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Challenging the obesity paradox: Extreme obesity and COPD mortality in the SUMMIT Trial

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"Take-home" message: In a population with moderate COPD, at heightened cardiovascular risk, and containing a substantial proportion of individuals with BMI ≥40kg/m^2, BMI and mortality demonstrate a U-shaped (rather than J-shaped) relationship.

Abstract

Populations with COPD demonstrate higher survival in overweight and obese compared with normal weight; the "obesity paradox." Relationships in less severe COPD are unclear, as is the impact of cardiovascular risk, and few studies include individuals at extremes of obesity.

We examined the relationship between body mass index (BMI, defined as underweight: <20kg/m^2, normal: 20-25kg/m^2, overweight: 25-<30kg/m^2, obese class I: 30-<35kg/m^2, class II: 35-<40kg/m^2, class III: $\geq$40kg/m^2), morbidity, and mortality in the SUMMIT trial population (n=16,485), characterized by moderate COPD and heightened cardiovascular risk with a substantial proportion with class III obesity. The association between BMI category and time to event was modeled via proportional hazards (reference normal weight) adjusted for demographics and cardiorespiratory disease.

Consistent with the paradox, underweight individuals demonstrated higher mortality (HR 1.31 (95%CI 1.04-1.64)), with lower mortality among overweight (HR 0.62 (95%CI 0.52-0.73)) and obese class I (HR 0.75 (95%CI 0.62-0.90)). However, mortality increased in obese class III (HR 1.36 (95%CI 1.00-1.86)). Death was primarily attributable to cardiovascular causes.

Within a large, multinational cohort with moderate COPD and increased cardiovascular risk, the phenomenon of reduced mortality with obesity did not persist at BMI>40kg/m^2, suggesting that obesity may not remain protective at the extremes in this population.

Introduction

Prior studies in COPD populations demonstrate improved survival in overweight and obese compared with normal weight individuals, and increased mortality in the underweight.[1, 2] This reverse "J-shaped" curve is referred to as the "obesity paradox," and has been described in several other chronic disease states. [3-5] In the general population, however, the relationship between body mass index (BMI) and survival is "U-shaped" with an increase in mortality noted both with underweight compared with normal weight individuals, and again with increasing BMI/obesity. [6, 7] It remains unclear why the "U-shaped" curve has not been reflected in populations with COPD. Several hypotheses are proposed to explain this discrepancy, including sparse data on patients with COPD at the extremes of obesity.

Furthermore, the paradox has been most apparent in patients with severe disease (defined by lower FEV_1). [2, 8] Whether the paradox applies to patients with milder disease is uncertain. Relationships between BMI and cause-specific mortality in COPD are largely undefined, and associations with morbidity in the same population is often unexplored. Cardiovascular disease is a common comorbidity in COPD[9, 10] and a major cause of death, [11, 12] but cardiovascular risk is often not described in studies of the obesity paradox.

The SUMMIT Trial was conducted in a large, international population with moderate COPD at heightened cardiovascular risk.[13] Over 16,000 patients were randomized to inhaler therapies including fluticasone furoate and/or vilanterol, with similar mortality rates regardless of treatment assignment. Standardized adjudication of all deaths and cardiovascular events was performed. COPD exacerbations were captured as protocol-defined events. A substantial number of individuals (over 500) had class III obesity (BMI $\geq$ 40 kg/m^2), presenting an ideal opportunity to investigate the obesity paradox over a wide range of BMI. Because cause of death and cardiopulmonary morbidity events were also captured as outcomes, we additionally investigated the association between BMI category and cause-specific mortality rates, COPD exacerbation rates, and cardiovascular event rates.

Methods

Study Subjects

All participants in the SUMMIT Trial[13] in the Intent to Treat population were included in the present analysis, with basic eligibility criteria including: age 40-80 years, moderate COPD (defined as forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) $\leq$ 0.70, and FEV_1 of 50-70% of predicted values, [14, 15] at least 10 pack-years smoking history, and modified Medical Research Council [mMRC] score of 2 or greater), and history of or risk factors for cardiovascular disease. A complete listing of eligibility criteria is published elsewhere. [16] All participants in the current analysis provided written, informed consent for trial participation. The SUMMIT Trial was approved by local ethics committees and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Study Design

We present a post-hoc analysis of trial results. As detailed in previous trial descriptions, [13, 16] 16,485 patients from 43 countries were included in the intention-to-treat efficacy population, and randomized 1:1:1:1 to once daily inhaled placebo, fluticasone furoate (100 μg), vilanterol (25 μg), or the combination of fluticasone and vilanterol. Participants were seen every 3 months after randomization to document vital status and adverse events. The trial opened enrollment on January 24, 2011 and completed data collection July 15, 2015.

Body mass index (BMI) was obtained at enrollment. Overweight (BMI 25-<30 kg/m^2), obese class I (BMI 30-<35 kg/m^2), class II (BMI 35-<40 kg/m^2) and class III (BMI $\geq$40 kg/m^2) were defined by World Health Organization (WHO) criteria. Normal weight was considered BMI 20-<25 kg/m^2, with underweight as <20 kg/m^2 and separately as <18.5 kg/m^2 (sensitivity analysis, WHO criteria[17]).

The primary outcome in this analysis and in the original trial was all-cause mortality, defined as time to on- and post-treatment death. A secondary outcome of cause-specific mortality was adjudicated by a clinical endpoint committee using a combination of study data, death certificates, autopsy findings, and health records. Respiratory morbidity outcomes included on-treatment moderate COPD exacerbations, defined by symptoms requiring antibiotic or systemic corticosteroid administration, on-treatment severe COPD exacerbations, defined by deterioration requiring

hospital admission, and pneumonia, defined by a comprehensive list of pneumonia MedDRA preferred terms applied to investigator-reported adverse events. [18] A pre-defined on-treatment composite cardiovascular event outcome included cardiovascular death, myocardial infarction, unstable angina, stroke, or transient ischemic attack.

Analysis

Variable distribution was examined and summary statistics calculated within each BMI category. Using the normal weight category as reference, the association between BMI category and time to event was evaluated using Cox proportional hazards modelling, with competing risk methods applied for cause-specific mortality outcomes. Analyses were adjusted for age, sex, region, race, ischemic heart disease indicator, vascular disease indicator, smoking status, cardiovascular entry criteria (history and risk by age), previous COPD exacerbations, percent predicted FEV_1, treatment arm and BMI (categorical). [13] Interaction between treatment arm and BMI (categorical) was tested and was not significant.

Analyses were completed using SAS Version 9.4. Statistical significance was defined as $p < 0.05$.

Results

In total, 16,485 participants were included in the analysis. A quarter (26.1%) of the sample were classified as normal weight (n=4306), with 6.7% (n=1111) underweight, 34.3% overweight (n=5662), and 32.8% obese (n=5406). Baseline characteristics stratified by BMI category are shown in Tables 1 and 1S. Age, lung function, and treatment assignment were similar across categories. Obese groups tended towards a higher proportion of women, Caucasian race, United States origin, and prevalent (2+) COPD exacerbations in the year prior to enrollment. Obese groups also demonstrated higher diabetes prevalence (including diabetes with target organ disease), hypercholesterolaemia, and hypertension, though curiously lower prevalence of prior stroke. Conversely, normal and underweight strata tended towards a higher proportion of Asian race and origin, higher current smoking, and higher rates of peripheral arterial disease. Obese individuals were more likely to report use of any of the long-acting inhaler therapies (beta-agonist, muscarinic antagonist, inhaler corticosteroids), and most reported cardiovascular therapies (Table 2S).

Compared with the pre-defined normal weight strata (BMI 20-<25 kg/m^2), overweight and class I obese individuals demonstrated 38% (95% CI: 52-73%) and 25% (95% CI: 62-90%) lower risk of death during the duration of the trial, respectively (Figure 1). Conversely, individuals who were underweight demonstrated a 31% (95% CI: 4-64%) increase in the risk of death (with similar rates when <20 kg/m^2 was split further into categories of Underweight II (<18.5 kg/m^2) and Underweight I (18.5-<20 kg/m^2), Table 4S), and individuals with class III obesity demonstrated a 36% (95% CI: 0-86%) increase in the risk of death compared with those with a normal BMI (Figure 1). In all BMI strata, rates of death due to cardiovascular disease were higher than those attributable to respiratory causes (Table 2, 4S). Respiratory deaths contributed more to mortality in the underweight (where 2.2% of patients died of respiratory causes; HR 1.44, 95%CI: 0.86-2.41) than the obese class III category (where 1.0% of patients died; HR 1.31, 95%CI: 0.54-3.16). Being overweight compared to normal BMI was associated with a decreased hazard of both respiratory (HR 0.51, 95% CI: 0.32-0.81) and cardiovascular (HR 0.69, 95% CI: 0.53-0.88) mortality.

Regarding morbidity, being overweight was associated with a lower risk of severe COPD exacerbation (HR 0.85, 95% CI: 0.73-0.98) or pneumonia (HR 0.76, 95% CI: 0.63-0.91) during treatment, while class II obesity was associated with a higher risk of moderate/severe COPD exacerbation (HR 1.14, 95% CI: 1.01-1.28). Underweight was conversely associated with a higher risk of pneumonia (HR 1.33, 95% CI: 1.05-1.67) compared to normal weight. No other significant, unique associations between BMI strata and moderate/severe or severe COPD exacerbations or cardiovascular events were noted in the main analyses (Table 3) or sensitivity analyses (Table 5S).

Discussion

Data from the large, international SUMMIT Trial including patients with moderate COPD at heightened cardiovascular risk demonstrates that BMI is associated with risk of all-cause mortality at the extremes; specifically among underweight (BMI<20 kg/m^2) and obese class III (BMI$\geq$40 kg/m^2). Moderate levels of obesity and overweight are associated with lower risk of death. Risk of death due to respiratory causes is highest among underweight individuals, though the leading cause of death in all BMI categories is cardiovascular, with the highest risk among obese class III. A "U-shaped" curve (with a protective association with overweight) was not consistently identified for morbidity outcomes.

The findings support and extend several studies demonstrating that underweight is a substantial risk factor for mortality in patients with COPD. [1, 8, 19-21] It has been argued that there is reverse causation with increasing severity of illness coinciding with weight loss and underweight status.[20] While the ability of nutritional supplementation and weight gain to reduce COPD mortality remains unclear[22, 23] the relationship between underweight and mortality exists even within patients with mild or moderate disease, [8] suggesting that disease severity alone may not account for increased mortality among underweight. Furthermore, findings in the SUMMIT population are consistent with prior studies demonstrating a protective association between overweight and obesity and COPD mortality.[2, 24-26] The protective associations with higher BMI are typically strongest with increasing disease severity, [8] and are reflected here in a population with moderate disease. In all categories, cardiovascular mortality predominated, consistent with population studies demonstrating cardiovascular disease as a leading cause of death in patients with COPD[11, 12, 27] and reasonable in this population at heightened cardiovascular risk.

Because of the large number of participants in the trial, there were a substantial number with class III obesity. Although class I obesity was associated with a lower mortality risk, individuals with class III obesity demonstrated increased risk for mortality. Indeed, weight gain in obese patients has previously been associated with increased mortality in individuals with severe COPD. [28] While overall increased mortality rates above 40 kg/m^2 might be expected based on well-known associations with hypertension, hypercholesterolemia, and diabetes, the prevalence of these conditions were similar between BMI classes II and III at trial initiation, suggesting a potential alternative explanation. Other comorbidities not captured in the SUMMIT data may play a role. For example, class III obesity is also associated with higher rates of sleep apnea, [29] which is linked to increased mortality and is an important comorbidity in COPD.[30, 31] Further, COPD phenotype may play a role in BMI-mortality relationships; patients with an emphysematous phenotype are more likely to be underweight, while patients with a chronic bronchitis phenotype are more likely to be overweight. [32] While these diagnoses are not mutually exclusive, it is possible that disease phenotypes are partially responsible for the associations noted.

Fewer studies in the current literature have examined associations between BMI and COPD morbidity outcomes, though several have combined morbidity and mortality into a single variable.[24, 33] These studies overall demonstrate increased respiratory morbidity in the underweight (i.e. hospitalizations,[33] hospital length of stay, [24] pneumonia[18]), although at least one prior analysis suggests higher odds of severe COPD exacerbation at the opposite end of the BMI

spectrum, class III obesity.[34] Extreme obesity may confer disadvantageous changes in pulmonary function such as increased airway resistance and reduced lung volumes, [35] relevant to individuals with COPD with already compromised respiratory mechanics. It is plausible that this may contribute to respiratory morbidity and exacerbations. Interestingly, in the SUMMIT Trial population overweight was associated with a lower risk of pneumonia. This is consistent with previous findings in the TORCH trial[36] demonstrating lower rates of pneumonia in higher BMI groups. [18] Furthermore, overweight associated with a lower risk of severe COPD exacerbations, but no increased risk was noted in underweight or class III obese populations. In contrast to overweight, lower mortality rates in class I obesity were not matched with reduced morbidity for the measured outcomes, suggesting the potential for an unmeasured morbidity signal. We did not find an association between BMI category and cardiovascular event risk; previous studies of cardiovascular morbidity outcomes in COPD by BMI are sparse, but suggest higher prevalence of heart failure with obesity, though not necessarily stroke or coronary heart disease, [34, 37, 38] which comprise the majority of the events captured in the SUMMIT Trial. The discordance between morbidity and mortality outcomes in relation to BMI deserves further attention, and the selection of outcomes is important in defining any future nutritional intervention trials.

Strengths include a study design that allowed for longitudinal assessment of a large number of participants including a critical population with obesity class III, limited in prior COPD studies. Patients with severe and very severe COPD were excluded, providing the opportunity to investigate the paradox in a dedicated cohort with less-severe COPD which may mitigate confounding of lower weight by higher disease severity. Cardiovascular risk was defined, allowing for adjustment but also mitigating competing respiratory risk in cause-specific mortality analyses. Deaths within the study were carefully adjudicated, with high ascertainment of vital status and confidence in primary and secondary outcomes. Ability to define cause-specific morbidity and mortality outcomes in a single population is unique. International representation increases generalizability of results, while precise characterization of lung function and rigorous assessment of cardiovascular health enhances validity of application among populations with moderate COPD at heightened cardiovascular risk.

Weakness are acknowledged. While cardiovascular comorbidities were well-defined, additional comorbidities were not captured, limiting assessment of potential contributing factors. Furthermore, the relatively small number of cardiovascular events (compared with all-cause mortality) may have limited power to distinguish between BMI groupings. In this study, a BMI of 20 kg/m^2 was chosen as the lower limit of the normal weight category for primary

analyses. This cut point may reduce comparability with other disease states, and falls between the BMI of 21 kg/m^2 in the BODE index[39] and 18.5 kg/m^2 in WHO guidelines[17] to define at-risk/underweight populations. However, 20 kg/m^2 has been used in previous studies demonstrating the obesity paradox in populations with COPD,[24, 25] and is of proposed benefit in facilitating international comparisons.[40] This approach combined with sensitivity analyses using the cut point of BMI 18.5 kg/m^2, provides increased granularity and generalizability. History of smoking was an inclusion criteria in the trial, and so differential associations among smokers/non-smokers and resultant selection bias by smoking was not explored.[41] Residual confounding by region may exist. Underweight individuals were more likely to be enrolled in Asia, whereas obese class II/III individuals were more likely enrolled in Europe and the United States, and outcomes may be influenced by local patterns of medical care and exposures. Adjustment for additional covariates not available within the SUMMIT data may provide more precision in estimates, and reveal factors that adjust or modify the obesity-mortality association in the direction of protection or harm. Multi-collinearity was not assessed. While multi-collinearity has the potential to decrease precision and skew estimates, presented crude death rates mirror the adjusted pattern, and variable inclusion was determined on the basis of clinical relevance and aim to isolate direct BMI associations, avoiding mediation and confounding where possible. Further, collider stratification bias should be considered as a partial or complete methodologic explanation for findings of a protective association with obesity, and bears mention and consideration as an alternative to causality.[42,43] COPD subphenotyping, including imaging or symptom data, was not available for further stratification or adjustment. Finally, all patients were selected for inclusion in a randomized controlled trial and may therefore differ from patients in the general population; caution is warranted in application to populations outside of the trial inclusion criteria.

In conclusion, we have demonstrated that a U-shaped curve in the association between BMI category and mortality in an international population with moderate COPD at heightened cardiovascular risk. This relationship extends prior studies demonstrating increased risk of mortality in underweight, and a protective association between overweight and moderate obesity. However, we provide evidence supporting recurrence of increased mortality risk with extreme obesity, at BMI $\geq$40 kg/m^2. Understanding the impact of overweight and obesity on COPD is paramount in the context of rising numbers of individuals with COPD [44] and shifts in prevalence of overweight and obesity worldwide. [45] The relationship described emphasizes the need to better understand the impact of BMI-driven nutritional supplementation and weight loss interventions when applied to populations with COPD.

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Data availability statement
Information on GSK's data sharing commitments and requesting access to anonymized individual participant data and associated documents can be found at www.clinicalstudydatarequest.com.

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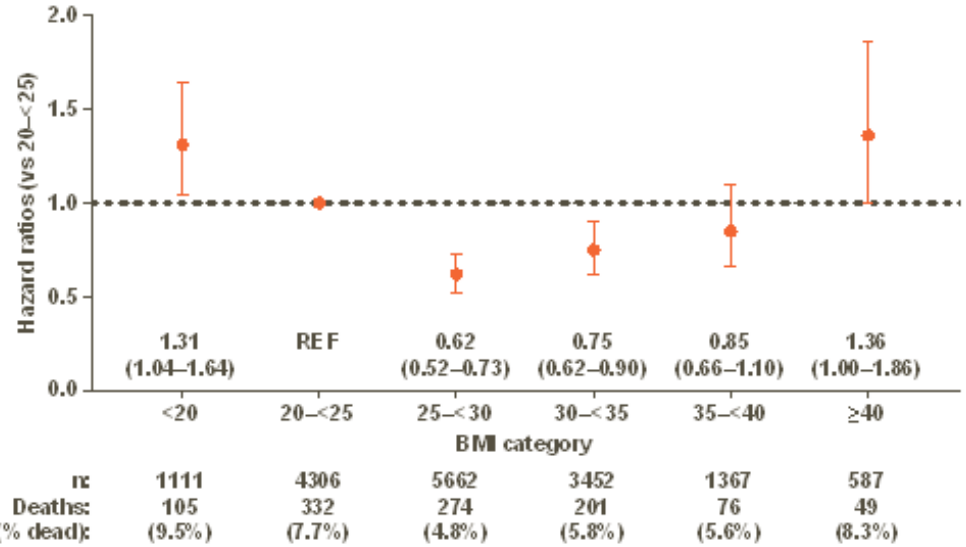
Figure 1. All cause mortality by BMI categories



n:	1111	4306	5662	3452	1367	587
Deaths:	105	332	274	201	76	49
(% dead):	(9.5%)	(7.7%)	(4.8%)	(5.8%)	(5.6%)	(8.3%)

Hazard ratios from model using 20–<25 as a reference group. Adjusted for: age, sex, region, race, ischemic heart disease, vascular disease, smoking status, cardiovascular history/risk, previous COPD exacerbations, percent predicted FEV_1, treatment arm, BMI.

Table 1. Baseline characteristics of study participants by BMI category

	Underweight <20 kg/m^2 (n=1111)	Normal 20-<25 kg/m^2 (n=4306)	Overweight 25-<30 kg/m^2 (n=5662)	Class I Obesity 30-<35 kg/m^2 (n=3452)	Class II Obesity 35-<40 kg/m^2 (n=1367)	Class III Obesity ≥40 kg/m^2 (n=587)
Demographics						
Body-mass index (kg/m^2)	18.3 (1.3)	22.9 (1.4)	27.4 (1.4)	32.1 (1.4)	37.0 (1.4)	44.0 (4.0)
Age (years)	65.4 (8.4)	65.8 (8.0)	65.5 (7.9)	65.0 (7.5)	63.4 (7.8)	62.3 (7.8)
Women	229 (21%)	941 (22%)	1373 (24%)	946 (27%)	455 (33%)	252 (43%)
Race						
White	468 (42%)	2941 (68%)	4841 (85%)	3236 (94%)	1314 (96%)	557 (95%)
Asian	625 (56%)	1262 (29%)	694 (12%)	126 (4%)	13 (<1%)	3 (<1%)
Other	18 (2%)	103 (2%)	127 (2%)	90 (3%)	40 (3%)	27 (5%)
Region						
United States	75 (7%)	443 (10%)	859 (15%)	655 (19%)	344 (25%)	214 (36%)
Europe	340 (31%)	2322 (54%)	3700 (65%)	2365 (69%)	889 (65%)	302 (51%)
Asia	625 (56%)	1245 (29%)	681 (12%)	120 (3%)	12 (<1%)	3 (<1%)
Rest of World	71 (6%)	296 (7%)	422 (7%)	312 (9%)	122 (9%)	68 (12%)
Current Smokers	617 (56%)	2281 (53%)	2589 (46%)	1389 (40%)	570 (42%)	232 (40%)
Smoking history (pack-years)	39.1 (23.6)	40.4 (23.4)	40.2 (23.8)	41.8 (25.1)	42.4 (27.1)	41.9 (26.3)
Lung Function						
Post-BD FEV_1 (L) at Screening	1.5 (0.4)	1.6 (0.4)	1.7 (0.4)	1.7 (0.4)	1.7 (0.4)	1.7 (0.4)
% Predicted post-BD FEV_1 at Screening	60.0 (6.3)	59.8 (6.2)	59.8 (6.1)	59.4 (5.9)	59.2 (6.1)	58.9 (6.1)
FEV_1 reversibility (% of pre-BD FEV_1) at Screening	7.6 (12.2)	8.1 (12.2)	8.1 (11.6)	8.0 (12.0)	9.0 (12.4)	9.0 (12.2)
Pre-study COPD exacerbations in 12 months before study						
0	717 (65%)	2675 (62%)	3390 (60%)	2065 (60%)	828 (61%)	346 (59%)
1	233 (21%)	1009 (23%)	1418 (25%)	888 (26%)	338 (25%)	134 (23%)
2+	161 (14%)	622 (14%)	854 (15%)	499 (14%)	201 (15%)	107 (18%)
Cardiovascular inclusion criteria*						
Manifest disease						
Coronary artery disease	445 (40%)	2056 (48%)	2951 (52%)	1868 (54%)	745 (54%)	314 (53%)
Peripheral arterial disease	245 (22%)	841 (20%)	1096 (19%)	629 (18%)	234 (17%)	100 (17%)
Previous stroke	147 (13%)	439 (10%)	546 (10%)	309 (9%)	108 (8%)	46 (8%)
Previous myocardial infarction	144 (13%)	653 (15%)	967 (17%)	666 (19%)	246 (18%)	98 (17%)
Diabetes with target organ disease	58 (5%)	237 (6%)	458 (8%)	414 (12%)	230 (17%)	106 (18%)
At risk						
Hypercholesterolaemia	547 (49%)	2467 (57%)	3579 (63%)	2300 (67%)	906 (66%)	391 (67%)
Hypertension	833 (75%)	3506 (81%)	4931 (87%)	3183 (92%)	1274 (93%)	538 (92%)
Diabetes mellitus	200 (18%)	818 (19%)	1395 (25%)	1103 (32%)	588 (43%)	272 (46%)
Peripheral arterial disease	130 (12%)	420 (10%)	564 (10%)	309 (9%)	100 (7%)	54 (9%)
SUMMIT treatment assignment						
Fluticasone furoate	298 (27%)	1086 (25%)	1420 (25%)	860 (25%)	336 (25%)	135 (23%)
Vilanterol	280 (25%)	1061 (25%)	1400 (25%)	881 (26%)	325 (24%)	171 (29%)
Fluticasone furoate/vilanterol	280 (25%)	1052 (24%)	1437 (25%)	857 (25%)	344 (25%)	151 (26%)
Placebo	253 (23%)	1107 (26%)	1405 (25%)	854 (25%)	362 (26%)	130 (22%)

Data are mean (SD) or n (%). FEV_1=forced expiratory volume in 1 s. COPD=chronic obstructive pulmonary disease. *Patients could have several cardiovascular diseases or risks at study entry.

Table 2. Total On- and Post-treatment Cause-Specific Mortality by BMI Category

	Underweight <20 kg/m^2 (n=1111)	Normal 20-<25 kg/m^2 (n=4306)	Overweight 25-<30 kg/m^2 (n=5662)	Class I Obesity 30-<35 kg/m^2 (n=3452)	Class II Obesity 35-<40 kg/m^2 (n=1367)	Class III Obesity ≥40 kg/m^2 (n=587)
Respiratory Mortality						
Deaths (%)	24 (2.2%)	49 (1.1%)	27 (0.5%)	23 (0.7%)	8 (0.6%)	6 (1.0%)
Hazard Ratio (95% CI)	1.44 (0.86, 2.41)	REF	0.51 (0.32, 0.81)	0.77 (0.46, 1.30)	0.80 (0.37, 1.72)	1.31 (0.54, 3.16)
Cardiovascular Mortality						
Deaths (%)	41 (3.7%)	132 (3.1%)	119 (2.1%)	94 (2.7%)	35 (2.6%)	24 (4.1%)
Hazard Ratio (95% CI)	1.30 (0.90, 1.87)	REF	0.69 (0.53, 0.88)	0.90 (0.68, 1.19)	1.04 (0.71, 1.53)	1.87 (1.19, 2.94)

REF=Reference, Hazard ratio (95% confidence interval) per Cox-proportional hazards. Adjusted model accounts for age, sex, region, race, ischemic heart disease indicator, vascular disease indicator, smoking status, cardiovascular entry criteria (history and risk by age), previous COPD exacerbations, % predicted FEV_1, treatment arm, BMI

Table 3. On-treatment System-Specific Morbidity by BMI Categories

	Underweight <20 kg/m^2 (n=1111)	Normal 20-<25 kg/m^2 (n=4306)	Overweight 25-<30 kg/m^2 (n=5662)	Class I Obesity 30-<35 kg/m^2 (n=3452)	Class II Obesity 35-<40 kg/m^2 (n=1367)	Class III Obesity ≥40 kg/m^2 (n=587)
Moderate/Severe COPD Exacerbation						
Events (%)	325 (29.3%)	1206 (28.0%)	1551 (27.4%)	1005 (29.1%)	429 (31.4%)	188 (32.0%)
Hazard Ratio (95% CI)	1.01 (0.89, 1.14)	REF	0.97 (0.90, 1.05)	1.02 (0.93, 1.11)	1.14 (1.01, 1.28)	1.05 (0.89, 1.23)
Severe COPD Exacerbation						
Events (%)	128 (11.5%)	367 (8.5%)	384 (6.8%)	265 (7.7%)	105 (7.7%)	44 (7.5%)
Hazard Ratio (95% CI)	1.18 (0.96-1.46)	REF	0.85 (0.73-0.98)	1.02 (0.87-1.21)	1.14 (0.90-1.43)	1.07 (0.77-1.49)
Pneumonia						
Events (%)	106 (9.5%)	260 (6.0%)	235 (4.2%)	153 (4.4%)	58 (4.2%)	26 (4.4%)
Hazard Ratio (95% CI)	1.33 (1.05-1.67)	REF	0.76 (0.63-0.91)	0.83 (0.67-1.03)	0.84 (0.62-1.14)	0.80 (0.52-1.22)
Composite Cardiovascular Events						
Events (%)	46 (4.1%)	191 (4.4%)	231 (4.1%)	154 (4.5%)	47 (3.4%)	19 (3.2%)
Hazard Ratio (95% CI)	1.01 (0.73-1.40)	REF	0.90 (0.74-1.10)	0.98 (0.78-1.22)	0.88 (0.64-1.23)	0.93 (0.57-1.50)

REF=Reference, Hazard ratio (95% confidence interval) per Cox-proportional hazards. Adjusted model accounts for age, sex, region, race, ischemic heart disease indicator, vascular disease indicator, smoking status, cardiovascular entry criteria (history and risk by age), previous COPD exacerbations, % predicted FEV_1 , treatment arm, BMI

Moderate COPD exacerbation: exacerbation treated with antibiotics and/or systemic corticosteroids

Severe COPD exacerbation: required hospitalization

Composite Cardiovascular Events: pre-defined secondary endpoint contains myocardial infarction, stroke, transient ischemic attack, unstable angina, and on-treatment cardiovascular death

Online Supplement.

Table 1S. Baseline characteristics of underweight participants: sensitivity analysis

	Underweight II <18.5 kg/m^2 (n=534)	Underweight I 18.5-<20 kg/m^2 (n=577)		Underweight <20 kg/m^2 (n=1111)
Demographics				
Body-mass index (kg/m^2)	17.2 (1.1)	19.3 (0.4)		18.3 (1.3)
Age (years)	65.7 (7.9)	65.1 (8.7)		65.4 (8.4)
Women	99 (19%)	130 (23%)		229 (21%)
Race				
White	184 (34%)	284 (49%)		468 (42%)
Asian	341 (64%)	284 (49%)		625 (56%)
Other	9 (2%)	9 (2%)		18 (2%)
Region				
United States	36 (7%)	39 (7%)		75 (7%)
Europe	125 (23%)	215 (37%)		340 (31%)
Asia	341 (64%)	284 (49%)		625 (56%)
Rest of World	32 (6%)	39 (7%)		71 (6%)
Current Smokers	308 (58%)	309 (54%)		617 (56%)
Smoking history (pack-years)	38.1 (22.6)	40.1 (24.5)		39.1 (23.6)
Lung Function				
Post-bronchodilator FEV_1 (L) at Screening	1.5 (0.4)	1.6 (0.4)		1.5 (0.4)
% Predicted post-bronchodilator FEV_1 at Screening	59.7 (6.6)	60.2 (6.1)		60.0 (6.3)
FEV_1 reversibility (as a % of pre-bronchodilator FEV_1) at Screening	7.7 (13.5)	7.6 (10.9)		7.6 (12.2)
Pre-study COPD exacerbations in 12 months before study				
0	355 (66%)	362 (63%)		717 (65%)
1	103 (19%)	130 (23%)		233 (21%)
2+	76 (14%)	85 (15%)		161 (14%)
Cardiovascular inclusion criteria*				
Manifest disease				
Coronary artery disease	192 (36%)	253 (44%)		445 (40%)
Peripheral arterial disease	99 (19%)	146 (25%)		245 (22%)
Previous stroke	61 (11%)	86 (15%)		147 (13%)
Previous myocardial infarction	74 (14%)	70 (12%)		144 (13%)
Diabetes with target organ disease	24 (4%)	34 (6%)		58 (5%)
At risk				
Hypercholesterolaemia	263 (49%)	284 (49%)		547 (49%)
Hypertension	412 (77%)	421 (73%)		833 (75%)
Diabetes mellitus	98 (18%)	102 (18%)		200 (18%)
Peripheral arterial disease	49 (9%)	81 (14%)		130 (12%)
Pre-study COPD therapy				
Long-acting β agonist	151 (28%)	182 (32%)		333 (30%)
Long-acting muscarinic agonist	63 (12%)	66 (11%)		129 (12%)
Inhaled corticosteroids	152 (28%)	167 (29%)		319 (29%)
Concomitant cardiovascular therapy				
Any medication	500 (94%)	538 (93%)		1038 (93%)
Anti-thrombotic medication	237 (44%)	297 (51%)		534 (48%)
Lipid-lowering medication	319 (60%)	335 (58%)		654 (59%)
Renin-angiotensin aldosterone inhibitor therapy	244 (46%)	305 (53%)		549 (49%)
B blockers	102 (19%)	111 (19%)		213 (19%)
Calcium channel blockers	250 (47%)	246 (43%)		496 (45%)
Nitrates	70 (13%)	101 (18%)		171 (15%)
Diuretics	118 (22%)	132 (23%)		250 (23%)
SUMMIT treatment assignment				
Fluticasone furoate	142 (27%)	156 (27%)		298 (27%)
Vilanterol	131 (25%)	149 (26%)		280 (25%)
Fluticasone furoate/vilanterol	133 (25%)	147 (25%)		280 (25%)
Placebo	128 (24%)	125 (22%)		253 (23%)

Data are mean (SD) or n (%). FEV_1=forced expiratory volume in 1 s. COPD=chronic obstructive pulmonary disease. *Patients could have several cardiovascular diseases or risks at study entry.

Table 2S. Baseline therapy of study participants by BMI category

	Underweight <20 kg/m^2 (n=1111)	Normal 20-<25 kg/m^2 (n=4306)	Overweight 25-<30 kg/m^2 (n=5662)	Class I Obesity 30-<35 kg/m^2 (n=3452)	Class II Obesity 35-<40 kg/m^2 (n=1367)	Class III Obesity ≥40 kg/m^2 (n=587)
Pre-Study COPD Therapy						
Long-acting β agonist	333 (30%)	1425 (33%)	2100 (37%)	1378 (40%)	557 (41%)	240 (41%)
Long-acting muscarinic agonist	129 (12%)	647 (15%)	967 (17%)	692 (20%)	286 (21%)	134 (23%)
Inhaled corticosteroids	319 (29%)	1377 (32%)	1978 (35%)	1326 (38%)	517 (38%)	251 (43%)
Concomitant cardiovascular therapy						
Any medication	1038 (93%)	4099 (95%)	5526 (98%)	3410 (99%)	1357 (99%)	581 (99%)
Anti-thrombotic medication	534 (48%)	2400 (56%)	3320 (59%)	2232 (65%)	896 (66%)	379 (65%)
Lipid-lowering medication	654 (59%)	2794 (65%)	3880 (69%)	2496 (72%)	974 (71%)	411 (70%)
Renin-angiotensin aldosterone inhibitor therapy	549 (49%)	2700 (63%)	4083 (72%)	2767 (80%)	1129 (83%)	484 (82%)
β blockers	213 (19%)	1279 (30%)	2020 (36%)	1417 (41%)	617 (45%)	264 (45%)
Calcium channel blockers	496 (45%)	1708 (40%)	2177 (38%)	1319 (38%)	592 (43%)	234 (40%)
Nitrates	171 (15%)	659 (15%)	873 (15%)	520 (15%)	222 (16%)	79 (13%)
Diuretics	250 (23%)	1268 (29%)	2101 (37%)	1695 (49%)	771 (56%)	396 (67%)

Data are mean (SD) or n (%).

Table 4S. Total On- and Post-treatment Mortality by BMI Category in Underweight, Sensitivity Analysis

	Underweight II <18.5 kg/m^2 (n=534)	Underweight I 18.5-<20 kg/m^2 (n=577)		Underweight <20 kg/m^2 (n=1111)
All-Cause Mortality				
Deaths (%)	54 (10.1%)	51 (8.8%)		105 (9.5%)
Hazard Ratio (95% CI)	1.42 (1.05, 1.91)	1.22 (0.90, 1.64)		1.31 (1.04, 1.64)
Respiratory Mortality				
Deaths (%)	15 (2.8%)	9 (1.6%)		24 (2.2%)
Hazard Ratio (95% CI)	1.70 (0.93, 3.11)	1.16 (0.55, 2.41)		1.44 (0.86, 2.41)
Cardiovascular Mortality				
Deaths (%)	22 (4.1%)	19 (3.3%)		41 (3.7%)
Hazard Ratio (95% CI)	1.51 (0.94, 2.42)	1.12 (0.69, 1.83)		1.30 (0.90, 1.87)

The category of Underweight (<20 kg/m^2) has been split into two new categories: Underweight II (<18.5 kg/m^2) and Underweight I (18.5-<20 kg/m^2). The Hazard ratios shown are in comparison to the reference category of Normal (20-<25 kg/m^2). For clarity, Underweight (<20 kg/m^2) has been shown again in this table from Figure 1 and Table 2.
Hazard ratio (95% confidence interval) per Cox-proportional hazards. Adjusted model accounts for age, sex, region, race, ischemic heart disease indicator, vascular disease indicator, smoking status, , cardiovascular entry criteria (history and risk by age), previous COPD exacerbations, % predicted FEV_1 treatment arm, BMI

Table 5S. On-treatment System-Specific Morbidity by BMI Categories in Underweight, Sensitivity Analysis

	Underweight II <18.5 kg/m^2 (n=534)	Underweight I 18.5-<20 kg/m^2 (n=577)		Underweight <20 kg/m^2 (n=1111)
Moderate/Severe COPD Exacerbation				
Events (%)	158 (29.6%)	167 (28.9%)		325 (29.3%)
Hazard Ratio (95% CI)	1.00 (0.85, 1.19)	1.01 (0.86, 1.19)		1.01 (0.89, 1.14)
Severe COPD Exacerbation				
Events (%)	64 (12.0%)	64 (11.1%)		128 (11.5%)
Hazard Ratio (95% CI)	1.18 (0.90, 1.54)	1.19 (0.91, 1.56)		1.18 (0.96, 1.46)
Pneumonia				
Events (%)	57 (10.7%)	49 (8.5%)		106 (9.5%)
Hazard Ratio (95% CI)	1.39 (1.03, 1.87)	1.26 (0.92, 1.72)		1.33 (1.05, 1.67)
Composite Cardiovascular Events				
Events (%)	22 (4.1%)	24 (4.2%)		46 (4.1%)
Hazard Ratio (95% CI)	1.02 (0.65, 1.59)	1.00 (0.65, 1.54)		1.01 (0.73, 1.40)

The category of Underweight (<20 kg/m^2) has been split into two new categories: Underweight II (<18.5 kg/m^2) and Underweight I (18.5-<20 kg/m^2). The Hazard ratios shown are in comparison to the reference category of Normal (20-<25 kg/m^2). For clarity, Underweight (<20 kg/m^2) has been shown again in this table from Table 3.
Hazard ratio (95% confidence interval) per Cox-proportional hazards. Adjusted model accounts for age, sex, region, race, ischemic heart disease indicator, vascular disease indicator, smoking status, cardiovascular entry criteria (history and risk by age), previous COPD exacerbations, % predicted FEV_1, treatment arm, BMI
Moderate COPD exacerbation: exacerbation treated with antibiotics and/or systemic corticosteroids
Severe COPD exacerbation: required hospitalization
Pneumonia: pre-defined MedDRA preferred terms applied to investigator-reported adverse events
Composite Cardiovascular Events: pre-defined secondary endpoint contains myocardial infarction, stroke, transient ischemic attack, unstable angina, and on-treatment cardiovascular death