Nutritional status and muscle mass loss in patients with COPD, association with lung function, symptoms, comorbidities and long-term survival: data from the National Database Study

Eva Volakova[1], Vladimir Koblizek[2], Michal Svoboda[3], Karel Hejduk[3], Marek Plutinsky[4], Kristian Brat[4], Martina Kulirova[2], Jaromir Zatloukal[1]

Aim. To assess nutritional status and muscle mass loss in patients with chronic obstructice pulmonary disease (COPD) from the Czech National Database of COPD and to evaluate the association of nutritional parameters with COPD phenotype, lung function, COPD-related symptoms and long-term survival.

Methods. A total of 343 patients with known body composition parameters – body mass Index (BMI), fat-free mass index (FFMI) and mid-art muscle circumference (MAMC) – were included in the analysis. Descriptive statistical methods were used to assess differences between groups, and overall survival was assessed using the Kaplan-Meier method after 9 years of follow-up.

Results. Nutritional imbalances were common in patients with COPD. Underweight and muscle mass loss were associated with emphysematous and pulmonary cachexia phenotypes, worse lung function, more symptoms and exacerbations, osteoporosis and depression. Overweight and obesity were associated with a chronic bronchitis phenotype and cardiovascular and metabolic comorbidities. Obese patients had higher forced exspiratory volume in 1 second (FEV_1) and diffusing capacity of the lung for carbon monoxid (DL_{CO}), but lower forced exspiratory capacity (FVC). Malnutrition increased the risk of death. Cachexia and underweight reduced median survival from 72.0 to 43.5 (P=0.049) and 39.8 (P=0.010) months, respectively, compared to normal nutrition. Muscle mass loss by MAMC of ≥20% was the strongest predictor of mortality, increasing the risk of death by 5.5-fold compared to patients with normal muscle mass (P<0.001). Patients with overweight and obesity had a 40% (P=0.026) and 30% lower risk of death, respectively, compared to patients with normal nutrition.

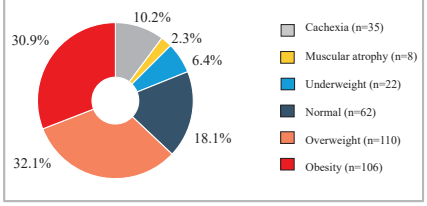
Conclusions. Patients with COPD often have nutritional imbalances. That is an important determinant of clinical characteristics and outcomes in patients with COPD. Further research is needed to better understand these differences.

NUTRITIONAL STATUS IS ASSOCIATED WITH CLINICAL CHARACTERISTICS AND AFFECTS SURVIVAL IN COPD PATIENTS

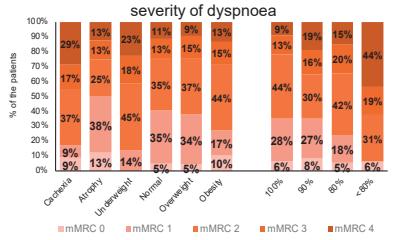
We assessed nutritional status and muscle mass loss and their impact to clinical characteristics and survival in 343 patients with COPD from the Czech national database of COPD.

Measured parameters were: body mass index (BMI), fat-free mass index (FFMI), and mid-arm muscle circumference (MAMC). To assess FFMI and MAMC methods of skinfold anthropometry were used.

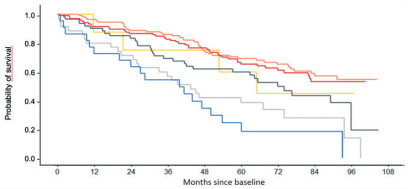
Descriptive statistical methods were used to assess differences between groups. Overall survival was assessed using the Kaplan-Meier method after 9 years of follow-up.



Patients with different nutritional status have different severity of dyspnoea



Survival in nutritional groups according to BMI and FFMI



Only 18.1% of the COPD patients had normal nutrition parameters.

Different clinical outcomes were observed between underweight and overweight patients.

Underweight and muscle mass loss were associated with pulmonary cachexia and emphysematous phenotypes, worse lung function, more symptoms and exacerbations, osteoporosis and depression.

Malnutrition increased the risk of death. Cachexia and underweight compared to normal nutrition reduced median survival from 72.0 to 43.5 (P=0.049) and 39.8 (P=0.010) months, respectively. Patients with significant muscle mass loss had a 5.5-fold increased risk of death compared to patients with normal muscle mass (P<0.001).

Overweight and obesity were associated with a chronic bronchitis phenotype, cardiovascular and metabolic comorbidities. Obese patients had higher FEV_1 and DLCO, although FVC was lower.

Overweight and obesity reduced the risk of death by 40% (P=0.026) and 30% (P=0.071), respectively, compared to patients with normal nutrition.

Patients with COPD often have nutritional imbalances. Survival is poorest in underweight patients and those with muscle wasting.

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Key words: nutrition, muscle mass loss, body mass index, fat-free mass index, mid-arm muscle circumference, chronic obstructive pulmonary disease, COPD phenotype, comorbidities, survival

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[1]Department of Respiratory Diseases, University Hospital Olomouc and Faculty of Medicine and Dentistry, Palacky University Olomouc, Olomouc, Czech Republic
[2]Pulmonary Department, University Hospital Hradec Kralove and Faculty of Medicine, Charles University in Prague, Hradec Kralove, Czech Republic
[3]Institute of Biostatistics and Analyses, Faculty of Medicine, Masaryk University, Brno, Czech Republic
[4]Department of Respiratory Diseases, University Hospital Brno and Faculty of Medicine, Masaryk University, Brno, Czech Republic
Corresponding author: Jaromir Zatloukal, e-mail: jaromir.zatloukal@fnol.cz

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung disease characterised by chronic respiratory symptoms and persistent, often progressive airflow obstruction. It is a major cause of chronic morbidity and mortality and, currently the third leading noncommunicable cause of death worldwide[1]. Associated comorbidities affect the outcome in COPD patients[1-4]. Two clinical phenotypes of COPD, namely "pink puffer" and "blue bloater", have been described in the early description of the disease, with recognised differences in respiratory symptoms and body composition[4,5].

Body mass index (BMI) is known as a part of the BODE (BMI, airflow Obstruction, Dyspnea, Exercise capacity) composite prognostic index, which has been developed to better predict outcomes in patients with COPD compared with assessment based on airflow obstruction alone[6]. In addition, low BMI has also been described as an independent predictor of mortality in patients with COPD (ref.[7]). However, some studies suggest that a more comprehensive assessment, including other parameters such as fat-free mass index (FFMI), may be more accurate[8]. COPD patients with different nutritional status have been shown to have different respiratory symptoms, comorbidities, causes of death and also different risk of death[4,9,10].

Few long-term survival analyses by nutritional status in COPD patients have been published, never in the Czech population with COPD. Therefore, we decided to evaluate the nutritional status in COPD patients from the National COPD Database, to evaluate the differences in nutritional status between COPD phenotypes, to evaluate the relationship between different nutritional categories and lung function, COPD-related symptoms, exacerbations and comorbidities, and finally to evaluate the long-term survival in COPD patients from the National COPD Database. We also decided to assess whether FFMI and MAMC improved the prediction of mortality risk compared with BMI alone, as has been described in similar studies[11,12].

METHODS

Study participants

Patient data included in this analysis were taken from the Czech Multicentre Research Database (CMRD) of COPD. The Database has been registered with the National Institute for Drug Control under the identifier 1301100001 and on ClinicalTrials.gov as NCT01923051. The study was approved by the Multicentre Ethics Committee of the University Hospital in Brno on 16 January 2013 under the project registration code "CHOPN" and by all institutional review boards of each participating centre. CMRD of COPD was designed as a prospective, observational, multicentre study with the primary endpoint to assess all-cause mortality in enrolled patients with COPD. All participants signed a written informed consent form prior to enrolment to participate in the study and to withdraw from the study.

The study design, inclusion and exclusion criteria have been described in detail previously[13]. A total of 784 consecutive patients with physician-diagnosed COPD, post-bronchodilator forced expiratory volume in 1 second (FEV_1)≤60% of predicted value, not newly diagnosed and free of exacerbations for at least 8 weeks prior to enrolment, were enrolled in the CMRD between August 2013 and December 2016 at 12 participating centres in tertiary hospitals. In this analysis, baseline data of patients with known body composition parameters were analysed, to evaluate nutritional status, its association with clinical characteristics and its impact on survival in patients with COPD. For the study design, see Figure S1 in the Supplementary Appendix.

Evaluation of nutritional parameters and muscle mass

Calibrated instruments were used to measure height and weight in metres and kilograms and to calculate BMI (kg/m^2). Skinfold anthropometry (SFA) and calibrated calipers were used to assess FFMI (kg/m^2), with triple measurements at four standard skin sites (triceps, biceps, subscapular, suprailiac) (ref.[14]). Body density was estimated using the Durnin and Womersley method[15] and FM was calculated using the Siri equation[16]. The threshold for low FFMI was defined as FFMI<16 kg/m^2 for men and FFMI<15 kg/m^2 for women[17]. In addition to BMI and FFMI, mid-arm muscle circumference (MAMC) was calculated as a parameter of muscle mass loss from the triceps skinfold and mid-arm circumference of the non-dominant upper arm[12,18].

Definition of nutritional categories and muscle mass loss

Patients were divided into nutritional categories according to BMI and FFMI (for men/women) as follows: 1) cachexia (BMI <21 kg/m^2 and FFMI <16/15 kg/m^2), 2) muscle atrophy (21≤ BMI <30 kg/m^2 and FFMI <16/15 kg/m^2), 3) underweight (BMI <21 kg/m^2 and FFMI ≥16/15 kg/m^2), 4) normal nutritional parameters (21≤ BMI <25 kg/m^2 and FFMI ≥16/15 kg/m^2), 5) overweight (25≤ BMI <30 kg/m^2 and FFMI ≥16/15 kg/m^2) and 6) obesity (BMI ≥30 kg/m^2 and FFMI ≥16/15 kg/m^2). Significant muscle mass loss by MAMC was defined as MAMC ≤20 cm in men and MAMC ≤18.5 cm in women, as a muscle mass loss of at least 20% compared to physiological muscle mass. Patients were divided into groups

according to MAMC corresponding to 100, 90, 80 and ≤80% of the physiological muscle mass.

COPD phenotyping, evaluation of lung function, symptoms, exacerbations and comorbidities

COPD phenotyping was performed by the physician. Six clinical phenotypes were defined according to the Czech national COPD guidelines[19]: 1) emphysematous phenotype, 2) chronic bronchitis phenotype, 3) asthma and COPD overlap (ACO) phenotype, 4) bronchiectasis and COPD overlap (BCO) phenotype, 5) frequent exacerbations phenotype, and 6) pulmonary cachexia phenotype. The guidelines allow patients to have more than one COPD phenotype, e.g. emphysematous and frequent exacerbations phenotypes at the same time.

Pulmonary function tests were performed according to the relevant ERS/ATS guidelines[20-22]. Of all the lung function parameters measured in patients enrolled in the CMRD, this study evaluated the relationship between nutritional categories and: a) forced expiratory volume in 1 second (FEV_1), b) ratio of forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC), c) forced vital capacity (FVC), and d) transfer factor of the lung for carbon monoxide (CO), also known as diffusing capacity of the lung for CO (DL_{CO}).

The COPD Assessment Test (CAT) to assess symptoms and the modified Medical Research Council dyspnoea scale (mMRC) to assess dyspnoea severity were completed.

Medical records were reviewed for history of exacerbations in the year prior to enrolment and for comorbidities by physicians.

Statistical analyses

All statistical analyses were performed at the Institute of Biostatistics and Analyses, Brno. Categorical parameters were described by absolute and relative frequencies. Interdependence between two categorical parameters was tested using Pearson's chi-squared test or Fisher's exact test. Quantitative parameters are described as means (standard deviation = SD), median (5% and 95% quantile). Differences in quantitative parameter values between groups were tested by the Kruskal-Wallis test. Overall survival was analysed using the Kaplan-Meier method and differences between groups were tested using the log-rank test or the Cox proportional hazards model. Probabilities of survival at 12, 24, 36, 48 and 60 months were analysed. Statistics are presented with 95% confidence intervals and results with *P*-values <0.05 were considered significant. All analyses were performed using IBM SPSS Statistics 28 and R software (version 4.2.1).

RESULTS

Patient characteristics

Data of 343 patients with assessed BMI, FFMI and MAMC were included in this analysis. Patients were predominantly male (73.8%), former or current smokers (93%), mean age at enrolment was 66.6 years, mean age at diagnosis was 58.0 years, mean BMI was 27.3 kg/m^2, median baseline FEV_1 was 45.0% of predicted. Overall, 53.6% of the patients had at least one exacerbation in the past year, including 26.5% of the patients with a severe exacerbation requiring hospitalisation. More baseline characteristics of the patients included in the analysis are in Table 1.

According to BMI and FFMI, a total of 16.6% of the patients were in categories with BMI≤21 kg/m^2, of which 10.2% also had low FFMI and were in the cachexia category and 6.4% had normal FFMI and were in the underweight category. A total of 2.3% of the patients had normal BMI and low FFMI and were in the muscle atrophy category, 8.1% of patients had normal nutritional parameters, 32.1% of the patients were overweight and 30.9% of the patients were obese. According to MAMC, significant muscle mass loss, corresponding to ≤80% of the physiological muscle mass was observed in 20.7% of the patients. See also Fig. S2 in the Supplementary Appendix.

Nutritional categories and COPD phenotypes

The representation of nutritional categories according to FFMI and BMI and groups by MAMC between clinical phenotypes is shown in Figure S3 in the Supplementary Appendix.

As one of the criteria for the pulmonary cachexia phenotype according to the Czech guidelines is a BMI <21 kg/m^2, patients with the pulmonary cachexia phenotype were exclusively in the nutritional categories of cachexia and underweight. In our cohort, of the 57 patients with the pulmonary cachexia phenotype, a total of 35 patients (61.4%) were in the cachexia nutritional category, and 22 patients (38.8%) were in the underweight category (*P*<0.001). In the muscle mass loss group by MAMC, a total of 42 patients had the pulmonary cachexia phenotype, representing 59.2% of all patients with significant muscle mass loss by MAMC (*P*<0.001).

In addition to the pulmonary cachexia phenotype, patients with nutritional categories associated with low BMI and/or low FFMI (cachexia, muscle atrophy and underweight) or muscle mass loss by MAMC had predominantly the emphysematous phenotype, BCO and frequent exacerbations phenotype. Normal nutritional parameters predominated in patients with ACO. Overweight and obesity were predominant in the chronic bronchitis phenotype, as was pfysiological muscle mass (*P*<0.001), Fig. S3 in the Supplementary Appendix.

Table 2 shows the prevalence of nutrition categories in COPD phenotype groups, comparing those with and without a nutrition category for each of the COPD phenotypes.

Nutritional categories and lung function

Underweight patients and patients with muscle atrophy had lower FEV_1 (36% and 37% vs. 49% of predicted, respectively, *P*=0.046), patients with cachexia had lower DLCO (32% vs. 54% of predicted, *P*<0.001) and all, patients with cachexia, muscle atrophy or underweight had a lower FEV_1/FVC ratio (0.4 vs. 0.6, *P*<0.001) compared

Table 1. Baseline characteristics.

Baseline characteristics, n=343		
Gender	Male, n	253 (73.8%)
Age	years, mean (SD)	66.6 (8.4)
Body mass index	kg/m^2, mean (SD)	27.3 (6.0)
Smoking	Ex-smoker, n	252 (73.5%)
	Smoker, n	67 (19.5%)
	Never smoker, n	24 (7.0%)
Dyspnea	mMRC 0, n	23 (6.7%)
	mMRC 1, n	86 (25.1%)
	mMRC 2, n	135 (39.4%)
	mMRC 3, n	52 (15.2%)
	mMRC 4, n	47 (13.7%)
COPD Assessment Test, median (95% CI)		17.0 (4.0; 29.0)
Exacerbations	All, mean (SD)	1.19 (1.62)
	Patients with at least 1 exacerbation, n	184 (53.6%)
	Moderate, mean (SD)	0.79 (1.28)
	Patients with at least 1 moderate exacerbation, n	146 (42.6%)
	Severe, mean (SD)	0.40 (0.78)
	Patients with at least 1 severe exacerbation, n	91 (26.5%)
Lung function	FEV_1, % of predicted value, median (95% CI)	45.0 (25.2; 58.6)
	FVC, % of predicted value, median (95% CI)	72.8 (44.1; 103.9)
	VC_{max}, % of predicted value, median (95% CI)	76.0 (50.6; 109.0)
	FEV_1/FVC, median (95% CI)	0.49 (0.32; 0.70)
	FEV_1/VC_{max}, median (95% CI)	0.46 (0.29; 0.65)
	RV, % of predicted value, median (95% CI)	197.0 (112.0; 284.0)
	TLC, % of predicted value, median (95% CI)	119.0 (70.0; 158.0)
	RV/TLC, % of predicted value, median (95% CI)	63.0 (44.0; 82.4)
	IC/TLC, % of predicted value, median (95% CI)	33.0 (17.0; 87.0)
	DL_{CO}, % of predicted value, median (95% CI)	47.0 (23.0; 89.0)
	K_{CO}, % of predicted value, median (95% CI)	63.0 (26.0; 114.0)
	FeNO, ppb, median (95% CI)	16.0 (4.0; 61.0)
6-MWT, distance, metres, median (95% CI)		360.0 (120.0; 480.0)
COPD phenotypes according to Czech national guidelines		
	Chronic bronchitis phenotype, n	206 (60%)
	Emphysematous phenotype, n	208 (75.1%)
	Bronchiectasis and COPD overlap (BCO), n	79 (28.9%)
	Asthma and COPD overlap (ACO), n	11 (3.9%)
	Frequent exacerbation phenotype, n	107 (31.2%)
	Pulmonary cachexia phenotype, n	57 (16.6%)
Nutritional categories according to BMI and FFMI		
	Cachexia, n	35 (10.2%)
	Muscle atrophy, n	8 (2.3%)
	Underweight, n	22 (6.4%)
	Normal, n	62 (18.1%)
	Overweight, n	110 (32.1%)
	Obesity, n	106 (30.9%)
Muscle mass loss in % of physiological muscle mass by MAMC		
	Physiological – 100%	186 (54.2%)
	Physiological – 90%	86 (25.1%)
	Muscle mass loss – 80%	55 (16.0%)
	Muscle mass loss – 70%	14 (4.1%)
	Muscle mass loss – 40–60%	2 (0.6%)

FEV_1, Forced expiratory volume in the first second; FVC, Forced vital capacity; $Vc_{max,}$ Maximal vital capacity; RV, Residual volume; TLC, Total lung capacity; IC, Inspiratory capacity; DLCO, Diffusing capacity of the lung for carbon monoxide; KCO, Diffusion coefficient for carbon monoxide; FeNO, Fraction of exhaled nitric oxide; 6-MWT, Six minute walking test; BMI, Body mass index; FFMI, Fat-free mass index; MAMC, Mid-arm muscle circumference.

Table 2. Nutritional categories and COPD phenotypes[#].

	Nutrition category by BMI anf FFMI						Muscle mass in % of physiological muscle mass by MAMC			
	Cachexia	Muscle atrophy	Underweight	Normal	Overweight	Obesity	Normal, 100%	Normal, 90%	Muscle mass loss, 80%	Muscle mass loss, <80%
Chronic bronchitis phenotype[#]										
Not present^	21 (15.3%)	5 (3.6%)	7 (5.1%)	23 (16.8%)	38 (27.7%)	43 (31.4%)	77 (56.2%)	28 (20.4%)	19 (13.9%)	13 (9.5%)
Present[$]	14 (6.8%)	3 (1.5%)	15 (7.3%)	39 (18.9%)	72 (35.0%)	63 (30.6%)	109 (52.9%)	58 (28.2%)	36 (17.5%)	3 (1.5%)
*P**	**0.017**	0.274	0.504	0.669	0.194	0.905	0.581	0.127	0.453	**0.001**
Emphysematous phenotype[#]										
Not present^	2 (2.9%)	0 (0.0%)	2 (2.9%)	4 (5.8%)	21 (30.4%)	40 (58.0%)	49 (71.0%)	16 (23.2%)	2 (2.9%)	2 (2.9%)
Present[$]	25 (12.5%)	5 (2.5%)	16 (8.0%)	42 (21.0%)	66 (33.0%)	46 (23.0%)	98 (49.0%)	56 (28.0%)	34 (17.0%)	12 (6.0%)
*P**	**0.020**	0.333	0.173	**0.003**	0.766	**<0.001**	**0.002**	0.529	**0.002**	0.530
Bronchiectasis and COPD overlap (BCO) phenotype[#]										
Not present^	15 (8.0%)	2 (1.1%)	10 (5.3%)	32 (17.1%)	64 (34.2%)	64 (34.2%)	113 (60.4%)	49 26.2%)	18 (9.6%)	7 (3.7%)
Present[$]	11 (14.1%)	2 (2.6%)	8 (10.3%)	14 (17.9%)	21 (26.9%)	22 (28.2%)	33 (42.3%)	23 (29.5%)	16 (20.5%)	6 (7.7%)
*P**	0.172	0.584	0.180	0.860	0.312	0.389	**0.010**	0.650	**0.025**	0.213
Asthma and COPD overlap (ACO) phenotype[#]										
Not present^	32 (11.7%)	7 (2.6%)	18 (6.6%)	46 (16.8%)	87 (31.9%)	83 (30.4%)	149 (54.6%)	63 (23.1%)	48 (17.6%)	13 (4.8%)
Present[$]	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (45.5%)	3 (27.3%)	3 (27.3%)	5 (45.5%)	6 (54.5%)	0 (0.0%)	0 (0.0%)
*P**	0.619	0.999	0.999	**0.030**	0.999	0.999	0.557	**0.027**	0.221	0.999
Frequent exacerbation phenotype[#]										
Not present^	22 (9.3%)	7 (3.0%)	11 (4.7%)	42 (17.8%)	73 (30.9%)	81 (34.3%)	137 (58.1%)	54 (22.9%)	37 (15.7%)	8 (3.4%)
Present[$]	13 (12.1%)	1 (0.9%)	11 (10.3%)	20 (18.7%)	37 (34.6%)	25 (23.4%)	49 (45.8%)	32 (29.9%)	18 (16.8%)	8 (7.5%)
*P**	0.444	0.443	0.058	0.880	0.533	**0.044**	**0.036**	0.180	0.874	0.105
Pulmonary cachexia phenotype[#]										
Not present^	0 (0.0%)	8 (2.8%)	0 (0.0%)	62 (21.7%)	110 (38.5%)	106 (37.1%)	181 (63.3%)	76 (26.6%)	24 (8.4%)	5 (1.7%)
Present[$]	35 (61.4%)	0 (0.0%)	22 (38.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (8.8%)	10 (17.5%)	31 (54.4%)	11 (19.3%)
*P**	**<0.001**	0.361	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.182	**<0.001**	**<0.001**

BMI, Body mass index; FFMI, Fat-free mass index; MAMC, Mid-arm muscle circumference.

[#]Clinical phenotypes according to the Czech National COPD Guidelines[19]; six clinical phenotypes may overlap. Patients in whom the presence or absence of emphysema or bronchiectasis was not confirmed on CT scan were not included.

^Number of patients without the COPD phenotype in the nutritional category (percentage of patients in the nutritional category out of all patients without the COPD phenotype).

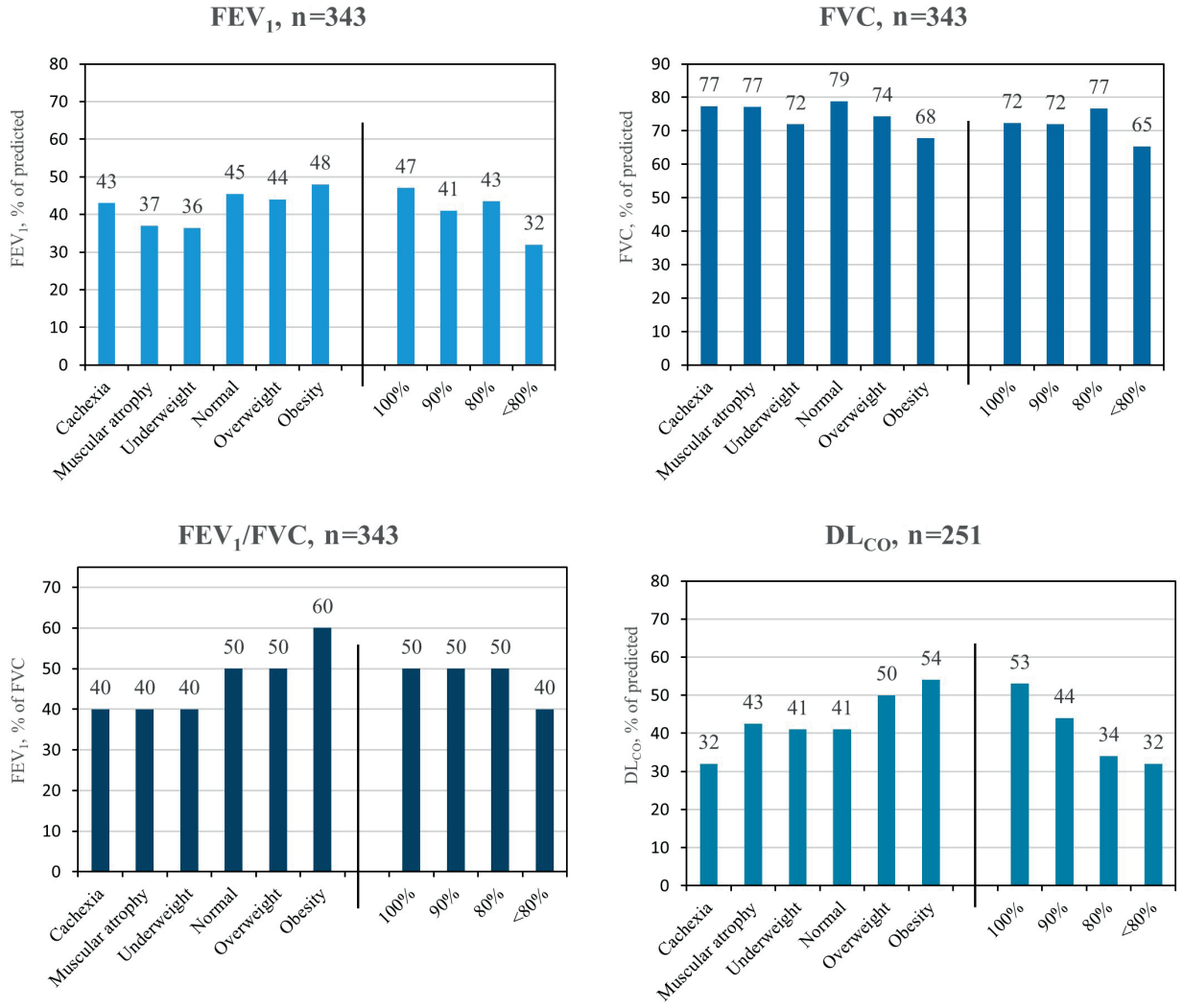
[$]Number of the patients with the COPD phenotype in the nutritional category (percentage of patients in the nutritional category out of all patients with the COPD phenotype).

* Fisher's exact test.

to obese patients. Obese patients had the lowest FVC of all groups (P=0.030). Patients with muscle mass loss of more than 20% of physiological muscle mass by MAMC had lower FEV_1 (32% vs. 47% of predicted, P=0.004), lower FEV_1/FVC ratio (0.4 vs. 0.5, P<0.001) and also lower DLCO (32% vs. 53% of predicted, P<0.001) compared to patients with 100% of physiological muscle mass. There were no differences in FVC between groups by MAMC, see Fig. 1.

Nutritional categories and dyspnoea, COPD-related symptoms by CAT, and exacerbations

Patients with the most severe dyspnoea (mMRC 4) were more common in the cachexia and underweight groups than in the normal weight or overweight groups (29% and 23% vs. 11% and 9%), and also predominated in the group of patients with significant muscle loss by MAMC, where 44% of the patients had severe dyspnoea (P=0.001). Conversely, mild dyspnoea (mMRC 1), predominated in the patients with normal muscle mass, and



	Nutritional categories by BMI and FFMI							Muscle mass in % of physiological muscle mass by MAMC				
Median (95% CI)	Cachexia	Atrophy	Underweight	Normal	Overweight	Obesity	*P*#	100%	90%	80%	<80%	*P*#
FEV_1, % predicted	43.3 (25,7–59.4)	36.9 (24.7–58.5)	36.4 (23.7–56.4)	44.8 (24.8–58.9)	44.0 (27.6–58.6)	47.5 (25.1–58.2)	**0.046**	46.8 (27.5–59.0)	4̈0.5 (25.0–58.2)	42.8 (24.7–59.4)	32.2 (13.8–57.1)	**0.004**
FVC, % predicted	77.4 (48.7–117.0)	77.2 (30.6–106.1)	71.9 (53.4–100.1)	78.9 (47.7–104.8)	74.3 (45.0–103.9)	67.8 (40.4–94.2)	**0.030**	72.4 (44.1–103.9)	72.0 (45.4–103.5)	76.7 (43.0–103.1)	65.4 (33.2–120.3)	0.731
FEV_1, % of FVC	40 (30–70)	40 (30–70)	40 (30–60)	50 (30–60)	50 (30–70)	60 (40–70)	**<0.001**	50 (30–70)	50 (30–70)	50 (30–60)	40 (30–70)	**<0.001**
DL_{CO}, % predicted	32.0 (8.0–71.0)	43.0 (27.0–44.0)	41.0 (12.0–68.0)	41.0 (23.0-78.0)	50.0 (27.0–92.0)	54.0 (30.0–89.0)	**<0.001**	53.0 (27.0–91.0)	44.0 (27.0–78.0)	34.0 (10.0-63.0)	32.0 (20.0–59.0)	**<0.001**

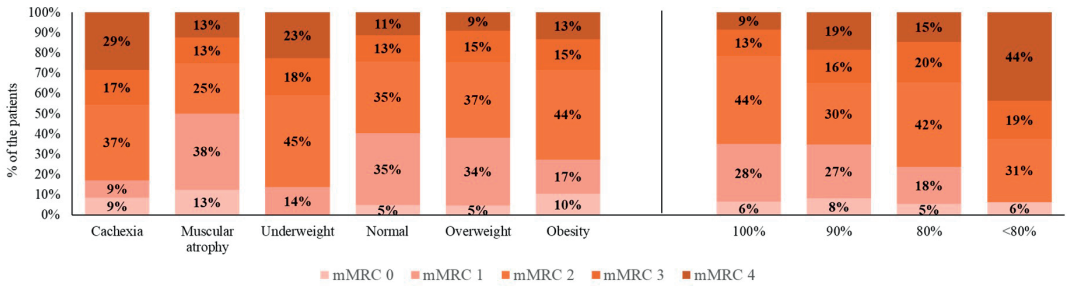
Fig. 1. Lung function in nutritional categories and in groups according to MAMC.
MAMC, Mid-arm muscle circumference; BMI, Body mass index; FFMI, Fat-free mass index, FEV_1, Forced expiratory volume in the first second; FVC, Forced vital capacity; FEV_1/FVC, Forced expiratory volume in the first second to forced vital capacity ratio; DL_{CO}, Diffusing capacity of the lungs for carbon monoxide.
#Kruskal-Wallis test.

there were no patients with mild dyspnoea in the group with significant muscle loss by MAMC (*P*=0.027).

Patients with normal nutritional status according to FFMI and BMI had fewer symptoms and the lowest CAT score (CAT 15), whereas CAT scores increased in patients in the cachexia, muscle atrophy, and underweight categories (CAT 18, 19, and 21, respectively), but also in overweight and obese patients (CAT 16 and 17, respectively). When assessed by MAMC, patients with significant muscle mass loss had more symptoms (CAT 23) than those without muscle mass loss (CAT 16). These differences did not reach statistical signifikance, Fig. 2.

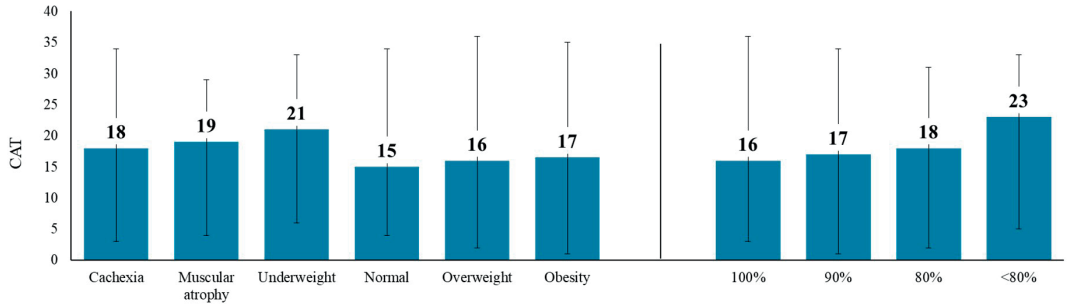
The highest prevalence of exacerbations was observed in the underweight group, where a total of 81.8% of the patients had experienced at least one exacerbation in the past year, in contrast to the normal weight group, where only 48.4% of the patients had experienced an exacerbation in the past year (*P*=0.043). Similarly, severe exacerbations requiring hospitalisation were the most common in the underweight group, with 50.0% of the patients experi-

A. Number and percentage of patients with dyspnea by mMRC in nutritional groups and groups by MAMC, n=343



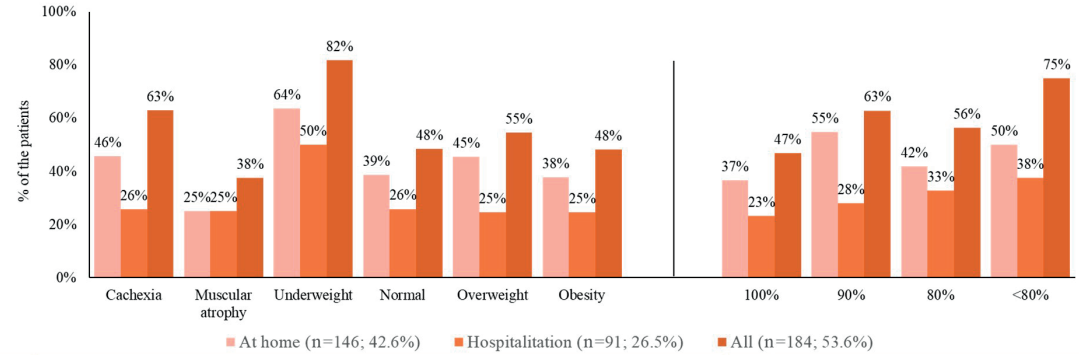
	Nutritional categories by BMI and FFMI							Muscle mass in % of physiological muscle mass by MAMC				
mMRC	Cachexia	Atrophy	Underweight	Normal	Overweight	Obesity	*P**	100%	90%	80%	<80%	*P**
0	3 (8.6%)	1 (12.5%)	0 (0.0%)	3 (4.8%)	5 (4.5%)	11 (10.4%)	0.299	12 (6.5%)	7 (8.1%)	3 (5.5%)	1 (6.3%)	0.932
1	3 (8.6%)	3 (37.5%)	3 (13.6%)	22 (35.5%)	37 (33.6%)	18 (17.0%)	**0.001**	53 (28.5%)	23 (26.7%)	10 (18.2%)	0 (0.0%)	**0.027**
2	13 (37.1%)	2 (25.0%)	10 (45.5%)	22 (35.5%)	41 (37.3%)	47 (44.3%)	0.754	81 (43.5%)	26 (30.2%)	23 (41.8%)	5 (31.3%)	0.174
3	6 (17.1%)	1 (12.5%)	4 (18.2%)	8 (12.9%)	17 (15.5%)	16 (15.1%)	0.983	24 (12.9%)	14 (16.3%)	11 (20.0%)	3 (18.8%)	0.494
4	10 (28.6%)	1 (12.5%)	5 (22.7%)	7 (11.3%)	10 (9.1%)	14 (13.2%)	0.069	16 (8.6%)	16 (18.6%)	8 (14.5%)	7 (43.8%)	**0.001**

B. Median CAT in nutritional groups and groups by MAMC, n=338



	Nutritional categories by BMI and FFMI							Muscle mass in % of physiological muscle mass by MAMC				
Median (95% CI)	Cachexia	Atrophy	Underweight	Normal	Overweight	Obesity	*P*#*	100%	90%	80%	<80%	*P*#*
CAT	18 (3–34)	19 (4–29)	21 (6–33)	15 (4–34)	16 (2–36)	17 (1–35)	0.060	16 (3–36)	17 (1–34)	18 (2–31)	23 (5–33)	0.058

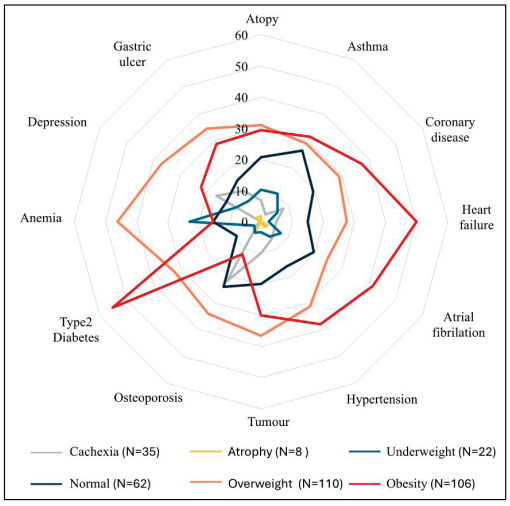
C. Number and percentage of patients with at least one exacerbation in last year in nutritional categories and groups by MAMC, n=343



Patients with ≥1 exacerbation in last year, N (%)	Nutritional categories by BMI and FFMI							Muscle mass in % of physiological muscle mass by MAMC				
	Cachexia	Atrophy	Underweight	Normal	Overweight	Obesity	*P**	100%	90%	80%	<80%	*P**
At home	16 (45.7%)	2 (25.0%)	14 (63.6%)	24 (38.7%)	50 (45.5%)	40 (37.7%)	0.240	68 (36.6%)	47 (54.7%)	23 (41.8%)	8 (50.0%)	**0.040**
Hospitalization	9 (25.7%)	2 (25.0%)	11 (50.0%)	16 (25.8%)	27 (24.5%)	26 (24.5%)	0.280	43 (23.1%)	24 (27.9%)	18 (32.7%)	6 (37.5%)	0.325
All	22 (62.9%)	3 (37.5%)	18 (81.8%)	30 (48.4%)	60 (54.5%)	51 (48.1%)	**0.043**	87 (46.8%)	54 (62.8%)	31 (56.4%)	12 (75.0%)	**0.023**

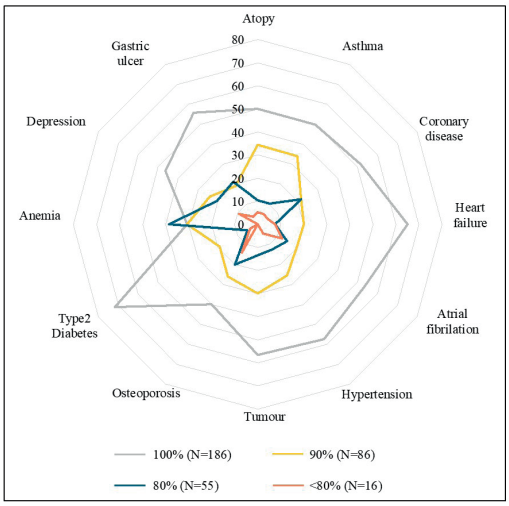
Fig. 2. Dyspnoea, symptoms and exacerbations in nutritional categories and in groups according to MAMC.
BMI, Body mass index; FFMI, Fat-free mass index; MAMC, Mid-arm muscle circumference; CAT, COPD Assessment Test; mMRC, Modified Medical Council Scale for assessment of dyspnoea; CI, Confidence Interval; *Fisher's exact test; #Kruskal-Wallis test.

A. Categories by BMI and FFMI and comorbidities



		Nutritional categories by BMI and FFMI						
		Cachexia	Atrophy	Underweight	Normal	Overweight	Obesity	*P*
Atopy	No	31 (10.9%)	7 (2.5%)	16 (5.6%)	50 (17.5%)	92 (32.3%)	89 (31.2%)	0.727
	Yes	4 (6.9%)	1 (1.7%)	6 (10.3%)	12 (20.7%)	18 (31.0%)	17 (29.3%)	
Asthma	No	34 (11.1%)	8 (2.6%)	18 (5.9%)	52 (17.0%)	99 (32.5%)	94 (30.8%)	0.296
	Yes	1 (2.6%)	0 (0.0%)	4 (10.5%)	10 (26.3%)	11 (28.9%)	12 (31.6%)	
Coronary disease	No	28 (10.8%)	8 (3.1%)	17 (6.5%)	46 (17.7%)	86 (33.1%)	75 (28.8%)	0.487
	Yes	7 (8.4%)	0 (0.0%)	5 (6.0%)	16 (19.3%)	24 (28.9%)	31 (37.3%)	
Heart failure	No	33 (10.9%)	8 (2.6%)	21 (6.9%)	56 (18.5%)	99 (32.7%)	86 (28.4%)	0.175
	Yes	2 (5.0%)	0 (0.0%)	1 (2.5%)	6 (15.0%)	11 (27.5%)	20 (50.0%)	
Atrial fibrilation	No	33 (10.9%)	7 (2.3%)	19 (6.3%)	54 (17.9%)	100 (33.1%)	89 (29.5%)	0.516
	Yes	2 (4.9%)	1 (2.4%)	3 (7.3%)	8 (19.5%)	10 (24.4%)	17 (41.5%)	
Hypertension	No	22 (15.4%)	4 (2.8%)	11 (7.7%)	29 (20.3%)	47 (32.9%)	30 (21.0%)	**0.006**
	Yes	13 (6.5%)	4 (2.0%)	11 (5.5%)	33 (16.5%)	63 (31.5%)	76 (38.0%)	
Tumour	No	32 (10.2%)	8 (2.6%)	21 (6.7%)	56 (17.9%)	99 (31.6%)	97 (31.0%)	0.991
	Yes	3 (10.0%)	0 (0.0%)	1 (3.3%)	6 (20.0%)	11 (36.7%)	9 (30.0%)	
Osteoporosis	No	24 (8.2%)	6 (2.0%)	20 (6.8%)	50 (17.1%)	93 (31.7%)	100 (34.1%)	**0.002**
	Yes	11 (22.0%)	2 (4.0%)	2 (4.0%)	12 (24.0%)	17 (34.0%)	6 (12.0%)	
Type2 diabetes	No	34 (12.8%)	8 (3.0%)	20 (7.5%)	55 (20.8%)	85 (32.1%)	63 (23.8%)	**<0.001**
	Yes	1 (1.3%)	0 (0.0%)	2 (2.6%)	7 (9.0%)	25 (32.1%)	43 (55.1%)	
Anemia	No	35 (10.6%)	8 (2.4%)	19 (5.8%)	60 (18.2%)	104 (31.5%)	104 (31.5%)	0.139
	Yes	0 (0.0%)	0 (0.0%)	3 (23.1%)	2 (15.4%)	6 (46.2%)	2 (15.4%)	
Depression	No	26 (9.0%)	7 (2.4%)	17 (5.9%)	55 (19.0%)	90 (31.1%)	94 (32.5%)	0.235
	Yes	9 (16.7%)	1 (1.9%)	5 (9.3%)	7 (13.0%)	20 (37.0%)	12 (22.2%)	
Gastric ulcer	No	29 (10.0%)	7 (2.4%)	18 (6.2%)	54 (18.6%)	92 (31.6%)	91 (31.3%)	0.972
	Yes	6 (11.5%)	1 (1.9%)	4 (7.7%)	8 (15.4%)	18 (34.6%)	15 (28.8%)	

B. Muscle mass groups by MAMC and comorbidities



		Muscle mass in % of ideal nutritional status by MAMC				
		100%	90%	80%	<80%	*P*
Atopy	No	157 (55.1%)	66 (23.2%)	49 (17.2%)	13 (4.6%)	0.248
	Yes	29 (50.0%)	20 (34.5%)	6 (10.3%)	3 (5.2%)	
Asthma	No	167 (54.8%)	73 (23.9%)	51 (16.7%)	14 (4.6%)	0.466
	Yes	19 (50.0%)	13 (34.2%)	4 (10.5%)	2 (5.3%)	
Coronary disease	No	143 (55.0%)	68 (26.2%)	37 (14.2%)	12 (4.6%)	0.422
	Yes	43 (51.8%)	18 (21.7%)	18 (21.7%)	4 (4.8%)	
Heart failure	No	160 (52.8%)	78 (25.7%)	52 (17.2%)	13 (4.3%)	0.202
	Yes	26 (65.0%)	8 (20.0%)	3 (7.5%)	3 (7.5%)	
Atrial fibrilation	No	164 (54.3%)	78 (25.8%)	49 (16.2%)	11 (3.6%)	0.135
	Yes	22 (53.7%)	8 (19.5%)	6 (14.6%)	5 (12.2%)	
Hypertension	No	71 (49.7%)	35 (24.5%)	30 (21.0%)	7 (4.9%)	0.190
	Yes	115 (57.5%)	51 (25.5%)	25 (12.5%)	9 (4.5%)	
Tumour	No	169 (54.0%)	77 (24.6%)	51 (16.3%)	16 (5.1%)	0.697
	Yes	17 (56.7%)	9 (30.0%)	4 (13.3%)	0 (0.0%)	
Osteoporosis	No	166 (56.7%)	73 (24.9%)	45 (15.4%)	9 (3.1%)	**0.007**
	Yes	20 (40.0%)	13 (26.0%)	10 (20.0%)	7 (14.0%)	
Type2 diabetes	No	130 (49.1%)	71 (26.8%)	51 (19.2%)	13 (4.9%)	**0.001**
	Yes	56 (71.8%)	15 (19.2%)	4 (5.1%)	3 (3.8%)	
Anemia	No	182 (55.2%)	82 (24.8%)	50 (15.2%)	16 (4.8%)	0.110
	Yes	4 (30.8%)	4 (30.8%)	5 (38.5%)	0 (0.0%)	
Depression	No	161 (55.7%)	73 (25.3%)	44 (15.2%)	11 (3.8%)	0.207
	Yes	25 (46.3%)	13 (24.1%)	11 (20.4%)	5 (9.3%)	
Gastric ulcer	No	157 (54.0%)	76 (26.1%)	44 (15.1%)	14 (4.8%)	0.584
	Yes	29 (55.8%)	10 (19.2%)	11 (21.2%)	2 (3.8%)	

Fig. 3. Nutritional categories and comorbidities.
Number and percentage of patients with present comorbidity (Yes) or without comorbidity (No) in nutritional categories according to BMI and FFMI and muscle mass loss groups by MAMC.
BMI, Body mass index; FFMI, Fat-free mass index; MAMC, Mid-arm muscle circumference.

encing an exacerbation. Patients with significant muscle mass loss according to MAMC were also more likely to have at least one exacerbation in the past year compared to those with physiological muscle mass. Overall, 75.0% of the patients with significant muscle mass loss had at least one exacerbation in the past year and 37.5% had at least one severe exacerbation in the past year, compared to 46.8% and 23.1% of the patients with physiological muscle mass and at least one exacerbation or at least one severe exacerbation, respectively (P=0.023). While the number of patients with severe exacerbations did not differ between BMI and FFMI categories after excluding underweight patients, ranging from 24.5% to 25.8%, the number of the patients with severe exacerbations increased with the severity of muscle mass loss by MAMC, see Fig. 2.

Nutritional categories and comorbidities

Cardiovascular comorbidities were more common in overweight and obese patients. Among patients with heart failure, 27.5% and 50.0% were overweight and obese, respectively, and only 5.0%, 0.0%, and 2.5% of the patients were in the cachexia, muscle atrophy, and underweight categories, respectively. Similarly, among patients with hypertension, 31.5% and 38.0% were overweight and obese, respectively, and only 6.5%, 2.0%, and 5.5% of the patients were in the cachexia, muscle atrophy, and underweight

categories, respectively (*P*=0.006). Among patients with type 2 diabetes, 32.1% and 55.1% of the patients were overweight and obese, respectively, and only 1.3%, 0.0% and 2.6% of the patients were in the cachexia, muscle atrophy and underweight categories, respectively (*P*<0.001). Otherwise, type 2 diabetes was present in 68 out of 216 patients (31.5%) who were overweight or obese, and in only 1 out of 35 patients (2.9%) with cachexia.

Patients with cachexia were more likely to have osteoporosis and depression. Osteoporosis was present in 11 out of 35 patients (31.4%) with cachexia and only in 23 out of 216 patients (10.6%), who were overweight or obese (*P*=0.002). Depression was present in 9 out of 35 patients (25.7%) with cachexia and in 32 out of 216 patients (14.8%), who were overweight or obese.

When assessed by MAMC, type 2 diabetes was present in 56 out of 186 patients (30.1%) with physiological muscle mass, but only in 3 out of 16 patients (18.7%) with significant muscle mass loss (*P*=0.001). Osteoporosis was present in only 20 out of 186 patients (10.7%) with physiological muscle mass, but in 7 out of 16 patients (43.7%) with significant muscle mass loss by MAMC (*P*=0.007), Fig. 3.

There were no differences in nutritional categories according to BMI and FFMI or groups by MAMC and smoking status. More patients with muscle mass loss were in the GOLD 4 group (with post-bronchodilator FEV_1 <30% of predicted). Older patients were more likely to have muscle mass loss (*P*=0.001), Fig. S4 in the Supplementary Appendix.

Survival COPD patients according to nutritional categories

In this study, Kaplan-Meier survival analysis was performed for all patients with 9 years of follow-up. When assess by BMI and FFMI, patients with BMI <21 kg/m^2, i.e. in cachexia and underweight categories, had the worst survival, while the overweight and obese patients had the best survival. Cachexia reduced median survival from 72.0 to 43.5 months and was associated with a 1.7-fold increased risk of death (HR 1.7, 95% CI 1.0–2.9; *P*=0.049), compared to patients with normal parameters. The difference was even more pronounced in underweight patients, who had survival reduced from 72.0 to 39.8 months and a 2.2-fold increased risk of the death, compared to patients with normal parameters (HR 2.2, 95% CI 1.2–4.0; *P*=0.010). Conversely, overweight and obesity reduced the risk of death by 40% (HR 0.6, 95% CI 0.4–0.9; *P*=0.026) and 30% (HR 0.7, 95% CI 0.4–1.0; *P*=0.071), respectively, compared to patients with normal nutritional parameters according to BMI and FFMI, Fig. 4.

Muscle mass loss by MAMC to 80% of physiological muscle mass (reduction muscle mass of 20%) was associated with a 2.5-fold increased risk of death (HR 2.5, 95% CI 1.7–3.8; *P*<0.001), and significant muscle loss by MAMC, to <80% of pgysiological muscle mass (reduction of ≥20%) was associated with up to a 5.5-fold increased risk of death (HR 5.5, 95% CI 3.2–9.6; *P*<0.001), compared to groups with physiological muscle mass, Fig. 4.

When survival was assessed by BMI alone, patients with a BMI<21kg/m^2 had the worst survival and those with a 25≤BMI<30 kg/m^2 had the best survival; BMI<21kg/m^2 increased the risk of death 1.9-fold (HR 1.9, 95% CI 1.2–3.0; *P*=0.006) and reduced median survival from 72.0 to 41.6 months, compared to patients with normal BMI (21≤BMI<25 kg/m^2). Conversely, patients with 25≤BMI<30 kg/m^2 had reduced the risk of death by 40% (HR 0.6, 95% CI 0.4–0.9; *P*=0.025), compared to those with normal BMI (*P*=0.025), Fig. 4.

DISCUSSION

This study assessed the nutritional status of a cohort of 343 patients with moderate and severe COPD from the National COPD Database. While previously published studies have focused on a specific part of the problem, this study provides a comprehensive assessment that gives a holistic view of the issue. It assesses the relationship of nutritional status not only with lung function, exacerbations, or comorbidities, but also, more recently, with COPD-associated symptoms. An additional benefit is the long-term follow-up and survival data over a uniquely long period, 9 years in total. The results show that less than one fifth of COPD patients have a normal nutritional status, highlighting the urgency of addressing this issue in COPD patients. At the same time, based on an independent evaluation, it highlights the potential for bias in the results when using a simple BMI-only assessment that does not take into account the highly prognostic parameter of muscle wasting, which may be a source of error in assessing survival in individual groups based on BMI alone.

The association of COPD with an older population may contribute to the high prevalence of nutritional imbalances in patients with COPD.

Consistent with previous studies[23], we observed a high prevalence of overweight and obesity in patients with COPD, representing 63% of all patients in our cohort. Patients with normal nutritional parameters appear to represent a smaller proportion of the patients with COPD, in our cohort it was only 18.1% of the all patients. This finding supports the importance of nutritional assessment in patients with COPD.

To determine muscle wasting, we used skinfold anthropometry, which has previously been shown to be a simple, inexpensive, available and accurate method for determining FFM (ref.[14]). Different cut-offs for low FFMI may contribute to some differences in previous studies. According to these studies, the lower limit of normal for FFMI varies between 14.6–15 kg/m^2 in women and 16–18.7 kg/m^2 in men[8,17,24], and varies not only by gender, but also by age[24]. When we used FFMI cut-offs of 16 kg/m^2 for men and 15 kg/m^2 for women, 18.9% of the patients were in categories associated with malnutrition, with low BMI and/or low FFMI (cachexia, muscle atrophy or underweight categories). Significant muscle mass loss by MAMC (muscle loss of at least 20% of physiological muscle mass) had 20.7% of all patients in our cohort. The prevalence of

malnutrition in patients with COPD in similar studies was even higher, with 27% of patients with malnutrition[25], or varying between 12.4% and 28.1% in a meta-analysis of 2,565 patients[26].

In this study, we used the national classification of clinical COPD phenotypes, which defines a total of six COPD phenotypes. For one of these, the pulmonary cachexia phenotype, BMI <21 kg/m^2 is one of the classification criteria[19]. Our results show, that low FFMI and significant muscle mass loss occur in about two thirds of the patients with BMI <21 kg/m^2. Low FFMI in this patients does not further worsen survival, and patients in the nutritional category of cachexia even had slightly better survival compared to underweight patients (with low BMI and normal FFMI). Thus, in the group of patients with BMI <21 kg/m^2, low BMI appears to be an independent risk factor for increased mortality.

However, it should be noted that there is a difference in the frequency of patients in each nutritional category according to BMI and FFMI. There is a higher probability of statistical error with a small number of patients in the malnutrition groups and the simultaneous combination of two independent variables. This may have influenced some of the results. From this perspective, we consider the assessment by MAMC to be more accurate.

A non-linear relationship between BMI and mortality in COPD patients was described in one meta-analysis, using a random effects model and cut-off for higher risk of death in COPD patients was set a BMI of <21.75 kg/m^2 (ref.[27]). It appears that the group of COPD patients with an arbitrarily defined normal BMI ≥21 kg/m^2 includes patients with an increased risk of death. These patients may contribute to the overall worse survival in patients with COPD and normal BMI, compared to overweight or obese COPD patients. Although only 2.3% of patients in our study were in the muscle atrophy category and had a low FFMI despite a normal BMI, a similar study found up to 8% of the patients with parameters of muscle atrophy[28]. In the other study[8], assessing the distribution of low FFMI and including 1,898 patients with COPD, among subjects with normal BMI, 26.1% had an FFMI lower than the lowest 10th percentile of the general population. It was associated with increased all-cause mortality and also COPD-related mortality. Particularly in the group of patients with normal or even higher BMI, it seems to be important to focus on the assessment of other risk factors such as low FFMI, as these patients may experience a phenomenon known as sarcopenic obesity[12], worsening outcomes in these patients. At the same time, it may also be difficult to distinguish these patients as they do not show a predilection for any of the clinical phenotypes[9].

We observed similar differences in the associations between nutritional categories and clinical COPD phenotypes as were described previously[3]. Poor nutritional status and muscle mass loss were associated with emphysema, bronchiectasis and frequent exacerbations. Patients with malnutrition had worse lung function, more symptoms and osteoporosis and depression as the most common comorbidities. On the other hand, overweight and obesity were associated with the chronic bronchitis phenotype and cardiovascular and metabolic comorbidities. Our observations support the need for nutritional support and rehabilitation in malnourished patients with COPD and cardiovascular prevention in obese COPD patients. This is important as the prevalence of overweight and obesity in patients with COPD is high.

Interestingly, ACO patients appear to be the lowest risk group in terms of nutritional risk. There were no malnourished patients in this phenotype. This may be explained by the predominance of a different type of inflammation in patients with overlapping COPD and asthma.

Our assessment of muscle mass loss by MAMC confirmed muscle mass loss as an independent risk factor for mortality in patients with COPD, with an increasing risk of death with increasing muscle mass loss. In our study, significant muscle mass loss by MAMC was the strongest predictor of mortality, increasing the risk of death more than fivefold. Muscle weakness in patients with sarcopenia is likely to contribute to respiratory failure and respiratory causes of death in malnourished COPD patients. The frequent association of muscle wasting with low BMI may also explain why nutritional intervention alone has limited results in COPD patients, and better results are achieved when nutritional support and rehabilitation are combined[29], and the timing of nutritional support also appears to be important[30].

The description of the mechanisms leading to cachexia in patients with COPD is inconsistent and many theories have been proposed[31]. The clinical and nutritional phenotypes are likely to be rooted in different immune phenotypes and these need to be better characterised. Five clusters of comorbidities in COPD patients have been described by Vanfleteren, with less comorbidity, cardiovascular, cachectic, metabolic and psychological comorbidity groups[4]. The proportions of pro-inflammatory cytokines were observed in some clusters, such as tumour necrosis factor (TNF) receptors in the metabolic cluster, and IL-6 in the cardiovascular cluster, while TNF receptor 1 was less common in the cachectic cluster[4].

The differences between nutritional categories in COPD patients and COPD-related outcomes, and the impact of nutritional status on mortality in COPD, appear to be well described. However, the factors contributing to these differences are still not fully understood and further research is needed to clarify them.

The strength of this study is the relatively large cohort of participants with moderate or severe COPD and the long-term follow-up of the patients. The study included consecutive patients from real life and reflected the conditions of routine clinical practice.

The limitations were that nutritional parameters were not assessed in all participating centres of the CMRD project, as this was only an optional part of the project. Skin anthropometry in the multicentre study was also performed by different people, which could slightly affect the individual accuracy of the measurements. Finally, as the last patient in the CMRD was enrolled in December 2018, the assessment of lung function according to the

recommendations of a new 2021 interpretation strategy for lung function tests[32] could not be applied.

CONCLUSIONS

Malnutrition and overnutrition are common in patients with COPD. They are associated with certain COPD phenotypes and comorbidities. Malnourished patients with COPD have worse lung function, more exacerbations and worse survival. Underweight is often associated with muscle atrophy, but even normal-weight patients can have muscle atrophy, which increases the risk of death. Muscle mass loss was an independent predictor of the risk of death. Combined assessment of nutritional status in patients with COPD using BMI and assessment of muscle mass loss improves the prediction of mortality risk. Further research is needed to clarify the factors that contribute to the different nutritional status in COPD patients.

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Author contributions: EV, VK, KH, JZ: study design; EV, JZ, VK, MP, KB, MK: data collection; MS: stastical analysis; EV, JZ: contributed to drafting; VK, MP, MK, KB: critically revised the manuscript. All authors approved the final version for publication.

Conflict of interest statement: EV has received COPD research funding/travel grants from AstraZeneca within past 36 months, and received consulting/lectures/advisory board payment from AstraZeneca within past 36 months. VK has received COPD research funding/travel grants from Angelini, Chiesi and AstraZeneca within the past 36 months, and received consulting/lectures/advisory board payment from Chiesi, Sanofi, Roche, Pfizer, MSD, GSK, AstraZeneca, Berlin Chemie, and Boehringer Ingelheim regarding the COPD field within past 36 months. KB has received consulting/lectures/advisory board payment from AstraZeneca, Boehringer Ingelheim, Chiesi, Angelini and Sanofi within past 36 months. JZ has received COPD research funding from AstraZeneca within past 36 months, and received consulting/lectures/advisory boards payment from AstraZeneca, Angelini, Chiesi and Sanofi within past 36 months. MP a MK have nothing to disclose. The authors reports no other conflicts of interest related to this work. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SUPPLEMENTARY DATA

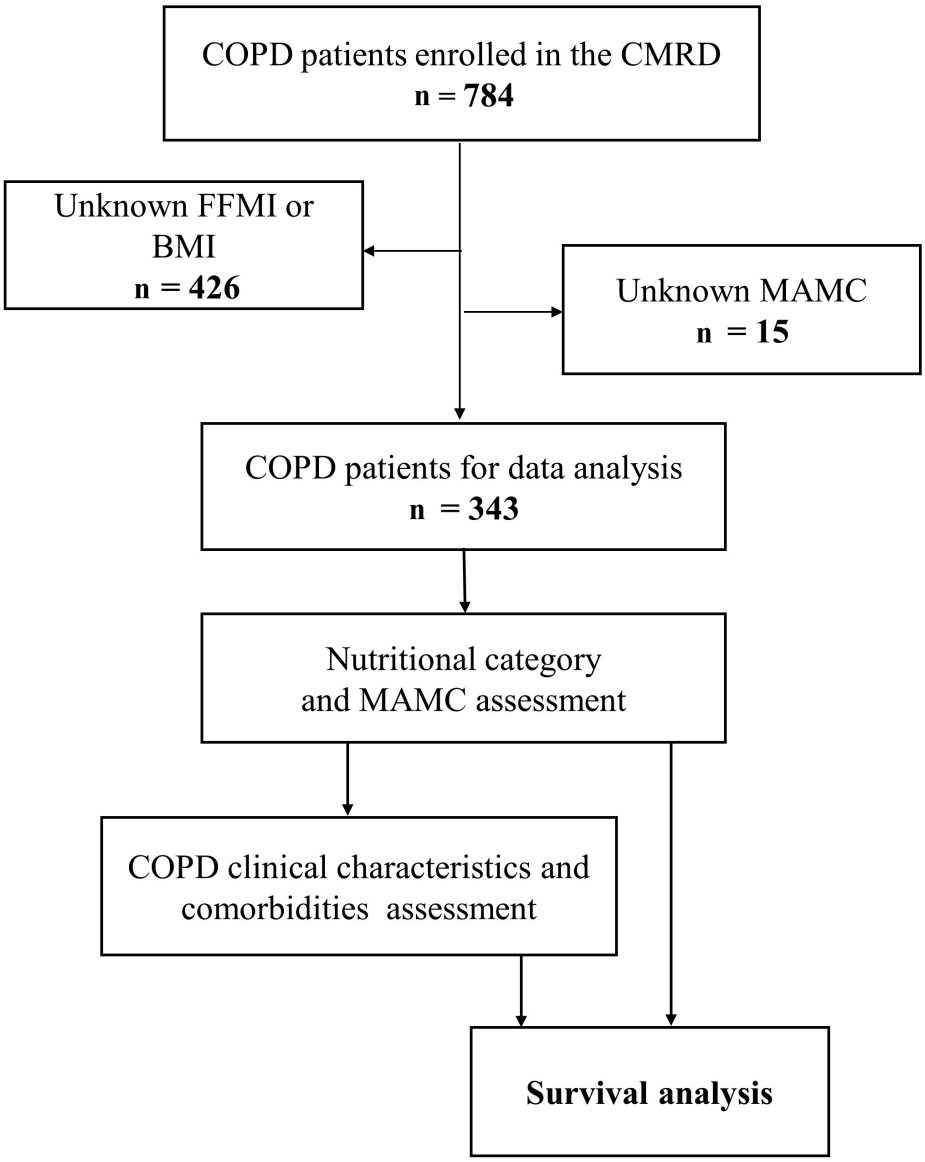
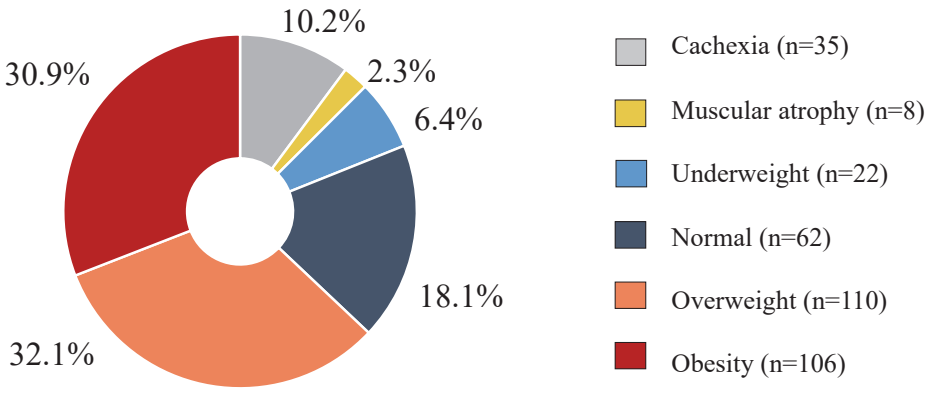


Fig. S1. Study design.

A. Nutritional categories according to FFMI and BMI, n=343.

FFMI	BMI			
	<21	21–25	25–30	>30
♂ < 16; ♀ < 15	Cachexia	Muscular atrophy	Muscular atrophy	Impossible
♂ ≥ 16; ♀ ≥ 15	Underweight	Normal	Overweight	Obesity



B. Muscle mass groups according to MAMC, n=343.

		Status						
		Physiological		Muscle loss		Significant muscle loss		
% of normal		100	90	80	70	60	50	40
MAMC	♂	25.5	23.0	20.0	18.0	15.0	12.5	10.0
	♀	23.0	21.0	18.5	16.0	14.0	11.5	9.0

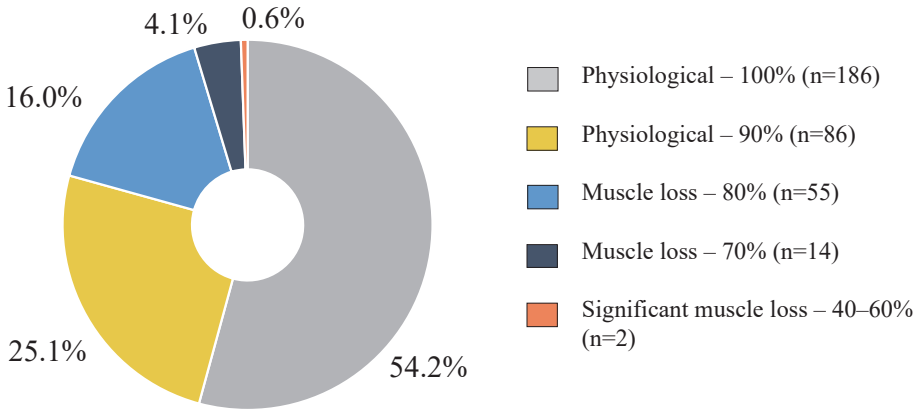


Fig. S2. Definition of nutritional categories by FFMI and BMI and muscle mass loss by MAMC and representation of patients in groups.
BMI, Body mass index; FFMI, Fat-free mass index; MAMC, Mid-arm muscle circumference.

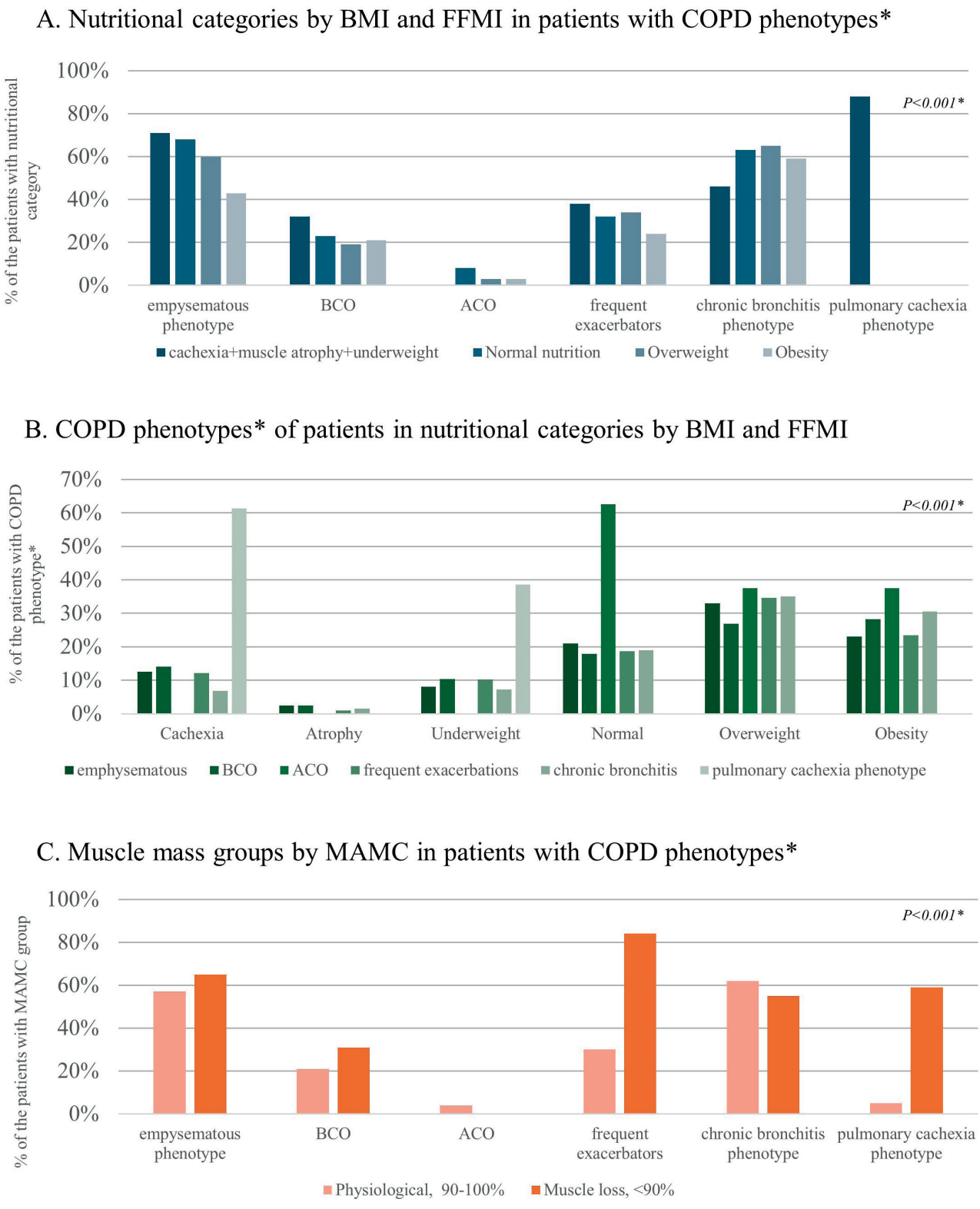
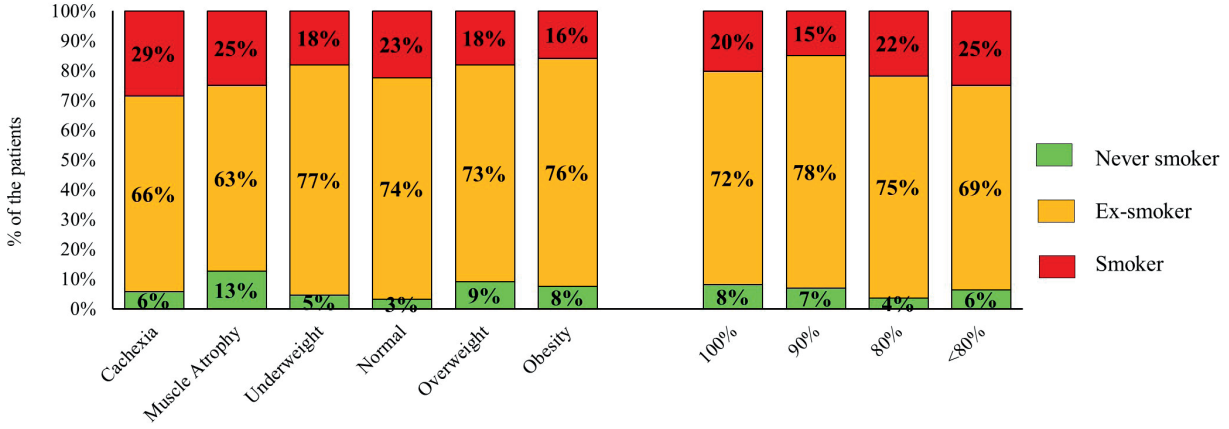


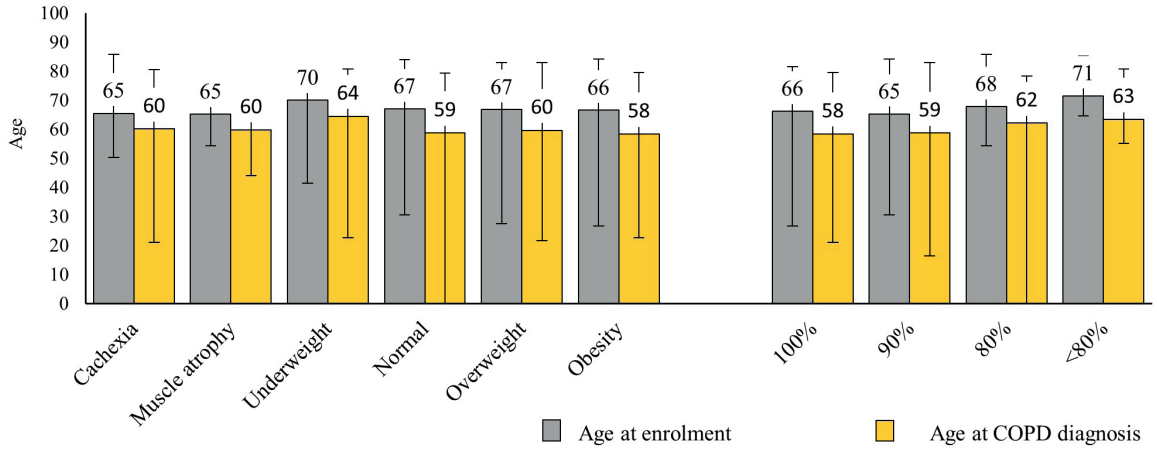
Fig. S3. Nutritional categories and COPD phenotypes*.
BMI, Body mass index; FFMI, Fat-free mass index; MAMC, Mid-arm muscle circumference;
*Clinical phenotypes according to the Czech National COPD Guidelines[19]:
ACO, Asthma and COPD overlap; BCO, Bronchiectasis and COPD overlap.
*Pearson's chi-squared test.

A. Smoking status in patients with the nutritional categories and groups by MAMC



Smoking status	Nutritional categories by BMI and FFMI							Muscle mass in % of physiological muscle mass by MAMC				
	Cachexia	Atrophy	Underweight	Normal	Overweight	Obesity	*P**	100%	90%	80%	<80%	*P**
Never smoker	2 (5.7%)	1 (12.5%)	1 (4.5%)	2 (3.2%)	10 (9.1%)	8 (7.5%)	0.652	15 (8.1%)	6 (7.0%)	2 (3.6%)	1 (6.3%)	0.787
Ex-smoker	23 (65.7%)	5 (62.5%)	17 (77.3%)	46 (74.2%)	80 (72.7%)	81 (76.4%)	0.789	133 (71.5%)	67 (77.9%)	41 (74.5%)	11 (68.8%)	0.692
Smoker	10 (28.6%)	2 (25.0%)	4 (18.2%)	14 (22.6%)	20 (18.2%)	17 (16.0%)	0.601	38 (20.4%)	13 (15.1%)	12 (21.8%)	4 (25.0%)	0.598

B. Age in patients with the nutritional categories and groups by MAMC



Age	Nutritional categories by BMI and FFMI							Muscle mass in % of physiological muscle mass by MAMC				
	Cachexia	Atrophy	Underweight	Normal	Overweight	Obesity	*P*#**	100%	90%	80%	<80%	*P*#**
Enrolment	65 (50–86)	65 (54–74)	70 (41–82)	67 (30–84)	67 (28–83)	66 (27–84)	0.320	66 (27–81)	65 (30–84)	68 (54–86)	71 (65–85)	**0.001**
Diagnosis	60 (21–80)	60 (44–65)	64 (23–81)	59 (0–79)	60 (22–83)	58 (23–79)	0.267	58 (21–79)	59 (16–83)	62 (0–78)	63 (55–81)	**0.006**

Fig. S4. Smoking status and age in the nutritional categories and groups by MAMC, n=343.
BMI, Body mass index; FFMI, Fat-free mass index; MAMC, Mid-arm muscle circumference.
*Fisher's exact test, #Kruskal-Wallis test.