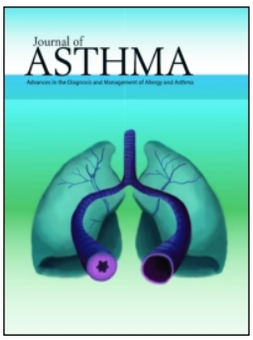

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Association of obstructive sleep apnea with all-cause readmissions after hospitalization for asthma exacerbation in adults aged 18–54 years: a population-based study, 2010–2013

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ABSTRACT

Objective: To investigate associations between obstructive sleep apnea (OSA) and readmission risk after hospitalization for asthma exacerbation.

Methods: We conducted a retrospective, population-based cohort study using State Inpatient Databases from seven U.S. states (Arkansas, California, Florida, Iowa, Nebraska, New York, and Utah) from 2010 to 2013. We identified all adults (aged 18–54 years) hospitalized for asthma exacerbation. The outcome measure was all-cause readmissions within one year after hospitalization for asthma exacerbation. To determine associations between OSA and readmission risk, we constructed negative binomial regression models estimating the incidence rate ratio (IRR) for readmissions and Cox proportional hazards models estimating hazard rate (HR) for the time-to-first readmission.

Results: Among 65,731 patients hospitalized for asthma exacerbation, 6,549 (10.0%) had OSA. Overall, OSA was associated with significantly higher incident rate of all cause readmission (1.36 vs. 0.85 readmissions per person-year; unadjusted IRR 1.60; 95%CI 1.54–1.66). Additionally, OSA was associated with higher incident rates of readmissions for five major diseases—asthma (IRR 1.21; 95%CI 1.15–1.27), COPD (IRR 2.03; 95%CI 1.88–2.19), respiratory failure (IRR 3.04; 95%CI 2.76–3.34), pneumonia (IRR 1.67; 95%CI 1.49–1.88), and congestive heart failure (IRR 3.78; 95%CI 3.36–4.24), compared to non-OSA. The Cox model demonstrated that patients with OSA had significantly higher rates for all-cause readmission compared to those without OSA (HR 1.56; 95% CI 1.50–1.62). These associations remained significant after adjustment for confounders.

Conclusions: The observed association of OSA with a higher risk of readmissions after hospitalization for asthma exacerbation underscores the importance of identifying coexistent OSA in this population and optimizing both OSA and asthma management.

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Introduction

Asthma and obstructive sleep apnea (OSA) are important chronic health problems (1–3). Asthma exacerbations impose considerable morbidity on patients and constitute a major healthcare burden in the U.S. (4–6). There are approximately 350,000 hospitalizations each year (7), and 14.5% of hospitalized patients were readmitted within 30 days after discharge (8). In parallel, OSA—another major chronic disease affecting 10–20% of population in developed nations (9)—is related to higher morbidity of cardiovascular and pulmonary diseases (10,11).

Emerging evidence suggests that asthma patients with OSA have worse asthma control compared to those without OSA (12–14). These cross-sectional studies with small sample sizes ($n < 500$) have shown that coexistent OSA is associated with a higher asthma severity (12), *Asthma Control Questionnaire* score (13), and frequency of self-reported exacerbations (14). Despite the apparent clinical and public health importance of these sleep and pulmonary disorders, to the best of our knowledge, no study has longitudinally examined the relation of OSA with readmissions after asthma exacerbation.

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To address this knowledge gap, by using state-level population-based data of patients with asthma, we investigated the association of coexistent OSA with the frequency of all-cause readmissions within a 365-day follow-up period after hospitalization for asthma exacerbation.

Methods

Study design and setting

We conducted a retrospective cohort study using state-level population-based data from the Healthcare Cost and Utilization Project (HCUP) State Inpatient Database (SID) of seven geographically dispersed U.S. states (Arkansas, California, Florida, Iowa, Nebraska, New York, and Utah) from 2010 to 2013. The HCUP is a family of healthcare databases developed through a federal-state-industry partnership and sponsored by the Agency for Healthcare Research and Quality. The HCUP is the largest collection of longitudinal hospital care data in the U.S., with all-payer, encounter-level information. The HCUP SIDs capture all hospitalizations, regardless of source or disposition, from acute care, nonfederal, general, and other specialty hospitals within the participating states. Additional details of the HCUP SIDs can be found elsewhere (15). These data of seven states from 2010 to 2013 were selected for their high data quality, geographic distribution, and mainly because their data included unique encrypted patient identifiers that enable longitudinal follow-up of specific individuals across years. The institutional review board of Massachusetts General Hospital approved this study.

Study sample

We identified all hospitalized adult patients (age 18–54 years) with a principal discharge diagnosis of asthma, as defined by the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnosis code of 493.xx (1,5,16,17). We excluded patients aged ≥55 years because of potential difficulty distinguishing between asthma and chronic obstructive pulmonary disease (COPD) (16,18,19). In the current analysis, we used only the first hospitalizations of the eligible patients during the study period. We also excluded patients who left the hospital against medical advice, those who died in-hospital at their index hospitalization, those who were transferred to another acute-care facility, and out-of-state residents.

Measurements

The SID contain information on patient characteristics, including demographics (age, sex, and race/ethnicity), primary insurance type (payer), quartiles for estimated household income, patient residence, *ICD-9-CM* diagnosis and procedure codes, patient comorbidities (29 Elixhauser comorbidity measures and arrhythmia), hospital course (e.g. hospital length-of-stay, in-hospital death), and disposition. The variables categories were sex (female and male), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanics, and others), primary health insurance (Medicare, Medicaid, private, and others), and patient residence (metropolitan and non-metropolitan).

Primary exposure

The primary exposure was coexistent OSA at the index hospitalization for asthma exacerbation, as defined by the *ICD-9-CM* diagnosis codes of 327.23, 780.53, and 780.57 in any diagnosis field, according to the prior literature (20–22).

Outcome measures

The primary outcome measure was readmission attributable to any cause within one year of discharge from the index hospitalization for asthma exacerbation. We investigated the frequency of readmissions within one year of discharge from the index hospitalization. Additionally, we also investigated the cause-specific readmissions for five major disease conditions (asthma, COPD, respiratory failure, pneumonia, and congestive heart failure [CHF]) (8) within one year of discharge from the index hospitalization. To make data presentation and interpretation more meaningful, we consolidated the principal discharge diagnoses (>14,000 *ICD-9-CM* diagnosis codes) into 285 mutually exclusive diagnostic categories by using the AHRQ-defined *Clinical Classifications Software* (*CCS*) (23). Then, as done previously (8), we identified cause-specific readmissions for asthma (*CCS* code 128), COPD (*CCS* code 127), respiratory failure (*CCS* code 131), pneumonia (*CCS* code 122), and CHF (*CCS* code 108).

Statistical analysis

First, we compared the patient characteristics between patients with and without OSA by using Wilcoxon rank sum test or chi-squared test, as appropriate. To examine the associations of OSA with the incidence rate of readmissions during the one-year follow-up period, we constructed unadjusted and adjusted negative binomial regression models that account for over-dispersion. The log of the follow-up period was used

as the offset to adjust for unequal follow-up periods (e.g. some patients had a shorter follow-up period from in-hospital death). In the models, we conducted sequential adjustments. First, we constructed an unadjusted model that included only OSA status as the independent variable (model 1). Second, we fit a multivariable model adjusting for age, sex, race/ethnicity, primary insurance, quartiles for median household income, patient residence (metropolitan vs. non-metropolitan), length-of-stay at the index hospitalization, and state of residence (model 2). Third, we fit a model adjusting for these covariates as well as 29 Elixhauser comorbidities and arrhythmia (model 3) (24,25) because the comorbidities were known to be associated with readmissions after hospitalization for asthma exacerbation (18,26). We also accounted for potential patient clustering within hospitals by using generalized estimating equations (GEE).

Furthermore, we performed a series of sensitivity analyses. First, to examine the association between OSA and the time-to-the first readmission, we fit Cox proportional hazards models with GEE accounting for patient clustering within hospitals. Patients who did not have an outcome were censored at 365 days from discharge. We fit three Cox proportional hazards models with sequential adjustment for potential confounders (models 1–3) similar to the primary analysis. The proportionality of hazards assumption was not violated per log-cumulative hazards plots. We also estimated survival function of two groups by the Kaplan-Meier method and compared the between-group survival estimates by log-rank test. Second, we repeated the analysis with stratifications by age category (18–39 years and 40–54 years), sex, and obesity (27,28) to investigate the interaction between OSA and these variables. Obesity was defined by the *ICD-9-CM* diagnosis codes of 278.00, 278.01, V85.3x, and V85.4x in any diagnosis field (29). Lastly, we repeated the analyses with stratification by state of residence to investigate the consistency of inferences across the seven study states. All analyses used STATA 14.0 (STATA Corp, College Station, TX). All p values were two-tailed, with $p < 0.05$ considered statistically significant. All analyses were performed as available data analyses because the missing rates of all variables were less than 5% (Supplemental Table 1).

Results

Patient characteristics

We identified 70,865 patients hospitalized for asthma exacerbation in the seven states. From these, we excluded 3,121 patients who left the hospital against medical advice, 104 patients who died in-hospital at their index hospitalization, 407 patients who were transferred to another acute-care facility, and 1,502 patients who were out-of-state residents. Finally, a total of 65,731 patients were eligible for the current analyses. Overall, the median age was 44 years (interquartile range [IQR], 33–50 years), 29.7% were male, and 42.6% were non-Hispanic white; 10.0% had OSA. Patient characteristics differed between OSA and non-OSA groups (Table 1). Patients with OSA were older (median [IQR], 47 [41–51] vs. 43 [32–49] years) and more likely to be male (33.3% vs. 29.3%) and non-Hispanic white (49.3% vs. 42.1%) compared to those without OSA. Additionally, patients with OSA were also more likely to have comorbidities, such as CHF (16.6% vs. 3.6%), diabetes (40.2% vs. 15.1%), hypertension (62.9% vs. 31.5%), obesity (72.5% vs. 19.4%), and longer hospital length-of-stay (proportion of patients hospitalized for ≥4 days, 47.0% vs. 29.3%) compared to those without OSA (all $p < 0.001$).

Incidence rates for readmission

The overall incidence rate of one-year all-cause readmission was 0.90 per person-year. Patients with OSA had a significantly higher incidence rate of readmission compared to those without OSA (incident rate 1.36 vs. 0.85 per person-year; unadjusted incidence rate ratio [IRR] 1.60; 95%CI 1.54–1.66; $p < 0.001$; Table 2 [model 1]). In a multivariable model (model 2) adjusting for socio-demographic factors, hospital length-of-stay, and state of residence attenuated the association (IRR 1.25; 95%CI 1.20–1.30; $p < 0.001$). With an additional adjustment for comorbidities (model 3), the association further attenuated (IRR 1.09; 95%CI 1.05–1.14; $p < 0.001$). In the sensitivity analyses stratified by age, sex, and obesity, the results were consistent across all strata. Specifically, patients aged <40 years had lower incidence rate (0.65/person-year) and higher IRR than patients aged ≥40 years (incidence rate: 1.06/person-year), whereas more similar incidence rates were observed between sex and obesity groups. Statistically significant effect modifications were observed in age, sex, and obesity (Table 2). Additionally, in the sensitivity analysis stratified by state of residence, there was no significant interaction ($P_{\text{interaction}}$=0.17; Supplemental Table 2).

Survival analysis for days to first readmission

Overall, 23,604 (35.9%) patients had at least one readmission within one year after their index

Table 1. Characteristics of patients hospitalized for asthma exacerbation by OSA status.

	All	OSA	Non-OSA	
Characteristics	$n = 65,731$	$n = 6,549$ (10.0%)	$n = 59,182$ (90.0%)	p Value
Age (year), median (IQR)	44 (33–50)	47 (41–51)	43 (32–49)	<0.001
Women	46,039 (70.3)	4,369 (66.7)	41,670 (70.7)	<0.001
Race/ethnicity				<0.001
Non-Hispanic white	26,938 (42.6)	2,979 (49.3)	23,959 (42.1)	
Non-Hispanic black	18,402 (29.1)	1,996 (30.0)	16,406 (28.8)	
Hispanic	13,609 (21.5)	1,092 (16.0)	12,517 (22.0)	
Others	4,354 (6.8)	280 (4.2)	4,074 (7.1)	
Primary health insurance				<0.001
Medicare	8,162 (12.4)	1,573 (24.0)	6,589 (11.1)	
Medicaid	23,027 (35.0)	2,165 (33.1)	20,862 (35.2)	
Private	20,214 (30.8)	1,964 (30.0)	18,250 (30.9)	
Others	845 (21.8)	845 (12.9)	13,451 (22.8)	
Median household income quartile				0.07
1 (lowest)	24,152 (38.9)	2443 (38.7)	21,709 (38.9)	
2	15,267 (24.6)	1,559 (24.7)	13,708 (24.6)	
3	13,541 (21.8)	1,438 (22.8)	12,103 (21.7)	
4 (highest)	9,192 (14.8)	878 (13.9)	8,314 (14.9)	
Patient residence				0.36
Metropolitan	61,252 (93.2)	6,086 (92.9)	55,166 (93.2)	
Non-metropolitan	4,479 (6.9)	463 (7.1)	4,016 (6.8)	
Selected comorbidities[a]				
CHF	3,243 (4.9)	1,087 (16.6)	2,156 (3.6)	<0.001
Depression	8,856 (13.5)	1,355 (20.7)	7,501 (12.7)	<0.001
Diabetes	11,557 (17.6)	2,632 (40.2)	8,925 (15.1)	<0.001
Hypertension	22,739 (34.6)	4,121 (62.9)	18,618 (31.5)	<0.001
Obesity	16,203 (24.7)	4,750 (72.5)	11,453 (19.4)	<0.001
Renal failure	1,495 (2.3)	374 (5.7)	1,121 (1.9)	<0.001
Hospital length-of-stay				<0.001
<2 days	15,633 (23.8)	842 (12.9)	14,791 (25.0)	
2–3 days	29,695 (45.2)	2,627 (40.1)	27,068 (45.7)	
≥4 days	20,403 (31.0)	3,080 (47.0)	17,323 (29.3)	
Hospital state				<0.001
Arkansas	2,084 (3.2)	191 (2.9)	1,893 (3.1)	
California	11,721 (17.8)	1,119 (17.1)	10,602 (17.9)	
Florida	22,386 (34.1)	2,614 (39.9)	19,772 (33.4)	
Iowa	1,432 (2.2)	200 (3.1)	1,232 (2.1)	
Nebraska	979 (1.5)	123 (1.9)	856 (1.4)	
New York	26,083 (39.7)	2,183 (33.3)	23,900 (40.4)	
Utah	1,046 (1.6)	119 (1.8)	927 (1.6)	

Notes: IQR, interquartile range.
Data are shown as *n* (%) unless otherwise specified.
[a]Selected from 29 Elixhauser comorbidity measures and arrhythmia.

hospitalization. The Kaplan-Meier survival estimates were significantly different in the risk of all-cause readmission between OSA and non-OSA groups ($p < 0.001$, Figure 1). In the unadjusted Cox proportional hazards model (model 1), patients with OSA had a significantly higher risk of readmission compared to those without OSA (hazard ratio [HR] 1.56; 95%CI 1.50–1.62; $p < 0.001$; Table 3). Similar to the primary analysis results, the difference attenuated but remained significant with the sequential adjustment (both $p < 0.001$). These significant associations also persisted with stratification by age, sex, and obesity, with a significant effect modification observed by age ($P_{\text{interaction}} < 0.05$, Table 3).

Cause-specific readmission

The most frequent cause for readmissions within one year after hospitalization was asthma, followed by COPD, respiratory failure, pneumonia, and CHF. Patients with OSA had a significantly higher incidence rate of readmission for asthma, with an IRR of 1.21 (95%CI 1.15–1.27; $p < 0.001$, Table 4). Likewise, patients with OSA had a significantly higher incidence rate of readmission for COPD (IRR 2.03; 95%CI 1.88–2.19; $p < 0.001$), respiratory failure (IRR 3.04; 95%CI 2.76–3.34; $p < 0.001$), pneumonia (IRR 1.67; 95%CI 1.49–1.88; $p < 0.001$), and CHF (IRR 3.78; 95%CI 3.36–4.24; $p < 0.001$). These significant associations persisted with sequential adjustment (all $p < 0.05$). We also investigated the cause of the first readmission. While there was no significant difference in the hazards for readmission by asthma between the OSA and non-OSA groups (HR 1.01; 95% CI 0.95–1.09; $p = 0.71$), patients with OSA had a significantly higher rate of readmission for COPD (HR 1.88; 95% CI 1.65–2.13; $p < 0.001$), respiratory failure (HR 2.65; 95% CI 2.27–3.09; $p < 0.001$), pneumonia (HR

Table 2. Associations of OSA with incident rate of all-cause readmissions during one-year period after index hospitalization for asthma exacerbation, overall and stratified by age category, sex, and obesity.

	Incidence rate (readmissions/person-year)			Unadjusted model (model 1)		Adjusted model (model 2)[a]		Adjusted model (model 3)[b]		
	All ($n = 65,731$)	OSA ($n = 6,549$)	Non-OSA ($n = 59,182$)	IRR (95% CI)	*p* Value	IRR (95% CI)	*p* Value	IRR (95% CI)	*p* Value	$P_{interaction}$
Overall ($n = 65,731$)	0.90	1.36	0.85	1.60 (1.54–1.66)	<0.001	1.25 (1.20–1.30)	<0.001	1.09 (1.05–1.14)	<0.001	
Age category										
<40 years ($n = 25,134$)	0.65	1.21	0.62	1.97 (1.83–2.12)	<0.001	1.44 (1.33–1.56)	<0.001	1.14 (1.04–1.24)	0.01	<0.001
≥40 years ($n = 40,597$)	1.06	1.40	1.01	1.40 (1.34–1.45)	<0.001	1.20 (1.15–1.26)	<0.001	1.08 (1.03–1.14)	0.001	
Sex[c]										
Men ($n = 19,418$)	0.95	1.34	0.90	1.51 (1.42–1.60)	<0.001	1.20 (1.12–1.28)	<0.001	1.08 (0.99–1.17)	0.05	0.01
Women ($n = 46,039$)	0.89	1.37	0.84	1.63 (1.56–1.70)	<0.001	1.28 (1.22–1.34)	<0.001	1.10 (1.05–1.16)	<0.001	
Obesity										
Obesity ($n = 16,198$)	1.10	1.38	0.98	1.42 (1.35–1.49)	<0.001	1.22 (1.16–1.28)	<0.001	1.10 (1.04–1.16)	0.001	<0.001
Non-obesity ($n = 49,533$)	0.84	1.31	0.82	1.59 (1.49–1.69)	<0.001	1.25 (1.17–1.34)	<0.001	1.12 (1.05–1.21)	0.001	

Notes: OSA, obstructive sleep apnea; IRR, incidence rate ratio; CI, confidence interval.
Incidence rate ratios and *p* values were calculated by negative binomial regression models. *P* for interaction was calculated by using model 3.
[a]Adjusted for age, sex, race/ethnicity, insurance status, estimated household income, residential status, hospital length-of-stay, and hospital state, with GEE to account for patient clustering within hospitals.
[b]Adjusted for Elixhauser comorbidity measures and arrhythmia in addition to the covariates that are adjusted in the model 2.
[c]274 patients with missingness on sex data.

1.44; 95% CI 1.20–1.73; $p < 0.001$), and CHF (HR 3.89; 95% CI 3.16–4.79; $p < 0.001$; Supplement Figure 1 and Supplemental Table 3).

Discussion

In this population-based study of 65,731 patients hospitalized for asthma exacerbation in the seven U.S. states, we found that patients with OSA had a 60% higher risk and incidence rate of all-cause readmissions during one year after their index hospitalization which was attenuated to 9% in the adjusted model, compared to those without OSA. Additionally, coexistent OSA was significantly associated with a higher frequency of readmissions for all five major causes (i.e. asthma, COPD, respiratory failure, pneumonia, and CHF). The significant association persisted after the sequential adjustment for potential confounders. To the best of our knowledge, this is the first longitudinal study that has demonstrated the association between coexistent OSA and the risk for readmissions in patients hospitalized for asthma exacerbation.

In the current study, while there was no significant difference in the days-to-first asthma-specific readmission outcome in the survival model, patients with OSA had a 20% higher incident rate of readmission for asthma which was attenuated to 6% in the adjusted model. Although the literature is limited, smaller cross-sectional studies have also reported the association between OSA and higher asthma chronic morbidity (12–14). For example, in a single-center study of 472 adults (18–75 years) with asthma in Madison, Teodorescu et al. reported that asthma patient with OSA had a higher Asthma Control Questionnaire score (13). Likewise, in another single-center study of 136 patients with difficult-to-treat asthma in the Netherlands, Ten Brinke et al. reported that OSA was associated with a higher frequency of self-reported asthma exacerbations, defined by the use of systemic corticosteroids (14). Our findings based on the large population-based data corroborate these prior studies, and extend them by demonstrating the longitudinal association of OSA with a higher frequency of all-cause and cause-specific readmissions after hospitalization for asthma exacerbation.

The underlying mechanisms of the observed OSA–readmission association warrant clarification. In the current study, with the sequential adjustment, a part of the association was attributable to the differences in demographics, socio-demographic factors, and hospital length-of-stay between the two populations (model 2). Additionally, the higher comorbidity

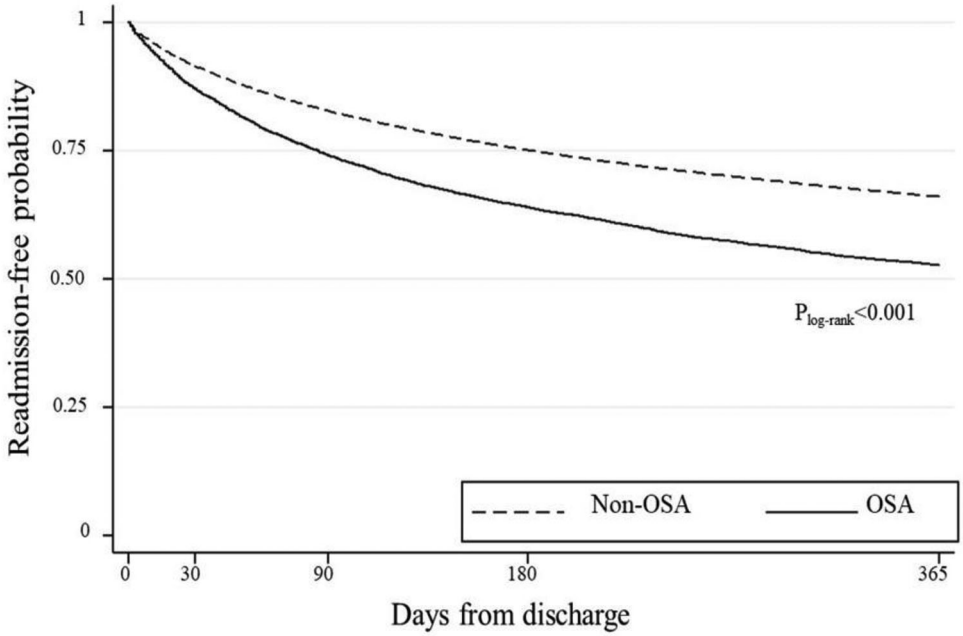

Figure 1. Kaplan-Meier survival estimates of all-cause readmission risk during one-year period after the index hospitalization for asthma exacerbation. Unadjusted survival curves showed that patients with OSA had a significantly higher risk of all-cause readmission during one-year period after the index hospitalization, compared to those without OSA ($P_{log\text{-}rank}$ <0.001).

prevalence in the OSA group further explained the higher readmission rate in this population (model 3). However, despite the rigorous adjustment, OSA remained a significant risk factor for one-year readmission in patients hospitalized for asthma exacerbation. This finding suggests that there are other factors predisposing patients with OSA to worse disease control and frequent readmissions for both of asthma and non-asthma diseases. These potential mechanisms are likely multifactorial, such as OSA-induced hypoxemia (30), sleep deprivation (31), increased lower airway resistance (32), neutrophilic airway inflammation (33), higher prevalence of gastro-esophageal reflux disease (34), or any combination of these factors. Additionally, we observed the effect modifications in OSA-readmission (frequency) association by age, sex, and obesity. According to a previous study using an unsupervised cluster analysis, an asthma phenotype characterized by older age, female sex, and obesity represented a difficult-to-manage asthma with more frequent exacerbations (35). The heterogeneity in asthma among the study sample may have contributed to the observed effect modifications.

In addition to the higher incidence rate of readmission for asthma, we also uncovered that coexistence of OSA is associated with a higher incidence rate of readmissions for the other major pulmonary and cardiovascular conditions, even after adjusting for comorbidities. These findings suggest that concurrent asthma and OSA may have synergistic detrimental effects to other respiratory and cardiovascular diseases. Increasing evidence suggests that both asthma and OSA are associated with compromised gas exchange (hypoxemia and hypercapnia) (36), increased susceptibility for respiratory infections due to impaired immune response (37,38), and impaired cardiac function via overlapping low-grade inflammation and oxidative stress (30,39–41). In contrast, OSA was not significantly associated with the time-to-first readmission caused by asthma. One potential explanation for the apparent discrepancy is that the in-hospital management for asthma exacerbation may have reduced the risk for readmission in both patients with and without OSA at least for some period (thereby reducing the HR for the first readmission by asthma) while OSA may have remained as a risk factor for frequent asthma exacerbations during a longer-term follow-up period. The identification of exact underlying mechanisms merits further investigation.

Potential limitations

Our study has several potential limitations. First, as we used administrative datasets, there may be misclassifications, such as misdiagnosis of asthma and OSA. Nevertheless, the *ICD-9-CM* codes for these conditions are widely used (20–22), and the HCUP data are rigorously tested and considered accurate (22,42–44). Furthermore, the prevalence of OSA in our population was comparable to that in previous asthma

Table 3. Hazard ratio for all-cause readmission during one-year period after index hospitalization for asthma exacerbation, according to coexistence of OSA, overall and stratified by age category, sex, and obesity.

	One-year readmission rate			Unadjusted model (model 1)		Adjusted model (model 2)[a]		Adjusted model (model 3)[b]		
	All ($n = 65,731$)	OSA ($n = 6,549$)	Non-OSA ($n = 59,182$)	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	$P_{interaction}$
Overall ($n = 65,731$)	35.9%	48.3%	34.5%	1.56 (1.50–1.62)	<0.001	1.25 (1.20–1.30)	<0.001	1.11 (1.07–1.16)	<0.001	
Age category										
<40 years ($n = 25,134$)	28.9%	42.8%	28.1%	1.72 (1.58–1.86)	<0.001	1.42 (1.30–1.55)	<0.001	1.17 (1.06–1.29)	0.002	0.001
≥40 years ($n = 40,597$)	40.2%	49.8%	38.%	1.40 (1.34–1.46)	<0.001	1.23 (1.17–1.28)	<0.001	1.10 (1.05–1.16)	<0.001	
Sex[c]										
Men ($n = 19,418$)	34.1%	46.2%	32.6%	1.57 (1.46–1.68)	<0.001	1.24 (1.15–1.33)	<0.001	1.11 (1.02-1.21)	0.01	0.95
Women ($n = 46,039$)	36.8%	49.3%	35.4%	1.56 (1.49–1.63)	<0.001	1.27 (1.21–1.33)	<0.001	1.12 (1.06–1.18)	<0.001	
Obesity										
Obesity ($n = 16,198$)	41.5%	49.1%	38.4%	1.40 (1.33–1.47)	<0.001	1.22 (1.16–1.29)	<0.001	1.12 (1.06–1.18)	<0.001	0.18
Non-obesity ($n = 49,533$)	34.1%	46.0%	33.6%	1.51 (1.41–1.62)	<0.001	1.25 (1.16–1.35)	<0.001	1.15 (1.07–1.24)	<0.001	

Notes: OSA, obstructive sleep apnea; HR, hazard ratio; CI, confidence interval.
A total of 23 604 (35.9%) patients had readmission during one-year period after index hospitalization for asthma exacerbation. Hazard ratios and p values were calculated by using Cox proportional hazard models. P for interaction was calculated by using model 3.
[a]Adjusted for age, sex, race/ethnicity, insurance status, estimated household income, residential status, hospital length-of-stay, and hospital state with GEE to account for patient clustering within hospitals.
[b]Adjusted for Elixhauser comorbidity measures and arrhythmia in addition to the covariates that are adjusted in the model 2.
[c]274 patients with missingness on sex data.

Table 4. Associations of OSA with incident rate of cause-specific readmissions during one-year period after index hospitalization for asthma exacerbation, overall.

	Incidence rate (readmissions/person-year)			Unadjusted model (model 1)		Adjusted model (model 2)[a]		Adjusted model (model 3)[b]	
Primary cause of readmission	All ($n = 65,731$)	OSA ($n = 6,549$)	Non-OSA ($n = 59,182$)	IRR (95% CI)	p Value	IRR (95% CI)	p Value	IRR (95% CI)	p Value
Asthma	0.28	0.33	0.28	1.21 (1.15–1.27)	<0.001	1.06 (1.00–1.21)	0.03	1.06 (1.00–1.13)	0.04
COPD	0.08	0.15	0.07	2.03 (1.88–2.19)	<0.001	1.41 (1.30–1.52)	<0.001	1.38 (1.26–1.52)	<0.001
Respiratory failure	0.04	0.10	0.03	3.04 (2.76–3.34)	<0.001	2.39 (2.15–2.64)	<0.001	2.08 (1.85–2.35)	<0.001
Pneumonia	0.03	0.05	0.03	1.67 (1.49–1.88)	<0.001	1.25 (1.10–1.41)	<0.001	1.15 (1.00–1.32)	0.04
CHF	0.02	0.07	0.02	3.78 (3.36–4.24)	<0.001	2.50 (2.21–2.83)	<0.001	1.39 (1.21–1.61)	<0.001

Notes: OSA, obstructive sleep apnea; COPD, chronic obstructive pulmonary disease; IRR, incidence rate ratio; CI, confidence interval.
Incidence rate ratios and p values were calculated by negative binomial regression models.
[a]Adjusted for age, sex, race/ethnicity, insurance status, estimated household income, residential status, hospital length-of-stay, and hospital state with GEE to account for patient clustering within hospitals.
[b]Adjusted for Elixhauser comorbidity measures and arrhythmia in addition to the covariates that are adjusted in the model 2.

cohort studies (12,14). Second, SIDs do not capture information on out-of-hospital deaths. While these events might have served as a competing risk on readmissions, the mortality rate in this population is low (0.15 per 1,000 person-year) (1). Additionally, we accounted for in-hospital deaths in the analysis. Third, as with any observational study, causal inference on the OSA–readmission relation may be confounded by unmeasured factors (e.g. access to ambulatory healthcare, patient's health behavior). Fourth, the studied sample is not a random sample of all patients with asthma in the U.S. However, the seven geographically dispersed states represent approximately 27% of the U.S. population, thereby supporting the generalizability of our inferences. Fifth, our data were based on seven states without detailed information on the access to and quality of care. Regardless, we have accounted for both primary insurance status and state of residence to address this issue. Finally, as our study sample was comprised of patients hospitalized for asthma exacerbation, the results may not be generalizable to patients with mild-to-moderate asthma exacerbation. Yet, our inferences remain directly relevant for an estimated 350,000 hospitalized patients with severe asthma exacerbation each year (4).

Conclusions

In a large population-based database of 65,731 patients hospitalized for asthma exacerbation across seven U.S. states, we found that patients with OSA had a significantly higher incidence rate of all-cause readmissions during one year after their index hospitalization, as compared to those without OSA. This association was also observed in cause-specific readmissions. There was an association between OSA and asthma readmission; however, the adjusted associations between OSA and readmission for non-asthma causes (e.g. COPD, respiratory failure, pneumonia, and CHF) were higher than the association for asthma readmissions. For clinicians, our findings underscore the importance of identifying coexistent OSA in this population and optimizing chronic asthma and OSA management. For researchers, our findings should facilitate further investigations into the mechanisms underlying the asthma-OSA link to develop novel preventive and therapeutic interventions in this population at high-risk for healthcare utilization.

Conflict of interest statements

Dr. Camargo has provided asthma-related consulting services to AstraZeneca, GlaxoSmithKline, Novartis, and Teva. Dr. Hasegawa has received a grant for asthma-related research from Novartis and Teva. The other authors have no relevant financial relationships to disclose.

Role of the authors

All authors have seen and approved the manuscript. Drs. Hirayama, Goto, and Hasegawa conceived the study. Drs. Hirayama and Goto, and Mr. Faridi analyzed the data. Dr. Hirayama drafted the manuscript. Drs. Camargo and Hasegawa supervised the conduct of the study. Finally, all authors contributed substantially to its revision and all authors had access to data.

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Supplementary Material

Association of obstructive sleep apnea with readmissions after hospitalization for asthma exacerbation in adults aged 18-54 years: A population-based study, 2010-2013

Supplemental Table 1. The missing rate in each variable.

Supplemental Table 2. Associations of obstructive sleep apnea with incident rate of all-cause readmissions during 1-year period after index hospitalization for asthma exacerbation, overall and stratification by state of residence

Supplemental Table 3. Hazard ratio for cause-specific readmission within 1-year period after index hospitalization for asthma exacerbation, according to coexistence of obstructive sleep apnea

Supplement Figure 1. Kaplan-Meier survival estimates of cause-specific readmission risk during 1-year period after the index hospitalization for asthma exacerbation

There was no significant difference in the risk of readmission for asthma (A) between patients with obstructive sleep apnea (OSA) and those without ($P_{log\text{-}rank}=0.71$). In contrast, patients with OSA had a significantly higher risk of readmission for chronic obstructive pulmonary disease (B), respiratory failure (C), pneumonia (D), and congestive heart failure (E) during 1-year period after the index hospitalization, compared to those without OSA (all $P_{log\text{-}rank}<0.001$).

Supplemental Table 1. The missing rate in each variable.

Characteristics	Missing rate (n, %)
Age	0 (0)
Women	274 (0.4)
Race/ethnicity	2,428 (3.7)
Primary health insurance	31 (0.04)
Median household income	2579 (3.9)
Patient residence	20 (0.03)
Elixhauser comorbidities	0 (0)
Hospital length-of-stay	0 (0)
Hospital state	0 (0)

Supplemental Table 2. Associations of obstructive sleep apnea with incident rate of all-cause readmissions during 1-year period after index hospitalization for asthma exacerbation, overall and stratification by state of residence

	Incidence rate (readmissions/person-year)			Unadjusted model	P-value
	All	**OSA**	**Non-OSA**	IRR (95% CI)	
States	n=65,731	n=6,549	n=59,182		
Arkansas (n=2,084)	0.89	1.46	0.83	1.74 (1.43-2.13)	<0.001
California (n=11,721)	1.03	1.60	0.97	1.67 (1.54-1.81)	<0.001
Florida (n=22,386)	0.96	1.38	0.90	1.54 (1.46-1.63)	<0.001
Iowa (n=1,432)	0.67	1.16	0.60	1.87 (1.27-2.75)	<0.001
Nebraska (n=979)	0.89	1.05	0.77	1.47 (1.16-1.91)	<0.001
New York (n=26,083)	0.82	1.26	0.78	1.63 (1.54-1.74)	<0.001
Utah (n=1,046)	0.76	1.07	0.74	1.43 (1.14-1.87)	<0.001

Abbreviations: OSA, obstructive sleep apnea; IRR, incidence rate ratio; CI, confidence interval

Incidence rate ratios and p-values were calculated by negative binomial regression models.

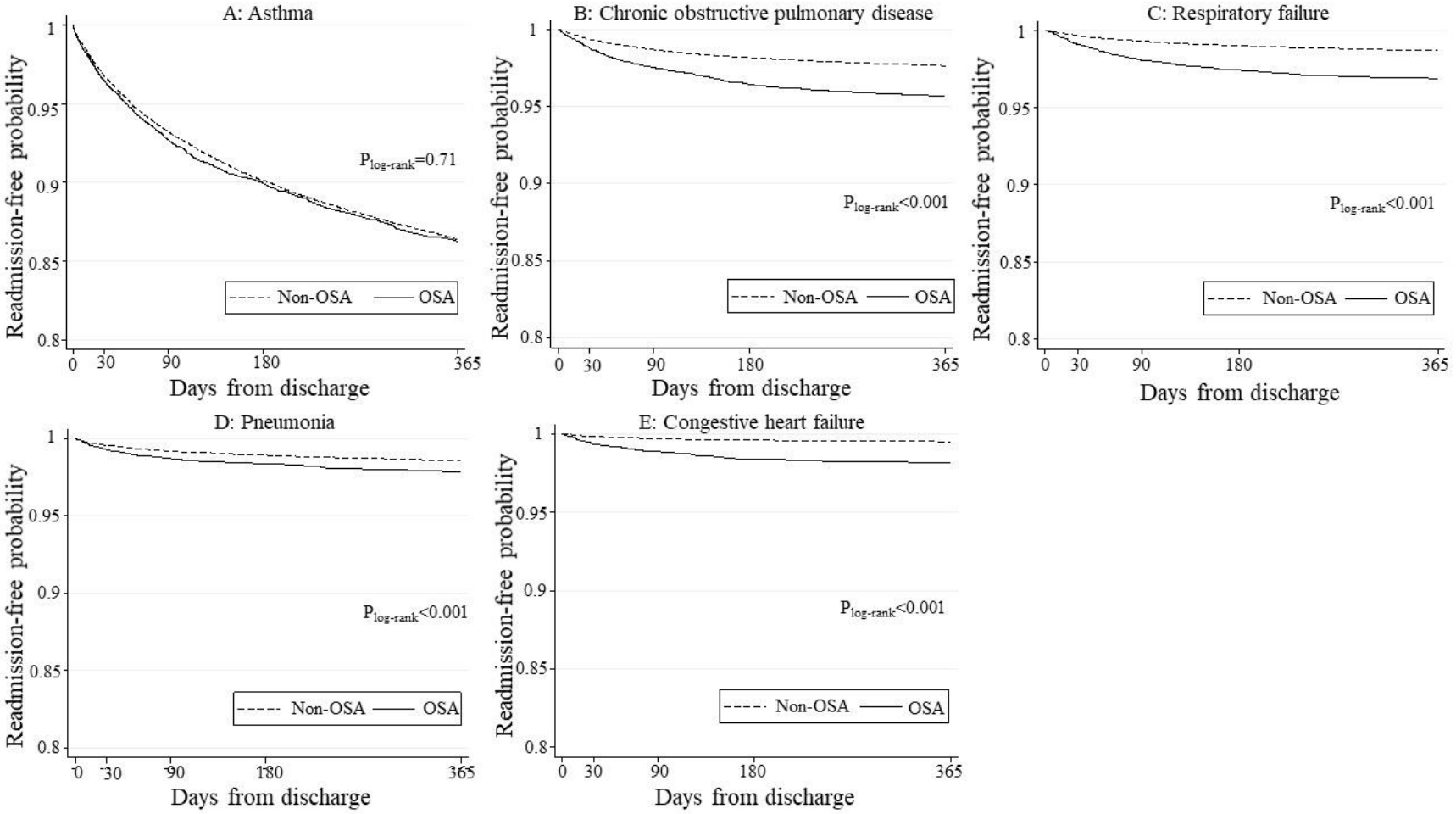
Supplemental Table 3. Hazard ratio for cause-specific readmission within 1-year period after index hospitalization for asthma exacerbation, according to coexistence of obstructive sleep apnea

	Readmission rate within one year			Unadjusted model (model 1)		Adjusted model (model 2)*		Adjusted model (model 3)†	
Primary cause of readmission	All (n=65,731)	OSA (n=6,549)	Non-OSA (n=59,182)	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Asthma	13.7%	13.7%	13.6%	1.01 (0.95-1.09)	0.71	0.98 (0.91-1.05)	0.55	1.02 (0.95-1.11)	0.57
COPD	2.6%	4.4%	2.4%	1.88 (1.65-2.13)	<0.001	1.23 (1.08-1.41)	0.002	1.32 (1.13-1.53)	<0.001
Respiratory failure	1.4%	3.2%	1.2%	2.65 (2.27-3.09)	<0.001	2.23 (1.89-2.63)	<0.001	1.94 (1.60-2.35)	<0.001
Pneumonia	2.2%	2.2%	1.5%	1.44 (1.20-1.73)	<0.001	1.13 (0.93-1.37)	0.21	1.11 (0.90-1.38)	0.32
Congestive heart failure	0.7%	2.0%	0.5%	3.89 (3.16-4.79)	<0.001	2.74 (2.20-3.41)	<0.001	1.44 (1.11-1.86)	0.01

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

Hazard ratios and p-values were calculated by using Cox proportional hazard models.

* Adjusted for age, sex, race/ethnicity, insurance status, estimated household income, residential status, hospital length-of-stay, and hospital state with generalized estimating equations to account for patient clustering within hospitals

† Adjusted for Elixhauser comorbidity measures and arrhythmia in addition to the covariates that are adjusted in the model 2

Supplemental Figure 1.