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Heterogeneity in clinical characteristics and co-morbidities in dyspneic individuals with COPD GOLD D: Findings of the *DICES* trial

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Summary
Introduction: Chronic obstructive pulmonary disease (COPD) is a complex and heterogeneous respiratory disease with important extra-pulmonary features and comorbidities. The aim of this study was to assess clinical heterogeneity in a well-defined subgroup of individuals with COPD GOLD D, including possible gender differences.
Methods: Pulmonary function, arterial blood gases, exercise performance, quadriceps muscle function, problematic activities of daily life, dyspnea, health status and comorbidities have been assessed in 117 individuals with a MRC dyspnea grade 4/5 and COPD GOLD D entering pulmonary rehabilitation.
Results: A broad range of values were found for diffusion capacity, exercise capacity, quadriceps muscle function and health status. Indeed, the high coefficients of variation were found for these outcomes. Problematic activities of daily life as well as objectified comorbidities also varied to a great extent. Moreover, significant gender differences were found for exercise performance, lower-limb muscle function and various comorbidities.

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Conclusion: The current findings emphasize that COPD is a heterogeneous disease whose clinical presentation varies significantly, even in individuals with very severe COPD with the same degree of dyspnea and all classified as GOLD D.

Trial registration: NTR2322.

Introduction

Chronic obstructive pulmonary disease (COPD) is an important cause of morbidity, disability-adjusted life years and mortality worldwide.[1] Generally, a significant heterogeneity in symptoms, clinical characteristics and comorbidities exist in patients with COPD.[2–7] Besides the degree of airflow limitation, symptoms, exacerbations and comorbidities contribute to the overall severity in patients with COPD.[7–9] The latest GOLD document stratifies patients into four groups (i.e., A to D) based on a combined assessment, including the degree of airflow limitation, future exacerbation risk and the burden of disease.[9]

The Medical Research Council (MRC) scale is a simple, readily available office tool to grade dyspnea.[10] In the latest GOLD document, the modified MRC has been used to determine the burden of disease.[9] Generally, clinical characteristics and extra-pulmonary features of COPD are different after stratification for MRC dyspnea grade.[11–14] For example, COPD patients with MRC dyspnea grades 4/5 have an increased risk for ischemic electrocardiographic changes,[14] worse exercise performance, higher scores for anxiety and depression and worse disease-specific health status[12] as compared to those with lower MRC dyspnea grades. Moreover, during domestic activities of daily life COPD patients with MRC dyspnea grades 4 or 5 use a significantly higher proportion of their peak aerobic capacity and ventilation accompanied with higher task-related dyspnea scores.[13] So, MRC dyspnea grades 4/5 provide a rough indication of the clinical status of patients with COPD. However, anecdotal clinical experience suggests that COPD is a complex, heterogeneous disease whose clinical presentation varies significantly despite having the same degree of dyspnea. Moreover, multiple studies have found that women with COPD report higher (=worse) scores on the MRC dyspnea scale than men with COPD for the same degree of airflow limitation.[15–17] This suggests that individuals with COPD GOLD D will have a heterogeneous clinical presentation, despite belonging to the same GOLD group.

Therefore, we sought to characterize the heterogeneity of individuals with COPD with GOLD D, including possible gender differences.

Methods

Patients and setting

Individuals with COPD who were referred by their chest physician for an interdisciplinary pulmonary rehabilitation program at CIRO+ were recruited.[18] Individuals with COPD as the primary diagnosis[8] and a MRC dyspnea grade 4 or 5 were eligible.[19] As these are the baseline findings of the ***DICES*** trial (***D***yspneic ***I***ndividuals with ***C***OPD: ***E***lectrical stimulation or ***S***trength training), participants also needed to have quadriceps weakness, defined as a peak torque $\leq$80% of the predicted value.[20] Individuals with known neuromuscular diseases; hip, leg and/or knee disorders including metal implants; cardiac pacemaker and/or internal cardiac defibrillator were ineligible. The Medical Ethical Committee of the Maastricht University Medical Centre+ (MEC 09-3-072) approved this study, which conformed to the principles outlined in the World Medical Association declaration of Helsinki which was revised in Seoul.[21] Details of the trial were registered at www.trialregister.nl (NTR2322) before subject enrollment. All patients gave written informed consent to participate.

Assessments

Medical history

During the medical history, the number of patient-reported COPD exacerbations in the 12 months prior to assessment, the usage of long-term oxygen therapy (LTOT) and all respiratory and non-respiratory medications prescribed by secondary care respiratory physicians were routinely recorded.[22]

Pulmonary function and arterial blood gases

Post-bronchodilator forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were determined using spirometry (MasterScreen® Body, Carefusion, Houten, the Netherlands). Diffusing capacity for carbon monoxide (DL_{CO}) was determined using the single breath method. All values were related to reference values.[23] Arterial oxygen tension (PaO_2), arterial carbon dioxide tension ($PaCO_2$) were measured with a blood gas analyzer (GEM4000, Instrumentation Laboratory, Peachtree City, USA).

Exercise performance

A supervised symptom-limited cardiopulmonary incremental cycle test on an electrically, braked cycle ergometer (Carefusion, Houten, the Netherlands) was conducted, as described before.[24] Peak aerobic capacity (only in subjects without oxygen supplement, $n = 55$) and peak work rate were determined. A constant work-rate cycling endurance test was performed at 75% of the peak work rate.[25] Functional exercise capacity was measured using the six-minute walk test, which was performed twice.[26] The best 6-min walk distance (6MWD) was used for further analyses.

Quadriceps muscle function

Quadriceps muscle function (peak strength and endurance) was measured using a Biodex (Biodex System 4 Pro, Biodex Medical Systems, Inc., New York, USA).[24] The reliability of this method in patients with COPD has been demonstrated

previously.[27] Peak muscle strength (Newtonmeter; Nm) and muscle endurance (Total work; TW) were measured isokinetically. The participants performed thirty volitional maximal contractions at an angular velocity of 90° per second. The measurement was performed twice, and best values were used for further analyses.

Problematic activities of daily life

The COPM, a semi-structured interview, was used to assess problematic activities of daily life (ADLs).[28] Problematic ADLs were categorized into four domains: self-care, productivity, leisure and mobility.[11]

Dyspnea and health status

The Medical Research Council (MRC) dyspnea scale was used to assess symptoms of dyspnea.[19] Health status was measured with the St. George's Respiratory Questionnaire (SGRQ).[29] Scores can range from 0 (optimal) to 100 points (worst).

Comorbidities

The degree of self-reported comorbidities was measured using the Charlson comorbidity index.[30] Moreover, the following comorbidities were objectified, as described before[7]:

Body composition abnormalities

Body mass index (BMI, defined as body weight divided by squared height) and fat-free mass index ((FFMI), defined as fat free mass divided by squared height) were determined, and classified as obesity (BMI $\geq$ 30 kg/m^2), underweight (BMI $<$ 21 kg/m^2), and/or muscle wasting (FFMI $<$ 14.62 kg/m^2 in women and FFMI $<$17.05 kg/m^2 in men).[31] In addition, bone mineral density (BMD of the hip, lumbar spine and whole body region, expressed as T-scores) were determined using dual-energy X-ray absorptiometry.[32] If the lowest of the three T-scores was <-2.5, the subject was defined as osteoporotic.[33]

Symptoms of anxiety and depression

Symptoms of anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS).[34] Scores can range from 0 (optimal) to 21 points (worst). A score of 10 points or more was defined as increased symptoms of anxiety and/or depression.[3,34]

Hyperglycemia, anemia, dyslipidemia and systemic inflammation

Routinely, a post-absorptive venous blood sample was collected from the patients in the fasted state to analyze glucose, hemoglobin, triglycerides, high density lipoprotein (HDL) and creatinine.

A fasting glucose level $>$5.6 mmol/L was defined as hyperglycemia[35]; anemia was defined as a hemoglobin level $<$13 g/dL (8.1 mmol/L, men) or $<$12 g/dL (7.5 mmol/L, women)[36]; dyslipidemia was defined as a triglyceride level above 1.7 mmol/L or a HDL cholesterol level below 1.03 mmol/L (men) or below 1.29 mmol/L (women).[37]

Renal impairment

Renal function was established by the estimated glomerular filtration rate (eGFR), using the Cockroft-Gault formula.[38] Chronic kidney disease was defined as eGFR $<$60 ml/min, corresponding with stage 3 chronic kidney disease according to the National Kidney Foundation Kidney Disease Outcome Quality Initiative (NKF KDOQI) guidelines.[39]

Cardiovascular abnormalities

Peripheral blood pressure was measured three times with interval of 5 min, after 15 min of supine rest in early morning time. Mean values were calculated. Hypertension grade 1 or higher was based on cut-off values of $>$140 mmHg for systolic blood pressure and $>$90 mmHg for diastolic blood pressure.[40]

A resting ECG was obtained and the Cardiac Infarction Injury Score (CIIS) was scored by a cardiologist (NHMKU-L) blinded for medical history and outcome measures. CIIS is an ECG classification system that was developed as a diagnostic tool to determine the presence of myocardial infarctions. It is based on the power of certain electrocardiographic characteristics to discriminate between myocardial infarction patients and healthy individuals. These characteristics are weighted and combined into a single score.[41] Myocardial infarction was defined as a CIIS $\geq$20.[41]

Statistical analysis

All statistical analyses were performed using SPSS for Windows, Version 17.0.1 (SPSS, Inc., Chicago, Il, USA) and GraphPad Prism Version 4.03 (GraphPad Software, Inc., La Jolla, USA). Data were presented as mean $\pm$ standard deviation, as median and interquartile range, or as frequencies, as appropriate. Gender differences were assessed using the Student's *t*-test, χ^2 test or Mann–Whitney *U* test. We additionally used the coefficient of variation (the ratio of the standard deviation to the mean) to present the degree of variability. *A priori*, the level of significance was set at $<$0.05.

Results

Characteristics of whole sample

In total, 120 individuals with COPD fulfilled all inclusion criteria and consented to participate in the ***DICES*** trial. Nevertheless, three individuals with COPD GOLD B were excluded from the current analysis to focus specifically on individuals with GOLD D.

The remaining 117 individuals with GOLD D had severe to very severe COPD and an impaired diffusion capacity (Table 1). 52% of the patients used long-term oxygen therapy and 72% patients reported 1 or more exacerbations in the previous 12 months (Fig. 1). Various types of respiratory and non-respiratory medications were used (Table 1 of the Online-Supplement). On average, participants had a decreased exercise capacity (Table 2), lower-limb muscle dysfunction (Table 3), and a decreased health status (SGRQ

Table 1 General characteristics.

		Total sample $n = 117$	Men $n = 61$	Women $n = 56$	*P*-value
Age	years	64.7 ± 8.1 (0.13)	66.7 ± 8.3	62.6 ± 7.5	0.005
FEV_1	liters	0.84 ± 0.34 (0.40)	0.94 ± 0.38	0.72 ± 0.26	<0.000
FEV_1	%predicted	33 ± 13 (0.39)	31 ± 13	34 ± 13	0.254
FEV_1/VC max	%	31 ± 11 (0.35)	30 ± 12	33 ± 9	0.139
DL_{CO}	%predicted	41 ± 15 (0.37)	41 ± 16	41 ± 14	0.997
RV	%	201 ± 53 (0.26)	198 ± 58	204 ± 47	0.537
PaO_2	kPa	9.7 ± 1.6 (0.16)	9.9 ± 1.7	9.4 ± 1.5	0.079
$PaCO_2$	kPa	5.7 ± 1.2 (0.21)	5.5 ± 1.2	5.9 ± 1.2	0.108
SaO_2	%	95 ± 2 (0.02)	96 ± 2	95 ± 3	0.111
LTOT	%	52	48	57	0.301

Values expressed as mean ± SD (coefficient of variation) or percentages.
Abbreviations: GOLD = Global Initiative on Obstructive Lung Diseases; LTOT = long-term oxygen therapy; FEV_1 = forced expiratory volume in one second; VC max = maximum vital capacity; DL_{CO} = diffusion capacity of the lung for carbon monoxide; RV = residual volume; PaO_2 = resting arterial oxygen tension; $PaCO_2$ = resting arterial carbon dioxide tension; SaO_2 = resting arterial oxygen tension; kPa = kilopascal.

total score: 63.8 ± 13.2 points). Even though all participants reported a MRC dyspnea grade of 4/5 and GOLD D, the clinical characteristics showed a broad range of values (Fig. 2A–E). Indeed, peak work rate ranged from 4 to 68 W; the 6-min walk distance ranged from 22 to 544 m; health status ranged from 22 to 88 points; anxiety scores ranged from 1 to 19 points; and depression scores ranged from 1 to 18 points. Moreover, the coefficient of variation ranged from 0.52 for bone mineral density to 0.49 for cycle endurance time and HADS anxiety score. Moreover, 42 problematic activities of daily were reported, with walking, showering, and household activities as the most prevalent (see Online Supplement Tables 2 and 3 for all details). Finally, 87% of the participants scored ≥1 objectified comorbidities (Charlson comorbidity index score: 1.57 ± 0.82 points). Hyperglycaemia, low muscle mass, and symptoms of anxiety were most prevalent (Table 4; Fig. 3).

Men *versus* women

The degree of airflow limitation (% predicted), DL_{CO} and arterial blood gases were similar between men and women (Table 1). Peak work load and peak VO_2 (after correction for lower-limb muscle mass) and 6MWD expressed (% predicted) were significantly higher in women compared to men (all $p < 0.05$; Table 2). The performance and satisfaction scores for self-reported problematic ADLs on the COPM were similar between men and women (3.5 ± 1.7 *versus* 3.5 ± 1.9 points; and 3.0 ± 1.8 *versus* 3.1 ± 2.1 points, respectively). Women reported walking, household activities and showering to be to the most important problematic ADLs, while men reported walking, showering and stair climbing. Disease-specific health status (SGRQ total score: 65.0 ± 12.1 *versus* 62.6 ± 14.3 points, respectively), BMI and bone mineral density were not different between men and women (Table 3). Women had significantly higher symptom scores of anxiety ($p = 0.024$), and a higher proportion of obesity, dyslipidemia and renal impairment (Fig. 3).

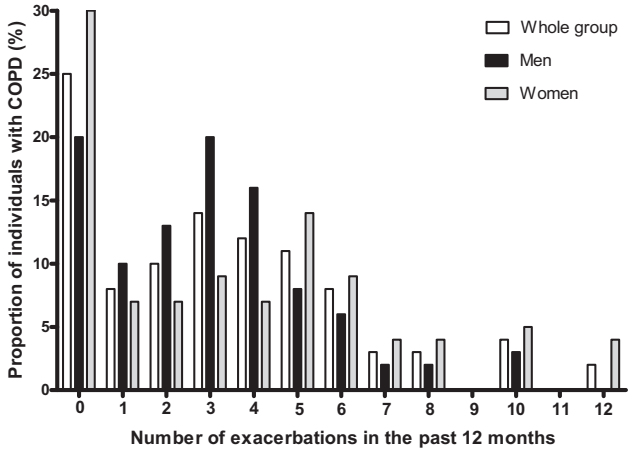

Figure 1 Number of exacerbations in the past 12 months.

Discussion

The current findings emphasize that COPD is a heterogeneous disease whose clinical presentation varies significantly, even in individuals with very severe COPD with the same degree of dyspnea and all classified as GOLD D. Moreover, significant gender differences were found for exercise performance, lower-limb muscle function and various comorbidities.

Previously, heterogeneity in clinical outcomes has been found after stratification for GOLD stage II to IV, suggesting that the degree of airflow limitation does not capture the clinical heterogeneity of COPD.[5,42] The current study shows a broad heterogeneity in exercise capacity, lower-limb muscle function, mood status, health status, exacerbations and comorbidities in individuals with COPD GOLD D and MRC dyspnea grade 4/5. The coefficient of variation for various clinical characteristics (i.e., FEV_1: 0.33 *versus* 0.39; 6MWD: 0.33 *versus* 0.31; and BMI: 0.22 *versus* 0.20[5]) seems comparable between the 2007 GOLD classification (based solely on degree of airflow limitation)[8] and the 2013 GOLD classification.[43] This suggests that the MRC dyspnea scale as

Table 2 Exercise performance.

Cardiopulmonary exercise test		Total	Men	Women	*P*-value
		$n = 101$	$n = 53$	$n = 48$	
Peak load	Watts	44 ± 13 (0.30)	48 ± 10	41 ± 14	0.006
Peak load/FFM	Watts/kg	0.96 ± 0.28 (0.29)	0.90 ± 0.21	1.03 ± 0.33	0.024
Peak VO_2	ml/min	820 ± 159 (0.19)	834 ± 153	802 ± 168	0.467
Peak VO_2/FFM	ml/min/kg	17.8 ± 4.0 (0.22)	16.0 ± 2.8	20.3 ± 4.0	<0.001
Constant work rate test		$n = 93$	$n = 51$	$n = 42$	
Cycle time	seconds	192 ± 95 (0.49)	199 ± 108	184 ± 76	0.468
6 min walk test		$n = 117$	$n = 61$	$n = 56$	
6MWD	meters	322 ± 92 (0.29)	314 ± 87	331 ± 97	0.321
6MWD <350 m	%	56	62	48	0.127
6MWD	%predicted	52 ± 16 (0.31)	47 ± 14	57 ± 17	0.002

Values expressed as mean ± SD (coefficient of variation) or percentages.
Abbreviations: peak VO_2 = peak oxygen uptake in ml/min.; peak VE = peak minute ventilation in liters; peak HR = peak heart rate; bpm = beats per minute; %MVV = percentage maximal voluntary ventilation; $tSaO_2$ = transcutaneous oxygen saturation; 6MWD = 6-min walk distance; kg = kilogram; min = minute; ml = milliliter.

well as the new GOLD classification may provide clinicians with a global impression of the clinical status of patients with COPD. However, patients with COPD need to be assessed individually to be able to provide a patient-tailored comprehensive COPD management program. Therefore, it seems reasonable to state that the new GOLD classification[9] cannot be the basis for personalized COPD management. The variability in clinical characteristics and comorbidities in this group of individuals with COPD GOLD D may partially explain the odds of survival in this subgroup.[44,45] Obviously, this needs to be corroborated prospectively.

Multimorbidity occurs frequently in the general population.[46] Comorbidities occur also frequently in patients with COPD entering pulmonary rehabilitation.[7,48] Comparable frequencies of comorbidities have been found in the current study (Fig. 3). This emphasizes again the complexity of patients with COPD entering pulmonary rehabilitation. For example, patients with COPD with increased symptoms of anxiety and/or depression have worse prognosis.[49,50] Moreover, individuals with COPD who also had osteoporosis at baseline had worst response on the 6-min walk test following pulmonary rehabilitation.[51]

Even though the degree of dyspnea, the degree of airflow limitation and the new GOLD group were similar between women and men in the present study, still significant gender differences were found. The female patients had a better exercise performance compared to men, after adjustment for FFM (Table 2). Even though the women were significantly younger (mean difference: 3 years), this does not seem to explain the mean difference in peak aerobic capacity (4.3 ml/min/kg FFM; 27%). Whether and to what extent this difference is due to changes in muscle structure and function, neurological function,[52] cardiovascular function,[53] hormonal exposures, health behaviors[54] or a combination thereof remains to be determined.

Women had a higher prevalence of obesity, anxiety, dyslipidemia and renal impairment. This suggests that

Table 3 Body composition and muscle function.

Body composition		Total	Men	Women	*P*-value
		$n = 117$	$n = 61$	$n = 56$	
BMI	kg/m^2	24.7 ± 5.0 (0.20)	24.1 ± 4.7	25.3 ± 5.2	0.217
FFMI	kg/m^2	16.5 ± 2.0 (0.12)	17.4 ± 1.9	15.5 ± 1.6	<0.001
Bone mineral density	T-score	−2.1 ± 1.1 (−0.52)	−2.0 ± 1.3	−2.1 ± 0.9	0.656
Isokinetic quadriceps muscle function		$n = 117$	$n = 61$	$n = 56$	
Peak torque	Nm	76.0 ± 26.4 (0.35)	86.6 ± 27.7	64.5 ± 19.3	<0.001
Peak torque	%predicted	54 ± 16 (0.30)	51 ± 16	57 ± 16	0.075
Peak torque/FFM	Nm/kg	1.6 ± 0.5 (0.31)	1.6 ± 0.5	1.6 ± 0.5	0.810
Total work	Joules	1175 ± 480 (0.41)	1308 ± 542	1029 ± 353	0.001
Total work/FFM	Joules/kg	25.2 ± 8.9 (0.35)	24.7 ± 9.4	25.9 ± 8.3	0.468

Values expressed as mean ± SD (coefficient of variation).
Abbreviations: BMI = body mass index; FFM = fat-free mass; FFMI = fat-free mass index; kg = kilogram; m^2 = squared meter; Nm = newtonmeter.

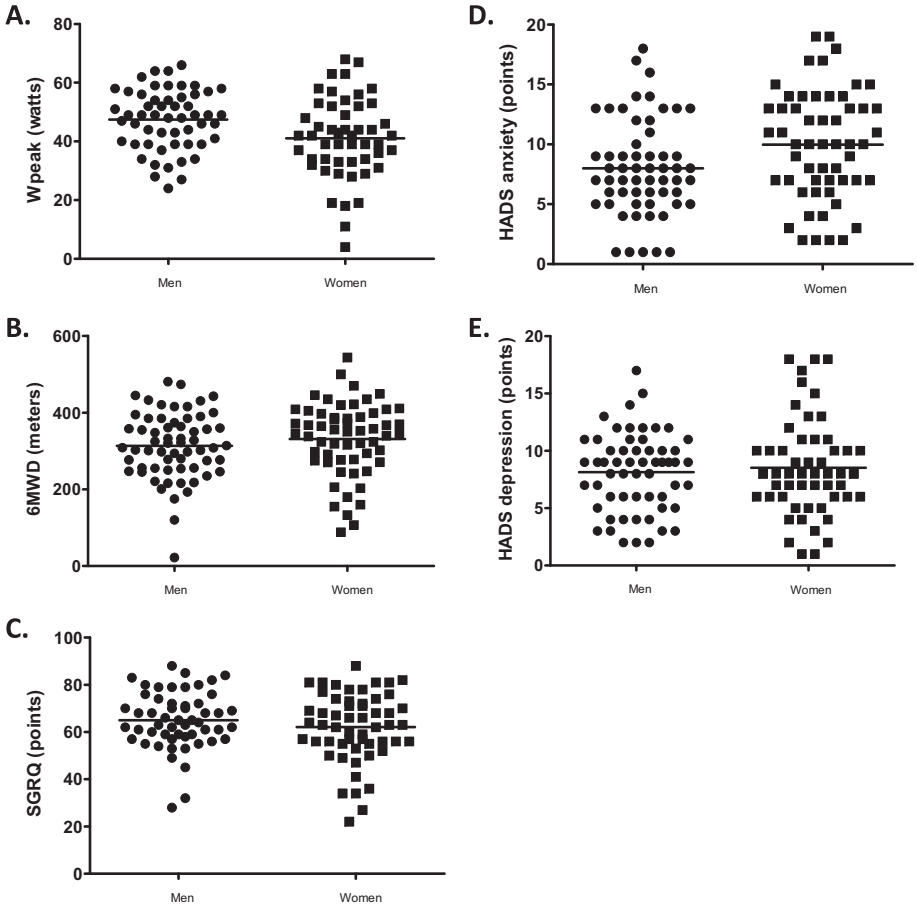

Figure 2 Heterogeneity in clinical characteristics. The distribution is shown for men (circles) and women (squares). The median is shown with a black line. A: Wpeak (peak work rate); B: 6MWD (6-min walk test); C: SGRQ (health status); D: HADS anxiety; E: HADS depression.

gender-specific patterns of comorbidities may exist in COPD. Whether and to what extent gender-differences in comorbidities may contribute to the overall severity of COPD patients remains to be determined. At first sight, health status does not seem to be influenced by these differences as mean SGRQ scores were similar between women and men in the present study.

Obviously, the inclusion criteria of the ***DICES*** trial limits the external validity of the present findings. Nevertheless, previous studies have already shown a large heterogeneity in clinical outcomes, like 6MWD, after stratification for MRC dyspnea grade or GOLD stage.[5,12] Therefore, the authors believe that the heterogeneous clinical presentation of COPD is not limited to individuals with MRC 4/5 and COPD GOLD D.

Table 4 Mood and health status.

HADS		Total	Men	Women	*P*-value
		$n = 110$	$n = 57$	$n = 53$	
Anxiety	points	8.9 ± 4.4 (0.49)	8.0 ± 4.0	9.9 ± 4.6	0.024
Anxiety ≥10 points	%	38	25	52	0.003
Depression	points	8.4 ± 3.8 (0.45)	8.1 ± 3.5	8.6 ± 4.2	0.497
Depression ≥10 points	%	32	31	34	0.749
SGRQ		$n = 109$	$n = 55$	$n = 54$	
Symptoms	points	66.3 ± 16.9 (0.25)	66.5 ± 16.3	66.2 ± 17.7	0.939
Activity	points	81.7 ± 16.4 (0.20)	83.3 ± 16.4	80.1 ± 16.4	0.321
Impact	points	53.1 ± 17.5 (0.33)	54.3 ± 15.8	51.9 ± 19.2	0.477
Total score	points	63.9 ± 13.2 (0.21)	65.0 ± 12.0	62.8 ± 14.3	0.388

Values expressed as mean ± SD (coefficient of variation) or percentages.
Abbreviations: HADS = Hospital Anxiety and Depression Scale; SGRQ = St. George's Respiratory Questionnaire.

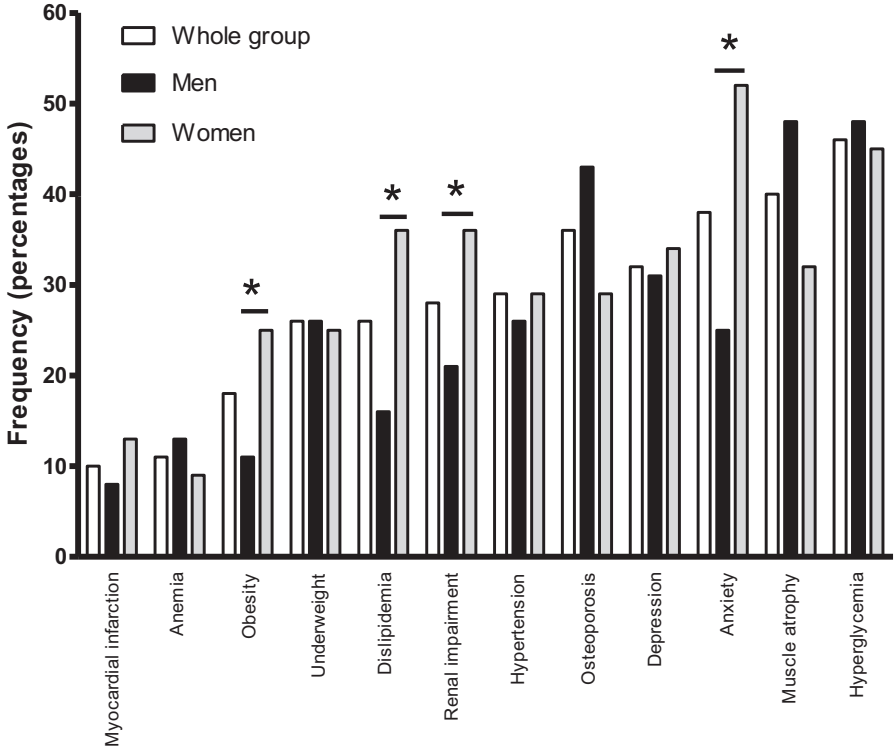

Figure 3 Prevalence of objectified comorbidities.

To conclude, COPD patients with severe dyspnea and classified as high risk with more symptoms according to the new GOLD classification have a highly variable clinical presentation. Moreover, this heterogeneity remains after stratification for sex. Finally, clinically relevant gender-differences exist, although the degree of dyspnea and the degree of airflow limitation were comparable between women and men. These findings emphasize that patients with COPD entering a pulmonary rehabilitation program need to be assessed interdisciplinary and individually to be able to provide a patient-tailored program. Moreover, the new GOLD classification seems inappropriate to capture the clinical heterogeneity of patients with COPD.

Declaration of interest

The authors do not have any conflict of interest with the contents of the present manuscript. The authors are responsible for the content and the writing of this paper.

Conflict of interest statement

The authors listed on the title page do not have possible conflicts of interest, sources of financial support, stock ownership, paid expert testimony, honoraria, corporate involvement, patent holdings, etc. which are related with the results of the present study.

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Appendix A. Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.rmed.2013.04.020.

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