0.001					0.654
Below High school	2886 (20.0%)		2695 (19.6%)	191 (31.3%)		397 (33.3%)		340 (33.0%)	57 (35.2%)	
High school graduate	3827 (26.6%)		3680 (26.7%)	147 (24.1%)		321 (27.0%)		275 (26.7%)	46 (28.4%)	
College or above	7682 (53.4%)		7409 (53.8%)	273 (44.7%)		473 (39.7%)		414 (40.2%)	59 (36.4%)	
Marital status, n (%)		0.1%			<0.001		0.3%			1
Married or partnered	9196 (63.9%)		8887 (64.5%)	309 (50.6%)		616 (51.9%)		532 (51.9%)	84 (51.9%)	
Other status	5187 (36.1%)		4885 (35.5%)	302 (49.4%)		572 (48.1%)		494 (48.1%)	78 (48.1%)	
Ever drinkers, n (%)	8788 (61.1%)	0.0%	8426 (61.1%)	362 (59.2%)	0.346	604 (50.7%)		528 (51.3%)	76 (46.9%)	0.298
Smoking Status, n (%)		0.4%			<0.001		0.2%			0.002
Never smokers	6963 (48.5%)		6796 (49.5%)	167 (27.3%)		268 (22.5%)		247 (24.1%)	21 (13.0%)	
Ever smokers	5538 (38.6%)		5288 (38.5%)	250 (40.9%)		543 (45.7%)		451 (43.9%)	92 (56.8%)	
Current smokers	1841 (12.8%)		1647 (12.0%)	194 (31.8%)		378 (31.8%)		329 (32.0%)	49 (30.2%)	

Physical activity score	9.0 (5.0, 15.0)		9.0 (5.0, 15.0)	7.0 (3.0, 12.0)	<0.001	7.0 (3.0, 11.0)		7.0 (3.0, 12.0)	5.5 (2.0, 9.0)	<0.001
BMI, kg/m^2	28.1 (25.0, 32.3)		28.1 (25.0, 32.2)	28.3 (24.2, 32.8)	0.737	28.6 (24.4, 33.6)		28.7 (24.6, 33.7)	28.3 (23.6, 33.0)	0.288
HTN, n (%)	8376 (58.2%)		7992 (58.0%)	384 (62.7%)	0.019	831 (69.8%)		716 (69.6%)	115 (71.0%)	0.717
DM, n (%)	3597 (25.0%)		3428 (24.9%)	169 (27.6%)	0.124	378 (31.7%)		323 (31.4%)	55 (34.0%)	0.515
Cancer, n (%)	1848 (12.8%)		1747 (12.7%)	101 (16.5%)	0.006	221 (18.6%)		186 (18.1%)	35 (21.6%)	0.283
Heart diseases, n (%)	2811 (19.5%)		2634 (19.1%)	177 (28.9%)	<0.001	447 (37.5%)		365 (35.5%)	82 (50.6%)	<0.001
Stroke, n (%)	995 (6.9%)		929 (6.7%)	66 (10.8%)	<0.001	177 (14.9%)		145 (14.1%)	32 (19.8%)	0.06
Nervous and psychiatric problems, n (%)	2587 (18.0%)		2403 (17.4%)	184 (30.1%)	<0.001	473 (39.7%)		413 (40.1%)	60 (37.0%)	0.454
Sleep quality score	2.0 (1.0, 4.0)	0.8%	2.0 (1.0, 4.0)	3.0 (2.0, 5.0)	<0.001	4.0 (2.0, 5.0)	1.1%	4.0 (2.0, 5.0)	4.0 (2.0, 6.0)	0.046
STOP-Bang score	3.0 (2.0, 4.0)		3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	<0.001	3.0 (3.0, 5.0)		3.0 (3.0, 5.0)	4.0 (3.0, 5.0)	0.576
High OSA risk, n (%)	5364 (37.3%)		5089 (36.9%)	275 (44.9%)	<0.001	572 (48.0%)		490 (47.6%)	82 (50.6%)	0.478

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HTN: hypertension; OSA, obstructive sleep apnea.

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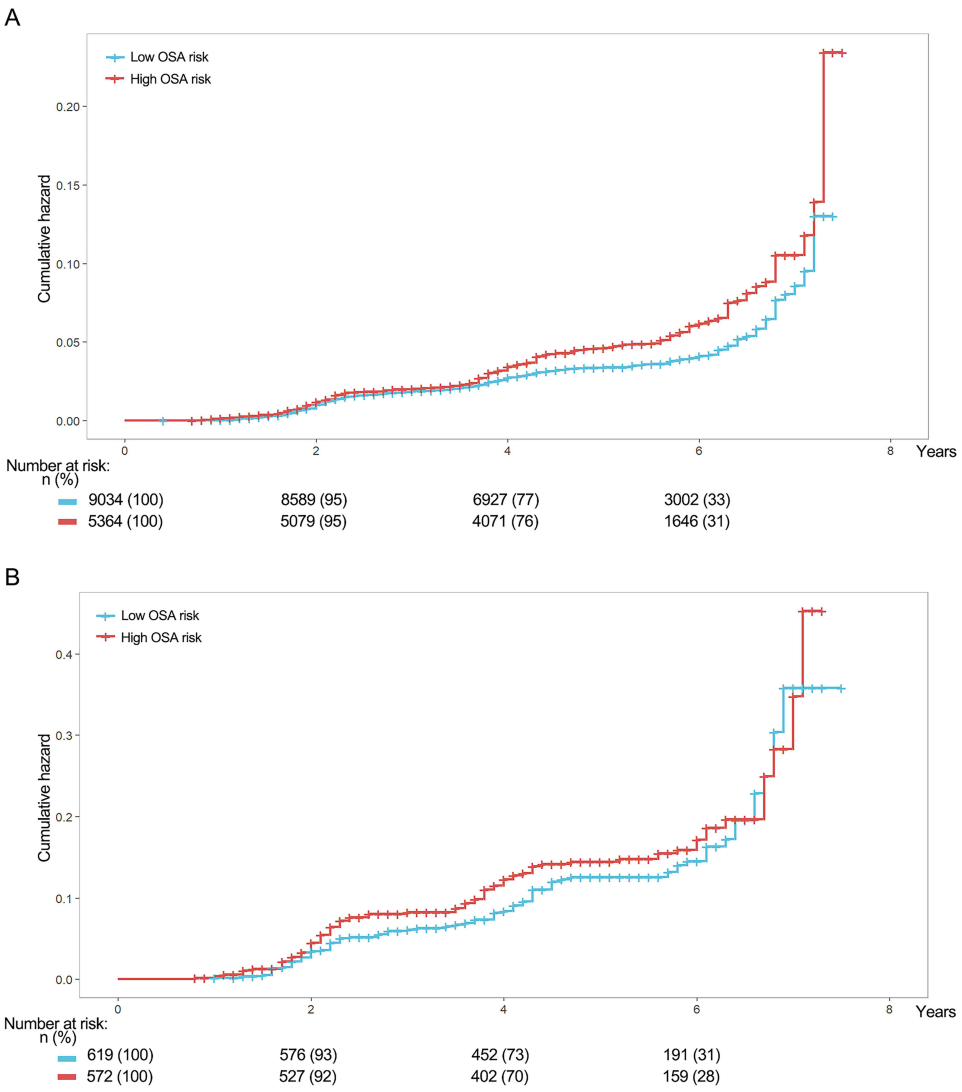

Figure 2 Cumulative hazard event curves for baseline OSA risk and COPD incidence (**A**) and progression to oxygen therapy (**B**).
Abbreviations: COPD, chronic obstructive pulmonary disease; HR, hazard ratio; OSA, obstructive sleep apnea.

The results of the sex-stratified analysis are presented in Table 4, indicating different effects of changes in OSA risk across different sexes. In the female group, the relationship between changes in OSA risk and COPD incidence remained significant. However, in the male group, changes in OSA risk did not significantly influence COPD incidence, regardless of baseline OSA risk.

Table 3 Association of OSA Risk with the Risks of Incident COPD

	STOP-Bang Indicators	Unadjusted		Adjusted 1[a]		Adjusted 2[b]	
		HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
All (n=14398)	High OSA risk vs low OSA risk[c]	1.396 (1.190, 1.637)	<0.001	1.390 (1.171, 1.651)	<0.001	1.255 (1.054, 1.496)	0.011
	STOP-Bang score	1.177 (1.107, 1.251)	<0.001	1.176 (1.098, 1.260)	<0.001	1.110 (1.034, 1.191)	0.004
Male (n=6201)	High OSA risk vs low OSA risk[c]	1.431 (1.106, 1.851)	0.006	1.478 (1.126, 1.940)	0.005	1.328 (1.004, 1.757)	0.047
	STOP-Bang score	1.241 (1.116, 1.382)	<0.001	1.282 (1.136, 1.446)	<0.001	1.199 (1.058, 1.359)	0.005

(*Continued*)

Table 3 (Continued).

	STOP-Bang Indicators	Unadjusted		Adjusted 1[a]		Adjusted 2[b]	
		HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Female (n=8197)	High OSA risk vs low OSA risk[c]	1.515 (1.217, 1.886)	<0.001	1.456 (1.140, 1.860)	0.003	1.274 (0.993, 1.635)	0.057
	STOP-Bang score	1.211 (1.116, 1.313)	<0.001	1.189 (1.079, 1.310)	<0.001	1.101 (0.996, 1.217)	0.059

Notes: [a]Adjusted for age, race, education, marital status, smoking status, drinking status, physical activity score and BMI; [b]Adjusted for age, race, education, marital status, smoking status, drinking status, physical activity score, BMI, HTN, DM, cancer, heart diseases, stroke, nervous and psychiatric problems, and sleep quality score; [c]Reference group.
Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; OSA, obstructive sleep apnea.

To evaluate whether changes in OSA risk also impact COPD progression, we further analyzed 824 participants. Among the 443 participants initially at low OSA risk, 94 (21.2%) progressed to high risk, while 349 (78.8%) remained stable Of the 381 participants with high baseline OSA risk, 285 (74.8%) remained at high risk, and 96 (25.2%) shifted to low risk. The cumulative risk of COPD progression to oxygen therapy across different OSA risk change groups is shown

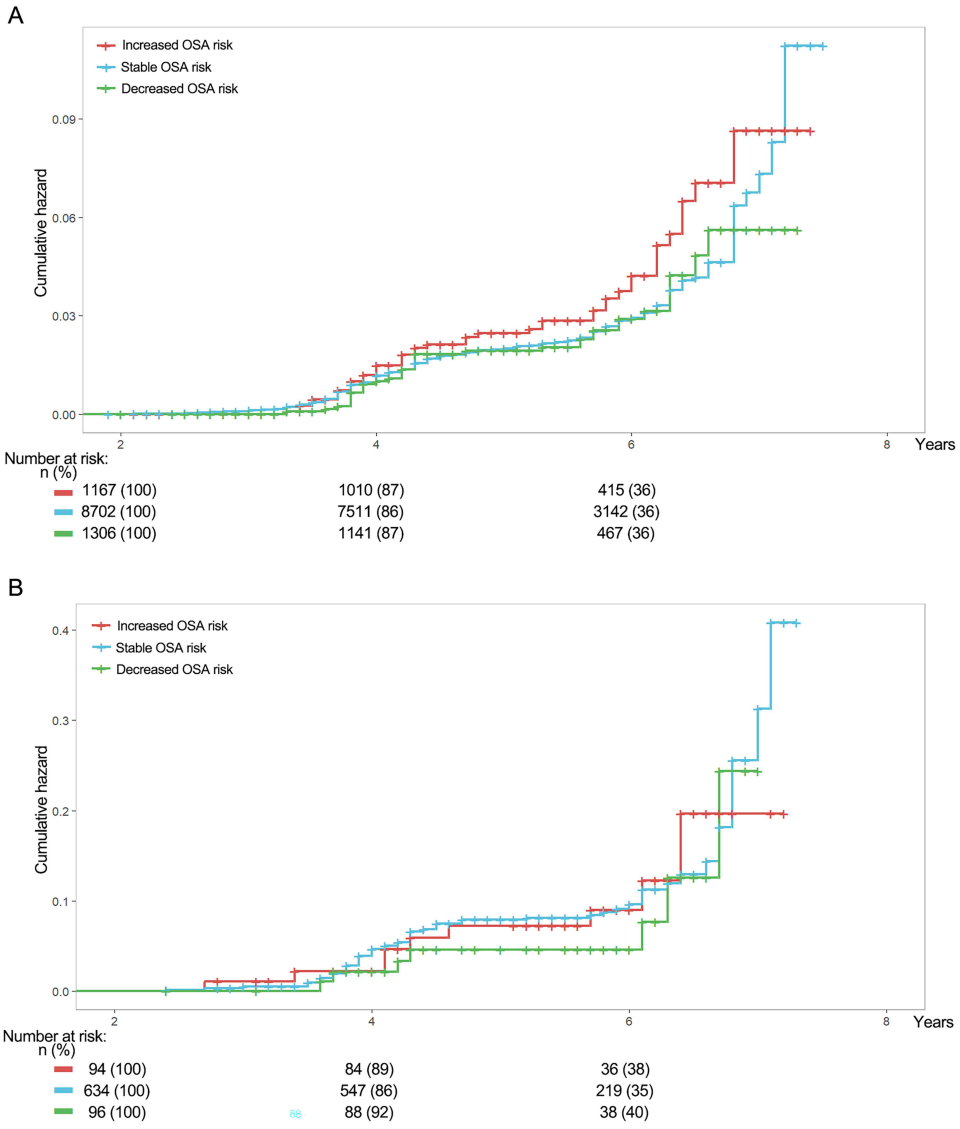

Figure 3 Cumulative hazard event curves for changes of OSA risk and COPD incidence (**A**) and progression to oxygen therapy (**B**).
Abbreviations: COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea.

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Table 4 Association of the Change of OSA Risk with the Risks of Incident COPD

	Subgroups of Baseline OSA risk	Reference Groups	Unadjusted		Adjusted 1[a]		Adjusted 2[b]	
			HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
All (n=11177)	Low OSA risk	Stable vs increased OSA risk[c]	0.542 (0.382, 0.769)	0.001	0.558 (0.388, 0.802)	0.002	0.603 (0.418, 0.871)	0.007
	High OSA risk	Decreased vs Stable OSA risk[c]	0.624 (0.428, 0.909)	0.014	0.569 (0.385, 0.843)	0.005	0.586 (0.396, 0.869)	0.008
Male (n=4851)	Low OSA risk	Stable vs increased OSA risk[c]	0.627 (0.353, 1.115)	0.112	0.580 (0.322, 1.043)	0.069	0.619 (0.341, 1.123)	0.114
	High OSA risk	Decreased vs Stable OSA risk[c]	0.843 (0.514, 1.384)	0.499	0.815 (0.486, 1.366)	0.437	0.820 (0.487, 1.381)	0.456
Female (n=6326)	Low OSA risk	Stable vs increased OSA risk[c]	0.463 (0.294, 0.729)	0.001	0.529 (0.326, 0.856)	0.01	0.589 (0.360, 0.963)	0.035
	High OSA risk	Decreased vs Stable OSA risk[c]	0.401 (0.225, 0.715)	0.002	0.360 (0.195, 0.666)	0.001	0.357 (0.191, 0.667)	0.001

Notes: [a]Adjusted for age, race, education, marital status, smoking status, drinking status, physical activity score and BMI; [b]Adjusted for age, race, education, marital status, smoking status, drinking status, physical activity score, BMI, HTN, DM, cancer, heart diseases, stroke, nervous and psychiatric problems, and sleep quality score; [c]Reference group.

Abbreviations: C I, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; OSA, obstructive sleep apnea.

in Figure 3B. Similar to the effects of baseline OSA risk, changes in OSA risk did not significantly influence COPD progression (Supplementary Table S3).

Sensitivity Analyses

We used multiple imputation to address missing data and conducted Cox regression analyses using the imputed datasets to validate the robustness of our findings. The results of the Cox regression analysis remained consistent and robust in the imputed cohorts, as shown in Supplementary Tables S4-S7.

Discussion

In this prospective cohort study, we analyzed the relationship between baseline OSA risk and changes in OSA risk with the incidence and progression of COPD. After adjusting for confounding factors, individuals with high baseline OSA risk were found to have a higher future risk of developing COPD compared to those with low OSA risk, although no significant association was found between high OSA risk and progression to oxygen therapy. This relationship was more influenced by baseline comorbidities in women. Additionally, a reduction in OSA risk was associated with a lower future risk of COPD, particularly in women, while the effect was not significant in men. Changes in OSA risk did not significantly impact the progression of COPD to oxygen therapy.

Our study identified a strong association between high OSA risk, changes in OSA risk, and an increased risk of developing COPD. While previous research has mainly focused on the OS, there has been limited exploration of OSA's impact on the incidence of COPD. Most previous studies have examined how OSA influences acute exacerbations of COPD. For example, Donovan et al found that patients with COPD who had a modified STOP-Bang score of ≥3 had worse long-term outcomes, including a higher adjusted risk of death or first hospitalization (HR: 1.61, 95% CI: 1.01–2.58) and more frequent COPD exacerbations (adjusted incidence rate ratio: 1.78, 95% CI 1.10–2.89).[14] Additionally, a 9-year longitudinal study reported that 61.4% of patients with OS had at least one hospitalization due to acute exacerbation of COPD, compared to 39.5% in the COPD group.[15] Beyond cohort studies, Wang et al used Mendelian randomization to explore the relationship between COPD and various comorbidities, finding that increased genetic risk for sleep apnea was associated with a higher genetic risk for COPD (odd ratio: 1.209, 95% CI = 1.087–1.345, $p < 0.001$).[27] This is consistent with our findings. Moreover, genetic predispositions to conditions like heart failure, sleep apnea symptoms, depression, and obesity may also heighten susceptibility to COPD.[27] Our analysis accounted for these confounding factors, further supporting the robustness of our results.

Moreover, our study revealed that the impact of OSA on COPD risk varies by sex. For baseline OSA risk, the association with COPD incidence was less influenced by comorbidities in men. Whereas in women, comorbidities had a more significant confounding effect. However, when focusing on changes in OSA risk, this association was significant

only in women, with men showing minimal response to such changes. Both diseases exhibit distinct sex characteristics. COPD was traditionally viewed as a disease predominantly affecting older men, but in the past 20 years, the prevalence and hospitalization rates in women have increased.[28] Studies have also shown that women are more adversely affected by the smoke exposure.[28] Women tend to develop COPD earlier and experience more severe respiratory symptoms.[29] In adults with OSA, men generally have a higher prevalence and greater severity of the condition, potentially due to anatomical differences in the upper airway and the influence of sex hormones on airway muscle tone and physiological responses to hypoxia and hypercapnia.[30] While the observed sex differences cannot yet be fully explained, these findings highlight the distinct ways in which diseases manifest in men and women, emphasizing the importance of sex-specific management and customized treatment strategies.

Mechanistically, the relationship between OSA and COPD is inherently complex.[13] From the perspective of COPD's impact on OSA, different clinical phenotypes of COPD can influence OSA in various ways. For example, Biselli et al found that patients with an emphysema phenotype and low BMI had a negative critical closing pressure of the upper airway during sleep, making OSA less likely.[31] In contrast, patients with chronic bronchitis and higher BMI are more prone to fluid retention, which can lead to upper airway obstruction during supine sleep, increasing the risk of OSA.[32,33] Additionally, smoking, a risk factor for COPD, can cause upper airway inflammation, further contributing to OSA.[34] From the perspective of OSA's impact on COPD, chronic intermittent hypoxia can trigger inflammation and oxidative stress, leading to ventilation-perfusion mismatches and increased respiratory effort.[35] Animal studies have confirmed that intermittent hypoxia can induce lung injury.[36] Lu et al also found that changes in the lung microbiome in patients with OSA increase their susceptibility to airway infections,[37] a factor closely linked to COPD and its acute exacerbations. From a shared risk factor perspective, OSA and COPD are strongly interconnected. Both conditions are influenced by common factors such as aging, smoking, obesity, oxidative stress, and inflammation.[38–42]

Our study has significant clinical and public health implications. The findings highlight the importance of incorporating OSA risk assessment into routine COPD management, particularly in older adults. Furthermore, these results suggest the need for greater awareness among clinicians regarding the interplay between OSA and COPD, which could enhance patient outcomes through integrated management strategies. From a health management perspective, assessing OSA risk in healthy middle-aged and older adults is beneficial for early identification of high-risk individuals. By implementing preventive measures and reducing OSA risk, the risk of COPD can be lowered. Since OSA risk is reversible, adopting comprehensive health strategies to improve sleep quality and reduce high OSA risk is of significant public health importance. These proactive steps can contribute to better long-term respiratory health outcomes and reduce the overall effect of COPD.

This study has several strengths. To our knowledge, it is the first to explore the relationship between changes in OSA risk and the incidence and progression of COPD. The research benefits from a large, nationally representative prospective cohort, ensuring a robust and well-structured design with a substantial sample size. Additionally, sensitivity analyses were performed to confirm the reliability of the findings. These factors together emphasize the study's robustness and the reliability of its findings.

This study has some limitations. First, similar to other cohort studies, COPD was identified based on self-reported physician diagnoses, which could introduce bias. However, a study by Graham Barr et al in 2002 demonstrated that COPD can be effectively studied in large populations through questionnaires.[43] Additionally, we used oxygen therapy as an indicator of COPD progression. Although this may not fully capture the complexity of the disease, it has been used in previous studies.[44] Future research could explore whether OSA impacts the need for oxygen therapy in other populations, should relevant data become available. Second, OSA risk was assessed using the STOP-BANG questionnaire without confirmatory polysomnography, which may have affected diagnostic accuracy. Moreover, COPD itself may influence the risk of OSA, potentially confounding the relationship between these two conditions and warranting further consideration.[45,46] Third, the study examined OSA risk changes between 2016 and 2020. The suitability of this time interval for assessing OSA risk requires further validation. The 2020 survey was chosen due to its minimal missing data, but as follow-up continues, different time points might be explored in future sensitivity analyses. Fourth, the current follow-up period may be relatively short for chronic diseases like OSA and COPD. Ongoing research with longer follow-up periods is necessary. Lastly, although this study is based on a prospective cohort and

accounts for relevant confounding factors, residual confounding is unavoidable. The follow-up period may be insufficient to establish causality between OSA and COPD. Future basic research is needed to address this limitation.

Conclusion

A high baseline OSA risk is associated with a greater risk of developing COPD. Additionally, changes in OSA risk are also correlated with COPD development. Individuals with increasing OSA risk are more prone to developing COPD, while those whose risk decreases have a lower chance. These associations show sex-specific variations. However, neither baseline OSA risk nor its changes in OSA risk appear to significantly influence the progression of COPD to the stage requiring oxygen therapy. This highlights the potential of managing OSA as a strategy to reduce COPD incidence. Future research should aim to uncover the mechanisms linking OSA and COPD and explore interventions targeting OSA to mitigate the risk of COPD.

Data Sharing Statement

The data used in this study were obtained from the the Health and Retirement Study, which is a publicly available dataset. The specific dataset can be accessed through the following link: https://hrs.isr.umich.edu/.

Ethics Approval and Informed Consent

The Health and Retirement Study was approved by the Ethics Review Committee of the University of Michigan. Informed consent was obtained from each subject in the cohort. This study was confirmed to be exempt from ethical approval by the Ethics Committee of Peking Union Medical College Hospital. The exemption is in accordance with Item 1 and Item 2 of Article 32 of the *Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects*, issued on February 18, 2023, China, as this study is based on publicly available and de-identified data.

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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.

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Disclosure

The authors report no conflicts of interest in this work.

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