The Association of Weight With the Detection of Airflow Obstruction and Inhaled Treatment Among Patients With a Clinical Diagnosis of COPD

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BACKGROUND: Most patients with a clinical diagnosis of COPD have not had spirometry to confirm airflow obstruction (AFO). Overweight and obese patients report more dyspnea than normal weight patients, which may be falsely attributed to AFO. We sought to determine whether overweight and obese patients who received a clinical diagnosis of COPD were more likely to receive a misdiagnosis (ie, lack of AFO on spirometry) and be subsequently treated with inhaled medications.

METHODS: The cohort comprised US veterans with COPD (*International Classification of Diseases, 9th Revision*, code; inhaled medication use; or both) and spirometry measurements from one of three Pacific Northwest Veterans Administration Medical Centers. The measured exposures were overweight and obesity (defined by BMI categories). Outcomes were (1) AFO on spirometry and (2) escalation or deescalation of inhaled therapies from 3 months before spirometry to 9 to 12 months after spirometry. We used multivariable logistic regression with calculation of adjusted proportions for all analyses.

RESULTS: Fifty-two percent of 5,493 veterans who had received a clinical diagnosis of COPD had AFO. The adjusted proportion of patients with AFO decreased as BMI increased ($P < .01$ for trend). Among patients without AFO, those who were overweight and obese were less likely to remain off medications or to have therapy deescalated (adjusted proportions: normal weight, 0.69 [95% CI, 0.64-0.73]; overweight, 0.62 [95% CI, 0.58-0.65; $P = .014$]; obese, 0.60 [95% CI, 0.57-0.63; $P = .001$]).

CONCLUSIONS: Overweight and obese patients are more likely to be given a misdiagnosis of COPD and not have their inhaled medications deescalated after spirometry demonstrated no AFO. Providers may be missing potential opportunities to recognize and treat other causes of dyspnea in these patients.

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ABBREVIATIONS: AFO = airflow obstruction; GOLD = Global Initiative for Chronic Obstructive Lung Disease; LLN = lower limit of normal; VA = Veterans Administration

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COPD and obesity are common and frequently coexisting conditions of increasing prevalence.^{1,2} Obese patients with COPD have greater symptom burden and receive more inhaled medications for any severity of airflow limitation.³ In general, obese patients are more likely than patients who are normal weight to report dyspnea, highlighting the difficulty in attributing symptoms of dyspnea to airflow obstruction (AFO) or to obesity and deconditioning.⁴ Despite this challenge, primary care clinicians report feeling comfortable diagnosing and treating patients with COPD based on history and examination alone, in the absence of confirmatory spirometry.^{5,6} Spirometry is recognized as the gold standard in the diagnosis of COPD,⁶⁻⁸ yet only one-third of patients with COPD have had spirometry in the 2 years prior to and

within 6 months after diagnosis.^{8,9} Diagnosis of COPD without spirometry may increase the possibility of misclassification and mistreatment, particularly among patients who have more than one etiology for dyspnea.

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Our goal was to assess whether in patients with clinically diagnosed COPD obesity is associated with a misdiagnosis defined as an absence of AFO on spirometry. Among such patients without AFO, we assessed whether obese patients were more likely than patients who are normal weight to receive potential inappropriate treatment defined as inhaled medications prescribed in the absence of AFO.

Materials and Methods

Study Design, Setting, and Subjects

This study was a secondary analysis of data collected from a cohort of US veterans from three Pacific Northwest Veterans Administration (VA) medical centers who received a clinical diagnosis of COPD and who had subsequent spirometry performed between January 2003 and December 2007. The index date was defined as the date of first spirometry within the study time period, and patients were subsequently followed for 2 years; the censoring date was January 1, 2009. Clinical diagnosis of COPD was defined by meeting at least one of the four criteria shown in Figure 1 and in e-Appendix 1. Exclusion criteria are also shown in Figure 1 and included in e-Appendix 1. Importantly, we excluded veterans with clinically diagnosed asthma (*International Classification of Diseases, 9th Revision*, codes 493.0, 493.1, 493.8, 493.9) to avoid potential misclassification. The institutional review board of the VA Puget Sound Healthcare System approved all protocols as well as a waiver of patient consent for this study (IRB project approval number 01386).

Data Collection

Data were collected from the VISN (Veterans Integrated Service Networks) 20 data warehouse, a relational database that includes data (clinical and nonclinical) for all patients receiving care at VA facilities throughout the Pacific Northwest. Spirometric measurements were obtained from the data warehouse or directly from the spirometer.

Exposures

BMI categories were as defined by the World Health Organization: (1) normal weight, $18.5 \leq \text{BMI} < 25.0 \text{ kg/m}^2$; (2) overweight, $25.0 \leq \text{BMI} < 30.0 \text{ kg/m}^2$; (3) class I obesity, $30.0 \leq \text{BMI} < 35.0 \text{ kg/m}^2$; (4) class II obesity, $35.0 \leq \text{BMI} < 40.0 \text{ kg/m}^2$; or (5) class III obesity, $\text{BMI} \geq 40.0 \text{ kg/m}^2$.¹⁰ For analyses of medication changes following spirometry, classes I to III obesity were collapsed into a single category of $\text{BMI} \geq 30.0 \text{ kg/m}^2$.

Outcomes

AFO was defined as a postbronchodilator value of FEV_1/FVC below the lower limit of normal (LLN).¹¹ Additional details are provided in e-Appendix 1. All analyses were done using the GOLD (Global Initiative for Chronic Obstructive Lung Disease) definition of AFO ($\text{FEV}_1/\text{FVC} < 70\%$).⁷

Among patients with COPD but no AFO, we examined whether inhaled medications were escalated or deescalated in the 9 to 12 months after the index date compared with the 3 months prior to the index date. Medication dispensation data were available for inhaled corticosteroids, long-acting β -agonists, ipratropium bromide, and short-acting β -agonists. Data on tiotropium use data were not collected because of the limited use of this medication within the VA during the study period.

Medication data were examined in 3-month blocks. Initial medication dispensation was in the 3 months prior to the index date. Therapeutic escalation or deescalation at 9 to 12 months after the index date was defined as stepping up or down by any degree within four levels defined as no medication, short-acting medication only, one long-acting medication, or two long-acting medications.

Statistical Analysis

We used multivariable logistic regression and calculated adjusted proportions using mean values for all covariates. Potential confounding covariates were added to models en bloc (e-Appendix 1) and were retained in the final models if $P \leq .10$. We performed additional sensitivity analyses that excluded 494 patients who entered the cohort based only on inhaled medication use to address the possibility that some of these patients may have been empirically treated for asthma not COPD. Finally, because postbronchodilator spirometry is needed to demonstrate incompletely reversible AFO among patients with COPD, we performed a sensitivity analysis restricting the cohort to patients who had a postbronchodilator FEV_1/FVC ratio available ($n = 4,634$).

Results

Description of the Cohort

A total of 14,541 veterans had spirometry at one of three Pacific Northwest VA hospitals during the study period. Of those, 3,967 met exclusion criteria. Of the remaining 10,574 patients, 5,493 met

inclusion criteria and made up the final cohort (Fig 1).

Patients were mostly older white men (Table 1). Of the 5,493 patients in the cohort, approximately 25% were normal weight, 35% were overweight, 23% had class I obesity, 10% had class II obesity, and 7% had class III

Figure 1 – Cohort formation. ICD.9 = International Classification of Diseases, 9th Revision.

obesity. Patients with a higher BMI were younger and less likely to have smoked in the year prior to the index date. The prevalence of comorbidities, such as sleep apnea, hypertension, and diabetes, was greater among patients with higher BMIs (Table 1).

Proportion of Veterans With a Clinical Diagnosis of COPD and AFO by BMI Class

The adjusted proportion of patients with AFO (defined by LLN criteria) detected by spirometry decreased with each level of obesity ($P < .01$ for trend) (Table 2). These results were robust when adjusted for age, smoking status in the prior year, white race, comorbidities, oral steroid use in the prior year, and site of care. The adjusted proportion of patients with AFO who were normal weight was 0.64 (0.61-0.66) compared with 0.53 (0.50-0.55, $P \leq .001$) among overweight patients, 0.44 (0.41-0.47, $P \leq .001$) among patients with class I obesity, 0.41 (0.37-0.46, $P \leq .001$) among patients with class II obesity, and 0.37 (0.32-0.43, $P \leq .001$) among patients with class III obesity (Table 2). Using the GOLD definition of airflow limitation produced similar results (data not shown).

Medication Escalation and Deescalation After Spirometry Showed No AFO

Of the 2,680 patients who did not have evidence of AFO by spirometry (LLN), 53% were prescribed one or more inhaled medications during the 3-months prior to spirometry (Table 3). As seen in Table 3, overweight and obese patients were more likely than normal weight patients to be on an inhaled medication prior to spirometry. Similarly, 9 to 12 months after spirometry, 41% of patients without AFO were on an inhaled medication, with more frequent prescription in overweight and obese patients.

We assessed deescalation of inhaled medication therapy and whether patients who did not have AFO remained off these medications. Overweight and obese patients were significantly less likely to experience deescalation of therapy or remain off therapy than were normal weight patients ($P < .01$ for trend) (Tables 4, 5). At the same time, overweight and obese patients were more likely to remain on maximal therapy or have intensification of treatment than were normal weight patients.

TABLE 1] Baseline Characteristics

Characteristic	Normal Weight (n = 1,377)	Overweight (n = 1,901)	Class I Obesity (n = 1,275)	Class II Obesity (n = 572)	Class III Obesity (n = 368)	P Value
Age, y	65.7 ± 11.4	66.2 ± 11.0	65.3 ± 10.9	64.0 ± 9.6	61.4 ± 8.8	≤ .001
Male sex	97.1	97.0	96.7	96.5	94.3	.10
White race	76.5	77.8	77.5	81.3	75.8	.19
History of smoking	53.7	42.8	37.1	36.7	33.4	≤ .001
Site						≤ .001
Site 1	34.1	34.6	31.9	30.1	25.8	
Site 2	54.9	50.4	51.5	54.6	54.4	
Site 3	11.0	15.0	16.6	15.4	19.8	
Comorbidities in prior year						
ACS	2.8	3.0	3.1	2.8	4.1	.76
CHF	10.9	13.4	17.0	21.2	30.4	≤ .001
Depression	20.4	21.2	22.2	21.2	29.1	.008
Diabetes	8.9	16.9	29.7	38.5	51.9	≤ .001
Sleep apnea	2.2	4.0	9.7	20.3	37.8	≤ .001
HTN	44.6	54.5	63.2	72.2	75.5	≤ .001
AFO (LLN) present	67.0	54.0	42.3	37.1	29.9	≤ .001
On oral steroids in prior year	14.2	13.7	15.8	14.3	19.3	.06

Data are presented as mean ± SD or %. Normal weight, $18.5 \leq \text{BMI} < 25 \text{ kg/m}^2$; overweight, $25 \leq \text{BMI} < 30 \text{ kg/m}^2$; class I obesity, $30 \leq \text{BMI} < 35 \text{ kg/m}^2$; class II obesity, $35 \leq \text{BMI} < 40 \text{ kg/m}^2$; and class III obesity, $\text{BMI} \geq 40 \text{ kg/m}^2$. ACS = acute coronary syndrome; AFO = airflow obstruction; CHF = congestive heart failure; HTN = hypertension; LLN = lower limit of normal.

($P = .09$ for trend) (Tables 4, 5). e-Figure 1 shows escalation and deescalation patterns for specific medication categories among all patients without AFO.

Sensitivity Analyses

We repeated the analyses in a subset of 4,999 patients who entered the cohort based on an *International Classification of Diseases, 9th Revision*, COPD codes (inclusion criteria 1-3 [e-Appendix 1]). Results were similar to those described previously (e-Appendix 1,

e-Tables 1, 2). Excluding the 859 patients who did not have postbronchodilator spirometry values, we found similar results (e-Tables 3, 4), with overweight and obese patients less likely to have AFO on subsequent spirometry and less likely to deescalate or remain off therapy in its absence. Overweight patients remained more likely to escalate or stay on maximal therapy despite a lack of AFO, although the association between obese patients and escalation of therapy no longer persisted.

TABLE 2] Adjusted Proportion of Veterans With COPD With AFO (Defined by LLN) on Subsequent Spirometry

BMI Class ^a	Proportion (95% CI)	P Value	Adjusted Proportion ^b (95% CI)	P Value ^c
Normal weight	0.67 (0.64-0.69)	Reference	0.64 (0.61-0.66)	Reference
Overweight	0.54 (0.52-0.56)	≤ .001	0.53 (0.50-0.55)	≤ .001
Class I obesity	0.43 (0.40-0.45)	≤ .001	0.44 (0.41-0.47)	≤ .001
Class II obesity	0.37 (0.33-0.41)	≤ .001	0.41 (0.37-0.46)	≤ .001
Class III obesity	0.30 (0.25-0.35)	≤ .001	0.37 (0.32-0.43)	≤ .001

See Table 1 legend for expansion of abbreviations.

^aNormal weight ($18.5 \leq \text{BMI} < 25 \text{ kg/m}^2$), overweight ($25 \leq \text{BMI} < 30 \text{ kg/m}^2$), class I obesity ($30 \leq \text{BMI} < 35 \text{ kg/m}^2$), class II obesity ($35 \leq \text{BMI} < 40 \text{ kg/m}^2$), class III obesity ($\text{BMI} \geq 40 \text{ kg/m}^2$).

^bAdjusted for mean values of age, smoking status in prior year, white race, comorbidities in the prior year (CHF, hypertension, depression, diabetes, sleep apnea), use of oral steroids in the prior year, and site of care.

^c $P < .001$ for trend.

TABLE 3] Percentage of Patients Without AFO on Inhaled Medications Before and After the Index Date

Patient Group	3 Mo Before Spirometry				9 to 12 Mo After Spirometry			
	Any Inhaled Medication	Short-Acting Only	One Long-Acting	Two Long-Acting	Any Inhaled Medication	Short-Acting Only	One Long-Acting	Two Long-Acting
All patients without AFO (n = 2,680)	52.6	34.3	14.5	3.8	40.9	23.6	12.5	4.8
Normal weight (n = 455)	44.2	29.5	12.6	2.2	33	20.2	10.1	2.6
Overweight (n = 875)	50.2	34.1	12.2	3.9	40.2	23	11.2	6.1
Obese (n = 1,350)	57	36.1	16.7	4.3	44.1	25.2	14.2	4.7

Data are presented as %. Normal weight, $18.5 \leq \text{BMI} < 25 \text{ kg/m}^2$; overweight, $25 \leq \text{BMI} < 30 \text{ kg/m}^2$; obese, $\text{BMI} \geq 30 \text{ kg/m}^2$. See Table 1 legend for expansion of abbreviation.

Discussion

We demonstrate that overweight and obese patients were more likely than normal weight patients to receive a misdiagnosis of COPD and more likely to be inappropriately treated with inhaled medications. This study is the first, to our knowledge, to show a dose-response relationship between BMI and COPD misdiagnosis. COPD and obesity are already associated with substantial economic costs, which will increase as the incidence of COPD and obesity continue to rise.^{12,13} Treating individuals who do not truly have COPD with costly medications that may be ineffective or potentially harmful could result in lower quality of care for this patient population at an increased expense. As the prevalence of both obesity and COPD increase, substantial financial resources expended for such care have negative implications for patients and health-care payers.

Accurate diagnosis of COPD is crucial to the delivery of efficient, cost-effective, and high-quality medical care. Although spirometry is considered the gold standard for COPD diagnosis and is a National Quality Forum-endorsed measure of care quality, many patients with COPD continue to be treated for COPD despite never

having had spirometry.^{8,9,14} In addition, misdiagnosis is common; many patients given a clinical diagnosis of COPD do not have AFO on spirometry.^{15,16}

We found that as BMI class increased, the proportion of patients with AFO on spirometry decreased, supporting an association between weight and misclassification of COPD consistent with prior studies. Walters et al¹⁵ found that among primary care patients with COPD, $\text{BMI} \geq 25 \text{ kg/m}^2$ was associated with a higher likelihood of COPD misdiagnosis when confirmatory spirometry was performed. In a study of adults undergoing confirmatory spirometry prior to discharge after hospitalization for COPD exacerbation, Prieto Centurion et al¹⁶ found that obese patients were four times as likely as normal weight patients to lack AFO. These findings have important implications because obese patients are at greater risk of diabetes, hypertension, coronary heart disease, and mortality compared with normal weight patients.¹⁷⁻¹⁹ Among obese patients misdiagnosed with COPD, missing the chance to diagnose and treat other conditions associated with dyspnea, particularly cardiovascular disease, may put them at even greater risk of poor health outcomes.

TABLE 4] Adjusted Proportion of Misdiagnosed Veterans (by BMI Class) Who Had Changes in Medication Regimen Between 3 Mo Prior to and 9 to 12 Mo After Spirometry: Model 1

BMI Class ^a	Proportion (95% CI)	P Value	Adjusted Proportion (95% CI) ^b	P Value
Normal weight	0.69 (0.65-0.73)	Reference	0.69 (0.64-0.73)	Reference
Overweight	0.62 (0.59-0.65)	.012	0.62 (0.58-0.65)	.014
Obese	0.59 (0.57-0.62)	$\leq .001$	0.60 (0.57-0.63)	.001

Model 1 had deescalation in therapy or remained off therapy.

^aNormal weight ($18.5 \leq \text{BMI} < 25 \text{ kg/m}^2$), overweight ($25 \leq \text{BMI} < 30 \text{ kg/m}^2$), and obese ($\text{BMI} \geq 30 \text{ kg/m}^2$).

^bAdjusted for mean values of white race, acute coronary syndrome in the prior year, oral steroid use in the prior year, and site of care. $P = .003$ for trend.

TABLE 5] Adjusted Proportion of Misdiagnosed Veterans (by BMI Class) Who Had Changes in Medication Regimen Between 3 Mo Prior to and 9 to 12 Mo After Spirometry: Model 2

BMI Class ^a	Proportion (95% CI)	P Value	Adjusted Proportion (95% CI) ^b	P Value
Normal weight	0.14 (0.11-0.17)	Reference	0.14 (0.11-0.18)	Reference
Overweight	0.20 (0.17-0.23)	.009	0.20 (0.18-0.23)	.008
Obese	0.19 (0.17-0.21)	.015	0.19 (0.17-0.21)	.02

Model 2 had escalation in therapy or stayed on maximal therapy.

^aNormal weight ($18.5 \leq \text{BMI} < 25 \text{ kg/m}^2$), overweight ($25 \leq \text{BMI} < 30 \text{ kg/m}^2$), and obese ($\text{BMI} \geq 30 \text{ kg/m}^2$).

^bAdjusted for mean values of oral steroid use in the prior year and site of care. $P = .09$ for trend.

Many primary care providers, often the only providers managing patients with mild to moderate COPD, do not follow established guidelines in the management of COPD, particularly regarding inhaled medication use.^{20,21} Salinas et al²¹ showed that only one of four primary care physicians adhered > 90% of the time to guideline recommendations regarding spirometry or long-acting bronchodilator use. Although spirometry is not frequently used in COPD diagnosis, (appropriate) prescription of inhaled medications increases after spirometry is used in the diagnosis of COPD in the primary care setting.^{5,22} Fewer data are available about cessation of inhaled medications if spirometry shows no evidence of AFO. The present results are concerning because inhaled medications used to treat COPD are not benign.²³⁻²⁵ Inhaled corticosteroids have been demonstrated to increase the risk of pneumonia, and older patients initiating a long-acting β -agonist or a long-acting anticholinergic have been shown to be at increased risk of acute coronary syndrome and heart failure.^{23,26,27}

In the present cohort, overweight and obese patients were less likely to experience deescalation or to stay off inhaled medications and were more likely to experience escalation of therapy or remain on maximal therapy after negative spirometry results compared with normal weight patients. This finding has implications for safety, cost, and quality of care. Patient overuse of inhaled medications is not uncommon in COPD; patients without COPD who receive and overuse inhaled medications may be at greater risk of dose-dependent adverse effects without the benefit of symptom relief.²⁸⁻³⁰ Furthermore, studies have shown that as the number of medications increases, medication adherence often decreases; thus, the addition of medications that are not indicated may affect patient adherence with other necessary medications, further compromising health.³¹ Overweight and obese patients could be especially vulnerable to such effects because they have more comorbidities, greater use of prescription medications, and higher pharmacy costs than normal weight patients.^{12,17,32}

It is possible that patients who did not have AFO did have emphysema or simple chronic bronchitis. Although there has been intensive study surrounding the clinical meaning of emphysema found on CT scans, in particular, there is no evidence that treating either of these conditions with inhaled medications in the absence of AFO is beneficial, and such treatment is not recommended by current guidelines.^{7,33-35}

The relationship between obesity and pulmonary function is complex. During cardiopulmonary exercise testing, obese patients with COPD do not report greater intensity of dyspnea or experience more exercise limitation than normal weight patients with similar AFO, perhaps because obesity can reduce functional residual capacity.³⁶ However, we have demonstrated that obese patients with COPD report more activity-related dyspnea (by modified Medical Research Council score) and worse health-related quality of life than do normal weight patients with the same severity of AFO.³ Severity of dyspnea may be related to degree of hyperinflation, which is affected by obesity as well as by COPD severity.³⁶ We did not have lung volume data, making it difficult to further speculate on how such relationships may have contributed to the results. It is also possible that inhaled bronchodilators may have differential effects on airways of obese patients who have higher small airway resistance at baseline due to lower lung volumes.³⁷ We also did not have data on waist-hip circumference; body fat distribution may influence respiratory dynamics and, therefore, symptoms.³⁷

Limitations

The present cohort comprising US veterans yielded a study population of largely white older men, which could limit generalizability. Additionally, the results apply only to those patients who had spirometry. Because pulmonologists are more likely to use spirometry in COPD diagnosis and management of inhaled medications, it is possible that the study underestimates the magnitude of the associations between obesity and COPD

misdiagnosis and between obesity and management of inhaled medications after spirometry.^{14,20} Additional limitations include those involved with the use of administrative data. However, use of the VA system allowed access to complete, integrated health-care records, including information on medication dispensation. Although we enrolled patients through 2007 and followed up through 2009, GOLD and other guidelines have recommended spirometry for a COPD diagnosis since 2001, and prior to that, this was included in American Thoracic Society treatment practice guidelines. More current articles continue to suggest that the majority of patients receive COPD diagnoses without spirometry, suggesting that practice patterns in this area have been relatively stable over the past several years.^{6,38,39}

We do not know whether veterans had additional spirometry after study entrance or at non-VA facilities. It is also possible that the providers adjusting patient medications were not aware of spirometry results, although the VA has an integrated system where notes and test results are centralized in a common electronic medical record. Some veterans without AFO at the index date may have gone on to have repeat spirometry that did show AFO that may have subsequently guided medication decisions, although we expect that repeat spirometry was uncommon. To address the possibility that

asthma may have been misclassified as COPD, we performed a sensitivity analysis excluding the 494 patients who entered the cohort only by inhaled medication use, and the results were unchanged.

Despite these limitations, the study has several strengths, including a large sample size that allowed us to examine the effects of BMI on misdiagnosis across five BMI classes and across three different centers, decreasing the likelihood that the results were influenced by local practice patterns. We also used both the LLN and the GOLD definitions of AFO, achieving similar results for both despite the limitations of each method.¹⁸ Regardless of the AFO criteria used, we found that as BMI increased, so did the likelihood of COPD misdiagnosis.

Conclusions

Overweight and obese patients are more likely than normal weight patients to be given a misdiagnosis of COPD and are more likely to be treated with inhaled medications even after spirometry shows no AFO. Missing the correct etiology of dyspnea or other symptoms indicative of COPD suggests that providers may be missing potential opportunities to recognize and treat other causes of dyspnea in overweight and obese patients, thereby missing opportunities to improve quality of care, reduce costs, and decrease medication use.

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Additional information: The e-Appendix, e-Figures, and e-Tables can be found in the Supplemental Materials section of the online article.

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