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Association between obesity and acute severity among patients hospitalized for asthma exacerbation

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Abstract

Background: Although studies have demonstrated relations between obesity and incident asthma, little is known about the association of obesity with acute severity in adults hospitalized for asthma exacerbation.

Objectives: To investigate the association of obesity with acute severity of asthma exacerbation.

Methods: This is a retrospective cohort study using population-based data of geographically-diverse eight US states from 2010 through 2013. We included adults (age 18-54 years) hospitalized for asthma exacerbation. The outcome measures were markers of acute severity – use of mechanical ventilation (defined by non-invasive positive pressure ventilation [NIPPV] and/or invasive mechanical ventilation) and hospital length-of-stay (LOS). To determine the association of obesity with each outcome, we fit multivariable models adjusting for patient-level confounders (e.g., age, sex, race/ethnicity, primary insurance, quartiles for household income, residential status, and comorbidities) and potential patient clustering within hospitals.

Results: Among the 72,086 patients hospitalized for asthma exacerbation, 24% were obese. Obesity was associated with a significantly higher risk of any mechanical ventilation use (8.3% vs. 5.0%; adjusted OR 1.77; 95%CI 1.63-1.92; P<0.001) driven by the higher risk of NIPPV use (7.2% vs. 3.4%; adjusted OR 2.14; 95%CI 1.96-2.35; P<0.001). Likewise, obese patients were more likely to have a hospital LOS of ≥3 days compared to non-obese patients (59.4% vs. 46.5%;

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adjusted OR 1.37; 95%CI 1.32-1.43; P<0.001). These findings were consistent with stratifications by age, sex, and race/ethnicity.

Conclusions: In this population-based study of adults hospitalized for asthma exacerbation, obesity was associated with higher acute severity.

Keywords

asthma; adults; obesity; epidemiology; acute severity; hospitalization

INTRODUCTION

Asthma and obesity are major health problems, with a significant impact on the US healthcare system. The prevalence of asthma remains high, affecting 8% (18 million) of American adults.[1] In addition, the burden of asthma-related healthcare utilization is substantial – approximately 385,000 annual hospitalizations with $2.3 billion direct cost each year.[2] In parallel, the US has also experienced an obesity epidemic.[3] It is anticipated that there will be a 33% increase in obesity prevalence over the next two decades.[4]

The literature has linked obesity to incident asthma[5] and *chronic* morbidity (e.g., suboptimal asthma control, frequent exacerbations,[6] and increased use of oral corticosteroids[7,8]). By contrast, only a few studies have examined the relations between obesity and *acute* asthma severity in adults.[9-12] Studies of emergency department patients with asthma exacerbation have reported that, in obese adults, the risk of hospitalization – a marker for acute severity – is no different[12,13] or higher[9,10] than non-obese patients. However, the inferences may have been limited by the small sample sizes, confounding, and potential issues of generalizability. Despite the clinical and public importance of asthma exacerbation, the relation of obesity with in-hospital acute severity in adults remains largely unclear.

In this context, we used large, population-based, all-payer databases from eight US states to investigate the association of obesity with the markers for acute severity and in-hospital mortality in adults hospitalized for asthma exacerbation. Specifically, we hypothesized *a priori* that obese adults hospitalized for asthma exacerbation have higher acute severity (defined by the use of mechanical ventilations and hospital length-of-stay [LOS]) when compared to non-obese patients.

METHODS

Study Design and Setting

We performed a retrospective cohort study using the Healthcare Cost and Utilization Project (HCUP) State Inpatient Databases (SIDs) from eight racially/ethnically- and geographically-diverse US states (Arkansas, California, Florida, Iowa, Nebraska, New York, Utah and Washington) from January 2010 through December 2013. The HCUP is the largest administrative longitudinal healthcare databases containing all-payer encounter-level information in the US. It is managed by the *Agency for Healthcare Research and Quality* and developed through a federal-state-industry partnership. The HCUP SIDs include all inpatient discharge records, regardless of source or disposition, from all acute care, non-

federal, general, and other specialty hospitals within the states. Additional information of HCUP SID can be found elsewhere.[14] The eight states were selected considering their geographic distribution and high data quality. The study period was chosen based on the availability of databases. This study was approved by the institutional review board of Massachusetts General Hospital.

Study Population

We included all adult patients (age 18-54 years) who had an unplanned hospitalization with a principal diagnosis of asthma, defined by the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnosis code of 493.xx.[9] We included only the first hospitalization for asthma exacerbation for each patient during the study period. We excluded patients who were underweight (defined as *ICD-9-CM* codes: 783.2, 783.21, 783.22, and v85.0)[15] as these patients may represent a unique phenotype compared with normal or overweight counterparts.[16,17] Additionally, we excluded patients who were aged ≥55 years, due to the difficulty of distinguishing asthma from chronic obstructive pulmonary disease (COPD),[9] and those who left hospital against medical advice.

Measurements

The databases include patient characteristics such as demographics (age, sex, race/ethnicity), primary insurance type, quartiles for estimated median household income, patient residence, *ICD-9-CM* diagnoses, patient comorbidities, procedures, hospital course, and disposition. Quartile classifications of estimated median household income of residents were based on the patient's ZIP code. Patient comorbidities were measured by the Elixhauser comorbidity measures,[11,18] a method of identifying comorbidities based on the *ICD-9-CM* diagnoses. The residential status was defined according to the National Center for Health Statistics.

Primary Exposure

The primary exposure was obesity, as defined by *ICD-9-CM* diagnosis codes of 278.00, 278.01, v85.31-v85.39, and v85.41-85.45.[19-21] These *ICD-9-CM* codes have a high specificity and positive predictive value to identify obesity (both >90%).[22]

Outcome Measures

The primary outcome measures were markers of acute severity – the use of mechanical ventilation (defined by non-invasive positive pressure ventilation [NIPPV] and/or invasive mechanical ventilation) and hospital LOS. The secondary outcome measure was in-hospital mortality during the hospitalization for asthma exacerbation. The use of NIPPV was identified by *ICD-9-CM* procedure code 93.90; the use of invasive mechanical ventilation was identified by the codes of 96.04 and 96.70-96.72.[23]

Statistical Analysis

We compared the patient characteristics between the obesity and non-obesity groups by using chi-squared and Wilcoxon signed rank test as appropriate. To examine the association between obesity and each outcome, we fit unadjusted and adjusted logistic regression models for each of the binomial responses with the use of generalized estimating equations

accounting for potential clustering of patients within hospitals. In the primary analysis, we modeled hospital LOS as a binomial response based on the median LOS (i.e., ≤2 days vs. ≥3 days). The cutoff value of 3 days was decided based on previous literature of patients hospitalized for asthma exacerbation where the overall mean hospital LOS being 2.7 days.[24] Additionally, the overall median LOS was 3 days in our data. In the adjusted models, we adjusted for age, sex, race/ethnicity, primary insurance, quartiles for household income, residential status, patient comorbidities (29 Elixhauser comorbidity measures[18] and arrhythmia[11]), hospital state, and calendar year. A set of potential confounders was chosen *a priori* based on clinical plausibility and *a priori* knowledge.

To examine the robustness of inferences, we performed series of sensitivity analyses. First, we repeated the analysis with stratification by age (<40 and ≥40 years), sex, and race/ethnicity (Non-Hispanic white, Non-Hispanic black, and Hispanic). Next, to examine the association between obesity and hospital LOS as a count variable, we fit unadjusted and adjusted negative binominal regression models with the use of generalized estimating equations. This model has advantages of need not to define an arbitrary cutoff point of LOS and accounts for overdispersion of data. Finally, to estimate the average causal effect of obesity on each outcome, we used stabilized inverse probability weighting (stabilized IPW).[25] Weighting the inverse probability to have an exposure (obesity) creates a synthetic sample where the exposure becomes independent from measured baseline covariates. Consequently, in the synthetic sample, obese and non-obese individuals become exchangeable. While conventional IPW may have a greater variability of the estimated effects in subjects with a very low or high probability score, stabilized IPW enables us to directly estimate both the main effect and variance from conventional regression models.[25] All analyses were performed by STATA 14.0 (STATA Corp, College Station, TX). All P values were two-tailed and considered statistically significant with P<0.05.

RESULTS

We identified 72,086 patients hospitalized for asthma exacerbation in the eight US states from January 2010 through December 2013. Overall, the median age was 43 years (IQR, 33-49 years), 70.2% were female, and 44.7% were non-Hispanic white. Among these, 17,479 patients (24.3%) were obese. The patient characteristics differed by obesity status. For example, obese patients were more likely to be female, Medicare beneficiaries, and living in lower household income areas compared to non-obese patients (all P<0.001). Additionally, obese patients were more likely to have several comorbidities, such as congestive heart failure, depression, and diabetes (all P<0.001), compared to non-obese patients.

Figure 1 illustrates the unadjusted and adjusted associations between obesity and each outcome. Obesity was associated with a significantly higher risk of overall mechanical ventilation use (8.3% vs. 5.0%; unadjusted OR 1.89; 95% CI 1.76-2.03; P<0.001). This association remained significant after adjusting for patient-level potential confounders (age, sex, race/ethnicity, primary insurance, quartiles for household income, residential status, patient comorbidities, hospital state, and calendar year) and potential clustering of patients within hospitals. When dividing overall mechanical ventilation use into NIPPV and invasive

mechanical ventilation, obesity was associated with a significantly higher risk of NIPPV use in both unadjusted (7.2% vs. 3.4%; unadjusted OR 2.53; 95% CI 2.32-2.75; P<0.001) and adjusted (adjusted OR 2.14; 95% CI 1.96-2.35; P<0.001) models. There was no statistically significant association with risk of invasive mechanical ventilation use in the adjusted model (P=0.12). As for hospital LOS, obese patients were more likely to have a hospital LOS of ≥3 days compared to non-obese patients (59.4% vs. 46.5%; adjusted OR 1.37; 95% CI 1.32-1.43; P<0.001). The number of asthma deaths was low (n=116), which limited statistical power, but, there was no significant difference in in-hospital mortality between obesity and non-obesity groups (0.15% vs. 0.16%, respectively; P=0.97).

In the sensitivity analyses, these results persisted with stratification by age, sex, and race/ethnicity (Supplemental Table 1) except for a lower risk of invasive mechanical ventilation use among obese men. While there were some statistically significant interactions of obesity with age and sex in the setting of large sample size (Supplemental Table 2), there was no substantial heterogeneity (or clinically meaningful interactions) in the observations across the age, sex, and race/ethnicity strata. Likewise, the associations were also consistent across the median household income and patient residence strata (Supplemental Table 3). Additionally, consistent with the primary analysis, the analysis modeling hospital LOS as a count variable (Supplemental Table 4) also showed that obese patients had a significantly longer hospital LOS, corresponding to a 24% increase (95%CI 22%-27% increase) in the unadjusted model and 13% increase (95%CI 11%-16% increase) in the adjusted model. Lastly, in the analysis using the stabilized IPW method, the results were consistent with the primary analysis, suggesting the causal association of obesity with acute severity of asthma exacerbation (Supplemental Table 5).

DISCUSSION

By analyzing population-based data from 72,086 patients hospitalized for asthma exacerbation in eight US states, we found that obese patients had significantly higher acute severity, including overall mechanical ventilation use and longer hospital LOS, when compared to non-obese patients. In contrast, there was no significant difference in in-hospital mortality between obese and non-obese patients although the number of asthma deaths was very low, which limited statistical power. These associations were consistent across the several sensitivity analyses with different statistical assumptions, including stabilized IPW. To the best of our knowledge, this is the first study that has investigated the relations of obesity with acute severity in adults hospitalized for asthma exacerbation.

Consistent with our inferences, within the limited literature, studies in the emergency department setting have reported the association of obesity and higher acute severity.[9,10] For example, a US-based multicenter chart-review study of 1,227 emergency department adult patients with asthma exacerbation reported that obesity was associated with a higher risk of hospitalization compared to non-obese adults.[9] Similarly, another single-center study of 426 adults with asthma exacerbation in Uruguay also reported significant obesity-hospitalization risk associations.[10] Likewise, an analysis of administrative data of US children (aged 2-18 years) hospitalized for asthma exacerbation demonstrated that obesity is associated with a higher risk of mechanical ventilation use and longer hospital LOS.[26] In addition, the

literature of all-cause hospitalizations has also documented that obese individuals have longer hospital LOS through an increased prevalence of comorbidities, complications, and longer recovery.[27,28] Our study corroborates these prior studies, and extends them by demonstrating, in a large population-based dataset, the robust association between obesity and acute severity in patients hospitalized for asthma exacerbation.

The underlying mechanism(s) of the observed obesity-acute severity relation warrants investigation. The literature has linked obesity to increased systemic inflammation by adipocyte-derived pro-inflammatory mediators (e.g., leptin),[29-31] increased airway obstruction and inflammation,[32-34] decreased corticosteroid responsiveness,[35-39] altered gut microbiome modulating host immune response,[40] obesity-associated restrictive ventilatory patterns and reduced expiratory reserve volume,[41] and higher prevalence of comorbidities (e.g., gastroesophageal reflux). Prior studies of bariatric surgery – the most effective weight reduction measure – and asthma have shown that bariatric surgery improves airway hyperresponsiveness in obese asthmatics,[42] and that bariatric surgery reverses the obesity-related increased pro-inflammatory mediator profiles,[29] both supporting the obesity-asthma morbidity causal link. Each of these mechanisms may affect this particular population to develop altered pulmonary pathophysiology and higher acute severity resulting in higher use of mechanical ventilation and longer LOS.[43,44] Interestingly, our study showed no significant association between obesity and the risk of invasive mechanical ventilation use even with sufficient statistical power (1,303 outcome events). This observation might be explained, at least in part, by the possibility that clinicians were more reluctant to attempt tracheal intubations on obese patients because obesity is a known risk factor for difficult intubation and extubation.[45-48]

We found no significant associations between obesity and in-hospital mortality despite the observed obesity-acute severity association. While a study of adults (aged >40 years) hospitalized with several conditions (e.g., asthma, cardiovascular diseases, cancer) reported that a higher body mass index (BMI) was associated with an increased risk of in-hospital mortality,[49] a meta-analysis of 17 studies has shown that obesity is associated with favorable survival outcomes in other respiratory conditions, such as COPD.[50] This apparent discrepancy in the literature might be partially attributable to the differences in study population, study designs, settings, or any combination of these factors. Alternatively, a limited statistical power from the low rate of in-hospital mortality among obese and non-obese patients in the present study (0.15% vs. 0.16%) may be an explanation for not detecting a statistically significant difference in this outcome measure. The potential protective effect of obesity on asthma merits further research.

POTENTIAL LIMITATIONS

The study has several potential limitations. First, the lack of information on BMI may have underestimated the prevalence of obesity. The sensitivity of *ICD-9-CM* codes for identifying obesity is shown to be poor,[51,52]while the specificity and positive predictive value for identifying obesity are both ≥90%.[22] It is possible that those classified as obese had a very high BMI, and that our inferences of obese patients having a higher acute severity may not be generalizable to patients with mild-to-moderate obesity. Second, as with any

observational studies, the observed associations may be confounded by unmeasured factors, such as smoking status, chronic severity of asthma, and institutional variability in resource use. Additionally, the observed associations between obesity and acute severity markers of asthma exacerbation remained significant after accounting for patient clustering at the hospital-level. Further, the significant associations persisted in the stabilized IPW, supporting causality in the association of interest. Third, the studied data were not a random sample of the entire population in the US. However, the data were racially/ethnically- and geographically-diverse. In addition, the eight states together represent approximately 30% of the US population[53], thereby supporting the generalizability of our inferences. Finally, as our study sample consisted of patients hospitalized for asthma exacerbation, our inferences may not be generalizable to patients with less severe asthma exacerbations. However, our findings remain highly relevant to the population of approximately 400,000 US adults hospitalized for asthma each year, involving high morbidity and healthcare utilization.[2]

CONCLUSIONS

By analyzing population-based data from 72,086 patients hospitalized for asthma exacerbation, we found that obese patients were more likely to have a higher acute severity – i.e., overall mechanical ventilation use and a longer hospital LOS – in comparison with non-obese patients. These associations persisted after adjusting for potential confounders and across the sensitivity analyses with different statistical assumptions. Our findings should facilitate further research into the mechanisms underlying the observed obesity-acute severity link to develop therapeutic interventions in this high-risk population. Lastly, our observations also underscore the importance of continued public health campaigns against obesity, which might curb asthma-related healthcare utilization.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

BMI	body mass index
COPD	chronic obstructive pulmonary disease
HCUP	Healthcare Cost and Utilization Project

ICD-9-CM	*International Classification of Diseases, Ninth Revision, Clinical Modification*
IPW	Inverse probability weighting
LOS	length-of-stay
NIPPV	non-invasive positive pressure ventilation
OR	odds ratio
SID	State Inpatient Databases

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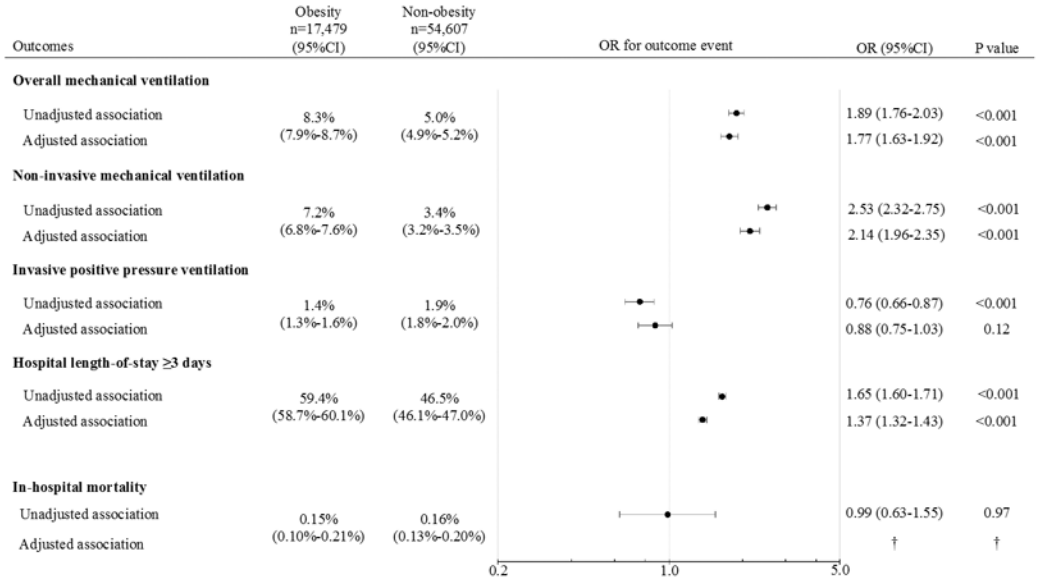

Figure 1. Unadjusted and adjusted associations of obesity with acute severity markers of asthma exacerbation and in-hospital mortality

In patients hospitalized for asthma exacerbation, obese patients were more likely to have makers of higher acute severity, including any mechanical ventilation use, non-invasive mechanical ventilation use, and hospital length-of-stay of ≥3 days, when compared to non-obesity. These associations remained significant after adjusting for the potential confounders and potential clustering within the hospitals. The number of asthma deaths was low (n=116), which limited statistical power, but there was no significant association between obesity and in-hospital mortality.

Abbreviations: CI, confidence interval; OR, odds ratio

† Adjusted model was not constructed because of the relatively few number of in-hospital mortality (n=116)

Table 1.

Characteristics of patients hospitalized for asthma exacerbation, according to obesity status

Characteristics	Obesity n=17,479 (24.3%)	Non-obesity n=54,607 (75.7%)	P value
Age (year), median (IQR)	45 (37-50)	43 (32-49)	<0.001
Female sex	13,798 (79.0)	36,586 (67.3)	<0.001
Race/ethnicity			<0.001
Non-Hispanic white	7,667 (45.3)	23,199 (44.5)	
Non-Hispanic black	5,154 (30.4)	14,154 (27.2)	
Hispanic	3,225 (19.1)	10,855 (20.8)	
Others	887 (5.2)	3,877 (7.4)	
Primary health insurance			<0.001
Medicare	3,030 (17.4)	6,000 (11.0)	
Medicaid	6,387 (36.6)	18,271 (33.5)	
Private	5,069 (29.0)	17,399 (31.9)	
No insurance	2,033 (11.6)	9,214 (16.9)	
No charge	333 (1.9)	1,208 (2.2)	
Others	613 (3.5)	2,489 (4.6)	
Median household income quartile			<0.001
1 (lowest)	6,921 (41.4)	19,408 (37.8)	
2	4,161 (24.9)	12,691 (24.7)	
3	3,497 (20.9)	11,363 (22.1)	
4 (highest)	2,125 (12.7)	7,940 (15.5)	
Patient residence			0.90
Metropolitan	16,148 (92.7)	50,369 (92.7)	
Non-metropolitan	1,270 (7.3)	3,978 (7.3)	
Selected comorbidities *			
Congestive heart failure	1,767 (10.1)	1,766 (3.2)	<0.001
Depression	3,097 (17.7)	6,941 (12.7)	<0.001
Diabetes	5,915 (33.8)	6,734 (12.3)	<0.001
Drug abuse	1,064 (6.1)	4,835 (8.9)	<0.001
Hypertension	9,292 (53.2)	15,421 (28.2)	<0.001
Renal failure	644 (3.7)	1,017 (1.9)	<0.001
Hospital state			<0.001
Arkansas	471 (2.7)	1,739 (3.2)	
California	3,287 (18.8)	8,753 (16.0)	
Florida	6,516 (37.3)	16,544 (30.3)	
Iowa	382 (2.2)	1,147 (2.1)	
Nebraska	199 (1.1)	836 (1.5)	
New York	5,286 (30.2)	21,296 (39.0)	
Utah	171 (1.0)	930 (1.7)	

Characteristics	Obesity n=17,479 (24.3%)	Non-obesity n=54,607 (75.7%)	P value
Washington	1,167 (6.87)	3,362 (6.2)	
Hospitalization year			0.054
2010	19,828 (36.3)	6,301 (36.1)	
2011	15,282 (28.0)	4,865 (27.8)	
2012	10,511 (19.3)	3,286 (18.8)	
2013	8,986 (16.5)	3,027 (17.3)	

Data are shown as n (%) unless otherwise specified

Abbreviation: IQR, interquartile range

*Selected from 29 Elixhauser comorbidity measures and arrhythmia