

Association of body mass index with mortality in COPD through exacerbations and cardiovascular events

Hyun Woo Lee ,¹ Sang Hyuk Kim,² Tae-Hyung Kim,³ Seung Won Ra,⁴ Won-Yeon Lee,⁵ Min Kwang Byun ,⁶ Chang-Hoon Lee ,⁷ Deog Kyeom Kim,¹ Kwang Ha Yoo,⁸ Yong Il Hwang ⁹

To cite: Lee HW, Kim SH, Kim T-H, *et al.* Association of body mass index with mortality in COPD through exacerbations and cardiovascular events. *BMJ Open Respir Res* 2026;**13**:e004358. doi:10.1136/bmjresp-2026-004358

► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/bmjresp-2026-004358>).

Received 7 April 2026
Accepted 30 July 2026

ABSTRACT

Introduction The mechanisms through which body mass index (BMI) influences the prognosis of chronic obstructive pulmonary disease (COPD) remain poorly understood. This study investigates whether BMI influences all-cause mortality in patients with COPD through mediating effects of exacerbations and cardiovascular events.

Methods Data were obtained from a multicentre prospective COPD cohort (NCT02800499). BMI was assessed both continuously and categorically as <23 (low), 23–27 (normal) and >27 kg/m² (high). The primary outcome was all-cause mortality and secondary outcomes were moderate-to-severe exacerbations and cardiovascular events. Mediation analyses were applied to quantify the contribution of these events to the association between BMI and all-cause mortality.

Results Among 3314 patients with COPD, those with low BMI had a higher risk of mortality (adjusted OR, 1.46; 95% CI 1.04 to 2.07), whereas no significant difference was observed among those with high BMI. Mediation analyses indicated that exacerbations partially mediated the relationship between BMI and all-cause mortality, explaining 11.9% of the increased mortality among patients with low BMI and 21.9% of the reduced mortality among those with high BMI. Meanwhile, cardiovascular events showed mediating effects in the opposite direction, contributing to 5.2% lower mortality among patients with low BMI and 11.5% higher mortality among those with high BMI.

Conclusions BMI was non-linearly associated with all-cause mortality in COPD. Exacerbations mediated the excess mortality risk among patients with low BMI, whereas the decreasing risk of cardiovascular events in this group contributed to a countervailing effect that tempered the overall association between low BMI and mortality.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide, imposing a substantial burden on patients and healthcare systems.¹ Beyond airflow limitation, COPD is increasingly recognised as a systemic disorder in which extrapulmonary factors

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Low body mass index (BMI) in chronic obstructive pulmonary disease (COPD) is associated with increased mortality, whereas high BMI paradoxically confers a survival advantage despite elevated cardiovascular risk, but the mechanisms underlying this non-linear pattern remain poorly understood.

WHAT THIS STUDY ADDS

⇒ Using counterfactual-based mediation analysis, this study demonstrates that exacerbations and cardiovascular events act as opposing mediators of the BMI–mortality relationship. In low-BMI patients, exacerbations partially account for excess mortality while cardiovascular events attenuate this effect, whereas in high-BMI patients, a lower exacerbation burden reduces mortality but increased cardiovascular risk partially offsets this benefit.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings suggest that BMI-stratified management strategies in COPD should prioritise exacerbation prevention and monitoring of body composition in underweight patients and systematic cardiovascular risk assessment in those with high BMI. Future intervention trials targeting BMI in COPD should incorporate competing mediation frameworks to capture opposing pathway effects that aggregate analyses would otherwise obscure.

such as nutritional status, muscle wasting and comorbidities significantly influence disease progression and survival.^{2–4} Recently, attention has been drawn to the potential importance of evaluating and managing cardiovascular risk and metabolic disorders in patients with COPD to improve prognosis.^{5–7}

Body mass index (BMI) has emerged as an important marker of overall health status in COPD. Low BMI has been associated with lower lung function, more severe symptoms, adverse outcomes including reduced respiratory muscle strength, heightened vulnerability



© Author(s) (or their employer(s)) 2026. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ Group.

For numbered affiliations see end of article.

Correspondence to

Dr Yong Il Hwang;
hyicyk@gmail.com

to infections, frequent exacerbations and increased mortality.^{8–12} Meanwhile, overweight or moderately obese patients showed improved survival compared with underweight individuals.^{13 14} However, higher BMI is also a well-established risk factor for cardiovascular disease, which has been a leading cause of death in patients with COPD.^{15–18} The coexistence of these opposing effects of BMI on mortality in COPD has been described as the ‘obesity paradox’, underscoring the presence of a non-linear relationship between BMI and mortality that is likely driven by distinct biological mechanisms.¹⁹

Although many studies have applied non-linear approaches to evaluate the association between BMI and mortality in COPD, the underlying mechanisms are not fully understood.²⁰ In particular, it remains uncertain whether BMI influences mortality directly or indirectly through mediating factors such as acute exacerbations or cardiovascular disease. Prior studies have reported these associations individually, but no study has formally quantified the relative contributions of exacerbations and cardiovascular events as competing mediating pathways within a single analytical framework. Clarifying these mechanisms is clinically important, as it may help identify high-risk patients who could benefit from nutritional interventions to prevent underweight-related vulnerability or from closer cardiovascular surveillance in those with elevated BMI.

Therefore, we investigated the association between BMI and all-cause mortality, incorporating non-linear modelling to capture potential threshold effects. We further assessed whether moderate-to-severe exacerbations and cardiovascular events mediate this relationship, in order to explain how BMI influences survival in COPD.

METHODS

Study design and population

We conducted a prospective longitudinal observational study within the Korean COPD Subtype Study (KOCOSS) including the patients with COPD across South Korea (ClinicalTrials.gov identifier: NCT02800499). The KOCOSS cohort recruited participants from 54 medical institutions using standardised protocols for baseline and follow-up assessments. Detailed information on the study design and methodology has been published previously.²¹

Eligible participants were adults aged 40 years or older with physician-diagnosed COPD, defined according to the Global Initiative for Chronic Obstructive Lung Disease criteria as the presence of persistent respiratory symptoms and a post-bronchodilator forced expiratory volume in 1 s to forced vital capacity ratio (FEV₁/FVC) of less than 0.70.²² At the time of enrolment, patients were required to be in a stable condition, with no acute exacerbation for at least 4 weeks prior to baseline evaluation.

Exclusion criteria included inability to complete pulmonary function testing, myocardial infarction or cerebrovascular event within the previous 3 months, pregnancy, rheumatoid disease, malignancy, irritable bowel disease

and systemic corticosteroid use for conditions other than COPD exacerbation within 8 weeks before enrolment.

Clinical and laboratory variables

At baseline, demographic and clinical information were collected according to standardised protocols, including age, sex, BMI, educational level, place of residence (capital city or non-capital area) and smoking status (never, former or current). Medical history and comorbid conditions were documented, with a focus on the Charlson comorbidity index as well as the presence of bronchiectasis and tuberculosis-destroyed lung. Symptom burden was assessed using the modified Medical Research Council (mMRC) dyspnoea scale, the COPD Assessment Test (CAT) and the St. George's Respiratory Questionnaire for COPD Patients (SGRQ-C). Exercise capacity was evaluated by the 6-Minute Walk Distance (6MWD). A history of exacerbation was recorded, including both moderate-to-severe and severe events.

Pulmonary function tests included post-bronchodilator FEV₁, FVC, and the FEV₁/FVC ratio, expressed as absolute values, percent predicted values and z-scores. Additional measurements included diffusing capacity for carbon monoxide (DL_{CO}), alveolar volume-adjusted diffusing capacity, and total lung capacity (TLC), each reported as absolute and percent predicted values.

Laboratory tests comprised complete blood cell counts with differential, including white cell count, neutrophil, lymphocyte, monocyte, basophil and eosinophil counts. Blood eosinophil count was further categorised by absolute counts and a threshold of >300 cells/μL.

Medication use was systematically documented, including inhaled therapies (long-acting beta-agonists (LABA), long-acting muscarinic antagonists (LAMA), inhaled corticosteroids (ICS), ICS/LABA combinations, LABA/LAMA combinations and triple therapy with ICS/LABA/LAMA) and oral medications (phosphodiesterase-4 inhibitors, methylxanthines, erdosteine, N-acetylcysteine and macrolides).

Body mass index categorisation

BMI was calculated as weight in kilograms divided by height in metres squared (kg/m²) at the time of enrolment. For categorical analyses, patients were stratified into three groups: low (<23 kg/m²), normal (23–27 kg/m², reference group) and high (>27 kg/m²). The selection of these cut-off values was based on evidence from a large-scale national health screening cohort in Korea, which demonstrated that all-cause mortality remained similar within the range of BMI 23–27 kg/m², whereas mortality increased progressively below 23 kg/m² and above 27 kg/m².²³

Outcome measurement

Primary outcome was all-cause mortality confirmed through linkage with nationwide death statistics from

Statistics Korea. Secondary outcomes were moderate-to-severe exacerbations and composite cardiovascular events. Moderate-to-severe exacerbations were defined as events requiring systemic corticosteroids, antibiotics or hospitalisation. Composite cardiovascular events were defined as newly occurring myocardial infarction, stroke or heart failure in patients without a prior history of these conditions. Clinical outcomes were ascertained at each annual follow-up visit and were additionally verified through medical record review.

Statistical analysis

Baseline characteristics were summarised according to BMI categories and compared using analysis of variance or the Kruskal-Wallis test for continuous variables and χ^2 tests for categorical variables, as appropriate. Continuous variables are presented as means with SDs or medians with IQRs, while categorical variables are presented as counts and percentages.

BMI was modelled using restricted cubic splines to assess potential non-linear relationships with mortality, exacerbations and cardiovascular events. The presence of non-linearity was evaluated by likelihood ratio tests comparing models with and without spline terms, and model fit was assessed using the Akaike information criterion (AIC).

Owing to the fixed follow-up window and the annual assessment of outcome status, logistic regression was applied uniformly across all outcome and mediator models, ensuring the methodological consistency required for valid counterfactual-based mediation analysis. Confounders were selected a priori based on established literature and clinical relevance to the relationship between BMI and COPD outcomes. Multivariable models were adjusted for potential confounders, including age, sex, educational level, smoking status, Charlson comorbidity index, history of prior exacerbations, lung function parameters, symptom burden (mMRC, CAT and SGRQ-C), 6MWD, laboratory parameters (blood counts) and medication use.

Mediation analysis was performed to quantify the extent to which exacerbations and composite cardiovascular events mediated the association between BMI and mortality. Natural direct and indirect effects were estimated using counterfactual-based mediation models, and the proportion mediated was calculated with corresponding CIs derived from bootstrapping. These analyses were conducted with the 'mediation' package in R.²⁴ Missing data were handled by complete case analysis, with each model fitted using all available observations for the variables of interest. Given the relatively low proportion of missing values and the absence of systematic patterns across covariates, no imputation procedure was applied.

All analyses were conducted using R software (V.4.5.0; R Foundation for Statistical Computing, Vienna, Austria). Two-sided P values <0.05 were considered statistically significant.

RESULTS

A total of 3476 patients with COPD were initially enrolled between January 2012 and December 2022. After excluding 112 patients without baseline lung function tests and 50 patients without CAT or SGRQ-C questionnaires, 3314 patients were included in the final analysis (online supplemental figure 1). Among them, 1633 (49.3%) were classified as the low BMI group (<23 kg/m²), 1250 (37.7%) as the normal BMI group (23–27 kg/m²) and 431 (13.0%) as the high BMI group (>27 kg/m²). The mean follow-up duration was 21.2±11.0 months.

Baseline characteristics

Baseline characteristics are presented in table 1. Patients with low BMI were more often male and current smokers, had a higher comorbidity burden including more frequent tuberculosis-destroyed lung and reported greater symptom burden with higher mMRC, CAT and SGRQ-C scores. They had shorter 6MWDs, more frequent prior exacerbations and worse lung function with lower FEV₁, FEV₁/FVC and DL_{CO}. TLC tended to be higher in the low BMI group. Laboratory findings revealed higher neutrophil counts and lower lymphocyte counts in the low BMI group. Treatment patterns differed, with greater use of inhaled triple therapy, phosphodiesterase-4 inhibitors and methylxanthines in the low BMI group, whereas LABA/LAMA use was more common in the high BMI group.

All-cause mortality

A total of 324 deaths were observed, corresponding to an overall mortality rate of 9.8%. The mortality rate was significantly higher in the low BMI group (12.6%) compared with 7.1% in the normal BMI group and 7.0% in the high BMI group (p<0.001). The low BMI group accounted for 63.6% of deaths, while only 9.3% of deaths occurred in the high BMI group. Clinical factors related to mortality are summarised in online supplemental table 1.

Restricted cubic spline analysis illustrated a non-linear association between BMI and all-cause mortality (figure 1A). Mortality risk rose sharply at BMI values below 23 kg/m², reached its nadir within the 23–27 kg/m² range and showed a modest but imprecise increase above 27 kg/m² due to wider CIs. Formal testing also supported the presence of non-linearity. Likelihood ratio tests comparing spline and linear models were statistically significant (p<0.05), and the AIC indicated better overall model performance for the spline specification.

In univariable analysis, each 1 kg/m² increase in BMI was associated with a lower risk of death (unadjusted OR (uOR)=0.908, 95% CI 0.877 to 0.940, p<0.001) (table 2). This association was attenuated in the multivariable model and did not reach statistical significance. When BMI was categorised, patients with BMI <23 kg/m² consistently showed a significantly higher risk of mortality compared with those with BMI 23–27 kg/m² in both univariable

Table 1 Baseline characteristics according to body mass index (BMI)

Variable	Low BMI <23 (n=1633)	Normal BMI 23–27 (n=1250)	High BMI >27 (n=431)	P value
Age, mean (SD)	68.6 (8.3)	68.4 (8.0)	68.3 (7.6)	0.713
Female, n (%)	103 (6.3)	104 (8.3)	46 (10.7)	0.005
BMI, mean (SD)	20.4 (1.9)	24.7 (1.1)	28.9 (2.0)	<0.001
Education				0.321
Less than or equal to elementary school, n (%)	489 (29.9)	324 (25.9)	131 (30.4)	
Middle school graduate, n (%)	355 (21.7)	284 (22.7)	89 (20.6)	
High school graduate, n (%)	557 (34.1)	461 (36.9)	149 (34.6)	
College graduate or higher, n (%)	232 (14.2)	181 (14.5)	62 (14.4)	
Residence				
Capital city, n (%)	276 (16.9)	255 (20.4)	78 (18.1)	0.055
Smoking status				<0.001
Never smoker, n (%)	127 (7.8)	122 (9.8)	62 (14.4)	
Ex-smoker, n (%)	1011 (61.9)	820 (65.6)	293 (68.0)	
Current smoker, n (%)	495 (30.3)	308 (24.6)	76 (17.6)	
Comorbidities				
Charlson comorbidity index				<0.001
1–2, n (%)	203 (12.4)	197 (15.8)	90 (20.9)	
≥3, n (%)	142 (8.7)	58 (4.6)	23 (5.3)	
Bronchiectasis, n (%)	194 (11.9)	142 (11.4)	40 (9.3)	0.318
Tuberculosis-destroyed lung, n (%)	47 (2.9)	22 (1.8)	5 (1.2)	0.036
Symptom and functional status				
mMRC, mean (SD)	1.4 (0.9)	1.2 (0.9)	1.3 (0.9)	<0.001
CAT, mean (SD)	14.7 (8.2)	13.5 (7.9)	13.0 (7.9)	<0.001
SGRQ-C, mean (SD)	31.6 (21.7)	27.3 (19.1)	28.7 (19.8)	<0.001
6MWD, mean (SD)	374 (98)	390 (102)	378 (89)	<0.001
Previous history of exacerbation				
Moderate-to-severe, n (%)	235 (14.4)	136 (10.9)	30 (7.0)	<0.001
Severe, n (%)	131 (8.0)	57 (4.6)	9 (2.1)	<0.001
Lung function parameters				
Post-BDR FEV ₁ , L, mean (SD)	1.64 (0.63)	1.82 (0.60)	1.88 (0.57)	<0.001
Post-BDR FEV ₁ , % predicted, mean (SD)	56.1 (19.4)	62.6 (17.7)	65.1 (17.6)	<0.001
Post-BDR FEV ₁ , z-score, mean (SD)	−2.17 (1.26)	−1.75 (1.18)	−1.58 (1.16)	<0.001
Post-BDR FVC, L, mean (SD)	3.21 (0.84)	3.27 (0.84)	3.18 (0.81)	0.064
Post-BDR FVC, % predicted, mean (SD)	79.4 (17.2)	78.9 (16.4)	75.4 (16.1)	<0.001
Post-BDR FVC, z-score, mean (SD)	−0.08 (1.34)	0.08 (1.25)	−0.10 (1.28)	0.002
Post-BDR FEV ₁ /FVC, %, mean (SD)	49.6 (13.5)	54.2 (11.7)	58.1 (10.7)	<0.001
Post-BDR FEV ₁ /FVC, z-score, mean (SD)	−2.86 (1.16)	−2.55 (0.97)	−2.23 (0.93)	<0.001
DL _{CO} , mL/min/mm Hg, mean (SD) (n=1385/1064/361)	12.0 (4.4)	14.6 (4.8)	15.2 (4.8)	<0.001
DL _{CO} , % predicted, mean (SD) (n=1385/1064/361)	59.4 (17.7)	69.7 (18.5)	72.8 (18.3)	<0.001
DL _{CO} /VA, mL/min/mmHg/L, mean (SD) (n=1379/1059/361)	2.8 (0.9)	3.4 (0.9)	3.6 (0.9)	<0.001
DL _{CO} /V _A , % predicted, mean (SD) (n=1379/1059/361)	68.7 (21.7)	82.0 (21.7)	86.1 (22.0)	<0.001

Continued

Table 1 Continued

Variable	Low BMI <23 (n=1633)	Normal BMI 23–27 (n=1250)	High BMI >27 (n=431)	P value
TLC, L, mean (SD) (n=1006/815/261)	6.2 (1.3)	5.8 (1.3)	5.6 (1.2)	<0.001
TLC, % predicted, mean (SD) (n=1006/815/261)	101.1 (14.2)	98.5 (17.0)	97.1 (15.1)	<0.001
Laboratory findings				
WBC, ×10 ⁹ /L, mean (SD) (n=1506/1156/406)	7.35 (2.45)	7.25 (2.10)	7.20 (2.29)	0.340
Neutrophil, ×10 ⁹ /L, mean (SD) (n=1469/1134/397)	4.51 (2.17)	4.26 (1.77)	4.21 (1.89)	0.001
Lymphocyte, ×10 ⁹ /L, mean (SD) (n=1477/1139/396)	1.95 (0.70)	2.11 (0.72)	2.10 (0.73)	<0.001
Monocyte, ×10 ⁹ /L, mean (SD) (n=1472/1135/393)	0.56 (0.32)	0.55 (0.20)	0.58 (0.21)	0.346
Basophil, ×10 ⁹ /L, mean (SD) (n=1473/1133/395)	0.05 (0.03)	0.05 (0.03)	0.05 (0.03)	0.564
Eosinophil, ×10 ⁹ /L, median (IQR) (n=1474/1135/395)	0.15 (0.090–0.27)	0.17 (0.10–0.29)	0.18 (0.10–0.27)	0.453
Eosinophil >0.30×10 ⁹ /L, n (%) (n=1474/1135/395)	292 (20.8)	245 (22.5)	83 (22.1)	0.572
Inhaled therapy				<0.001
LABA, n (%)	88 (5.4)	57 (4.6)	17 (3.9)	
LAMA, n (%)	281 (17.2)	239 (19.1)	79 (18.3)	
ICS/LABA, n (%)	164 (10.0)	149 (11.9)	54 (12.5)	
LABA/LAMA, n (%)	446 (27.3)	335 (26.8)	144 (33.4)	
ICS/LABA/LAMA, n (%)	373 (22.8)	215 (17.2)	61 (14.2)	
Oral medication				
PDE-4 inhibitor, n (%)	114 (7.0)	59 (4.7)	25 (5.8)	0.039
Methylxanthine, n (%)	402 (24.6)	273 (21.8)	85 (19.7)	0.050
Erdosteine, n (%)	60 (3.7)	48 (3.8)	10 (2.3)	0.320
N-acetylcysteine, n (%)	21 (1.3)	11 (0.9)	5 (1.2)	0.587
Macrolide, n (%)	5 (0.3)	3 (0.2)	3 (0.7)	0.354

For variables with missing values, the number of participants included in each analysis is indicated below the corresponding variable. BDR, bronchodilator; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; DL_{CO}, diffusing capacity of the lung for carbon monoxide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Research Council scale; 6MWD, 6-Minute Walk Distance; PDE-4, phosphodiesterase-4; SGRQ-C, St. George's Respiratory Questionnaire for COPD; TLC, total lung capacity; V_A, alveolar volume; WCC, white cell count.

(uOR=1.854, 95% CI 1.435 to 2.396, p<0.001) and multi-variable analyses (adjusted OR (aOR)=1.463, 95% CI 1.039 to 2.074, p=0.031). By contrast, patients with BMI >27 kg/m² showed no significant difference in mortality risk (aOR=1.131, 95% CI 0.650 to 1.919, p=0.654).

Exacerbation and cardiovascular event

Restricted cubic spline analysis revealed contrasting patterns in the associations of BMI with the two secondary outcomes. The risk of moderate-to-severe exacerbation increased sharply at lower BMI values, whereas the risk

of composite cardiovascular events gradually increased at higher BMI levels (figure 1B,C).

Over the follow-up, moderate-to-severe exacerbations occurred in 393 patients (24.1%) in the low BMI group, 228 patients (18.2%) in the BMI 23–27 kg/m² group and 70 patients (16.2%) in the high BMI group (p<0.001). The low BMI group accounted for 55.1% of all exacerbation events. In univariable analysis, each 1 kg/m² increase in BMI was associated with a reduced risk of exacerbation (uOR=0.942, 95% CI 0.919 to 0.966, p<0.001), and this association remained significant in the multivariable

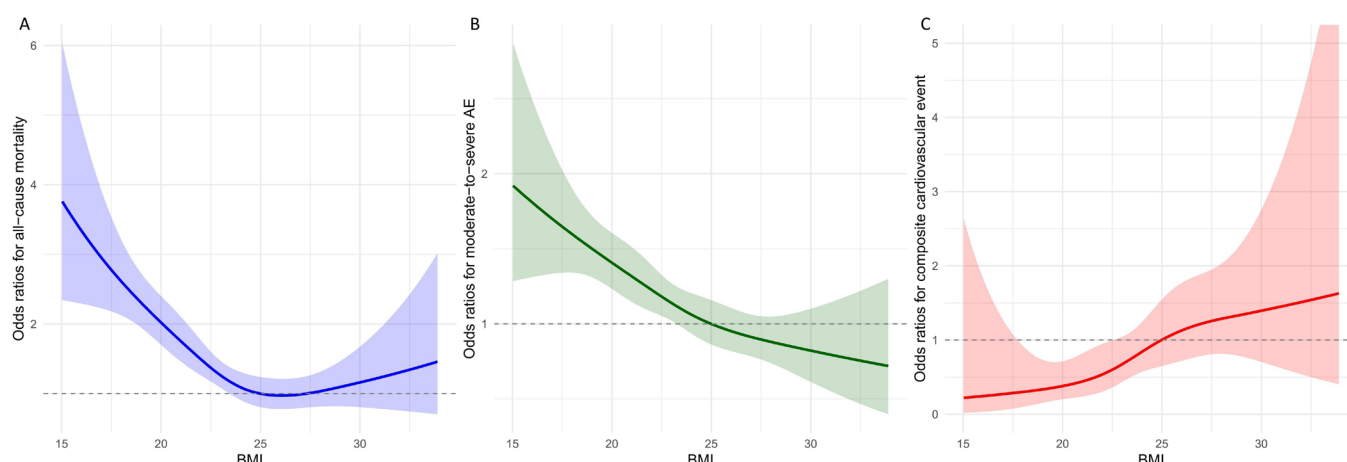


Figure 1 Restricted cubic spline analysis of body mass index (BMI) in relation to mortality, acute exacerbation and cardiovascular events. Non-linear association between BMI and outcomes ((A) all-cause mortality, (B) moderate-to-severe exacerbations and (C) composite cardiovascular events) in COPD, modelled by restricted cubic splines. Solid lines represent adjusted ORs and shaded areas indicate 95% CIs. AE, acute exacerbation.

model (aOR=0.970, 95% CI 0.941 to 0.9996, $p=0.047$) (table 3). Patients with BMI <23 had a higher risk of exacerbation compared with those with BMI 23–27 kg/m² in both univariable (uOR=1.424, 95% CI 1.188 to 1.706, $p<0.001$) and multivariable analyses (aOR=1.251, 95% CI 1.015 to 1.544, $p=0.036$), whereas BMI >27 kg/m² was not significantly associated with exacerbation risk.

Composite cardiovascular events were observed in 12 patients (0.7%) in the low BMI group, 20 patients (1.6%) in the normal BMI group and 9 patients (2.1%) in the high BMI group ($p=0.026$). In both univariable (uOR=1.128, 95% CI 1.042 to 1.221, $p=0.003$) and multivariable analyses (aOR=1.112, 95% CI 1.015 to 1.214, $p=0.020$), each 1 kg/m² increase in BMI was associated with greater cardiovascular risk (table 3). Patients with BMI <23 kg/m² showed a trend towards fewer cardiovascular events compared with those with BMI 23–27 kg/m², although this did not reach statistical significance (aOR=0.509, 95% CI 0.238 to 1.053, $p=0.073$).

Mediation analysis

Mediation analysis was conducted to examine the roles of moderate-to-severe exacerbations and composite cardiovascular events in the association between BMI and all-cause mortality (figure 2).

For low BMI (<23 kg/m²), the direct effect was associated with greater risk of mortality and exacerbations further strengthened this association by mediating 11.9% of the overall association between low BMI and higher mortality ($p=0.002$). In contrast, cardiovascular events mediated a small indirect effect in the opposite direction (−5.2%, $p<0.001$), which attenuated the overall association between low BMI and increased risk of mortality.

For high BMI (>27 kg/m²), the direct effect showed a trend towards lower mortality risk and exacerbations contributed to this protective association by mediating 21.9% of the overall effect of high BMI on reduced mortality ($p=0.004$). Meanwhile, cardiovascular events mediated a small indirect effect in the opposite direction

Table 2 ORs for all-cause mortality according to body mass index (BMI)

Variable	Univariable regression model		Multivariable regression model	
	uOR (95% CI)	P value	aOR (95% CI)*	P value
BMI (per 1 kg/m ²)	0.908 (0.877 to 0.940)	<0.001	0.958 (0.912 to 1.006)	0.086
BMI category (reference: BMI 23–27)				
BMI <23	1.854 (1.435 to 2.396)	<0.001	1.463 (1.039 to 2.074)	0.031
BMI >27	0.999 (0.658 to 1.516)	0.996	1.131 (0.650 to 1.919)	0.654

*Multivariable models were adjusted for age, sex, education level, smoking status, Charlson Comorbidity Index, bronchiectasis and tuberculosis-destroyed lung on chest CT, dyspnoea score (mMRC), symptom burden (CAT and SGRQ-C scores), 6-Minute Walk Distance, history of prior exacerbations, post-bronchodilator FEV₁/FVC z-score, diffusing capacity (DL_{CO} % predicted), total lung capacity (% predicted), neutrophil and lymphocyte counts, inhaled treatment regimen and methylxanthine use.

aOR, adjusted OR; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; DL_{CO}, diffusing capacity of the lung for carbon monoxide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; mMRC, modified Medical Research Council scale; SGRQ-C, St. George's Respiratory Questionnaire for COPD; uOR, unadjusted OR.

Table 3 ORs for moderate-to-severe exacerbation and composite cardiovascular event according to body mass index (BMI)

Outcome and variable	Univariable regression model		Multivariable regression model	
	uOR (95% CI)	P value	aOR (95% CI)*	P value
Moderate-to-severe exacerbation				
BMI (per 1 kg/m ²)	0.942 (0.919 to 0.966)	<0.001	0.970 (0.941 to 0.9996)	0.047
BMI category (reference: BMI 23–27)				
BMI <23	1.424 (1.188 to 1.706)	<0.001	1.251 (1.015 to 1.544)	0.036
BMI >27	0.847 (0.633 to 1.134)	0.264	0.926 (0.667 to 1.274)	0.640
Composite cardiovascular event				
BMI (per 1 kg/m ²)	1.128 (1.042 to 1.221)	0.003	1.112 (1.015 to 1.214)	0.020
BMI category (reference: BMI 23–27)				
BMI <23	0.466 (0.232 to 0.934)	0.031	0.509 (0.238 to 1.053)	0.073
BMI >27	1.376 (0.643 to 2.944)	0.411	1.388 (0.608 to 2.977)	0.413

*Multivariable models were adjusted for age, sex, education level, smoking status, Charlson Comorbidity Index, bronchiectasis and tuberculosis-destroyed lung on chest CT, dyspnoea score (mMRC), symptom burden (CAT and SGRQ-C scores), 6-Minute Walk Distance, history of prior exacerbations, post-bronchodilator FEV₁/FVC z-score, diffusing capacity (DL_{CO} % predicted), total lung capacity (% predicted), neutrophil and lymphocyte counts, inhaled treatment regimen and methylxanthine use.

aOR, adjusted OR; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; DL_{CO}, diffusing capacity of the lung for carbon monoxide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; mMRC, modified Medical Research Council scale; SGRQ-C, St. George's Respiratory Questionnaire for COPD; uOR, unadjusted OR.

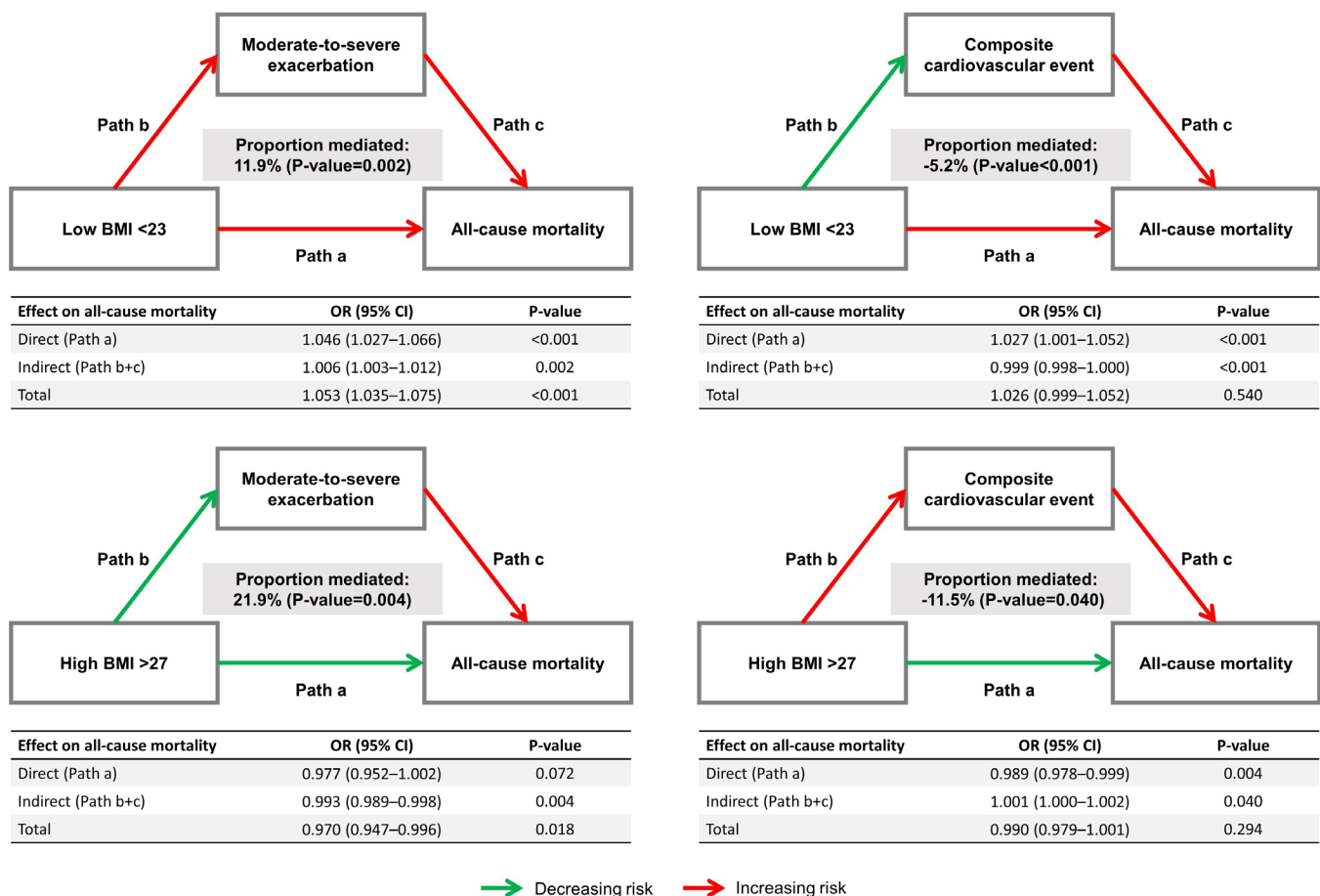


Figure 2 Mediation effects of acute exacerbation and cardiovascular events on the association between low body mass index and all-cause mortality. Although the exposure and outcome were identical across analyses, the estimated total effects differ because each model incorporated a different mediator. These discrepancies reflect the use of distinct mediation structures rather than changes in the underlying exposure–outcome association. BMI, body mass index.

(−11.5%, $p=0.040$), which weakened the overall association between high BMI and lower mortality.

DISCUSSION

Our study revealed that the association between BMI and all-cause mortality in COPD was better described as a non-linear model. Patients with low BMI had a higher risk of mortality and experienced more frequent moderate to severe exacerbations. Mediation analysis indicated that these exacerbations partly accounted for the excess mortality risk observed in patients with low BMI. In contrast, low BMI was associated with fewer cardiovascular events, which attenuated the overall impact of low BMI on mortality. Among patients with high BMI, the reduced risk of mortality was partly explained by a lower frequency of exacerbations. Conversely, high BMI was linked to an increased likelihood of cardiovascular events, which acted in the opposite direction by elevating mortality risk and weakening the protective association between high BMI and mortality. These findings suggest that nutritional support and prevention of exacerbations should be prioritised in patients with COPD and low BMI, whereas systematic screening and management of cardiovascular risk may be particularly beneficial for those with high BMI. To our knowledge, this is the first study to formally quantify exacerbations and cardiovascular events as competing mediating pathways in the BMI–mortality relationship in COPD, showing that these two pathways operate in opposing directions depending on BMI category. This mechanistic decomposition provides a more nuanced characterisation of the obesity paradox in COPD than has previously been reported.

Several biologic and clinical mechanisms likely underlie the observed association between low BMI and increased all-cause mortality in COPD, with increased susceptibility to exacerbations plausibly serving as a central link in this pathway. Low BMI in COPD may reflect a heterogeneous combination of processes, including advanced disease severity, systemic inflammation, cachexia, sarcopenia, smoking-related factors and comorbidity burden, rather than nutritional deficiency alone. Loss of fat-free mass and skeletal muscle, which are not captured by BMI, compromise respiratory muscle strength and reduce ventilatory reserve, thereby increasing vulnerability to exacerbations.^{25–27} Respiratory muscle weakness further diminishes the effectiveness of inhaled treatments, and each exacerbation accelerates systemic inflammation and worsens muscle and nutritional decline, potentially contributing to a cumulative deterioration in survival.^{28–30} Longitudinal data further show that BMI loss over time is associated with both greater exacerbation frequency and increased mortality.³¹ Considered alongside existing evidence, these observations suggest the importance of strategies targeting both exacerbation prevention and the preservation of muscle mass and nutritional status in patients with COPD and low BMI.

In our study, high BMI was associated with a lower risk of all-cause mortality in COPD patients and mediation analysis indicated that this apparent survival benefit was partly explained by a reduced frequency of moderate-to-severe exacerbations. Prior studies have shown that overweight and obese patients experience fewer exacerbations and have a lower risk of mortality following an exacerbation compared with those of normal weight.^{13,32} The post hoc analysis of SUMMIT trial further identified that even in patients with extreme obesity, survival was not adversely affected, reinforcing the notion that greater body mass may buffer the adverse effects of acute illness.¹⁸ Increased adiposity may contribute to improved survival through mechanisms such as enhanced energy reserves during acute exacerbations, attenuation of catabolic burden and modulation of systemic immune responses.³³ On the other hand, our study found that high BMI was associated with an increased incidence of cardiovascular events, consistent with extensive evidence linking obesity to cardiovascular comorbidity.¹⁵ Nevertheless, in our mediation model, the cardiovascular pathway did not significantly account for the overall mortality effect, suggesting that the protective influence of reduced exacerbation burden outweighed the adverse cardiovascular impact in this population. These findings suggest that while higher BMI may confer short-term protection against mortality by reducing exacerbation risk, it simultaneously increases cardiovascular burden. Clinically, these observations support a dual strategy for COPD patients with high BMI, combining systematic screening for cardiovascular disease, management of cardiovascular risk factors, while maintaining the potential protective effects that may be linked to preserved physiologic reserves.

This study has several limitations. First, mediation analysis rests on strong causal assumptions, including no unmeasured confounding of the exposure-mediator and mediator-outcome relationships and the absence of exposure-induced mediator-outcome confounding. These assumptions cannot be fully verified in an observational cohort, and the mediated effects reported here should be interpreted as hypothesis-generating rather than causally conclusive. Second, the mean follow-up duration was less than 3 years, which may have been insufficient to capture long-term trajectories of BMI change and the cumulative burden of cardiovascular consequences. This relatively short follow-up may have led to an underestimation of cardiovascular-mediated effects, and the mediation estimates involving the cardiovascular pathway should therefore be interpreted with caution. Third, the total number of composite cardiovascular events was small, which limits the statistical power and robustness of the mediation estimates involving the cardiovascular pathway. The cardiovascular mediation findings should therefore be interpreted with caution and regarded as preliminary, pending replication in larger cohorts with longer follow-up. Fourth, BMI is a readily accessible but limited anthropometric measure that cannot differentiate fat mass from fat-free mass, and

therefore does not capture body composition components that are more directly relevant to COPD prognosis, including skeletal muscle mass, sarcopenia and cachexia. The mechanistic discussion regarding respiratory muscle weakness and nutritional depletion is based on inferences from existing literature rather than direct measurements in this cohort, and the associations reported here should be interpreted as hypothesis-generating rather than mechanistically conclusive. Fifth, the BMI cut-offs applied in this study (<23, 23–27 and >27 kg/m²) were derived from Korean population data and differ from standard WHO definitions. While these thresholds are consistent with Asian-specific recommendations and are appropriate for the present cohort, they may limit the generalisability of the categorical findings to non-Asian populations, in whom different BMI thresholds may be more applicable. Sixth, low BMI in COPD may reflect advanced disease severity or frailty rather than represent an independent causal driver of mortality. Despite extensive multivariable adjustment, residual confounding from unmeasured factors such as frailty and physical activity cannot be excluded, and causal inference regarding the BMI–mortality relationship is not warranted from the present observational data.

CONCLUSIONS

Our study showed a non-linear association between BMI and all-cause mortality in COPD. Exacerbations contributed to the excess mortality risk in patients with low BMI, whereas reduced exacerbation burden partly explained the survival advantage observed at high BMI. These findings identify distinct risk profiles across BMI categories and suggest that exacerbation prevention should be prioritised in low BMI patients, while cardiovascular risk assessment warrants particular attention in those with high BMI.

Author affiliations

¹Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University College of Medicine, Seoul Metropolitan Government–Seoul National University Boramae Medical Center, Seoul, South Korea

²Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Internal Medicine, Korea University Guro Hospital, Korea University College of Medicine, Seoul, South Korea

³Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Hanyang University Guri Hospital, Guri, South Korea

⁴Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, South Korea

⁵Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Internal Medicine, Yonsei University Wonju Severance Christian Hospital, Wonju, South Korea

⁶Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea

⁷Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea

⁸Division of Pulmonary and Allergy and Critical Care Medicine, Department of Internal Medicine, Konkuk University Medical Center, Konkuk University School of Medicine, Seoul, South Korea

⁹Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Hallym University Sacred Heart Hospital, Anyang, South Korea

Contributors Study concept and design: HWL and YIH. Acquisition of data: SHK, THK, SWR, WYL, MKB, CHL, DKK and KHY. Analysis and interpretation of data: HWL and YIH. Drafting of the manuscript: HWL. Critical revision of the manuscript for important intellectual content: SHK, THK, SWR, WYL, MKB, CHL, DKK, KHY and YIH. Study supervision: YIH. Full data access and responsibility for data integrity and accuracy of the analysis: YIH. Approval of the final manuscript: all authors. YIH is the guarantor for this study. During manuscript preparation, ChatGPT-4o (OpenAI, San Francisco, California, USA) was used solely to review and correct grammatical errors in the authors' drafted text. No part of the research design, data analysis, interpretation or scientific content generation involved the use of AI tools.

Funding This work was supported by the Research Program funded by Korea National Institute of Health (Fund CODE: 2016ER670100, 2016ER670101, 2016ER670102, 2018ER67100, 2018ER67101, 2018ER67102, 2021ER120500, 2021ER120501, 2021ER120502, 2024ER120100, and 2024ER120101).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The study protocol received approval from the Institutional Review Board (IRB) at each hospital (Seoul Metropolitan Government–Seoul National University Boramae Medical Center IRB No. 06-2012-36). All participants provided written informed consent at the time of enrolment. This study adhered to the principles outlined in the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The data that support the findings of this study are available from the Korea COPD Subgroup Study (KOCOSS) team but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors on reasonable request and with permission of the KOCOSS team.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Hyun Woo Lee <https://orcid.org/0000-0003-4379-0260>

Min Kwang Byun <https://orcid.org/0000-0003-1525-1745>

Chang-Hoon Lee <https://orcid.org/0000-0001-9960-1524>

Yong Il Hwang <https://orcid.org/0000-0002-3502-5211>

REFERENCES

- Vos T, Lim SS, Abbafati C, *et al.* Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet* 2020;396:1204–22.
- Priya K, Vadivelu S, Ann Abraham E, *et al.* Correlation Between Chronic Obstructive Pulmonary Disease Severity and Nutritional Status: A Cross-Sectional Study From a Tertiary Care Center in South India. *Cureus* 2025;17:e86535.
- Schols AMWJ. Nutritional and metabolic modulation in chronic obstructive pulmonary disease management. *Eur Respir J Suppl* 2003;46:81s–6s.
- Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. *Eur Respir J* 2009;33:1165–85.

- 5 Rabe KF, Hurst JR, Suissa S. Cardiovascular disease and COPD: dangerous liaisons? *Eur Respir Rev* 2018;27:180057.
- 6 Lee HW, Kim SH, Rhee CK, *et al.* Impact of concurrent COPD and cardiovascular disease on mortality. *Respir Med* 2026;259:108895.
- 7 Sun J, Lee HJ, Lee JK, *et al.* Impact of inhaled corticosteroids on metabolic dysfunction-associated steatotic liver disease risk in COPD patients. *Respir Med Res* 2025;87:101171.
- 8 Lim JU, Lee JH, Kim JS, *et al.* Comparison of World Health Organization and Asia-Pacific body mass index classifications in COPD patients. *Int J Chron Obstruct Pulmon Dis* 2017;12:2465–75.
- 9 Wada H, Ikeda A, Maruyama K, *et al.* Low BMI and weight loss aggravate COPD mortality in men, findings from a large prospective cohort: the JACC study. *Sci Rep* 2021;11:1531.
- 10 Putcha N, Anzueto AR, Calverley PMA, *et al.* Mortality and Exacerbation Risk by Body Mass Index in Patients with COPD in TIOSPIR and UPLIFT. *Ann Am Thorac Soc* 2022;19:204–13.
- 11 Landbo C, Prescott E, Lange P, *et al.* Prognostic value of nutritional status in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;160:1856–61.
- 12 Kim NY, Kim DK, Park S, *et al.* Risk Factors of FEV₁/FVC Decline in COPD Patients. *J Korean Med Sci* 2025;40:e32.
- 13 Smulders L, van der Aalst A, Neuhaus EDET, *et al.* Decreased Risk of COPD Exacerbations in Obese Patients. *COPD* 2020;17:485–91.
- 14 Lainscak M, von Haehling S, Doehner W, *et al.* Body mass index and prognosis in patients hospitalized with acute exacerbation of chronic obstructive pulmonary disease. *J Cachexia Sarcopenia Muscle* 2011;2:81–6.
- 15 Powell-Wiley TM, Poirier P, Burke LE, *et al.* Obesity and Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation* 2021;143:e984–1010.
- 16 Huiart L, Ernst P, Suissa S. Cardiovascular morbidity and mortality in COPD. *Chest* 2005;128:2640–6.
- 17 Mannino DM, Thorn D, Swensen A, *et al.* Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Eur Respir J* 2008;32:962–9.
- 18 Brigham EP, Anderson JA, Brook RD, *et al.* Challenging the obesity paradox: extreme obesity and COPD mortality in the SUMMIT trial. *ERJ Open Res* 2021;7.
- 19 Iyer AS, Dransfield MT. The “Obesity Paradox” in Chronic Obstructive Pulmonary Disease: Can It Be Resolved. *Ann Am Thorac Soc* 2018;15:158–9.
- 20 Hernández Cordero AI, Sin DD. Why Is Body Mass Index Related to Chronic Obstructive Pulmonary Disease? Is It All in the Genes. *Am J Respir Crit Care Med* 2024;210:859–61.
- 21 Lee JY, Chon GR, Rhee CK, *et al.* Characteristics of Patients with Chronic Obstructive Pulmonary Disease at the First Visit to a Pulmonary Medical Center in Korea: The KOREA COPD Subgroup Study Team Cohort. *J Korean Med Sci* 2016;31:553–60.
- 22 Koo H-K, Rhee CK, Min KH, *et al.* A Decade of Healthcare Quality Assessment for Chronic Obstructive Pulmonary Disease in South Korea: Trends and Implications (2014–2023). *Tuberc Respir Dis* 2025;88:615–21.
- 23 Lee SM. Evaluation of obesity criteria for evidence-based obesity management policy South Korea: national health insurance service. Health Promotion Research Center; 2024. Available: http://www.khep.or.kr/files/2024_fall.pdf [Accessed 22 Sep 2025].
- 24 Tingley D, Yamamoto T, Hirose K, *et al.* Mediation: R package for causal mediation analysis. *J Stat Softw* 2014;59:1–38.
- 25 Engelen MP, Schols AM, Baken WC, *et al.* Nutritional depletion in relation to respiratory and peripheral skeletal muscle function in out-patients with COPD. *Eur Respir J* 1994;7:1793–7.
- 26 Hu C, Song B, Liu X, *et al.* The Association Between COPD, Acute Exacerbations of COPD, and Survival in COPD, with Fat-Free Body Mass Index: A Systematic Review and Meta-Analysis. *Int J Chron Obstruct Pulmon Dis* 2025;20:2589–600.
- 27 Swallow EB, Reyes D, Hopkinson NS, *et al.* Quadriceps strength predicts mortality in patients with moderate to severe chronic obstructive pulmonary disease. *Thorax* 2007;62:115–20.
- 28 Wang M, Ni X, Yu F. Impact of Body Mass Index on Risk of Exacerbation in Patients With COPD: A Systematic Review and Meta-Analysis. *Chron Obstr Pulm Dis* 2024;11:524–33.
- 29 Kim DH, Jeon E-T, Lee HJ, *et al.* Longitudinal Changes in Maximal Forced Inspiratory Flow and Clinical Outcomes in Patients With COPD. *Chest* 2025;167:76–86.
- 30 Laveneziana P, Palange P, ERS Research Seminar Faculty. Physical activity, nutritional status and systemic inflammation in COPD. *Eur Respir J* 2012;40:522–9.
- 31 Kim T, Shin SH, Kim H, *et al.* Longitudinal BMI change and outcomes in Chronic Obstructive Pulmonary Disease: a nationwide population-based cohort study. *Respir Res* 2024;25:150.
- 32 DeLapp DA, Glick C, Furmanek S, *et al.* Patients with Obesity Have Better Long-Term Outcomes after Hospitalization for COPD Exacerbation. *COPD* 2020;17:373–7.
- 33 Schols AMWJ, Broekhuizen R, Weling-Scheepers CA, *et al.* Body composition and mortality in chronic obstructive pulmonary disease. *Am J Clin Nutr* 2005;82:53–9.