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Authors

Channick, Jessica E
Jackson, Nicholas J
Zeidler, Michelle R
[et al.](#)

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Effects of Obstructive Sleep Apnea and Obesity on 30-Day Readmissions in Patients with Chronic Obstructive Pulmonary Disease

A Cross-Sectional Mediation Analysis

Jessica E. Channick¹, Nicholas J. Jackson², Michelle R. Zeidler^{1,3}, and Russell G. Buhr^{1,3,4}

¹Division of Pulmonary, Critical Care and Sleep Medicine, David Geffen School of Medicine, and ²Department of Medicine Statistics Core, University of California, Los Angeles, Los Angeles, California; and ³Department of Medicine and ⁴Center for the Study of Healthcare Innovation, Implementation, and Policy, Health Services Research & Development, Greater Los Angeles Veterans Affairs Healthcare System, Los Angeles, California

ORCID IDs: 0000-0002-9719-474X (J.E.C.); 0000-0002-9515-5050 (N.J.J.); 0000-0001-6159-7435 (R.G.B.).

Abstract

Rationale: Comorbidity is a significant driver of health status and healthcare utilization in chronic obstructive pulmonary disease (COPD). Obstructive sleep apnea (OSA) portends poorer outcomes, whereas obesity is protective.

Objectives: We describe the prevalence and influence of these comorbidities on COPD readmissions.

Methods: We collated discharge records for COPD exacerbations spanning 2010–2016 from the Nationwide Readmissions Database using Medicare's Hospital Readmissions Reduction Program criteria, with OSA–COPD overlap identified by concomitant diagnosis code for OSA. We used mixed-effects logistic regression to predict readmission odds. A cross-sectional mediation analysis was performed to evaluate the extent that OSA attenuated obesity's impact on readmission.

Results: Of 1,662,983 qualifying COPD discharges, 19.1% carried a diagnosis of obesity and 12.9% had OSA, with both diagnoses present in 7.8%. In unadjusted analyses, obesity

(odds ratio [OR], 1.04; 95% confidence interval [CI], 1.03–1.05; $P < 0.001$) and OSA (OR, 1.11; 95% CI, 1.10–1.13; $P < 0.001$) had increased readmission odds. In models adjusted for patient and hospital characteristics, 71% of readmission risk from obesity was attributable to OSA. When additionally adjusted for Charlson Comorbidity Index, we found that OSA remained a significant risk factor (OR, 1.05; 95% CI, 1.03–1.06; $P < 0.001$), whereas obesity remained protective (OR, 0.96; 95% CI, 0.94–0.97; $P < 0.001$) even after accounting for OSA.

Conclusions: A significant proportion of patients with COPD suffer comorbid OSA and obesity with resultant readmission risk. Interestingly, obesity's protective effect attenuates readmission odds from OSA. Taken together, OSA and aggregate comorbidity influence readmissions in patients with COPD. Testing for and treating OSA–COPD overlap may provide a mechanism to reduce avoidable readmissions.

Keywords: COPD; obesity; comorbidity; readmission; multilevel modeling

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Correspondence and requests for reprints should be addressed to Jessica E. Channick, M.D., Department of Medicine, Division of Pulmonary and Critical Care, David Geffen School of Medicine at UCLA, 10833 Le Conte Avenue, Room 43-229 CHS, Los Angeles, CA 90095. E-mail: jchannick@mednet.ucla.edu.

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The prevalence of obstructive sleep apnea (OSA) among patients with moderate to severe chronic obstructive pulmonary disease (COPD) may be as high as 65% (1, 2). The true prevalence of OSA–COPD overlap syndrome may be even higher because traditional tools and surveys used to screen for OSA tend to focus on typical symptoms and may not capture the predominant presentations in patients with underlying lung disease (3). This presumed underdiagnosis is concerning given the notable increased morbidity and mortality in overlap syndrome compared with OSA or COPD alone (4–6). The diagnosis of OSA in patients hospitalized for COPD exacerbation has also been shown to be an independent risk factor for 30-day hospital readmission (7).

Treatment of overlap syndrome, specifically with positive-pressure ventilation, has been shown to improve sleep quality, hypoventilation, and survival (8). Continuous positive airway pressure usage in overlap syndrome is an independent predictor of improvement in COPD exacerbation frequency and all-cause mortality (9, 10). Unrecognized or untreated OSA has both short- and long-term negative influence on the frequency and time to readmission in the COPD population (11). These readmissions are not only due to exacerbations of pulmonary pathologies. Cardiovascular-related and all-cause readmissions are also increased in the overlap syndrome population (12).

Although obesity definitively increases the risk of developing OSA, the increased morbidity and mortality of overlap syndrome may not be equally attributable to elevated body mass index (BMI). Papachatzakis and colleagues showed that BMI in those with OSA compared with people with OSA alone was not significantly different, suggesting that the increased morbidity and mortality of overlap syndrome should be attributed to factors other than obesity (13). In fact, obesity is an independent protective factor in some chronic illnesses, including COPD (14). In COPD, the attenuative effects of obesity on mortality are seen more convincingly in more severe disease with worsened impairment in forced expiratory volume in 1 second (15). Although higher BMI may be associated with lower mortality, the effect on exacerbation events and readmission is not well established (16). One prospective trial demonstrated a significant benefit in

exacerbation frequency and time to subsequent exacerbation at 5 years in their COPD population, further suggesting the presence of a strong obesity paradox in this population (17).

Given the high burden of these pathologies and the different effects of obesity and OSA on outcomes in patients with COPD, we sought to explore the interrelationship between these three conditions. In this study, we use a nationally representative readmission database to elucidate the interaction between OSA and obesity and how this impacts the rate of readmission in patients with COPD after discharge from hospital after a COPD exacerbation.

The results of this study in abstract form were accepted to the 2020 American Thoracic Society International Conference, which was cancelled because of coronavirus disease (COVID-19). This study was reviewed by the UCLA Institutional Review Board (IRB #18-001208) and was waived from review owing to the use of publicly available, deidentified data.

Methods

Data Source and Definitions

Data were collated from the Nationwide Readmissions Database (NRD) (18), which is a national all-payer 100% sample of discharges from multiple states provided through the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project (19). We aggregated pooled data from 2010 through 2016. Index admissions were defined using criteria outlined by the Centers for Medicare and Medicaid Services' Hospital Readmissions Reduction Program (HRRP) (20, 21). It should be noted that the NRD's structure allows identification of an individual patient *within* years, but precludes identification of an individual patient *across* years, hence the pooled cross-sectional rather than truly longitudinal approach.

The obesity comorbidity category indicator from the Elixhauser Comorbidity Index (22, 23) was used to determine presence of obesity using diagnostic codes (see Table E1 in the online supplement) previously validated for this purpose. Comorbidity was further operationalized using the Charlson Comorbidity Index from aggregated *International Classification of Diseases* (ICD) codes (24, 25), chosen over Elixhauser for this

application given that obesity is subsumed within the Elixhauser index and would have increased collinearity (26). An indicator variable for OSA was coded using ICD codes (see Table E1). ICD codes for other forms of sleep apnea including central or unspecified were excluded to improve specificity. As previously described, a readmission was defined as return to any acute care hospital for any cause within 30 days of index discharge from a qualifying COPD stay, as defined in the HRRP (26, 27).

Statistical Analysis

Descriptive bivariate statistics were computed comparing groups of patients with COPD who were and were not readmitted. Chi-square tests were used for categorical variables, whereas Welch's *t* test for unequal variance was used for continuous variables. Sample weights provided with the NRD (19) were used in calculation of frequencies to approximate a nationally representative sample. A series of mixed-effects logistic regression models were fit to estimate the main effect of the OSA on readmission odds, adjusted for other key patient and care characteristics, with a random intercept for hospital given the hierarchical nature of the data. As noted above, subjects in the database are identifiable only within each calendar year; therefore, we used each discharge event as the unit of analysis rather than specifying within-patient random effects for a repeated measures analysis. In addition, we tabulated comorbidities for each hospitalization at the time of each discharge rather than cumulatively across the year to prevent issues with the time a diagnosis was elucidated within each year.

A cross-sectional mediation analysis was performed to evaluate the degree of confounding effects of obesity accounted for by the presence of OSA. All tests of significance were two-tailed with a significance threshold of $P < 0.05$. A threshold of 15% missing data on any key variable was determined in advance to trigger multiple imputation, which was not reached for any variable of interest. All analyses were conducted in Stata version 15.1 (StataCorp).

Results

Sample Characteristics

The study population included 1,662,983 qualifying COPD index discharges (Table

Table 1. Pooled baseline characteristics of cohort, stratified by OSA and readmission status

	No OSA (N = 1,448,494)			OSA (N = 214,489)		
	Not Readmitted (n = 1,200,569)	Readmitted (n = 247,925)	Effect Size	Not Readmitted (n = 174,530)	Readmitted (n = 39,959)	Effect Size
Obesity diagnosis present, %	13.0	13.0	0.00	59.0	59.0	0.00
Age, yr, mean ± SD	68 ± 12	69 ± 12	0.08	64 ± 11	65 ± 11	0.05
Female sex, %	60.0	58.0	0.05	55.0	56.0	0.02
Payer, %						
Medicare	70.0	75.0	0.11	67.0	71.0	0.09
Medicaid	11.0	13.0	0.03	14.0	16.0	0.05
Private	12.0	8.1	0.13	14.0	10.0	0.14
Self-pay	3.5	2.1	0.09	2.2	1.2	0.08
Other	3.1	2.4	0.04	2.8	2.4	0.03
Discharge disposition, %						
Routine	69.0	60.0	0.18	68.0	58.0	0.21
Post-acute	13.0	16.0	0.11	11.0	16.0	0.12
Home health	0.7	0.8	0.01	0.7	0.8	0.01
Other	16.0	22.0	0.12	20.0	26.0	0.14
Length of stay, mean ± SD	4.4 ± 4.4	5.1 ± 5.0	0.15	5.1 ± 4.7	5.8 ± 5.6	0.13
Comorbidity indices, mean ± SD						
Charlson Index Score	2.1 ± 1.4	2.4 ± 1.6	0.21	2.4 ± 1.4	2.7 ± 1.5	0.19
Elixhauser Index Score	15.7 ± 14.4	19.8 ± 15.7	0.28	20.4 ± 15.8	24.9 ± 16.6	0.28
Care intensity, %						
Noninvasive ventilation	6.4	8.3	0.07	16.0	18.0	0.05
Mechanical ventilation	4.2	5.4	0.05	6.6	7.6	0.04
Tracheostomy placement	0.7	1.0	0.04	1.4	2.0	0.04
Cardiac arrest	0.2	0.3	0.01	0.3	0.3	0.01
CPR performed	0.1	0.2	0.01	0.2	0.2	0.01

Definition of abbreviations: CPR = cardiopulmonary resuscitation; OSA = obstructive sleep apnea; SD = standard deviation.

Effect sizes presented as Cohen's d for continuous variables or Cohen's h for categorical variables. Effect sizes of statistical significance ($P < 0.05$ using Welch's *t* test for continuous and chi-square tests for categorical variables) are bolded.

1). Of these encounters, 19.1% carried a diagnosis of obesity and 12.9% carried a diagnosis of OSA. Both diagnoses were present in 7.8% of encounters. The overall readmission rate for the study population was 17.3% within 30 days of index discharge.

Among the COPD cohort, obesity was more common in those with a concomitant diagnosis of OSA compared with those

without OSA. There was no significant difference in readmission frequency related to obesity in either the OSA (Welch's *t* test $P = 0.276$) or non-OSA ($P = 0.810$) strata (Table 1). Those with OSA-COPD overlap syndrome were younger and more frequently male. Medicare and Medicaid insurance status were more frequently associated with readmission regardless of presence of OSA. Length of stay was greater for those with

OSA than those without. Longer lengths of stay were associated with increased readmission frequency among both strata (Table 1). Aggregate comorbidity was significantly greater among the readmitted patients than those who were not readmitted. Comorbidity scores were also higher among those with OSA than those without OSA (Charlson 2.5 vs. 2.1, $P < 0.001$; Elixhauser 21.3 vs. 16.6, $P < 0.001$), despite OSA not

Table 2. Mediation of obesity effect on readmissions by OSA

	Obesity -> OSA (Path A) OR (95% CI)	OSA -> Readmission (Path B) OR (95% CI)	Obesity -> Readmission (Path C) OR (95% CI)	Obesity -> Readmission (Adjusting for OSA - Path C') OR (95% CI)	% Effect Mediated	
					% (95% CI)	P Value
Model 1	9.70 (9.54–9.86)	1.11 (1.10–1.13)	1.04 (1.03–1.05)	1.00 (0.99–1.01)	97.2 (83–100)	<0.01
Model 2	8.73 (8.59–8.88)	1.07 (1.06–1.09)	1.01 (1.00–1.03)	0.99 (0.98–1.00)	71.0 (55–87)	<0.01
Model 3	8.43 (8.29–8.57)	1.05 (1.03–1.06)	0.97 (0.96–0.98)	0.96 (0.94–0.97)	—	—

Definition of abbreviations: CI = confidence interval; OR = odds ratio; OSA = obstructive sleep apnea.

Model 1 unadjusted.

Model 2 adjusted for age, sex, income, time period (year and quarter), insurer, discharge disposition, hospital length of stay, care intensity (noninvasive ventilation, mechanical ventilation, cardiopulmonary resuscitation, cardiac arrest, and tracheostomy), hospital characteristics (ownership type, teaching hospital status, location, size, annual number of discharges, and proportion Medicaid patients).

Model 3 adjusted for model 2 covariates as well as Charlson Comorbidity Index.

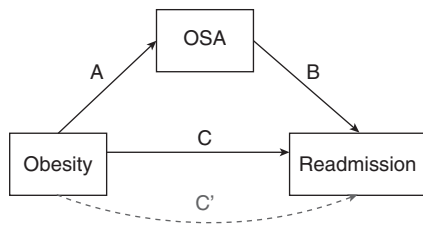


Figure 1. Mediation pathway diagram. Pathway A corresponds to the risk obesity exerts on the diagnosis of obstructive sleep apnea (OSA). Pathway B corresponds to the risk OSA exerts upon readmission odds. Pathway C corresponds to the total risk obesity exerts upon readmission risk without accounting for OSA. Pathway C' corresponds to the direct risk obesity exerts upon readmission when accounting for OSA. $C = C' + A \times B$; total effect = direct + indirect.

being included as a comorbidity domain in either comorbidity scoring system.

Cross-Sectional Mediation Analysis

The pathways we sought to better characterize are detailed in Figure 1. Pathway A represents obesity’s effect on having a diagnosis of OSA. Although not the primary finding of interest in our analyses, we have represented this pathway in our tables and diagrams for clarity and for comparison of effect sizes. Pathways B and C represent how having a diagnosis of OSA or obesity, respectively, affect the odds of readmission. The difference between pathways B and C (identified as pathway C’) account for the independent effect of obesity on readmission odds once accounting for OSA.

The results of the mediation analysis are detailed in Table 2. Concordant with existing

literature, there was a strong association with obesity and OSA (Table 2, column 1), corresponding to pathway A in our mediation diagram. Even after controlling for comorbidity and other factors, those with obesity had 8.4 times the odds of being diagnosed with OSA (odds ratio, 8.43; 95% confidence interval, 8.29–8.57; $P < 0.001$). We also found that there was a significant, independent risk for readmission from carrying a diagnosis of OSA, which persisted in our fully adjusted model, with 5% greater odds of readmission (Table 2, column 2, which corresponds with Figure 1, pathway B). On the contrary, obesity was associated with increased readmission odds in models adjusting for demographic, care intensity, and hospital characteristics, but once adjusting for aggregate comorbidity in our models, we observed a sign change to a protective effect, with 3% lower readmission odds than among those who were not obese (Table 2 and Figure 1, pathway C).

Finally, we fit a model to determine the net effect of obesity on readmission once adjusted for the deleterious effects of OSA (Table 2, column 4 and Figure 1, pathway C’). Adjusting for OSA fully attenuated the increased odds of readmission related to obesity in all of our models. We then calculated the degree that readmission odds of obesity were mediated by the presence of obstructed sleep apnea (Table 2, column 5). In the unadjusted models, when accounting for the effect of OSA, the association of obesity with readmission was reduced by 97.2%, suggesting the majority of the deleterious effects of obesity seen in model 1 are accounted for by the effects of OSA in the

obese population. This confounding effect is also demonstrated in model 2, which accounts for metrics of care intensity and hospital characteristics. Once controlling for OSA in model 2, the obesity association is attenuated and nonsignificant. The indirect effect was significant for all of these showing >70% of the effect of obesity on readmission being confounded by OSA.

Additional Analyses for Assessing the Risk of Obesity and OSA on Readmission

Stratified analyses provide an even stronger control for potential confounding and can help understand how both obesity and OSA contribute to readmission risk when examined in homogeneous risk groups. These analyses assess readmission risk when stratified by the comorbidity of interest. In Table 3, the presence of OSA is shown to increase the odds of readmission independent of concurrent obesity. Although this effect is somewhat reduced when adjusted for comorbidity and other patient and hospitalization factors, a diagnosis of OSA carried significantly increased odds of readmission, with a larger effect within obese patients.

We also evaluated the readmission odds based on a diagnosis of obesity, stratified by presence or absence of OSA (Table 4). In this analysis, we found that there was no significant increase in readmission risk with obesity even in presence of OSA, and once adjusting for comorbidity and other patient and hospital characteristics, a significant protective effect was observed.

Discussion

In this study of the Nationwide Readmissions Database, we describe how obesity and OSA contribute the risk of 30-day readmission in patients with an index hospitalization for COPD exacerbation.

Readmission Risk Assessment

In the unadjusted model, OSA and obesity appeared to be independent risk factors for readmission; however, as the model was adjusted for more patient-specific factors, we found that obesity alone decreased the odds of readmission. This suggests that OSA, in addition to higher comorbidity burden, confounds the previously seen increased obesity-readmission risk. In our mediation analysis, further corroborated in our

Table 3. OSA on readmission risk stratified by obesity status

	Not Obese OSA -> Readmission	Obese* OSA -> Readmission
Model 1	1.11 (1.08–1.13)	1.12 (1.10–1.15)
Model 2	1.08 (1.05–1.10)	1.08 (1.05–1.10)
Model 3	1.04 (1.02–1.06)	1.06 (1.04–1.08)

Definition of abbreviations: CI = confidence interval; OR = odds ratio; OSA = obstructive sleep apnea.

Data are shown as OR (95% CI).

Model 1 unadjusted.

Model 2 adjusted for age, sex, income, time period (year and quarter), insurer, discharge disposition, hospital length of stay, care intensity (Non-invasive ventilation, mechanical ventilation, cardiopulmonary resuscitation, cardiac arrest, and tracheostomy), hospital characteristics (ownership type, teaching hospital status, location, size, annual number of discharges, and proportion Medicaid patients).

Model 3 adjusted for model 2 covariates as well as Charlson Comorbidity Index.

*Obesity as defined by Elixhauser Comorbidity Index includes *International Classification of Diseases* (ICD) code for body mass index >30.

Table 4. Obesity on readmission risk stratified by OSA status

	No OSA Obesity -> Readmission	OSA Obesity -> Readmission
Model 1	1.00 (0.98–1.01)	1.01 (0.98–1.04)
Model 2	1.00 (0.98–1.01)	0.97 (0.94–1.00)
Model 3	0.96 (0.94–0.97)	0.95 (0.92–0.98)

Definition of abbreviation: OSA = obstructive sleep apnea.

Model 1 unadjusted.

Model 2 adjusted for age, sex, income, time period (year and quarter), insurer, discharge disposition, hospital length of stay, care intensity (Non-invasive ventilation, mechanical ventilation, cardiopulmonary resuscitation, cardiac arrest, and tracheostomy), hospital characteristics (ownership type, teaching hospital status, location, size, annual number of discharges, and proportion Medicaid patients).

Model 3 adjusted for model 2 covariates as well as Charlson Comorbidity Index.

stratified regression models (Tables 2 and 3), OSA is a persistent and independent risk factor for 30-day readmission even when patient and hospital characteristics are accounted for. These findings support our hypothesis that OSA increases odds of readmission among patients with COPD, whether obese or nonobese (Table 3). Given these results, one may conclude that focusing on the diagnosis and treatment of OSA may have significant benefit for the COPD population regarding readmission risk. Prior analysis of this cohort shows that 55% of the 30-day readmissions were driven by non-COPD diagnoses, which further emphasizes that a focus on diagnosis and treatment of concurrent comorbidity is crucial to reducing readmission in these patients (28).

Potential Protective Effects of Obesity

Although obesity is definitively a risk factor for worsened morbidity and mortality in the general population, there is strong evidence to suggest obesity is protective in patients with COPD for both all-cause mortality and exacerbation frequency (29, 30). There continues to be conflicting evidence as to whether this paradoxical benefit is dose-dependent versus a U-shaped distribution (17, 31). Although the true etiology of this benefit is unknown, hypotheses include the possibility of overweight and obese patients having increased muscle mass in addition to adiposity, neurohormonal effects of adipose tissue, and possible extra treatment in these patients if they are perceived by providers to have more comorbidities when admitted to the hospital (30). One study suggests the “pink puffer” phenotype of patients with

COPD tends to have more emphysematous disease, which has been previously shown to have higher associated mortality, in addition to lower BMI, when compared with the “blue bloaters,” and the increased mortality in lower BMI may be more representative of increased emphysematous destruction (15).

Previous literature has shown this paradoxical effect for mortality and exacerbation frequency, and our study showed a similar protective effect of obesity related to risk of readmission within 30 days of hospitalization for COPD exacerbation. When analyzing patients with OSA and obesity in our mediation analysis (Table 2), it appears that the paradoxical effect of obesity attenuates the risk of OSA regarding readmission. The findings of our stratified model (Table 4) further support that obesity confers a mild protective benefit against readmission, regardless of the presence of OSA. This suggests that the protective effect of obesity may be significant enough to outweigh the deleterious effects of OSA in patients hospitalized for COPD exacerbation. Furthermore, these results also imply that the increased odds for readmission in patients with obesity seen in unadjusted models are powerfully influenced by concurrent OSA or overall comorbidity.

Prevalence

Based on the data obtained in this study, 13.1% of patients with COPD have a concurrent diagnosis of OSA based on ICD codes, although previous literature suggests that the true prevalence of overlap syndrome may be much higher (1). In our study population, the prevalence of obesity by ICD

codes was 19.1%, which was notably lower than the prevalence in the general population, which is estimated to be 42.4% (32). We found concurrent diagnosis of OSA and obesity in 7.8% of the study population. Previous studies show the prevalence of OSA among obese patients in the general population is up to 45% (33). Our analysis was in line with the prior understanding that obesity is a strong risk factor for comorbid OSA.

Given the nature of the NRD, variations in coding practices likely contribute to lower prevalence seen in our study; however, other factors may also be at play. The lower prevalence of obesity seen in this study when compared with general population may highlight the trend for patients with COPD, especially in later stages, to have lower BMI secondary to nutritional deficiencies and the metabolic effects of the chronic illness (31). This is important to consider when screening for concurrent OSA given high BMI is commonly used as an important risk factor for OSA. The lower prevalence of overlap syndrome in our study population could also reflect the underdiagnosis of OSA in the COPD population. Patients with COPD may not present with the traditional symptoms of OSA, or symptoms such as daytime sleepiness or disturbed sleep may be attributed to their underlying COPD and chronic hypercarbia without considering coexisting OSA. This is an important consideration when treating patients with COPD, as a high clinical suspicion should be used given the significant rate of overlap syndrome and the particular morbidity and mortality associated with not treating OSA on this population (9, 10).

Limitations

Given the nature of the data used for this study, limitations are inherent, including inconsistent coding of primary and secondary diagnoses, which may lead to the lower rates of obesity seen in our OSA cohort as compared with prior literature (34). In addition, the database uses diagnostic codes and does not indicate presence or absence of treatment for OSA or COPD. Given the significant benefit of treatment in both of these conditions, it would be particularly interesting to see how readmission would be affected by treatment adherence. Unfortunately, this database does not allow for this level of granularity. Furthermore, reliable severity

data of these pathologies is also unobtainable when analyzing administrative data. Parsing the severity of any disease is difficult in any administrative data sets, although the large population size helps to offset this limitation and allows us to assess aggregate effects and generate hypotheses for further primary data collection and future study.

Another limitation of this analysis was the pooled cross-sectional nature of the database making it impossible to account for multiple admission from the same patient across years. Although this constraint may introduce a small degree of autocorrelation, we believed this was sufficiently offset by the

large sample size and thus likely did not impact the analyses to a significant degree.

Of note, the Hospital Readmissions Reduction Program applies penalties without accounting for disease severity or treatment status, so analyzing readmissions from this broader perspective may provide more pointed insights on health system-level effects related to the HRRP; however, additional studies on individual patient-level outcomes related to the diagnosis and treatment of OSA-COPD overlap are clearly warranted. Moreover, the cross-sectional nature of the data precludes us from establishing the temporal precedence of our variables, thereby potentially weakening the case for mediation.

Conclusions

Our study highlights an important comorbid factor that may be influencing health-related outcomes among patients with COPD. This also offers not only a better understanding of risk factors for readmission but a potential intervention point for the diagnosis and treatment of OSA-COPD overlap with the goal of averting preventable readmissions. Further investigation with prospective analyses of how treatment of OSA affects other COPD parameters such as exacerbation frequency and quality of life will be useful to better understand the degree to which this risk factor is modifiable. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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