

Rising Trends and Impact of Metabolically Healthy Obesity in Elderly Patients Hospitalized with Acute Exacerbation of COPD: A Nationwide Analysis (2016-2020)

Short Title: Metabolically Healthy Obesity in Elderly COPD

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ABSTRACT

Purpose: The prevalence and clinical impact of metabolically healthy obesity (MHO) in elderly patients hospitalized with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) remain unclear. We aimed to evaluate temporal trends, prevalence and outcomes associated with MHO in this population.

Methods: Using the National Inpatient Sample (2016-2020), we analyzed hospitalizations for AECOPD among patients aged ≥65 years. Patients were stratified into MHO and non-MHO cohorts. Primary outcomes included adjusted odds of all-cause mortality (ACM), respiratory failure (RF), mechanical ventilation (MV), pulmonary hypertension (PH) and heart failure with

reduced ejection fraction (HFrEF). Secondary outcomes included healthcare utilization. Multivariable regression analyses were performed.

Results: Among 221,700 AECOPD admissions, 5.7% were classified as MHO, increasing from 5.1% in 2016 to 6.5% in 2020. MHO patients were younger (median 71 vs 73 years) and more frequently female. They had higher rates of RF (45.3% vs 30.8%), MV (5.2% vs 2.7%) and PH (10.8% vs 9.1%) (all $p < 0.001$). Comorbidities including smoking, depression, autoimmune disease and hypothyroidism were more prevalent in the MHO group. Adjusted analyses demonstrated increased odds of RF, MV, PH and HFrEF among MHO patients. Length of stay and hospitalization costs were also higher. There were no significant differences in ACM or pulmonary embolism.

Conclusions: MHO is increasingly prevalent among elderly AECOPD patients and is associated with greater respiratory and cardiovascular complications and higher healthcare utilization, despite no difference in mortality. Further studies are needed to elucidate underlying mechanisms.

Keywords: Metabolically healthy obesity; Acute exacerbation of chronic obstructive pulmonary disease; Respiratory failure; Mechanical ventilation; Pulmonary hypertension

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality in the United States¹. It is characterized by its chronic and progressive nature, often accompanied by acute exacerbations that significantly impact both health and pulmonary function over time². These recurrent exacerbations of COPD are known to have adverse effects on the progression of the disease, accelerating the decline in respiratory function and resulting in an overall diminished quality of life.

The implications of obesity and its associated complications extend beyond reducing life expectancy and quality of life. Obesity is often linked to other metabolic abnormalities such as systemic hypertension, diabetes mellitus and cardiovascular diseases, contributing to reduced life expectancy³⁻⁵. Several studies have demonstrated an inverse relation between COPD mortality and body mass index (BMI), reporting improved survival in overweight and obese patients compared to those of average weight, which has been referred to as the “obesity paradox⁶⁻⁸”. Additionally, a few studies have indicated worse outcomes in patients with both obesity and COPD⁹. In contrast, others have shown no changes in mortality or exacerbation risks in COPD patients with obesity^{10,11}.

Certain studies suggest that obesity does not always lead to metabolic abnormalities, leading to Metabolically Healthy Obesity (MHO)¹². However, the prevalence of MHO varies due to the absence of universally accepted criteria¹³.

Obesity is common among individuals with COPD and has been linked to a higher risk of acute exacerbations¹⁴. Some studies have suggested an increased likelihood of metabolic syndrome among those with airflow obstruction¹⁵. However, the prevalence and impact of metabolically healthy obesity (MHO) on hospitalizations for acute exacerbation of chronic obstructive pulmonary disease in elderly individuals are not well understood. This nationwide study aims to investigate the patterns and consequences of MHO in elderly AECOPD admissions from 2016 to 2020, shedding light on its prevalence.

Methods

Source of data

The National Inpatient Sample (NIS) databases (2016-

2020) of the Healthcare Cost and Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality (AHRQ) were used. The NIS is the largest publicly accessible all-payer inpatient healthcare dataset in the US. It contains discharge data representing approximately 20% of US hospitals from more than 48 states, comprising an average of 7 million unweighted discharges per year and approximately 35 million weighted nationwide discharges. The NIS has one primary diagnosis and up to 34 secondary discharge diagnoses for each inpatient admission. The Institutional Review Board (IRB) approval was not mandatory since the NIS contains deidentified data. For further information about the database, please visit the HCUP website.

Study population

We identified AECOPD hospitalizations in the elderly (≥ 65 years) using the ICD-10-CM and Revised Clinical Classifications Software (CCSR) codes. The CCSR is a scheme that collapses many ICD-10-CM (International Classification of Diseases, Ninth Revision, Clinical Modification) codes into fewer clinically essential categories, which are more suitable for descriptive statistics than individual ICD-10-CM codes. The ICD-10-CM codes used were J44.0 and J44.1.

Study outcomes

We assessed and compared the baseline demographics, comorbidities and outcomes of AECOPD hospitalizations in non-obese and MHO (excluding cases with hypertension, diabetes and hyperlipidemia) individuals. The primary outcomes are adjusted odds of all-cause mortality (ACM), respiratory failure (RF), Mechanical ventilation (MV), pulmonary hypertension (PH) and Heart failure with reduced ejection (HFrEF). Secondary outcomes included the mean length of hospital stay (in days) and hospital charges (\$) associated with AECOPD.

Statistical analyses

Pearson Chi-square test for categorical variables and Mann-Whitney U test for continuous variables [non-normal distribution] were applied to compare the baseline demographics and hospital characteristics between the two groups (without MHO vs. with MHO) among AECOPD hospitalizations. The categorical and continuous variables were expressed in percentages and mean \pm SD, respectively. We applied the discharge weight (DISCWT)

provided in the database to generate the national estimates and used complex sample modules.

After controlling for age, sex, race, median household income, insurance payer, rural/urban setting and obesity, multivariate regression models were planned to assess the risk of MHO in patients hospitalized for AECOPD. We evaluated predictors of MHO and related in-hospital mortality by univariate analysis. Coexisting comorbidities and patient features were adjusted with Multivariable regression analyses. Adjusted odds ratio (OR), 95% confidence interval (CI) and two-sided p-value of 0.05 were considered to account for logistic regression results. We utilized IBM SPSS Statistics 25.0 (IBM Corp, Armonk, New

York) software for all the statistical analyses.

Results

Baseline characteristics of the study population

Of 221,700 admissions for AECOPD, 5.7% were attributed to individuals with MHO. The AECOPD hospitalizations with MHO primarily consisted of females (6.6% vs. 4.6%) and had a younger median age (71 years vs. 73 years) compared to the cohorts without MHO. Most patients were from lower socioeconomic groups (32.6%) and Medicare beneficiaries (90%) compared to those without MHO. Whites comprised the majority of the study cohorts (87.1%) (**Table 1**).

Table 1: Baseline Characteristics of AECOPD Hospitalized Elderly with and without Metabolically Healthy Obesity (MHO), 2016-2020, National Inpatient Sample.

Variables	Non-Obese N=208955	Metabolically Healthy Obesity N=12745	P-Value
Age at Admission, Median [IQR]	73(69-80)	71(67-76)	<0.001 ^a
Indicator of Sex			<0.001 ^b
Male	44.0%	35.1%	
Female	56.0%	64.9%	
Payer Type			<0.001 ^b
Mediacare	90.0%	90.5%	
Medicaid	1.9%	1.8%	
Private incl HMO	7.3%	7.3%	
Self-Pay	0.8%	0.4%	
No charges	0.0%	0.0%	
Race			<0.001 ^b
White	87.1%	87.7%	
Black	6.2%	5.9%	
Hispanic	4.8%	5.1%	
Asian or Pacific Islander	1.3%	0.6%	
Native American	0.6%	0.7%	
Median Household Income National Quartile for Patient Zip Code			<0.001 ^b
0-25	34.2%	32.6%	
26-50	29.8%	28.7%	
51-75	21.2%	23.7%	
76-100	14.8%	15.0%	
Comorbidities			
Smoking	45.0%	49.0%	<0.001 ^b
Peripheral Vascular Disease	5.9%	5.0%	<0.001 ^b
Valvular disease	1.1%	1.2%	0.623 ^b
Prior MI	4.1%	4.0%	0.594 ^b
Prior TIA_Stroke without Neurologic deficit	4.2%	4.2%	0.704 ^b
Autoimmune Conditions	3.7%	5.7%	<0.001 ^b
Depression	11.8%	15.9%	<0.001 ^b
Drug Abuse	2.1%	2.4%	0.048 ^b
Hypothyroidism	12.1%	17.2%	<0.001 ^b
Other thyroid disorders	1.1%	1.1%	0.941 ^b
Renal failure, severe	0.2%	0.3%	<0.001 ^b
Alcohol abuse	3.8%	3.1%	<0.001 ^b
Bariatric Surgery Status	0.3%	1.6%	<0.001 ^b
Outcome			
All-Cause mortality	2.3%	1.8%	<0.001 ^b

Respiratory Failure	42.0%	51.0%	<0.001 ^b
HFrEF	3.2%	4.1%	<0.001 ^b
Pulmonary embolism	0.6%	0.6%	0.398
Pulmonary hypertension	5.4%	8.8%	<0.001 ^b
Disposition of patient (uniform)			<0.001 ^b
routine	58.0%	56.1%	
Transfer to other short term	1.6%	0.9%	
Other transfers incl SNF ICF	16.3%	16.8%	
Home Healthcare	20.2%	23.7%	
Length of Stay (Days), Median (IQR)	3(2-5)	4(2-6)	<0.001 ^a
Hospital Cost (USD), Median (IQR)	25696\$ (15318\$-44282\$)	31248\$ (18644\$-54482\$)	<0.001 ^a

AECOPD= A cute Exacerbation of Chronic Obstructive Pulmonary Disease, MI= Myocardial infarction, TIA= Transient Ischemic Attack, SNF= Skilled Nursing Facility, ICF= Intermediate Care Facility, HFrEF= Heart Failure with reduced ejection fraction, IQR= Inter Quartile Range

^a.Statistical test: Mann-Whitney U Test, p value <0.05 is significant.

^b.Statistical test: Pearson Chi Square Test, p value <0.05 is significant.

Baseline comorbidities

Co-morbid conditions such as smoking (49% vs. 45%), depression (15.9% vs. 11.8%), autoimmune conditions (5.7% vs. 3.7%) and hypothyroidism (17.2% vs. 12.1%), were more prevalent in the MHO group as compared to the non-MHO group (all p<0.001) (Table 2). Demographics and results are illustrated in the central figure (Figure 1).

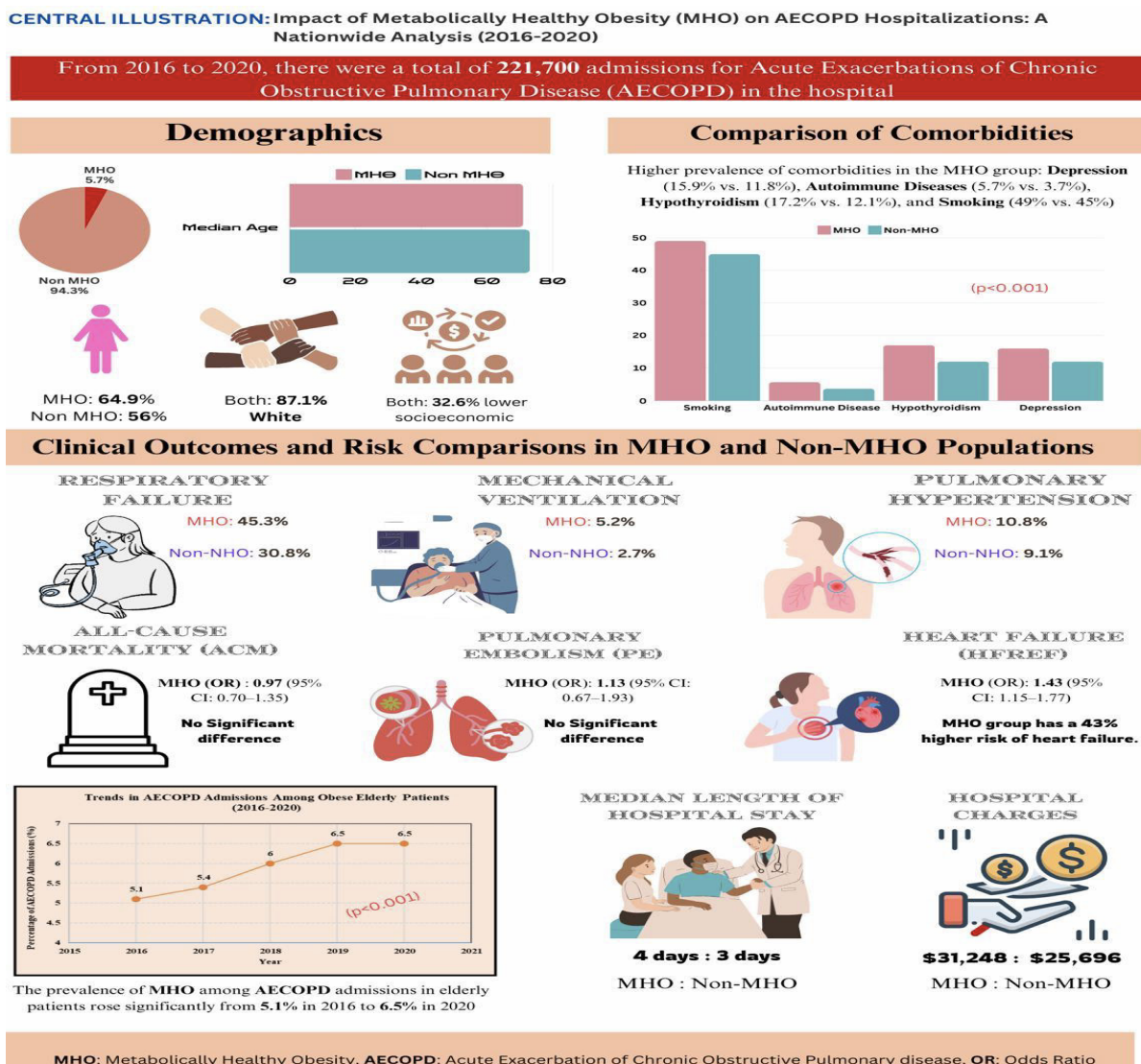


Figure 1: Central illustration explaining the demographics and findings

Table 2: Multivariable odds of AECOPD hospitalized Elderly with vs without metabolically healthy obesity, 2016-2020, National Inpatient Sample.

95%CI				
In Hospital Outcomes	Adjusted Odds Ratio	LL	UL	P-Value
All-Cause Mortality	0.97	0.70	1.35	0.856
Respiratory Failure	1.31	1.21	1.43	<0.001
Mechanical Ventilation	1.32	1.03	1.69	0.026
HFrEF	1.43	1.15	1.77	0.001
Pulmonary Embolism	1.13	0.67	1.93	0.642
Pulmonary Hypertension	1.73	1.48	2.01	<0.001

AECOPD: Acute Exacerbation of Chronic Obstructive Pulmonary Disease, HFrEF= Heart Failure with reduced Ejection Fraction, LL= Lower Limit, UL= Upper Limit, p<0.05 significant at 95% Confidence Interval.

Multivariate Logistic Regression Model adjusted for age, sex, payer type, race, median household income national quartile for patient ZIP code, alcohol abuse, autoimmune condition, depression, liver disease, moderate to severe, peripheral vascular disease, renal failure, severe, hypothyroidism, other thyroid disorders, valvular disease, smoking, prior MI, prior TIA_stroke without Neurologic deficit, bariatric Sx Status

Prevalence of MHO

The prevalence of MHOs significantly increased from 5.1% in 2016 to 6.5% in 2020. Notably, there were significant elevations in RF (30.8% to 45.3%), MV (2.7% vs. 5.2%) and PH (9.1% vs. 10.8%), all $p < 0.001$.

Gender comparison of MHO in AECOPD hospitalizations

Female patients hospitalized for AECOPD were more likely to have MHO than male patients (6.6% vs 4.6%).

Impact of MHO on in-hospital outcomes of AECOPD hospitalizations

On multivariate analysis, individuals with MHO have an increased risk of RF (OR: 1.31, 95% CI: 1.21-1.43, $p < 0.001$), PH (OR: 1.73, 95% CI: 1.48-2.01, $p < 0.001$) and HFrEF (OR: 1.43, 95% CI: 1.15-1.77, $p = 0.001$) compared to individuals without MHO. Similarly, individuals with MHO have an elevated risk of MV (OR: 1.32, 95% CI: 1.03- 1.69, $p = 0.026$) compared to individuals without MHO. On the other hand, there was no significant difference between individuals with MHO and without MHO on ACM (OR: 0.97, 95% CI: 0.70-1.35, $p = 0.86$) and PE (OR: 1.13, 95% CI: 0.67-1.93, $p = 0.64$) (Table 3).

Length of stay and expenditure in AECOPD hospitalizations with MHO

MHO cohorts have increased length of stay (4 vs. 3 days) and hospital expenses (\$31,248 vs. \$25,696) compared to non-MHO cohorts.

Discussion

Prior research has suggested a connection between lower BMI and adverse outcomes for individuals with chronic obstructive pulmonary disease (COPD). Over the 21st century, there has been an increase in the proportion of COPD patients receiving pharmaceutical treatment who are obese¹⁶. This study represents one of the most extensive nationwide investigations

to evaluate the influence of metabolically healthy obesity (MHO) on hospitalizations due to acute exacerbation of COPD (AECOPD) among the elderly. The main findings of this study are as follows: 5.7% of COPD-related hospitalizations involved MHO, with a majority of the affected individuals being from low socio-economic backgrounds and being beneficiaries of Medicare. Among COPD patients, a higher percentage of women (6.6% vs. 4.6%) had MHO and the study population predominantly consisted of individuals of white race (87.1%). It is widely accepted that obesity is associated with various adverse health conditions. This research showed an increased likelihood of MHO after adjusting for co-morbidities such as smoking (49% vs. 45%), depression (15.9% vs. 11.8%), autoimmune conditions (5.7% vs. 3.7%) and hypothyroidism (17.2% vs. 12.1%). Furthermore, the prevalence of MHO increased by 1.4% between 2016 and 2020, accompanied by increases in respiratory failure (14.5%), mechanical ventilation (2.5%) and pulmonary hypertension (1.7%). MHO had a significant impact on the elderly in terms of COPD-related hospitalizations, leading to increased occurrences of respiratory failure, pulmonary hypertension, heart failure with reduced ejection fraction and mechanical ventilation, in addition to prolonged hospital stays and higher healthcare expenses.

Numerous prior studies have postulated that the connection between Metabolically Healthy Obesity (MHO) and an elevated incidence of Acute Exacerbations of COPD (AECOPD) is partially attributed to the higher occurrence of comorbidities among obese individuals^{14,17,18}. Correspondingly, other findings indicate that the heightened risk of heart failure (HF) observed in obese patients with COPD is linked to the widespread systemic inflammation and metabolic disturbances associated with COPD. Alqarni, et al.¹⁴ found that obese patients with COPD exhibited a greater prevalence of comorbidities and higher rates of intensive care unit (ICU) admissions in comparison to normal-weight patients with COPD. A recent study by Uzunlar, et al.¹⁷ put forward the prevalence of various comorbidities in obese and non-obese COPD patients, with cardiovascular complications being predominant in the former. They proposed that the chronic inflammatory process plays a pivotal role in the onset of cardiovascular diseases, especially among patients with COPD, as inflammatory mediators propagate from the lungs to the systemic circulation, contributing to comorbidities.

Furthermore, Park, et al.¹⁸ highlighted the association of MHO with an increased risk of comorbidities, particularly cardiovascular ones, in COPD patients, suggesting that obesity negatively impacts COPD prognosis by increasing hospital readmissions and mortality rates. Likewise, Tian, et al.¹⁹ indicated an elevated risk of readmission in elderly COPD patients with MHO, while Lambert, et al.²⁰ suggested that the severity of obesity significantly influences COPD outcomes, with severe obesity leading to more severe exacerbations, increased healthcare utilization and prolonged hospital stays. Finally, Verberne, et al.²¹ demonstrated a connection between obesity and higher rates of hypertension, diabetes, osteoarthritis and heart failure in patients with mild-to-moderate COPD. However, there is limited evidence of coronary artery disease akin to our study.

The impact of Metabolically Healthy Obesity (MHO) on hospitalizations for Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD) has been investigated in various

studies. Gursel, et al.²² found that obese AECOPD patients were hospitalized at a higher rate, primarily due to pulmonary edema and less frequently due to pulmonary infections, compared to non-obese patients. Additionally, obese patients required higher levels and frequencies of mechanical ventilation (MV) to reduce their arterial carbon dioxide tension (PaCO₂) levels to less than 50 mmHg. Furthermore, studies by Apostolovic, et al.²³ revealed a high prevalence of COPD in elderly patients with heart failure (HF) and abdominal obesity, suggesting a significant correlation. COPD is characterized by sustained hypoxemia, which increases peripheral chemoreceptor activity and elevates sympathetic activity²⁴.

Moreover, higher oxidative stress and lung hyperinflation contribute to increased sympathetic activity in COPD patients. In the context of obesity, it is associated with increased sympathetic activity as leptin, produced by adipose tissue, acts on the hypothalamus²⁵. Consequently, obesity exacerbates the poor prognosis of AECOPD. Elevated sympathetic activity is linked to increased cardiovascular morbidity and end-organ damage²⁶, leading to HF through cardiac remodelling and pulmonary hypertension due to chronic pulmonary artery vasoconstriction. Ultimately, this results in hypercapnic respiratory failure, necessitating increased frequencies of MV.

The research by Alqarni, et al.¹⁴ challenges our existing focus by suggesting that mild obesity may have protective effects on lung function. They propose that symptoms such as dyspnea and reduced quality of life in obese individuals may lead to earlier medical intervention compared to normal-weight individuals. Their study also highlights a three-to-fourfold increase in the risk of heart failure in obese patients with COPD. Similarly, Channick, et al.²⁷ suggest that obesity may act as a protective factor in COPD patients, impacting all-cause mortality and exacerbation frequency. These conflicting findings are based on the hypothesis that metabolically healthy obese (MHO) patients exhibit neurohormonal effects of fatty tissue, increased adipose mass leading to local tissue hypoxia and chronic inflammation and potential additional treatments upon hospital admission²⁸.

In terms of the demographic profile affected by MHO, studies by Lambert, et al.²⁰ align with our research, indicating a higher prevalence of MHO in female COPD patients. This trend can be attributed to the narrower airway caliber in women and airway hyper-responsiveness. Additionally, factors such as depression and anxiety were more prevalent in females, contributing to a poorer prognosis in this demographic group. Furthermore, women exhibit higher leptin levels, contributing to chronic systemic inflammation and increased COPD exacerbation frequency. Conversely, research by Tian, et al.¹⁹ demonstrated a comparable prevalence of MHO between male and female COPD patients regarding hospital readmissions.

These findings emphasize the significance of managing MHO to improve the quality of life in elderly patients hospitalized for acute exacerbations of COPD, particularly respiratory and cardiac complications, which are the primary causes of mortality in this demographic. Implementing strategies to prevent weight gain in high-risk patients is a viable management option, as improving health outcomes becomes challenging once obesity has been established or continues to increase. Monitoring weight fluctuations and changes in smoking status over time can aid in identifying trends and planning appropriate interventions for patient management.

The study is robust due to its innovative research question and the use of a comprehensive nationwide dataset. This extensive dataset enabled the study to identify AECOPD hospitalizations in older individuals using ICD-10-CM and CCSR codes, which were then grouped into clinically relevant categories for more accurate descriptive statistics. The study also accounted for confounding variables, including age, sex, race, median household income, insurance payer, rural/urban setting and obesity. However, the study has limitations. Firstly, using the NIS, an administrative dataset, increases the potential for administrative coding errors and selection bias, despite the use of validated codes. Additionally, due to the retrospective dataset, the study was unable to assess the severity of COPD and obesity. Consequently, the findings may not be universally applicable to the entire elderly population with COPD, as the risk of MHO and subsequent outcomes may vary depending on hospital bed size, location and availability of healthcare resources.

Conclusion

This study's findings reveal that nearly 5.7% of hospitalizations for acute exacerbations of chronic obstructive pulmonary disease (AECOPD) among elderly individuals in the United States from 2016 to 2020 were linked to metabolically healthy obesity (MHO). The study underscores an upward trend of MHO among older patients hospitalized for AECOPD. MHO is associated with an elevated risk of respiratory and cardiac complications, more extended hospital stays and increased healthcare costs. Despite these risks, MHO did not significantly impact overall mortality. Screening elderly AECOPD patients for MHO can enable the development of tailored treatment plans and interventions. Addressing both COPD exacerbations and obesity-related metabolic factors requires a comprehensive, multidisciplinary approach. These findings underscore the need for further research to elucidate the mechanisms underlying these associations.

Competing Interests

None of the authors has any conflict of interest.

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Authors' Contributions

VC and SN led the study and contributed to the analysis and writing of the original manuscript. RD supervised the project and helped with editing. The remaining authors contributed to the writing of the manuscript original draft and contributed in revision.

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Disclosure

All authors have no conflict of interest to disclose that is related to this article

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