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ORIGINAL RESEARCH

Association of Obesity with Symptoms and Quality of Life in COPD: Results from COSYCONET

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Background: Body weight plays an intricate role in COPD, as obesity can impair lung function and thus might affect COPD categorization. We asked to which extent overweight/obesity affects conventional COPD scores taking into account lung function and potential restrictive patterns (PRISm, preserved ratio and impaired spirometry).

Methods: Patients of the COSYCONET cohort were included. Outcomes were the modified Medical Research Council (mMRC) questionnaire, the COPD Assessment Test (CAT), CAT question #4 (dyspnea upon exertion), the St George's Respiratory Questionnaire (SGRQ) and its domains, and the EQ-5D-VAS (EuroQoL-5-dimension) questionnaire for generic quality of life. Body mass index (BMI) was categorized into <25, ≥25 to <30, and ≥30 kg/m^2. The relationship between outcomes and predictors including airway obstruction, lung hyperinflation, air trapping and CO diffusing capacity was assessed by generalized linear models in a repeated measures design.

Results: Data from visits 1, 3, 4 and 5 were available in n=2478, 1855, 1291 and 944 patients, respectively, of whom 169, 132, 95 and 63 fulfilled the PRISm criterion. For mMRC, CAT total, CAT dyspnoea (#4), EQ-5D-VAS, SGRQ total, Activity and Impact, scores were higher in the upper two BMI categories compared to the lower one ($p<0.05$ each), without further significant dependence on PRISm or an interaction between BMI and PRISm. For SGRQ Symptoms, only the upper BMI category showed a significantly higher score. All scores depended ($p<0.05$ each) on lung function and exacerbation history in terms of GOLD group E.

Conclusion: For common indicators of the burden from COPD, BMI played a significant role by increasing these scores even if confounders were taken into account. Compared to the lowest BMI category, there was a continuous increase with overweight and obesity. Categorization into PRISm did not influence the relationship between BMI and symptom scores. The underlying mechanisms probably involve mechanical but also systemic factors. Based on this, COPD categorizations based on the scores studied probably should consider the effects of BMI.

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Keywords: COPD, obesity, lung function, PRISm, symptoms, quality of life

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Introduction

Patients with chronic obstructive pulmonary disease (COPD) experience a broad spectrum of symptoms and limitations, including dyspnea, chest discomfort, impaired quality of life and reduced exercise capacity. In a substantial proportion of these patients, obesity is present,[1] which is known to affect lung function. An increased body mass index is, for example, often associated with signs of a restrictive ventilatory disorder and reduced lung hyperinflation.[2] While in COPD a decrease of hyperinflation could be associated with decreased dyspnea,[3–5] it is not unlikely that obesity per se increases dyspnea, or at least shortness of breath. Thus, it is intriguing to examine the effect of elevated body mass on symptom profiles in COPD. Beyond their scientific value, the results could be relevant if categorizations of disease severity are based on symptom scores.

Indeed, a recent study by Dupuis and colleagues[6] investigated dyspnea of COPD patients in terms of mMRC (modified Medical Research Council scale).[7] It was reported that in obese patients, mMRC did not increase across more severe spirometric COPD grades, as categorized according to Global Initiative for Chronic Obstructive Lung Disease (GOLD).[8,9] Taken overall, the findings suggested that obesity played no or only a minor role for the mMCRC score. However, there are further clinically useful COPD scores, such as the CAT (COPD Assessment Test)[10] and the SGRQ (St George's Respiratory Questionnaire) with its subdomains,[11] as well as indices of generic quality of life (EuroQoL-5-dimension, EQ-5D-3L),[12] all of which are not equivalent and offer a multidimensional profile of the disease. Moreover, airway obstruction, lung hyperinflation, air trapping and gas exchange capability are known to modulate symptoms, while they themselves might be affected by obesity in different ways. Therefore, the question remains whether symptom scores are associated with overweight or obesity in a genuine manner, ie, after lung function, as a central confounder, has been taken into account.

This leads to further questions regarding phenotypes that are linked to both, COPD and body weight. Most notable seems PRISm (preserved ratio impaired spirometry), which is defined via forced expiratory volume in 1 s (FEV_1) <80% predicted and FEV_1/FVC (ratio to forced vital capacity) ≥0.7.[13] Although PRISm patients do not fulfil the GOLD criterion of FEV_1/FVC <0.7, they share many characteristics with classical COPD patients, including symptoms, comorbidities and elevated mortality risk.[13,14] At the same time, they more often show elevated body weight, which is of interest, as obesity per se is known to favor a restrictive functional pattern.[14] These observations raise the question whether the association between body mass and symptom profile also depends on the functional category of PRISm and whether this association differs from that observed in classical COPD 1–4. The comparison of these phenotypes can be performed if data from a population comprising a broad range of patients are available, which is the case in the German COPD cohort COSYCONET.[15]

Based on these considerations, we investigated the relationship between body mass index (BMI) and a panel of indices describing symptom and disease burden in patients with COPD, additionally including PRISm patients. The underlying hypothesis was that overweight and obesity should lead to significant increases in various commonly used COPD scores. Data were taken from four consecutive visits of the longitudinal cohort COSYCONET,[15] which included a broad panel of clinical and functional assessments.

Materials and Methods

Study Population

Participants of the multi-center COPD cohort COSYCONET were examined, including patients of the former GOLD grade 0,[13,16] ie, individuals with chronic bronchitis but not fulfilling the GOLD criterion of airway obstruction (FEV_1/FVC) < 0.7. Some of these belong to the PRISm group. Details of the study cohort including the protocol, inclusion and exclusion criteria and panel of assessments have been published previously, as well as details of the study population.[15] For the present analyses, we used data from the enrolment visit 1, as well as the follow-up visits 3, 4 and 5 that were performed at 1.5-year intervals after 18, 36 and 54 months, respectively. The study was approved by the ethics committees of all participating centers and performed according to the revised Declaration of Helsinki. All participants gave their written informed consent. ClinicalTrials.gov: NCT01245933.

Assessments

The data included anthropometric information on age, sex, measured height, measured weight, and smoking status (current vs former or never). From height and weight, the BMI was calculated and, for further analyses, categorized into three groups: <25 (non-overweight/obese), 25 to <30 (overweight), ≥30 kg/m^2 (obese). Post bronchodilator lung function was assessed via forced spirometry according to recommendations;[17,18] this included the determination of forced expiratory volume in 1 sec (FEV_1), forced vital capacity (FVC), and their ratio FEV_1/FVC. Moreover, functional residual capacity (FRC) and the ratio of residual volume to total lung capacity ratio (RV/TLC) were measured via body plethysmograph.[19] In addition, lung diffusing capacity for carbon monoxide (transfer factor, TLCO) was determined.[18] All assessments followed standard operating procedures (SOP) described in the study protocol[15] and were performed in line with accepted recommendations. Predicted values were taken from the Global Lung Function Initiative (GLI)[18,20] or from European Coal and Steel Community (ECSC) reference values.[21]

For description, patients showing FEV_1/FVC <0.7 were categorized according to the spirometric GOLD grades 1–4.[8,9] Patients not fulfilling this criterion were categorized into two groups: PRISm as defined by FEV_1/FVC ≥0.7 and FEV_1 <80% predicted,[13] and non-PRISm as defined by FEV_1/FVC ≥0.7 and FEV_1 ≥80% predicted.

In the analyses, the non-PRISm and regular GOLD grades 1–4 patients were pooled to reveal potential influences attributable to PRISm, since the restrictive pattern defined via PRISm was of primary interest and lung function was kept as covariate anyway (see also sensitivity analyses). This implies that former GOLD 0 patients were included into the COPD group as far as they did not fulfil the PRISm criterion. We consider this approach as valid, as previous analyses have shown a continuum from grades 1–4 down to GOLD 0,[22,23] which justifies the inclusion of GOLD 0 patients in general. Thus, in the present study COPD refers to grades 1–4 and the former GOLD 0 group being not PRISm, while PRISm indicates the defined functional phenotype. Interestingly, there are current developments suggesting a multidimensional approach to diagnose COPD, involving major and minor criteria.[24] Although this was not applied in the current study, it is supportive for the view to rate COPD as continuum with broad spectrum of disease.

As outcome measures, the following instruments were used: the Modified Medical Research Council (mMRC) dyspnea score,[7] the COPD Assessment Test (CAT),[10] the St George's Respiratory Questionnaire (SGRQ) with its domains of Activity, Symptoms and Impact,[11] and for generic quality of life the EuroQoL-5-dimension questionnaire (EQ-5D-3L),[12] using its visual analog scale (VAS) ranging from 0 to 100 mm. Regarding the CAT, we also included specifically the responses to Question 4 (breathlessness when walking up a hill or one flight of stairs). The mMRC values were additionally used to categorize patients into GOLD groups A/B/E,[9] whereby the exacerbation risk was evaluated as proposed by GOLD and used in previous COSYCONET analyses.[25–29] An exacerbation history corresponding to Group E was assumed if at least two moderate exacerbations or at least one severe exacerbation had occurred in the 12 months previous to the study visit. The allocation to Group E was used as additional predictor.

The presence of comorbidities was determined from patients' reports of physician-based diagnoses as previously used in COSYCONET analyses.[30] As comorbidities of interest, we included asthma, sleep apnea, diabetes, and the diagnosis of either heart failure or coronary artery disease that were summarized into a single variable termed cardiac disease.[27,31]

Statistical Analysis

Numbers and percentages, or mean values and standard deviations were used for data description. Analyses were performed by generalized linear models (GLM) using a repeated measures design for consecutive visits, and the assumption of normal distribution with identity link for the outcomes. The analyses used the individual data from the visits 1, 3, 4 and 5 for all patients available at these visits. In addition, sensitivity analyses were performed using data only of patients who stayed in the study until visit 5. As covariates, FEV_1, FRC, RV/TLC and TLCO, all of them as % predicted, were included in the models, moreover sex, age, smoking status and GOLD E group, as well as the presence of sleep apnea, asthma, diabetes and cardiac disease, in addition to the binary PRISm indicator and the three BMI categories. For PRISm and BMI, an interaction term was also included. The effect estimates regarding PRISm and the BMI categories are presented as mean values and 95% confidence intervals (95% CI). Statistical significance was assumed for p-values <0.05. All analyses were performed using the statistical software package SPSS (Version 29, IBM, Armonk, NJ, USA).

Results

Patient Description

From COSYCONET visits 1, 3, 4 and 5, data sets as required for the multivariable models were available in n=2478, 1855, 1291 and 944 patients, respectively, of whom 169, 132, 95 and 63 fulfilled the PRISm criterion. Accordingly, 944 patients had data across all visits until visit 5, including 63 patients with PRISm. Patients' characteristics at visit 1 are given in Table 1.

Table 1 Baseline Characteristics of COPD Patients at Visit 1

Variable	All Patients (n=2478)
Sex (male/female %)	1487/991 (60/40%)
Age (yrs)	64.9 ± 8.6
Smoking (active)	620 (25%)
BMI (kg/m^2)	27.1 ± 5.3
BMI <25 kg/m^2 (%)	931 (37.6%)
BMI ≥25 and <30 kg/m^2 (%)	927 (37.4%)
BMI ≥30 kg/m^2 (%)	620 (25.0%)
FEV$_1$ (% predicted)	58.0 ± 20.7
FRC (% predicted)	142.9 ± 36.6
RV/TLC (% predicted)	132.0 ± 27.5
TLCO (% predicted)	59.4 ± 22.6
GOLD grades 0/1/2/3/4 (%)	387/195/924/799/173 (15.6/7.9/37.3/37.2/7.0%)
PRISm (%)	169 (6.8%)
Asthma (%)	452 (18.2%)
Sleep apnea (%)	278 (11.2%)
Cardiac disease (CAD or HF) (%)	461 (18.6%)
Diabetes (%)	336 (13.6%)
GOLD A/B/E (%)	1039/583/847 (42.1/23.6/34.3%)
mMRC (score)	1.52 ± 0.90
CAT total (score)	17.8 ± 7.3
CAT Question #4 (score)	3.7 ± 1.2
SGRQ total (score)	41.9 ± 19.8
SGRQ Activity (score)	55.8 ± 26.0
SGRQ Impact (score)	29.1 ± 20.3
SGRQ Symptoms (score)	54.8 ± 21.4
EQ-5D-VAS (mm)	57.6 ± 19.5

Notes: Mean values and standard deviations, or numbers and percentages are given.

Abbreviations: BMI, body mass index; PRISm, preserved ratio impaired spirometry; CAD, coronary artery disease; HF, heart failure; FEV$_1$, forced expiratory volume in 1 s; FRC, functional residual capacity; RV/TLC, residual volume over total lung capacity ratio; mMRC, modified Medical Research Council; CAT, COPD Assessment Test; CAT Question #4, "breathlessness when walking up a hill or one flight of stairs"; EQ-5D-VAS, visual analog scale (VAS) of the EuroQoL-5-dimension questionnaire (EQ-5D-3L); SGRQ, St George's Respiratory Questionnaire; GOLD, Global Obstructive Lung Disease.

Association Between Predictors and Measures of Symptoms and Quality of Life

The coefficients of the association between mMRC and the multiple predictors including PRISm and the three BMI categories are given in Table 2, and the effect estimates are shown in Figure 1A. There were significant ($p \leq 0.05$ each) associations with a multitude of variables including sex, age, smoking status, GOLD E, the four comorbidities, FEV_1, RV/TLC and TLCO in % predicted, as well as the upper two BMI categories (≥30 and 25–30 kg/m^2) compared to the lower one, but not for PRISm and without significant interaction between PRISm and BMI.

Analogous results were obtained for CAT, except that there was no significant association with age and diabetes. Again, the upper two BMI categories were associated ($p \leq 0.002$ each) with the outcome, without significant dependence on PRISm or interaction between PRISm and BMI (Figure 1B). Virtually identical results were observed for Question #4 of the CAT (Figure 1C).

Regarding generic quality of life in terms of the EQ-5D VAS, this score was significantly ($p < 0.001$ each) reduced in overweight and in obese patients compared to those with BMI <25 kg/m^2 but again there was no significant effect of PRISm or interaction with BMI (Figure 1D).

The associations between SGRQ scores and the various predictors, including PRISm and the three BMI categories, are presented in Table 3. The total SGRQ score as well as the Activity and Impact scores (Figures 1E–G) showed patterns of association similar to that of CAT, and this included the significant dependence on the highest and the middle BMI category ($p < 0.001$ each). Again, there was no dependence on PRISm or interaction between PRISm and BMI categories. However, the SGRQ Symptom score (Figure 1H) was significantly different ($p < 0.001$) only when comparing the highest (obesity) and the lowest (<25 kg/m^2) BMI categories. At the same time, there was a significant ($p = 0.031$) interaction term between the middle BMI category (overweight) and PRISm, indicating a marked increase by about 5.1 points if this combination was present, however with a non-significant ($p = 0.071$) main effect of PRISm by 2.6 points in the opposite direction.

Sensitivity Analyses

For this purpose, we included only patients who participated until visit 5. Regarding mMRC, CAT total, CAT #4, EQ-5D VAS, SGRQ total, Activity and Impact, the significant dependence on each of the two upper BMI categories compared to the category <25 kg/m^2 was maintained (always $p < 0.05$), without any dependence on PRISm or interaction between PRISm and BMI. Moreover, regarding SGRQ Symptoms, again this score was dependent only on the highest BMI category ($p < 0.001$), and there was a significant interaction term ($p = 0.024$) regarding the middle BMI category and PRISm. These results indicate that all findings obtained were robust against the drop-out of patients over the study period. Analyses were also repeated after excluding patients with low weight as defined by BMI <20 kg/m^2, and again, the same results were obtained regarding the dependence of the two variables BMI and PRISm. The same was true when only patients of visit 1 were included.

We also looked for associations of the other CAT questions. Regarding #1 (cough) and #2 (phlegm), there were no significant relationships. #6 (confidence in leaving home) and #8 (amount of energy felt), were significantly ($p < 0.001$ each) linked to obesity categories, but according to the magnitude of the regression coefficients, associations were only about half as strong as for #4 (dyspnea upon exertion). In contrast, the association for #5 (limitations in activity at home) was about as strong ($p < 0.001$) as that for #4.

Discussion

In the present study, we investigated the relationship between COPD symptom scores and body mass, while taking into account the potential effect of overweight or obesity on lung function. In addition, we addressed the impact of a restrictive pattern of lung function disorder, defined via PRISm, and its potential interaction with body weight. Regarding mMRC, CAT, CAT Question #4, SGRQ and two of its subdomains, as well as generic quality of life, overweight (BMI ≥25 and <30 kg/m^2) and obesity (≥30 kg/m^2) were significantly associated with impaired values compared to the reference category (<25 kg/m^2), while there was no significant dependence on the presence of PRISm. Moreover, the effects of obesity were generally stronger than those of overweight.

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Table 2 Results From Generalized Linear Models (GLM)

Outcomes	mMRC				CAT Total				CAT Question #4				EQ-5D-VAS			
Parameter	**B**	**95% CI**		**p value**	**B**	**95% CI**		**p value**	**B**	**95% CI**		**p value**	**B**	**95% CI**		**p value**
Predictors		**Lower**	**Upper**			**Lower**	**Upper**			**Lower**	**Upper**			**Lower**	**Upper**	
Sex female	0.124	0.071	0.177	**<0.001**	0.943	0.448	1.437	**<0.001**	0.185	0.105	0.264	**<0.001**	−0.020	−1.278	1.239	0.976
Age per 5 yrs	0.067	0.053	0.082	**<0.001**	−0.036	−0.179	0.107	0.622	0.003	−0.020	0.027	0.785	−0.727	−1.087	−0.367	**<0.001**
Smoking active	−0.068	−0.124	−0.012	**0.017**	0.807	0.313	1.301	**0.001**	−0.077	−0.160	0.006	0.070	0.106	−1.259	1.471	0.879
Asthma	0.077	0.018	0.136	**0.010**	1.265	0.768	1.763	**<0.001**	0.107	0.023	0.190	**0.012**	−3.791	−5.184	−2.397	**<0.001**
Sleep apnea	0.157	0.083	0.230	**<0.001**	1.454	0.829	2.078	**<0.001**	0.176	0.080	0.272	**<0.001**	−2.555	−4.227	−0.883	**0.003**
Cardiac disease (CAD or HF)	0.172	0.110	0.234	**<0.001**	1.719	1.200	2.238	**<0.001**	0.159	0.082	0.237	**<0.001**	−4.938	−6.389	−3.486	**<0.001**
Diabetes	0.138	0.063	0.213	**<0.001**	0.181	−0.452	0.813	0.576	−0.021	−0.122	0.081	0.687	−0.153	−1.787	1.482	0.855
GOLD E	0.186	0.145	0.228	**<0.001**	1.715	1.425	2.006	**<0.001**	0.127	0.077	0.177	**<0.001**	−3.798	−4.672	−2.924	**<0.001**
FEV_1 per 10 PP	−0.105	−0.122	−0.089	**<0.001**	−0.599	−0.737	−0.461	**<0.001**	−0.138	−0.163	−0.112	**<0.001**	1.395	0.984	1.806	**<0.001**
FRC per 10 PP	0.001	−0.009	0.010	0.908	−0.021	−0.093	0.051	0.562	0.006	−0.006	0.018	0.322	−0.016	−0.213	0.182	0.875
RV/TLC per 10 PP	0.038	0.025	0.051	**<0.001**	0.268	0.171	0.364	**<0.001**	0.022	0.006	0.039	**0.008**	−0.707	−0.999	−0.416	**<0.001**
TLCO per 10 PP	−0.067	−0.080	−0.054	**<0.001**	−0.317	−0.415	−0.218	**<0.001**	−0.082	−0.099	−0.064	**<0.001**	1.302	1.003	1.601	**<0.001**
BMI ≥30 kg/m^2	0.353	0.285	0.420	**<0.001**	1.577	1.032	2.122	**<0.001**	0.423	0.335	0.511	**<0.001**	−5.579	−7.115	−4.043	**<0.001**
BMI ≥25 and <30 kg/m^2	0.132	0.081	0.184	**<0.001**	0.630	0.234	1.027	**0.002**	0.177	0.110	0.243	**<0.001**	−2.636	−3.808	−1.464	**<0.001**
PRISm	0.031	−0.128	0.190	0.703	−0.281	−1.630	1.069	0.683	−0.033	−0.251	0.185	0.768	−3.605	−8.079	0.869	0.114
BMI≥30 kg/m^2 * PRISm	−0.057	−0.256	0.143	0.577	−0.309	−1.875	1.258	0.699	−0.003	−0.265	0.259	0.982	1.555	−3.451	6.560	0.543
BMI 25–30 kg/m^2 * PRISm	−0.014	−0.223	0.195	0.895	1.216	−0.259	2.691	0.106	0.077	−0.181	0.336	0.558	−0.192	−5.517	5.133	0.944

Notes: Regression coefficients B, 95% confidence intervals (CI) and p values are given. Bold p values indicate values < 0.05.

Abbreviations: GOLD, Global Obstructive Lung Disease; FEV_1, forced expiratory volume in 1 s; FRC, functional residual capacity; RV/TLC, residual volume over total lung capacity ratio; TLCO, transfer capacity for carbon monoxide; per 10 PP, per 10% of the corresponding predicted value; BMI, body mass index; PRISm, preserved ratio impaired spirometry; CAD, coronary artery disease; HF, heart failure; mMRC, modified Medical Research Council; CAT, COPD Assessment Test; CAT Question #4, "breathlessness when walking up a hill or one flight of stairs"; EQ-5D-VAS, visual analog scale (VAS) of the EuroQoL-5-dimension questionnaire (EQ-5D-3L).

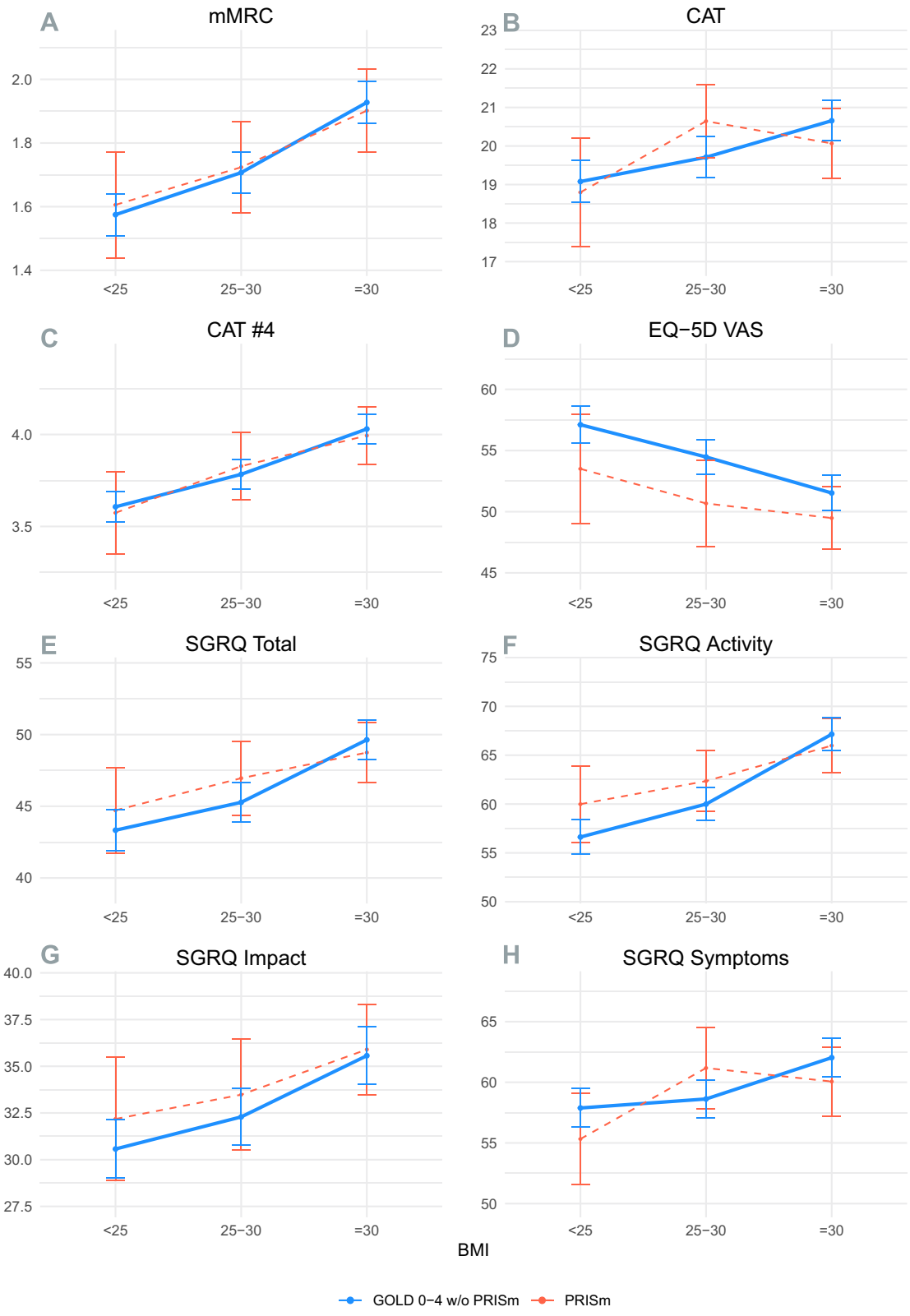

Figure 1 Mean values and 95% confidence intervals of the effects estimated from the generalized linear models including an interaction term between BMI and PRISm. mMRC = modified Medical Research Council (**A**), CAT = COPD Assessment Test (**B**), CAT Question #4 = "breathlessness when walking up a hill or one flight of stairs" (**C**), EQ-5D-VAS = visual analog scale (VAS) of the EuroQoL-5-dimension questionnaire (EQ-5D-3L) (**D**), SGRQ = St George's Respiratory Questionnaire ((**E**), total) and its Activity, Impact and Symptoms domains (**F**–**H**). The three BMI categories (<25, ≥25 and <30, ≥30 kg/m^2) are indicated. In addition, results are stratified according to the presence of PRISm as a restrictive type of functional disorder (FEV_1/FVC ≥0.7 and FEV_1 <80% predicted). Please note that non-PRISm includes patients of the classical GOLD grades 1–4 (FEV_1/FVC<0.7) as well as patients of the former GOLD grade 0 but without PRISm (FEV_1/FVC ≥0.7 and FEV_1 ≥80% predicted).

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Table 3 Results From Generalized Linear Models (GLM)

Outcomes	SGRQ Total				SGRQ Activity				SGRQ Impact				SGRQ Symptoms			
Parameter	B	95% CI		p value	B	95% CI		p value	B	95% CI		p value	B	95% CI		p value
Predictors		Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper	
Sex female	2.516	1.226	3.807	**<0.001**	6.410	4.828	7.991	**<0.001**	1.004	−0.363	2.370	0.150	−0.090	−1.574	1.394	0.905
Age per 5 yrs	0.945	0.575	1.316	**<0.001**	1.844	1.383	2.305	**<0.001**	0.694	0.309	1.080	**<0.001**	0.059	−0.371	0.488	0.789
Smoking active	−0.369	−1.575	0.837	0.549	−3.460	−5.038	−1.883	**<0.001**	−0.257	−1.569	1.055	0.701	5.403	3.925	6.881	**<0.001**
Asthma	3.121	1.696	4.545	**<0.001**	2.584	0.807	4.361	**0.004**	3.391	1.875	4.908	**<0.001**	4.771	3.229	6.314	**<0.001**
Sleep apnea	3.933	2.309	5.557	**<0.001**	4.264	2.307	6.221	**<0.001**	4.428	2.636	6.220	**<0.001**	3.001	1.108	4.894	**0.002**
Cardiac disease (CAD or HF)	4.397	2.984	5.810	**<0.001**	5.884	4.223	7.545	**<0.001**	4.154	2.625	5.684	**<0.001**	3.494	1.932	5.057	**<0.001**
Diabetes	0.914	−0.656	2.484	0.254	1.091	−0.773	2.955	0.251	0.741	−0.987	2.468	0.401	0.183	−1.667	2.034	0.846
GOLD E	4.403	3.713	5.092	**<0.001**	3.706	2.801	4.611	**<0.001**	4.881	4.072	5.691	**<0.001**	6.566	5.631	7.502	**<0.001**
FEV_1 per 10 PP	−2.405	−2.759	−2.051	**<0.001**	−3.554	−4.022	−3.086	**<0.001**	−1.723	−2.099	−1.347	**<0.001**	−1.999	−2.429	−1.570	**<0.001**
FRC per 10 PP	0.049	−0.135	0.234	0.599	0.260	0.030	0.490	**0.026**	−0.080	−0.287	0.128	0.453	−0.007	−0.220	0.206	0.948
RV/TLC per 10 PP	0.704	0.457	0.951	**<0.001**	0.722	0.415	1.029	**<0.001**	0.773	0.492	1.054	**<0.001**	0.636	0.341	0.931	**<0.001**
TLCO per 10 PP	−1.096	−1.363	−0.829	**<0.001**	−1.848	−2.194	−1.501	**<0.001**	−1.019	−1.303	−0.735	**<0.001**	−0.413	−0.708	−0.117	**0.006**
BMI ≥30 kg/m^2	6.307	4.922	7.692	**<0.001**	10.524	8.753	12.296	**<0.001**	4.993	3.441	6.545	**<0.001**	4.149	2.455	5.843	**<0.001**
BMI ≥25 and <30 kg/m^2	1.945	0.933	2.958	**<0.001**	3.370	2.020	4.720	**<0.001**	1.716	0.579	2.854	**0.003**	0.742	−0.544	2.027	0.258
PRISm	1.386	−1.396	4.168	0.329	3.367	−0.310	7.044	0.073	1.606	−1.494	4.706	0.310	−2.557	−6.173	1.058	0.166
BMI≥30 kg/m^2 * PRISm	−2.275	−5.539	0.988	0.172	−4.533	−8.891	−0.174	0.042	−1.274	−5.011	2.463	0.504	0.588	−3.850	5.025	0.795
BMI 25–30 kg/m^2 * PRISm	0.299	−3.097	3.694	0.863	−1.008	−5.421	3.405	0.654	−0.416	−4.262	3.430	0.832	5.113	0.476	9.750	**0.031**

Notes: Regression coefficients B, 95% confidence intervals (CI) and p values are given. Bold p values indicate values < 0.05.

Abbreviations: GOLD, Global Obstructive Lung Disease; FEV_1, forced expiratory volume in 1 s; FRC, functional residual capacity; RV/TLC, residual volume over total lung capacity ratio; TLCO, transfer capacity for carbon monoxide; per 10 PP, per 10% of the corresponding value predicted; BMI, body mass index; PRISm, preserved ratio impaired spirometry; CAD, coronary artery disease; HF, heart failure; SGRQ, St George's Respiratory Questionnaire.

We thus could quantify the effect of body weight per se, after adjusting for various anthropometric characteristics as well as indices of airway obstruction, lung hyperinflation, air trapping and CO diffusing capacity, thereby taking into account differential effects of body weight on a variety of functional indices. The mean increase in score points from the lowest to the highest BMI category was about 6.3 points for SGRQ total, 1.6 points for CAT and 0.35 points for mMRC (see Table 2 and Table 3). Although being small in magnitude compared to the total range of scores, the changes seem large enough to be considered when using these scores for categorization of COPD severity. Certainly, the importance of these changes should not be overstated but, on the other hand, they appear large enough to affect categorizations based on cut-off values of these scores in a number of patients. If patients are attributed to higher categories than their lung disease deserves, this could lead to over-treatment in view of the fact that the common COPD medication primarily addresses the lung, irrespective of potential beneficial side-effects on the heart.[32]

The influence of body mass on lung function has long been known. Especially, obesity is associated with a reduction in FRC as well as expiratory reserve volume (ERV), with additional reduction in vital capacity but virtually unchanged values of FEV_1/FVC.[33–35] The reduction in FRC can lead to airway collapse and inhomogeneous ventilation during the expiratory phase even of resting ventilation, which is reflected in expiratory airway obstruction. This can be clearly demonstrated using body plethysmography, and the fact that the obstruction is primarily due to FRC reduction can be demonstrated by its disappearance when end-expiratory volume is voluntarily raised.[36] Of course, this type of obstruction can occur not only in subjects without respiratory disease but also in patients with asthma or COPD, thereby contributing to symptoms and weakening the ability of medication to alleviate symptoms.[37,38] In addition, the impact can be seen in apparently inadequate estimations of COPD-associated lung hyperinflation, if reference values for FRC are chosen that take body weight into account.[39] Thus, it was important that the panel of lung function indices used for adjustment was broad and included lung hyperinflation and air trapping.

It was not known previously, to which extent the effect of body mass on clinical scores differs between various instruments that are commonly used in COPD. We therefore included a whole panel of such instruments. A simple tool of widespread use is the mMRC.[7] Notably, in our data, it showed a clear dependence on body mass but not on PRISm. A similar dependence was observed for the CAT,[10] though only in patients who were not in the PRISm group. At the same time, there was remarkable heterogeneity between single CAT questions. For example, Question #3 (chest tightness) did not show any dependence on body mass (data not shown), while Question #4 (Dyspnea upon exertion) exhibited a pattern very similar to that of the mMRC, including the fact that there was no association with PRISm. Noteworthy, the association of BMI categories with CAT #5 was about as strong as that with #4, while that with #6 and #8 was weaker, and that with #1 and #2 absent. The observation of marked heterogeneity between CAT questions is in line with previous results demonstrating that the single CAT questions play different roles in relation to various outcomes and characteristics of COPD.[29,40]

Regarding SGRQ,[11] the total score as well as the Activity and Impact domains behaved in a similar way as mMRC, without a significant modulation by the presence of PRISm, but the Symptoms domain was only significantly elevated with the highest BMI category representing obesity. Generic quality of life in terms of the VAS of the EQ-5D[12] was also dependent on body mass in the same way in which mMRC or CAT #4 behaved, but there was an additional parallel downward shift in PRISm patients which, however, did not reach statistical significance. Overall, the results were similar across the different instruments used to assess the symptomatic burden from COPD, and all of the scores showed a clear dependence on body mass, mostly with a steady increase from the lowest BMI category to overweight to obesity.

It is intriguing that PRISm, as commonly defined,[9,13] had only a minor effect, or no discernible effect at all. Previous observations demonstrated that this category was helpful to identify patients at increased risk within the group of patients not fulfilling the $FEV_1/FVC < 0.7$ criterion. In the COSYCONET cohort, PRISm patients essentially showed all essential characteristics of COPD and were found to be similar to patients of classical GOLD grades 1 or 2.[22,23] As we adjusted for a panel of functional impairments, we kept patients within the analysis who showed $FEV_1/FVC \leq 0.7$ as well as $FEV_1 \geq 80\%$ predicted, ie, former GOLD 0 patients without PRISm. Moreover, their omission from the analysis did not affect the results (data not shown). Our observations are in line with the fact that PRISm patients are very similar to those of "classical" COPD of grades 1–4 and might be considered as having COPD, particularly in view of their varying categorization over time.[13,14]

It is also noteworthy that in none of the regression analyses, except for SGRQ activity, FRC as a measure of lung hyperinflation showed a significant association (see Table 3), in contrast to RV/TLC as a measure of trapped air that always showed significant associations. Lung hyperinflation is known to play a pivotal role for dyspnea in patients with COPD[41,42] and might even be involved in promoting the cessation of smoking.[28] It seemed, however, to be of less importance for the scores investigated in the present study, provided that air trapping was included in the covariates. This was confirmed when repeating the analyses while omitting RV/TLC, since then FRC % predicted became statistically significant for all scores included (data not shown). Thus, our observations do not contradict the major role of lung hyperinflation but only suggest a more specific impact of air trapping, despite the fact that air trapping and hyperinflation are associated, although there might occur some discordance between the two, for example, in patients with COPD and bronchiectasis.[43]

In addition to lung function, there were other obvious predictors of symptom burden, such as sex, age, active smoking, as well as the presence of comorbidities such as asthma, sleep apnea and cardiac disease in terms of coronary artery disease or heart failure. It is also plausible that a higher exacerbation frequency or severity as expressed via GOLD E was linked to impaired scores of all the instruments used. The multiple adjustments performed in this manner render it likely that the observed associations with overweight or obesity reflected true residual effects of body mass that were not mediated via its associations with confounders.

Limitations

Although various study visits were included, the present study is essentially of cross-sectional nature, and it was not the aim to assess potential associations between changes over time. Using the repeated visits with an appropriate statistical model, we increased the power of the study. Of note, the results of either visit 1 alone or of analyses excluding the drop-outs were essentially the same as presented in the tables and figure. Despite this, it should be noted that the patients lost to follow-up differed from those remaining in the study by being more severely ill, on average. To determine to which extent this was associated with overweight or obesity, was beyond the aim of the present analysis. It certainly would have been of interest to include medication into the analysis, but this was outside the scope of the analysis since COSYCONET patients show a high intensity of treatment[23,44] which renders analyses without a proper control group difficult. Of course, the possibility of unmeasured confounding cannot be excluded. Beyond BMI, more specific measures and consequences of body composition including fat-free mass are known[45] but in the present study we wanted to focus on the simple, robust and generally available parameter BMI. Although sensitivity analyses have been performed, the power to detect potential PRISm-related interactions was limited due to the number of patients.

Conclusion

Using data from a large COPD cohort, the association of various clinical scores with body mass in terms of BMI was studied while adjusting for multiple lung function and anthropometric parameters. For mMRC, CAT total, CAT Question #4 (Dyspnea upon exertion), EQ-5D-VAS, SGRQ total and its Activity and Impact domains, scores were significantly higher with obesity ($\geq$30 kg/m^2) or overweight (25–30 kg/m^2) compared to the lower BMI category ($<$25 kg/m^2); for SGRQ Symptoms, only the upper category showed a significantly higher score. There was no relevant dependence on a restrictive pattern of functional disorder as defined via PRISm. These observations indicate that for common clinical indicators of the burden from COPD in terms of symptoms, limitations and quality of life, BMI played a role by increasing these scores even if lung function and exacerbations had been taken into account. The findings may have implications for clinical risk stratification and personalized management of COPD patients, particularly in populations with a high prevalence of overweight and obesity. COPD categorizations based on the scores as analyzed probably should consider effects of BMI.

Data Sharing Statement

COSYCONET is an ongoing, long-term, multi-center observational study the data of which are not intended to be available without demand. If there is interest in the analysis of specific questions, however, there is a formalized procedure for submitting an application to the study office, which will be evaluated by the steering committee on scientific grounds. There is no limitation for this application except proven expertise in COPD studies.

Ethics Approval and Consent to Participate

The study protocol was approved by the central ethical committee in Marburg (Ethikkommission FB Medizin Marburg) and the respective local ethical committees: Bad Reichenhall (Ethikkommission Bayerische Landesärztekammer); Berlin (Ethikkommission Ärztekammer Berlin); Bochum (Ethikkommission Medizinische Fakultät der RUB); Borstel (Ethikkommission Universität Lübeck); Coswig (Ethikkommission TU Dresden); Donaustauf (Ethikkommission Universitätsklinikum Regensburg); Essen (Ethikkommission Medizinische Fakultät Duisburg-Essen); Gießen (Ethikkommission Fachbereich Medizin); Greifswald (Ethikkommission Universitätsmedizin Greifswald); Großhansdorf (Ethikkommission Ärztekammer Schleswig-Holstein); Hamburg (Ethikkommission Ärztekammer Hamburg); MHH Hannover/Coppenbrügge (MHH Ethikkommission); Heidelberg Thorax/Uniklinik (Ethikkommission Universität Heidelberg); Homburg (Ethikkommission Saarbrücken); Immenhausen (Ethikkommission Landesärztekammer Hessen); Kiel (Ethikkommission Christian-Albrechts-Universität zu Kiel); Leipzig (Ethikkommission Universität Leipzig); Löwenstein (Ethikkommission Landesärztekammer Baden-Württemberg); Mainz (Ethikkommission Landesärztekammer Rheinland-Pfalz); München LMU/Gauting (Ethikkommission Klinikum Universität München); Nürnberg (Ethikkommission Friedrich-Alexander-Universität Erlangen Nürnberg); Rostock (Ethikkommission Universität Rostock); Berchtesgadener Land (Ethikkommission Land Salzburg); Schmallenberg (Ethikkommission Ärztekammer Westfalen-Lippe); Solingen (Ethikkommission Universität Witten-Herdecke); Ulm (Ethikkommission Universität Ulm); Würzburg (Ethikkommission Universität Würzburg). The study was performed in accordance with the Declaration of Helsinki, and all participants gave their written informed consent.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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