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ORIGINAL RESEARCH

Mortality and Exacerbation Risk by Body Mass Index in Patients with COPD in TIOSPIR and UPLIFT

Nirupama Putcha[1], Antonio R. Anzueto[2], Peter M. A. Calverley[3], Bartolomé R. Celli[4], Donald P. Tashkin[5], Norbert Metzdorf[6], Achim Mueller[7], and Robert A. Wise[1]

[1]Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland; [2]Department of Pulmonary Medicine and Critical Care, University of Texas and South Texas Veterans Health Care System, San Antonio, Texas; [3]Clinical Science Centre, Institute of Ageing and Chronic Disease, University of Liverpool, Liverpool, United Kingdom; [4]Pulmonary Division, Brigham and Women's Hospital, Boston, Massachusetts; [5]Department of Medicine, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California; [6]Respiratory Medicine, Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany; and [7]Biostatistics and Data Sciences Europe, Boehringer Ingelheim Pharma GmbH and Company KG, Biberach an der Riss, Germany

ORCID IDs: 0000-0002-0688-1836 (N.P.); 0000-0002-7007-588X (A.R.A.); 0000-0003-4676-9993 (P. M.A.C.); 0000-0002-5607-4872 (D.P.T.); 0000-0002-0676-9019 (N.M.); 0000-0001-9795-8634 (A.M.); 0000-0002-8353-2349 (R.A.W.).

Abstract

Rationale: There is an association between body mass index (BMI) and mortality in chronic obstructive pulmonary disease (COPD), with underweight individuals having higher mortality risk. Mortality and exacerbation risks among individuals with higher BMI are unclear.

Objectives: To examine the relationship between BMI and adverse outcomes in COPD.

Methods: This *post hoc* analysis included data from TIOSPIR (Tiotropium Safety and Performance in Respimat) ($N = 17{,}116$) and tiotropium-treated patients in UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium) ($N = 2{,}986$). BMI classes (underweight [BMI < 20 kg/m^2], normal weight [BMI 20 to <25 kg/m^2], overweight [BMI 25 to <30 kg/m^2], obesity class I [BMI 30 to <35 kg/m^2], obesity class II [BMI 35 to <40 kg/m^2], and obesity class III [BMI ≥ 40 kg/m^2]) were examined for adjusted associations with mortality, exacerbation, and nonfatal cardiovascular event risk using over 50,000 patient-years of cumulative follow-up data. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox regression models.

Results: In TIOSPIR, obesity prevalence was 22%, overweight 32%, and underweight 12%. The proportion of females was highest in obesity classes II and III. Overweight and obese participants had better baseline lung function versus other BMI classes; underweight participants were more likely to be current smokers. Underweight participants had a significantly higher risk of death (HR, 1.88; 95% CI, 1.62–2.20; $P < 0.0001$) and severe exacerbations (HR, 1.31; 95% CI, 1.16–1.47; $P < 0.0001$) versus normal-weight participants; however, overweight and obese participants were at lower to no additional risk. Results from UPLIFT were similar to TIOSPIR.

Conclusions: These results suggest that there is a strong association between body weight, COPD events, and risk of death. A holistic management approach taking into account respiratory and cardiovascular risk factors and nutritional status is needed to improve the general well-being of patients with COPD.

Keywords: body mass index; COPD; exacerbation; mortality; obesity

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Correspondence and requests for reprints should be addressed to Nirupama Putcha, M.D., M.H.S., Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, 5501 Hopkins Bayview Circle, JHAAC 4B.73, Baltimore, MD 21224. E-mail: nputcha@jhmi.edu.

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The global prevalence of obesity has nearly tripled since 1975 (1) and has been a rising public health concern in many countries (1, 2). A concomitant rise in obesity has been observed in specific patient populations, including patients with chronic obstructive pulmonary disease (COPD) (3, 4). Although the prevalence of obesity in COPD likely varies by disease severity, some studies report that it is higher than in the general population, even after matching for age, sex, and other demographic factors (4).

Body mass index (BMI) is a measure commonly used to categorize a person's weight. Variations in BMI may play a role in the pathophysiology of COPD and influence patient outcomes (2). For example, individuals with COPD and obesity experience higher rates of dyspnea, increased use of inhaled medication, poorer quality of life (QoL), and an increased prevalence of other respiratory diseases, including asthma (5–7). A meta-analysis of over 200 studies including healthy nonsmokers in four continents found a strong association between being overweight or obese and increased all-cause mortality across all regions (8). Being underweight is also associated with higher mortality risk relative to normal-weight patients (9). However, contradictory evidence suggests a "protective" effect associated with being overweight. A systematic review and meta-analysis of studies in the general population indicated an association between being overweight (BMI 25 to <30 kg/m^2) and lower all-cause mortality relative to those of normal weight, whereas obesity (BMI ≥ 30 kg/m^2) was associated with higher all-cause mortality (10). This phenomenon, known as the "obesity paradox," has also been demonstrated in some COPD studies, indicating that excess body mass may have a protective effect against mortality (11, 12). However, this protective effect may depend on COPD disease severity and be more prevalent in patients with severe airflow limitation (9).

The impact of obesity on mortality and exacerbation risk in COPD has not yet been assessed in a large, well-characterized cohort from multiple continents with longitudinal follow-up. Furthermore, there is a paucity of studies including very obese people. The TIOSPIR (Tiotropium Safety and Performance in Respimat) and the UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium) trials are among the largest and longest COPD trials. TIOSPIR was specifically designed with adequate power to analyze all-cause mortality and time to first COPD exacerbation in a large patient population, with broad inclusion criteria that closely reflect the real-world population of patients with COPD (13). These results enabled further analysis of specific patient subpopulations (14, 15). This study aims to determine whether BMI is an important susceptibility factor for adverse outcomes in patients with COPD (who are receiving maintenance bronchodilator treatment), focusing on data from the large-scale TIOSPIR trial and supported by the UPLIFT trial.

Elements of the data have been previously presented at international conferences (16, 17).

Methods

Study Design and Population

The TIOSPIR trial (NCT01126437) was a large ($N = 17{,}116$), 2–3-year, randomized, double-blind, parallel-group, double-dummy, event-driven trial comparing the efficacy and safety of once-daily tiotropium Respimat 5 μg and 2.5 μg versus once-daily tiotropium HandiHaler 18 μg in moderate to very severe COPD. The UPLIFT trial (NCT00144339) was a 4-year, randomized, double-blind, placebo-controlled, parallel-group trial evaluating the effect of tiotropium HandiHaler 18 μg once-daily versus placebo on lung function, QoL, exacerbations, and mortality in patients ($N = 5{,}993$) with moderate to very severe COPD. Detailed methods have been published previously for TIOSPIR (13, 18) and UPLIFT (19). In both trials, participants were aged 40 years or more, had confirmed diagnosis of COPD (70% or less predicted postbronchodilator forced expiratory volume in 1 second [FEV_1], and FEV_1/forced vital capacity [FVC] ratio of 0.70 or less) and at least 10 pack-years of smoking history. Details of inclusion–exclusion criteria have been published (18, 19). There were no inclusion–exclusion criteria related to BMI in either trial.

Assessments

Participants from TIOSPIR and UPLIFT were categorized into six BMI classes at baseline: underweight (BMI < 20 kg/m^2), normal weight (BMI 20 to <25 kg/m^2), overweight (BMI 25 to <30 kg/m^2), obesity class I (BMI 30 to <35 kg/m^2), obesity class II (BMI 35 to <40 kg/m^2), and obesity class III (BMI ≥ 40 kg/m^2) (20).

Adverse events, including exacerbations and deaths, were reviewed by independent data and safety monitoring committees; deaths were additionally adjudicated by a mortality adjudication committee blinded to study group assignments. COPD exacerbations were defined as moderate (i.e., treatment with antibiotics or systemic steroids without hospitalization) or severe (i.e., involving hospitalization or causing death). Exacerbations included in this analysis were recorded from treatment commencement to last dose of study drug in both trials. Mortality was recorded to the study end. Serious, nonfatal cardiovascular (CV) events were counted from treatment commencement to 30 days after the last dose of study drug. Pharmacovigilance endpoints used to define respiratory death, cardiac death, and nonfatal CV events are described in Tables E1 and E2 (*see* online supplement).

Data from the TIOSPIR trial were pooled, as primary results showed no differences in outcomes between the three tiotropium treatment arms in other *post hoc* analyses (13, 15). UPLIFT was used as a validating cohort for the TIOSPIR findings. In this analysis, only tiotropium-treated patients from UPLIFT were included, because tiotropium reduced mortality and exacerbations versus placebo in this trial.

Statistical Analysis

In this *post hoc* analysis, statistical significance and all presented *P* values are considered nominal. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for time to all-cause death, respiratory death, CV death, first serious nonfatal CV event, and first moderate and/or severe exacerbation using Cox regression models (however, the study was not designed and powered to assess the statistical significance of correlations between BMI class and adverse events). Kaplan–Meier analysis was used to show the risk of an event occurring over time. The main analysis adjusted for several covariates considered *a priori* confounders: age, sex, region, smoking status, smoking history (pack-years), Global Initiative for Chronic Obstructive Lung Disease stage, medication use (long-acting β_2-agonist only, inhaled corticosteroid only, both inhaled corticosteroid and long-acting β_2-agonist, or neither), and cardiac history. BMI was coded as a disjoint categorical

variable with all classes included simultaneously. Participants with missing covariate data were excluded (TIOSPIR: 48 patients; UPLIFT: 9 patients). SAS was used for all analyses.

Results

Baseline Characteristics

Baseline characteristics for the 17,116 participants from TIOSPIR are presented in Table 1. Mean follow-up time for all-cause mortality was 838.2 days (TIOSPIR) and 1,359.5 days (UPLIFT). In TIOSPIR, 12.1% of participants were underweight, 33.4% normal weight, 32.2% overweight, and 22.3% obese (15.3% obesity class I; 4.9% obesity class II; and 2.1% obesity class III). Similar proportions were observed in UPLIFT (Table E3). In TIOSPIR, age did not vary greatly between the different groups, although obesity class III participants tended to be younger (mean 60.4 yr vs. 65.5 yr in the normal-weight group). The proportion of females and participants from North America increased with increasing BMI; there was a higher proportion of underweight and normal-weight participants from Asia (36.0% and 19.9% among underweight and normal weight, respectively, vs. 7.3% overweight, 2.6% obesity class I, 1.2% obesity class II, and 0% obesity class III) (Table 1). Number of pack-years increased with increasing BMI; however, underweight participants were more likely to be current smokers than overweight participants (43.7% of underweight participants were current smokers vs. 35.9% of overweight and 39.9% of normal-weight participants) (Table 1). Similar patterns in baseline characteristics were found in UPLIFT (Table E3).

Baseline postbronchodilator FEV_1, FEV_1% predicted, and FEV_1/FVC ratio were higher in overweight and obese participants versus underweight and normal-weight participants in TIOSPIR (Table 1). The FEV_1/FVC ratio was 0.45 in underweight participants and 0.58 in obesity class III; the FVC% predicted was lower in participants at either end of the BMI spectrum (i.e., underweight and obesity class III) versus normal weight (Table 1). In UPLIFT, FVC% predicted was lower in obesity class III versus other BMI classes (Table E3).

In TIOSPIR, generally a higher proportion of overweight/obese participants had a history of CV disease and were using CV medications at baseline versus underweight/normal-weight participants (Table 1). This was also observed in UPLIFT (Table E3).

Mortality Risk by BMI Class

Risk of all-cause death. Underweight participants in TIOSPIR had a significantly higher risk of all-cause mortality versus normal-weight participants (HR, 1.88; 95% CI, 1.62–2.20) (Figures 1 and 2A). Conversely, overweight participants had a significantly lower risk of all-cause mortality versus normal-weight participants (HR, 0.74; 95% CI, 0.64–0.86) (Figure 1). The protective effect of being overweight decreased with increasing obesity class in TIOSPIR, with obesity class III at the same risk as normal-weight participants (HR, 1.02; 95% CI, 0.67–1.55). Consistent with TIOSPIR, underweight participants in UPLIFT had a significantly higher risk of all-cause mortality versus normal-weight participants, and overweight participants had a significantly lower risk (Figures E1 and E2A). Similarly, the protective effect of being overweight decreased with increasing BMI; obesity class III participants had a significantly higher risk of all-cause mortality versus overweight participants (HR, 2.56; 95% CI, 1.11–5.90).

Risk of respiratory death. In TIOSPIR, underweight participants had a more than twofold higher risk of respiratory death (HR, 2.27; 95% CI, 1.80–2.86) compared with normal-weight participants, and overweight participants had a 48% lower risk of respiratory death (HR, 0.52; 95% CI, 0.40–0.69) (Figures 1 and E3A), with both results significant (similar significant results were found in UPLIFT) (Figures E1 and E2B). Overall, results in the obese categories indicated no clear association between increasing BMI and the risk of respiratory death.

Risk of CV death. Underweight participants in TIOSPIR had a significantly higher risk of CV death versus normal-weight participants (HR, 1.73; 95% CI, 1.25–2.40), and overweight participants had a lower, though nonsignificant, risk (HR, 0.87; 95% CI, 0.65–1.15). There was an increasing risk of CV death with increasing BMI; obesity class III participants had a significantly higher risk of CV death versus overweight participants (HR, 2.08; 95% CI, 1.04–4.17). Consistent with TIOSPIR, underweight participants in UPLIFT had a significantly higher risk of CV death versus normal-weight participants, and overweight participants had a lower, though nonsignificant, risk (Figures E1 and E2C). The risk of CV death versus normal weight in UPLIFT increased from overweight to obesity class III, reaching significance for obesity classes II and III (Figure E1).

Risk of severe and moderate exacerbations. In TIOSPIR, underweight participants had a significantly higher risk of severe exacerbations than normal-weight participants (HR, 1.31; 95% CI, 1.16–1.47) (Figures 2B and 3), and this was also observed in UPLIFT (Figures E2D and E4). In TIOSPIR, the risk of severe exacerbations was significantly lower in overweight participants (HR, 0.81; 95% CI, 0.73–0.90). There was no clear association between BMI and the risk of moderate exacerbations in obese participants in either trial (Figures 3 and E4).

Risk of a serious nonfatal CV event in TIOSPIR and UPLIFT. In TIOSPIR, the risk of serious nonfatal CV events was similar in underweight (HR, 1.00; 95% CI, 0.79–1.27) and overweight (HR, 0.96; 95% CI, 0.82–1.12) versus normal-weight participants. As seen for fatal CV events, the risk of nonfatal CV events increased with increasing BMI, with obesity class II reaching significance versus normal weight (HR, 1.33; 95% CI, 1.03–1.73; Figures 3 and E3C). Comparison of obese versus overweight participants showed a significantly higher risk of nonfatal CV events in all obesity classes (I–III) versus overweight participants (obesity class I HR, 1.24; 95% CI, 1.04–1.48; obesity class II HR, 1.39 95% CI 1.08–1.79; obesity class III HR, 1.50; 95% CI, 1.05–2.15 versus overweight). A similar pattern was present in UPLIFT (Figure E4).

Discussion

This secondary analysis of two large international COPD studies of participants from multiple continents, including a large number of morbidly obese individuals (BMI $\geq$40 kg/m^2), adds to the current literature by demonstrating that BMI can affect mortality and exacerbation risk in patients with COPD (21–23). An increased risk of CV-related mortality was observed for participants at either end of the BMI scale (BMI $<$ 20 kg/m^2 and BMI $\geq$ 35 kg/m^2) compared with normal-weight participants (though not reaching significance in TIOSPIR for BMI $\geq$ 35 kg/m^2). Underweight participants had a significantly increased risk of all-cause

Table 1. Patient baseline characteristics by BMI class in TIOSPIR

			Overweight and Obese			
	Underweight (BMI < 20)* n = 2,063	Normal Weight† (BMI 20 to <25)* n = 5,721	Overweight (BMI 25 to <30)* n = 5,509	Obesity Class I (BMI 30 to <35)* n = 2,624	Obesity Class II (BMI 35 to <40)* n = 841	Obesity Class III (BMI ⩾ 40)* n = 358
Gender, male, *n* (%)	1,449 (70.2)	4,169 (72.9)	4,037 (73.3)	1,851 (70.5)	547 (65.0)	184 (51.4)
Age, years, mean (SD)	64.6 (9.3)	65.5 (9.2)	65.4 (9.0)	64.6 (8.7)	63.4 (8.6)	60.4 (8.1)
Race, *n* (%)						
White	1,206 (58.5)	4,324 (75.6)	4,868 (88.4)	2,432 (92.7)	795 (94.5)	338 (94.4)
Black	44 (2.1)	80 (1.4)	58 (1.1)	45 (1.7)	15 (1.8)	14 (3.9)
Asian	756 (36.6)	1,165 (20.4)	421 (7.6)	74 (2.8)	11 (1.3)	1 (0.3)
Region, *n* (%)						
Europe/Africa/Aus/NZ	821 (39.8)	3,118 (54.5)	3,452 (62.7)	1,632 (62.2)	472 (56.1)	144 (40.2)
Latin America	115 (5.6)	379 (6.6)	321 (5.8)	144 (5.5)	30 (3.6)	11 (3.1)
North America	385 (18.7)	1,087 (19.0)	1,336 (24.3)	781 (29.8)	329 (39.1)	203 (56.7)
Asia	742 (36.0)	1,137 (19.9)	400 (7.3)	67 (2.6)	10 (1.2)	0 (0.0)
Current smokers, *n* (%)	902 (43.7)	2,281 (39.9)	1,977 (35.9)	912 (34.8)	304 (36.1)	143 (39.9)
Smoking history, pack-years, mean (SD)	41.0 (21.9)	42.8 (23.7)	44.2 (25.0)	45.3 (26.2)	47.6 (28.0)	49.4 (31.0)
Postbronchodilator pulmonary function data						
FEV_1, L, mean (SD)	1.1 (0.4)	1.3 (0.5)	1.4 (0.5)	1.5 (0.5)	1.5 (0.5)	1.4 (0.5)
FEV_1/FVC ratio, mean (SD)	0.5 (0.1)	0.5 (0.1)	0.5 (0.1)	0.5 (0.1)	0.6 (0.1)	0.6 (0.1)
FVC, L, mean (SD)	2.5 (0.8)	2.7 (0.9)	2.8 (0.9)	2.7 (0.8)	2.6 (0.8)	2.5 (0.8)
FEV_1% predicted, mean (SD)	41.7 (14.8)	47.3 (14.5)	51.0 (13.9)	52.2 (13.5)	53.1 (13.8)	53.5 (13.9)
FVC% predicted, mean (SD)	74.6 (20.9)	79.5 (20.4)	80.1 (19.2)	78.1 (17.9)	77.5 (19.8)	75.6 (17.5)
Duration of COPD, years, mean (SD)	7.1 (6.2)	7.3 (6.2)	7.7 (6.3)	7.5 (6.2)	7.4 (5.8)	6.6 (5.5)
mMRC dyspnea scale number, *n* (%)						
0	159 (7.7)	473 (8.3)	513 (9.3)	187 (7.1)	57 (6.8)	16 (4.5)
1	703 (34.1)	2,237 (39.1)	2,128 (38.6)	941 (35.9)	266 (31.6)	99 (27.7)
2	715 (34.7)	2,044 (35.7)	2,013 (36.5)	1,051 (40.1)	336 (40.0)	111 (31.0)
3	436 (21.1)	860 (15.0)	771 (14.0)	405 (15.4)	159 (18.9)	107 (29.9)
4	50 (2.4)	94 (1.6)	80 (1.5)	37 (1.4)	22 (2.6)	24 (6.7)
Sputum-producing cough, *n* (%)	1,284 (62.2)	3,673 (64.2)	3,520 (63.9)	1,688 (64.3)	518 (61.6)	203 (56.7)
GOLD stages, *n* (%)						
I	9 (0.4)	26 (0.5)	32 (0.6)	13 (0.5)	12 (1.4)	7 (2.0)
II	600 (29.1)	2,451 (42.8)	2,933 (53.2)	1,489 (56.7)	473 (56.2)	198 (55.3)
III	957 (46.4)	2,414 (42.2)	2,045 (37.1)	896 (34.1)	292 (34.7)	129 (36.0)
IV	489 (23.7)	770 (13.5)	421 (7.6)	170 (6.5)	39 (4.6)	15 (4.2)
CV disease history‡, *n* (%)	359 (17.4)	1,242 (21.7)	1,587 (28.8)	858 (32.7)	298 (35.4)	125 (34.9)
MI, *n* (%)	77 (3.7)	266 (4.6)	387 (7.0)	199 (7.6)	75 (8.9)	22 (6.1)
Cardiac arrhythmia, *n* (%)	152 (7.4)	523 (9.1)	621 (11.3)	357 (13.6)	123 (14.6)	49 (13.7)
IHD/CAD, *n* (%)	173 (8.4)	677 (11.8)	993 (18.0)	508 (19.4)	170 (20.2)	73 (20.4)
Stroke, *n* (%)	30 (1.5)	129 (2.3)	137 (2.5)	66 (2.5)	22 (2.6)	4 (1.1)
Use of CV medication, *n* (%)	608 (29.5)	2,372 (41.5)	3,178 (57.7)	1,723 (65.7)	601 (71.5)	271 (75.7)
Number of patients with moderate/severe exacerbations in previous year, *n* (%)						
0	990 (48.0)	2,885 (50.4)	2,855 (51.8)	1,407 (53.6)	478 (56.8)	204 (57.0)
1	615 (29.8)	1,646 (28.8)	1,583 (28.7)	714 (27.2)	221 (26.3)	97 (27.1)
2	260 (12.6)	736 (12.9)	640 (11.6)	305 (11.6)	93 (11.1)	44 (12.3)
3	111 (5.4)	279 (4.9)	266 (4.8)	118 (4.5)	33 (3.9)	10 (2.8)
4	41 (2.0)	96 (1.7)	110 (2.0)	44 (1.7)	10 (1.2)	1 (0.3)
⩾5	46 (2.2)	73 (1.3)	53 (1.0)	33 (1.3)	5 (0.6)	2 (0.6)

Definition of abbreviations: Aus = Australia; BMI = body mass index; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; IHD = ischemic heart disease; MI = myocardial infarction; mMRC = modified Medical Research Council; NZ = New Zealand; SD = standard deviation; TIOSPIR = TIOtropium Safety and Performance In Respimat.

*All BMI expressed as kg/m^2.

†Highlighted normal weight data are the reference dataset for subsequent comparisons.

‡Cardiovascular history is defined as a history of MI, IHD/CAD, cardiac arrhythmia, or heart failure.

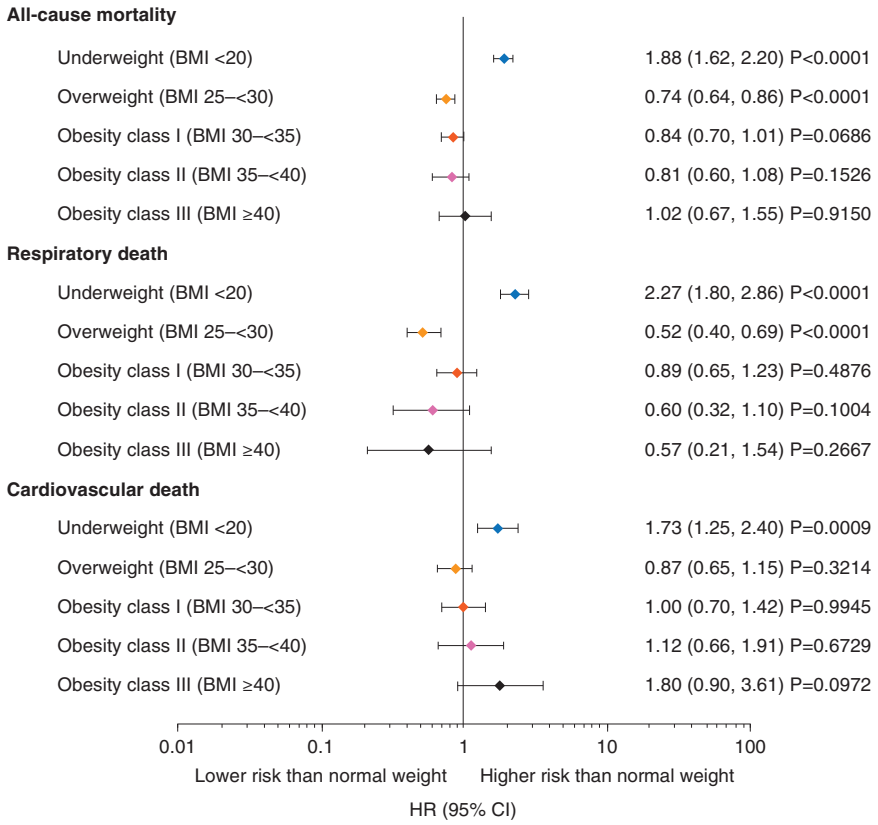
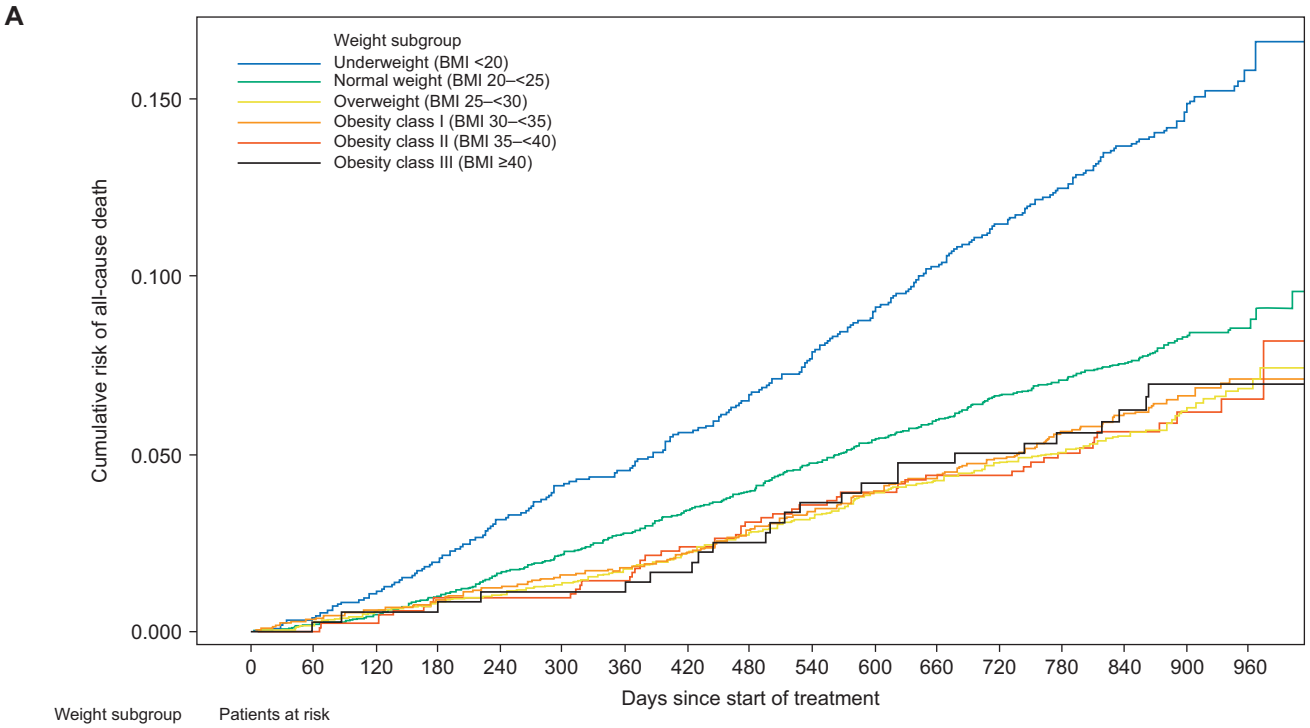


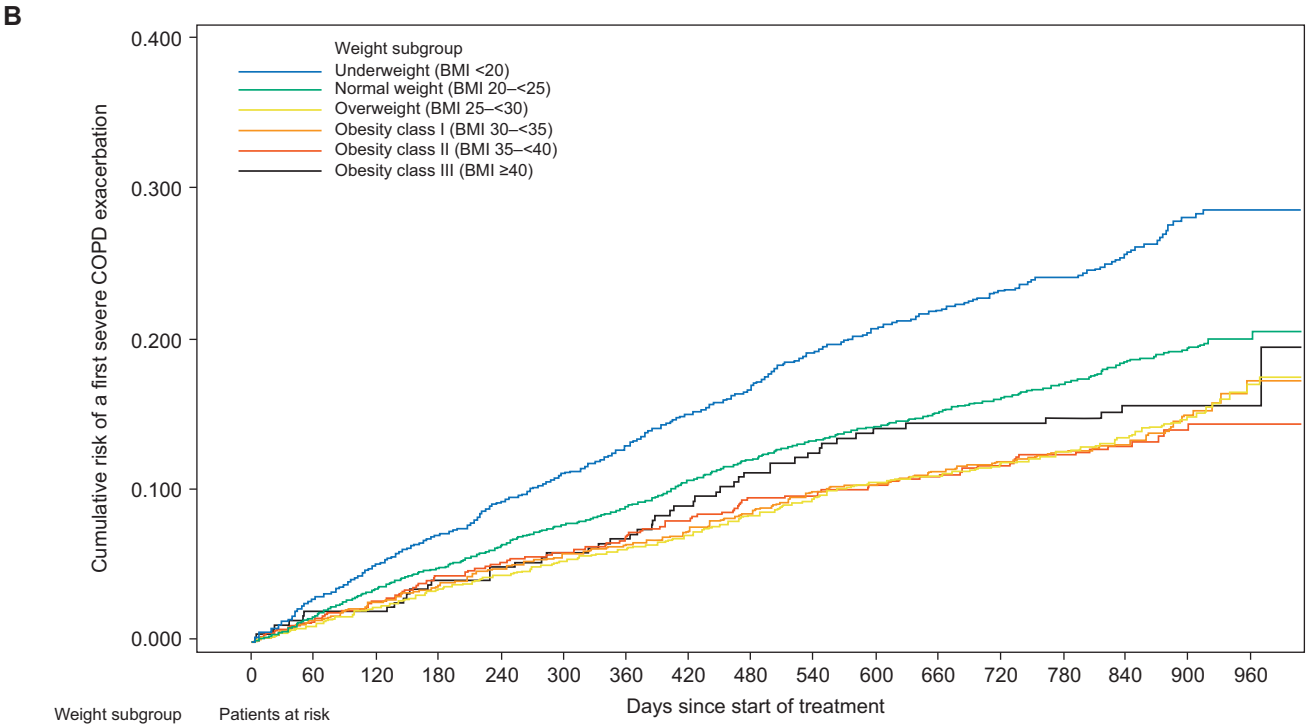
Figure 1. Relative risk of death (including vital status follow-up) for participants in TIOSPIR by body mass index (BMI) class versus normal-weight (BMI 20 to <25 kg/m^2), set as hazard ratio (HR) = 1. All BMI expressed as kg/m^2. Cox regression with "BMI class" as factor and adjusted for other covariates: age class, sex, region, smoking status, smoking history (pack-years), Global Initiative for Chronic Obstructive Lung Disease stages, medication variable (long-acting β_2-agonist only, inhaled corticosteroid only, both inhaled corticosteroid and long-acting β_2-agonist, or neither), and cardiac history. CI = confidence interval; TIOSPIR = TIOtropium Safety and Performance In Respimat.

mortality, respiratory-related mortality, CV-related mortality, and severe exacerbations compared with normal-weight participants. Conversely, overweight and obese (BMI ⩾ 25 kg/m^2) participants had lower or no additional risk of all-cause death, respiratory-related death, or severe exacerbations versus normal-weight participants. It is of note that the protective effect of being overweight or obese against all-cause mortality in these studies was reduced in morbidly obese patients. Overall, these data suggest that underweight patients are at increased risk for COPD-related events (exacerbations or respiratory-related death) and CV-related mortality; patients with higher BMI may be at higher risk of fatal and nonfatal CV events, but they appear to have no increased risk of respiratory-related events (exacerbations or respiratory-related deaths).

The finding that underweight participants with COPD had a significantly higher risk of death and exacerbations versus normal-weight participants is consistent with previous studies (9, 11). However, underweight status may not be the sole driver of such adverse outcomes. In this study, underweight participants had poorer lung function and were more likely to be current smokers. Although adjustments were made to account for these differences in the models, residual confounding was possible. Nonetheless, the effect size and consistency of these results between studies suggests underlying mechanisms for this association should be considered. For example, underweight individuals may have disease phenotypes that are more commonly associated with adverse outcomes. Previous cluster analyses from a Spanish and a French cohort, and the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points) study, demonstrated a higher risk of death and exacerbations among individuals with a more "severe respiratory disease" phenotype; this subgroup had lower BMIs than other phenotypic clusters (24–26). Whether the impact of respiratory disease causes low BMI and cachexia is unclear. Work by Celli and colleagues described a phenotype of individuals with COPD having "extrapulmonary tissue loss," which included individuals similar to those described here, having lower BMI, lower FEV_1, higher exacerbation risk and mortality, but a higher burden of emphysema on computed tomography imaging, and certain biomarkers indicating higher burden of tissue damage and repair (27). All individuals in this subgroup showed a higher risk of mortality. Such studies provide important insight into the potential mechanisms leading to low BMI in this subtype and demonstrate how differences in comorbidities among different BMI groups may influence outcomes. A recent multicenter observational study with over 1,600 patients showed that different BMI categories are associated with diverse clinical expressions of COPD and comorbidity



Weight subgroup	Patients at risk																
Underweight (BMI <20)	2063	2055	2039	2021	1997	1977	1969	1946	1928	1900	1877	1849	1686	1532	1039	477	165
Normal weight (BMI 20–<25)	5721	5708	5689	5659	5621	5589	5555	5516	5483	5434	5397	5365	5098	4701	3341	1537	494
Overweight (BMI 25–<30)	5509	5498	5479	5458	5448	5430	5405	5379	5344	5321	5283	5261	5077	4803	3669	1570	496
Obesity class I (BMI 30–<35)	2624	2616	2609	2601	2592	2583	2575	2564	2547	2532	2518	2505	2435	2304	1789	837	290
Obesity class II (BMI 35–<40)	841	841	839	833	833	832	828	820	814	810	807	803	785	742	591	284	103
Obesity class III (BMI ≥40)	358	357	356	356	354	354	354	352	349	345	343	341	337	330	284	140	50



Weight subgroup	Patients at risk																
Underweight (BMI <20)	2063	1909	1808	1731	1651	1586	1536	1479	1424	1357	1312	1280	1174	766	613	326	45
Normal weight (BMI 20–<25)	5721	5380	5177	4998	4855	4706	4562	4410	4265	4143	4057	3981	3759	2581	2110	1108	158
Overweight (BMI 25–<30)	5509	5214	5024	4883	4788	4679	4582	4495	4382	4247	4155	4101	3919	2936	2405	1180	174
Obesity class I (BMI 30–<35)	2624	2497	2410	2346	2296	2240	2198	2154	2087	2037	1999	1967	1894	1480	1213	630	97
Obesity class II (BMI 35–<40)	841	797	773	744	734	720	701	685	664	651	641	631	603	477	407	218	39
Obesity class III (BMI ≥40)	358	336	330	321	315	310	299	289	280	272	263	262	257	226	185	114	22

Figure 2. Kaplan–Meier curves by body mass index (BMI) in TIOSPIR for (*A*) all-cause mortality and (*B*) severe COPD exacerbation. All BMI expressed as kg/m^2. COPD = chronic obstructive pulmonary disease; TIOSPIR = TIOtropium Safety and Performance In Respimat.

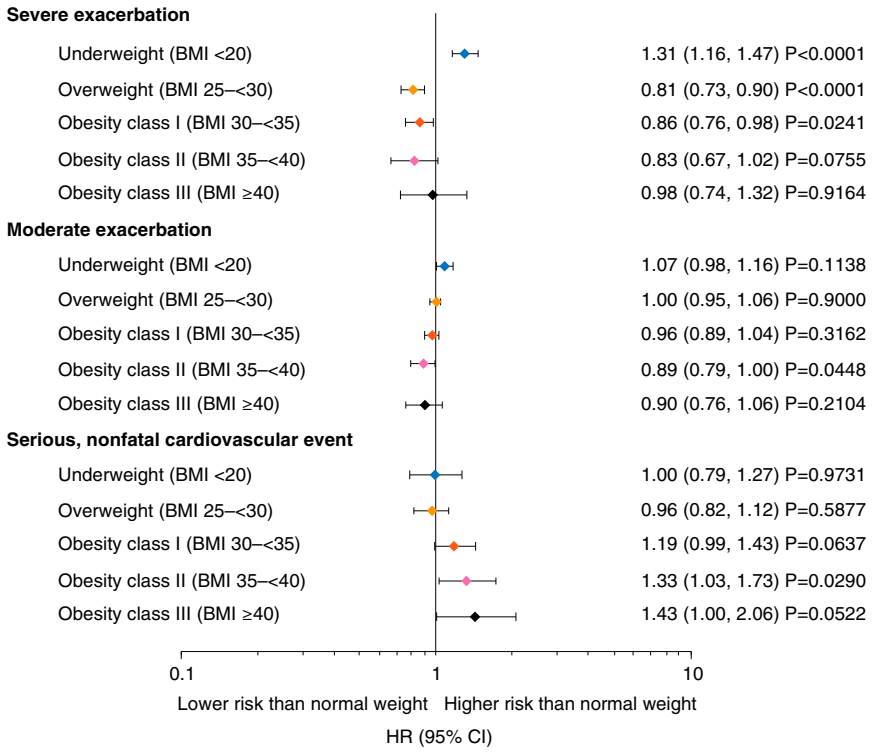


Figure 3. Relative risk of COPD exacerbations and nonfatal cardiovascular events for participants in TIOSPIR by body mass index (BMI) class versus normal-weight (BMI 20 to <25 kg/m^2), set as hazard ratio (HR) = 1. All BMI expressed as kg/m^2. Cox regression with "BMI class" as factor and adjusted for other covariates: age class, sex, region, smoking status, smoking history (pack-years), Global Initiative for Chronic Obstructive Lung Disease stages, medication variable (long-acting β_2-agonist only, inhaled corticosteroid only, both inhaled corticosteroid and long-acting β_2-agonist, or neither), and cardiac history. CI = confidence interval; COPD = chronic obstructive pulmonary disease; TIOSPIR = TIOtropium Safety and Performance In Respimat.

patterns (28). Patients who were underweight (BMI ⩽ 21 kg/m^2) had the highest rate of respiratory-related mortality despite having among the lowest total number of comorbidities compared with other BMI categories (28). Nutritional support leading to weight gain can lead to improved COPD outcomes for underweight patients (29). However, weight gain leading to ectopic fat accumulation could be detrimental to cardiovascular and metabolic health in COPD, and development of lifestyle modification programs focusing on both nutritional quality and physical activity/exercise should be considered (30, 31).

Analysis of nonfatal CV events showed higher risk among obesity class II in TIOSPIR and UPLIFT. These results are consistent with previous studies, including a recent multicenter observational study that reported a higher prevalence of cardiac and metabolic comorbidities in patients with BMI ⩾ 35 kg/m^2 (28). In addition, cluster analyses in patients with COPD from both Spanish and French cohorts identified a cluster of individuals with obesity and a higher risk of CV endpoints, as well as more systemic manifestations of disease (24, 25). These findings are unsurprising given the magnitude of evidence reporting an increased risk of CV disease with obesity; obesity influences various CV risk factors, has adverse effects on CV structure and function, and is a major risk factor for hypertension, heart failure, and coronary heart disease (32–34). In obese patients, purposeful weight reduction is supported for prevention and treatment of CV diseases (33). Long-term dietary interventions in obese individuals have been shown to promote and sustain long-term weight loss and reduce CV risk (35), while in obese COPD patients, dietary energy restriction coupled with resistance exercise training demonstrated significant improvements in BMI, exercise tolerance, and health status (36).

Suggestions as to why overweight or obese individuals show this paradoxical reduction in respiratory mortality and morbidity include earlier presentation of symptoms, greater likelihood of receiving optimal treatment, the cardioprotective metabolic effects of increased body fat, and benefits from greater metabolic reserves (9–12). In TIOSPIR and UPLIFT, the duration of COPD was relatively balanced between different BMI groups; these results are therefore not confounded by earlier presentation, although other explanations are possible.

Obesity has been suggested to provide benefits through a mechanism akin to chest wall strapping to improve airflow (37). In COPD, obesity is associated with lower lung volumes and increased airway conductance. This potential "chest wall strapping-like" effect of obesity could protect small airways and lower the risk of progression to emphysema or death (37). However, lung function measures can be affected by obesity; the FEV_1/FVC ratio, a parameter for airflow obstruction, is influenced by the lung volume-reducing effect of increasing weight (38). O'Donnell and colleagues note that

mild and moderate obesity have minimal impact on dyspnea, symptom-limited oxygen uptake, and respiratory mechanics during cardiopulmonary exercise testing, and that physiologic changes during exercise for individuals with COPD and obesity should raise questions about other contributing factors, including chronic comorbidities (39). Here, a clinically meaningful difference in FEV_1/FVC is shown, with ratios increasing with increased BMI. As an FEV_1/FVC ratio of less than 0.70 is required for diagnosis, having a higher ratio might obscure diagnosis of airflow obstruction in obese patients and affect rates of emphysema diagnosis (40). In underweight patients, potential contributors to the lower FEV_1/FVC ratio include air-trapping, hyperinflation, emphysema, diaphragmatic weakness from sarcopenia, and loss of the normal curvature of the diaphragm (41, 42).

A recent analysis of 3,631 patients from the COPDGene (Genetic Epidemiology of COPD) study showed that obesity (BMI $\geq$ 30 kg/m^2) was associated with worse COPD-related outcomes versus normal-weight and overweight patients (BMI 18.5 to 29.9 kg/m^2), including QoL, dyspnea, and incidence of severe exacerbations (43). Baseline characteristics of the current study indicate that patients with obesity class III have a higher burden of dyspnea and sputum-producing cough versus normal-weight and overweight individuals. In contrast to COPDGene, the current study found in TIOSPIR that overweight and slightly obese participants (BMI 25 to $<$35 kg/m^2) were at a lower risk of severe exacerbations versus normal-weight participants. This could be due to the controlled conditions and treatment with tiotropium in this study, which could result in fewer exacerbations in overweight and slightly obese patients, compared with what is reported in the COPDGene study. Adherence to medications is also likely to be higher under the trial conditions of this study, compared with the observational COPDGene study, and this could potentially have an influence on the results. Findings reported in this study are, however, in line with two recent analyses, which showed that a higher BMI is associated with fewer COPD exacerbations in the study population, although different BMI cutoffs were selected (22, 44).

Overall, these studies emphasize the need to closely monitor individuals with COPD at either extreme of the BMI spectrum. In addition, these data suggest that BMI and obesity should be considered in relation to other important phenotypic characteristics and comorbidities that could affect treatment outcomes.

BMI is a simple measure that can easily be incorporated into clinical decision-making. However, it does not give a complete picture of fat/lean mass distribution throughout the body (2, 20). Previous studies suggest that patients with COPD may have a different fat/lean mass distribution versus the general population (45). Measures of fat distribution, such as waist/hip ratio and waist circumference, have been linked with lung function in adults, suggesting that the location of fat may be important (20, 45). For CV outcomes, measurement of fat distribution is particularly important, as abdominal obesity is a better risk indicator of CV diseases than BMI (30). Other measurements of weight distribution, such as dual-energy X-ray absorptiometry, have shown that changes in body composition, including limb and trunk lean mass and distribution of fat deposits, are associated with COPD severity (45). Whether these techniques provide better prognostic information than BMI alone in a population such as ours remains to be determined.

Strengths and Limitations

One limitation of our study is that it was *post hoc* rather than a predefined subgroup analysis. Whether the outcomes we observed would apply to other populations who had been selected differently in a global clinical trial is uncertain. However, as the largest long-term, randomized study in a broad range of patients with COPD performed to date, TIOSPIR provided a substantial dataset for investigation of our hypothesis, supported by the dataset from UPLIFT. Another possible limitation is that the BMI cutoffs in this study may not account for differences in race in the patient population; it has been suggested that different populations (e.g., Asian people) should use lower cutoffs for overweight/obesity BMI categories (46). Indeed, it was noted that Asian patients in this study tended to be underweight. Additionally, detailed body composition assessment, including fat distribution, was not performed in this study. As BMI was measured at baseline and not longitudinally in TIOSPIR, we could not analyze BMI as a time-varying exposure, such as reported in the recent study by Peralta and colleagues (47). This limits any conclusions on the association of weight changes over time with outcomes, especially whether there was an accumulation of patients with "wasting syndrome" in the lower BMI classes. Lastly, data may be confounded as they were not adjusted for exercise capacity and lung volumes (hyperinflation), which can affect mortality and are themselves affected by the patient's weight.

This dataset is unique because of the high number of patients, including those who were underweight and morbidly obese (predominantly from TIOSPIR), who were observed under strictly controlled study conditions for 2–4 years; such a dataset has not been previously studied in COPD. Furthermore, the large, well-powered dataset and relatively open inclusion criteria allowed for the inclusion of comorbid CV disease, a common comorbidity in COPD.

Conclusions

BMI is a commonly used and recorded measurement both in clinical trials and general practice. In this analysis, after we adjusted for confounding factors such as age, sex, ethnicity, and smoking status, we demonstrated a strong association between body weight, COPD events, and risk of death. These data underscore the need for the holistic management of COPD patients that considers not just the management of their respiratory symptoms but also CV risk factors, nutritional status, and lifestyle modification to improve their general well-being. ■

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