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Evaluation of Exacerbation and Symptom-Free Time in Patients with COPD

Mirthe I. de Vries[a,b], Tanja W. Effing[c,d], Job van der Palen[e,f], Jade Schrijver[b,f], Paul van der Valk[b] and Anke Lenferink[a,b,g]

[a]Health Technology and Services Research, Faculty of Behavioral, Management and Social Sciences, Technical Medical Centre, University of Twente, Enschede, Netherlands; [b]Department of Pulmonary Medicine, Medisch Spectrum Twente, Enschede, Netherlands; [c]College of Medicine and Public Health, Flinders University, Adelaide, Australia; [d]School of Psychology, Faculty of Health and Medical Sciences, University of Adelaide, Adelaide, Australia; [e]Medical School Twente, Medisch Spectrum Twente, Enschede, Netherlands; [f]Cognition, Data and Education, Faculty of Behavioral, Management and Social Sciences, University of Twente, Enschede, Netherlands; [g]Clinical Research Centre, Rijnstate Hospital, Arnhem, Netherlands

ABSTRACT

In clinical practice, clinicians mainly focus on Chronic Obstructive Pulmonary Disease (COPD) exacerbations and symptoms, while patients may prefer to evaluate periods free of COPD exacerbations and deteriorated symptoms. The latter would suit the positive health approach that centralizes people and their beliefs. We aimed to identify patient characteristics and health outcomes relating to: 1) COPD exacerbation-free days; 2) days with no more symptoms than usual; and 3) combined COPD exacerbation and comorbid flare-up-free days (i.e. chronic heart failure, anxiety, depression flare-ups) using negative binomial regression analyzes. Data were obtained from two self-management intervention trials including COPD patients with and without comorbidities. 313 patients (mean age 66.0 years, 63.6% male, 68.7% comorbidity) were included. Better baseline chronic respiratory questionnaire (CRQ) fatigue (incidence rate ratio (IRR) = 1.03 (95% CI 1.01–1.05), $p = 0.02$) and mastery scores (IRR = 1.03 (95% CI 1.00–1.06), $p = 0.04$) and fewer courses of antibiotics (IRR = 0.95 (95% CI 0.94–0.96), $p < 0.01$) were related to more COPD exacerbation-free days. Additionally, better baseline CRQ fatigue (IRR = 1.05 (95% CI 1.00–1.10), $p = 0.04$) and mastery scores (IRR = 1.06 (95% CI 1.00–1.12), $p = 0.04$), fewer courses of antibiotics (IRR = 0.94 (95% CI 0.91–0.96), $p < 0.01$), and improved CRQ dyspnea scores over 12 months of follow-up (IRR = 1.07 (95% CI 1.01–1.12), $p < 0.01$) were correlated to more days free of deteriorated symptoms. Less baseline dyspnea (modified Medical Research Council score) (IRR = 0.95 (95% CI 0.92–0.98), $p < 0.01$) and fewer courses of antibiotics (IRR = 0.94 (95% CI 0.93–0.95), $p < 0.01$) were associated with more combined COPD exacerbation and comorbid flare-up-free days. Healthcare professionals should be aware that less fatigue and better mastering of COPD relate to more exacerbation and symptom-free time in COPD patients.

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is the third leading cause of death worldwide [1]. COPD is a progressive lung condition characterized by persistent airflow obstruction and respiratory symptoms, such as dyspnea, cough, and sputum production [2]. In addition to daily symptom burden, patients suffer from episodes of deterioration in respiratory symptoms that persist for consecutive days, called exacerbations [3,4]. COPD exacerbations differ between and within COPD patients in terms of frequency, severity, symptoms, and recovery time [5,6]. Some of these differences may be explained by the stage of COPD [7] or a difference in the trigger of exacerbations (e.g. smoking, air pollution, viral infection) [3]. COPD exacerbations lead to higher morbidity, mortality, hospitalizations, reduced health-related quality of life (HRQoL), declined lung function, and increased healthcare costs [4,8–11].

Many COPD patients have been diagnosed with comorbidities, such as cardiovascular, metabolic, and/or psychological disorders [12–16]. COPD shares common risk factors (e.g. increasing age, smoking) and can attribute to (further) development of comorbidities (e.g. anxiety, heart failure) [15–17]. Comorbid flare-ups (e.g. dyspnea-, anxiety-, depression-related symptoms) can trigger, but also prolong COPD exacerbations [16,18–21]. In general, the presence of comorbidities increases patients' symptom burden [22] and the risk of hospitalizations and mortality [12–16].

Clinicians' goals often do not liaison well with patients' priorities in disease management [23,24]. Healthcare professionals might underestimate how symptoms affect patients' daily life as they mainly focus on reducing

CONTACT Anke Lenferink a.lenferink@utwente.nl Technical Medical Centre, Faculty of Behavioral, Management and Social Sciences, Health Technology and Services Research, University of Twente, P.O. Box 217, Enschede, 7500 AE, Netherlands.

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symptoms, frequency, and duration of COPD exacerbations to diminish the negative consequences on patients' health status [25,26]. From the patients' perspective, it may be more appropriate to assess the period they are free from deteriorated symptoms and COPD exacerbations (i.e. COPD exacerbation-free time). In this broader approach of positive health [27,28], not the disease, but patients and their interpretation of meaningful lives are the focus of attention. This may help patients to focus on what is still possible in daily life while coping with COPD [25,29] and may improve HRQoL [22,30].

To our knowledge, only one study has evaluated COPD exacerbation-free time, showing that COPD exacerbation-free weeks were related to patient characteristics (e.g. dyspnea severity) and health outcomes (e.g. HRQoL) [31]. However, because COPD exacerbation-free time data was only retrospectively collected every two weeks, information may have been lost [31]. Daily symptom registration could provide more accurate information about COPD exacerbations and symptoms. With extracted data from two previously conducted randomized controlled trials [32,33] in which daily symptom data were collected, we explored how COPD exacerbation-free days and days with no more symptoms than usual relate to patient characteristics and health outcomes. In addition, we investigated how combined COPD exacerbation and comorbid flare-up-free days related to patient characteristics and health outcomes in a subsample of COPD patients with comorbidities [33]. Based on previous evidence [31], we hypothesized that COPD exacerbation-free days would be moderately correlated to patient characteristics and health outcomes, but we expected to find even stronger associations regarding the number of days with no more symptoms than usual and combined COPD exacerbation and comorbid flare-up-free days with patient characteristics and health outcomes.

Methods

Study design

Secondary analyzes were performed on extracted data from two randomized controlled trials, the COPE-II (2004–2006) [32] and COPE-III study (2012–2016) [33], in which the effectiveness of self-treatment interventions including COPD exacerbation action plans were compared with control groups over a 12-month follow-up period [32,33]. Both COPE studies were approved by the Medical Ethical Committee Twente (02-04 and NL39516.044.12). The COPE-III study was also approved by the Southern Adelaide Clinical Human Research Ethics Committee (37-12). The COPE-II study was registered in the Netherlands Trial Registry (NTR325) and the COPE-III study in the public Australian New Zealand Clinical Trials Registry (ACTRN12612000514808). All patients gave written informed consent prior to study participation. For more detailed information regarding both COPE studies, we refer to previous publications [32–34].

Population

In the current analyzes, data of the COPE-II [32] and COPE-III study [33] were combined. Most in- and exclusion criteria of the two studies were comparable. However, whereas patients with severe comorbidities were excluded from the COPE-II study [32], COPE-III patients could only be included when they had at least one comorbidity (Ischemic Heart Disease (IHD), Chronic Heart Failure (CHF), Diabetes Mellitus (DM), anxiety, depression) [33,34].

At inclusion, all patients received a "what are my 'usual' symptoms" card that described their COPD symptom levels in a stable health state [32,33]. In the COPE-III study, patients were also asked to report the "usual" symptoms of individually diagnosed comorbidities [33,34]. Patients were educated in completing their daily diaries in which they had to report whether their symptoms were normal, slightly increased, or significantly increased compared to their usual symptoms in the last 24 h [32–34]. The daily symptom diaries were used to establish whether a COPD exacerbation had occurred (Table 1) [32,33]. Patients allocated to the self-treatment intervention group learned to monitor day-to-day symptom fluctuations and when to start self-treatment according to their tailored written exacerbation action plan [32,33].

Patients had to complete at least 25% of their daily diaries throughout the 12-month follow-up to be included in the current analysis.

Outcomes

Primary outcomes were as follows: (1) the number of COPD exacerbation-free days per patient per year; and (2) the number of days with no more symptoms than usual per patient per year. COPD exacerbation-free days were defined as the inverse of the number of COPD exacerbation days per patient per year. Days with no more symptoms than usual were determined by summing up the number of days patients indicated no negative change in symptoms in their daily symptom diaries [32,33]. The secondary outcome was the combined number of COPD exacerbation and comorbid flare-up-free days per patient per year. This outcome could only be obtained for the subsample of patients with comorbidities (COPE-III patients). For definitions of a COPD exacerbation and comorbid flare-up (i.e. CHF, anxiety, and depression) see Table 1.

The health outcomes used in the analyzes as independent variables were prospectively measured over a 12-month follow-up period in both the COPE-II [32] and COPE-III study [33]: exacerbation outcomes, healthcare use, medication use, dyspnea, anxiety, and depression.

Missing days

Missing diary data were proportionally imputed to enable calculating the primary and secondary outcomes. To illustrate, if a patient experienced 275 COPD exacerbation-free days over 300 days of follow-up, this was considered 335 COPD exacerbation-free days ((275/300)*365) over 365 days.

Table 1. Definition of a COPD exacerbation and comorbid flare-up.[a]

	Definition
COPD exacerbation	Onset was defined as "a significant negative change in two major symptoms (breathlessness, sputum production, sputum colour) or one major and one minor symptom (cough, wheeze, running nose, sore throat, fever (>38.5°)) from baseline, for at least two consecutive days." Recovery was defined as the first day of: 1) three successive days that the patient has returned to his usual health state; or 2) seven consecutive days on which the patient continuously reports no or only a slight increase in symptoms compared to baseline, with no fever or change in sputum colour [32–34].
Chronic Heart Failure flare-up	Onset was defined as a "clear negative change in at least one symptom (fluid retention: weight, swelling of ankles or abdomen, wake up at night short of breath) from baseline, for at least two consecutive days." The last day was defined as the first day of: 1) three consecutive successive days that the patient has returned to his usual baseline cardiac health state; 2) seven consecutive days on which patients continuously reported no or only a slightly increase of CHF symptoms compared to baseline [33,34].
Anxiety flare-up	Onset was defined as a "clear negative change in anxiety symptoms from baseline, for at least five consecutive days." The last day of the flare-up was defined as the first day of: 1) five consecutive successive days that the patient has returned to his usual baseline anxiety health state; 2) seven consecutive days on which patients continuously reported no or only a slightly increase of anxiety symptoms compared to baseline [33,34].
Depression flare-up	Onset was defined as a "clear negative change in depression symptoms from baseline, for at least five consecutive days." The last day of the flare-up was defined as the first day of: 1) five consecutive successive days that the patient has returned to his usual baseline depression health state; 2) seven consecutive days on which patients continuously reported no or only a slightly increase of depression symptoms compared to baseline [33,34].

Abbreviations: COPD = Chronic Obstructive Pulmonary Disease; CHF = Chronic Heart Failure.

[a]To be eligible for inclusion, COPE-III patients had to have at least one comorbidity (Ischemic Heart Disease (IHD), Chronic Heart Failure, Diabetes Mellitus (DM), anxiety, depression) [33,34]. The COPE-III study data [33] did however not provide insight in flare-ups of IHD and DM because: 1) changes in IHD-related symptoms required immediate action (because of safety) and were therefore seen as a once-off event and not as a flare-up; 2) actions for DM were only directed during medication treatment of a COPD exacerbation and no further DM diary data were collected, so no information regarding DM flare-ups could be extracted.

Statistical analyzes

Analyzes were conducted using IBM SPSS Statistics 26 software with $p < 0.05$ considered to be statistically significant. The normality of the data was assessed visually, using a histogram and Q-Q plot. To detect differences between COPE-II and COPE-III populations, chi-square tests were used for categorical variables, and independent *t*-tests or Mann–Whitney *U* tests for continuous variables. Negative binomial regression models were used to explore patient characteristics and health outcomes that related to over-dispersed primary and secondary outcomes. Potential relationships were selected by univariate regression analysis ($p < 0.15$). Multicollinearity ($r > 0.7$) was prevented by selecting the best-fitting variable based on log likelihood. Subsequently, selected variables were included in negative binomial regression models. Dominant variables were identified by backward elimination based on *p*-value ($p < 0.05$). The patient intervention group allocation was always kept in the model [32,33].

Sensitivity analyzes were conducted by only including patients who completed the 12-month follow-up diary data (173 (55.3%) patients: 98 (69.0%) COPE-II and 75 (43.9%) COPE-III patients).

Results

Of the 343 patients included in the COPE-II and COPE-III studies [32,33], 313 (91.3%) had 25% of their 12-month follow-up data complete and could be included. Of these, 140 (44.7%) patients had missing diary data with a median of 31.5 (12.3–92.8) missing days. 158 (50.5%) patients were assigned to the self-treatment intervention and 155 (49.5%) to the control group [32,33]. Patient characteristics of the included patients are reported in Table 2. The COPE-II and COPE-III populations differed significantly, except for sex, FEV_1, and CRQ dyspnea score.

Health outcomes are presented in Table 3, with the mMRC, CRQ, and HADS scores reported as the difference between baseline and 12-month follow-up score. The COPE-II population had more frequent and longer durations of COPD exacerbations than the COPE-III population. In addition, patients in the COPE-III study had significantly more hospitalization days and used less courses of corticosteroids and antibiotics compared to patients in the COPE-II study. The change in CRQ dyspnea score after 12-month follow-up was significantly different between the COPE populations. Whereas in the COPE-II population CRQ dyspnea scores increased, indicating less severe dyspnea, these scores decreased in the COPE-III population, suggesting more severe dyspnea.

The primary and secondary outcomes are shown in Table 4. The COPE-III population had significantly more COPD exacerbation-free days than the COPE-II population.

Table 5 shows patient characteristics that were related to COPD exacerbation-free days and days with no more symptoms than usual for all included patients, and the combined number of COPD exacerbation and comorbid flare-up-free days for the subsample of patients with comorbidities (COPE-III patients).

We found that having no comorbidities, and better baseline CRQ fatigue and mastery scores were significantly related to more COPD exacerbation-free days.

Better baseline CRQ fatigue and mastery scores were significantly associated with more days with no more symptoms than usual.

In the COPE-III population [33], less severe dyspnea was significantly correlated to more combined COPD exacerbation and comorbid flare-up-free days.

Table 2. Patient characteristics measured at baseline.

	Combined group ($n = 313$)	COPE-II ($n = 142$)	COPE-III ($n = 171$)	p-value
Age (years)	66.0 (±8.6)	63.4 (±7.9)	68.2 (±8.5)	<0.01*
Men	199 (63.6%)	84 (59.2%)	115 (67.3%)	0.14
Smoker	79 (25.2%)	47 (33.1%)	32 (18.7%)	<0.01*
Body mass index[a]	28.1 (±5.9)	26.6 (±4.7)	29.4 (±6.4)	<0.01*
COPD classification[a]				<0.01*
GOLD I	6 (1.9%)	6 (4.3%)	0 (0%)	
GOLD II	156 (50.0%)	60 (42.6%)	96 (56.1%)	
GOLD III	124 (39.7%)	59 (41.8%)	65 (38.0%)	
GOLD IV	26 (8.3%)	16 (11.3%)	10 (5.9%)	
FEV_1 (l)[a]	1.42 (±0.52)	1.42 (±0.53)	1.41 (±0.52)	0.84
FEV_1 (%)	51.2 (±15.5)	50.2 (±15.7)	52.0 (±15.3)	0.30
FEV_1/FVC	46.6 (±13.1)	44.2 (±12.2)	48.5 (±13.5)	<0.01*
mMRC dyspnea score[b]	1.74 (±1.13)	1.32 (±1.10)	2.09 (±1.03)	<0.01*
HRQoL domains (CRQ)				
Emotional functioning	4.88 (±1.14)	5.05 (±1.10)	4.74 (±1.15)	0.02*
Mastery	5.11 (±1.14)	5.35 (±1.11)	4.91 (±1.13)	<0.01*
Dyspnea	4.35 (±1.42)	4.50 (±1.42)	4.23 (±1.40)	0.08
Fatigue	4.05 (±1.27)	4.35 (±1.28)	3.80 (±1.21)	<0.01*
HADS domains[a]				
Anxiety	5.80 (±4.02)	4.71 (±3.70)	6.70 (±4.07)	<0.01*
Depression	5.63 (±3.94)	4.53 (±3.76)	6.53 (±3.87)	<0.01*
Comorbidities	215 (68.7%)	44 (31.0%)	171 (100%)	<0.01*
Cardiovascular disease[c]	137 (43.8%)	30 (21.1%)	107 (62.6%)	<0.01*
Ischaemic heart disease	NA	ND	80 (46.8%)	
Chronic heart failure	NA	ND	40 (23.4%)	
Anxiety[d]	51 (16.3%)	15 (10.6%)	36 (21.1%)	0.01*
Based on HADS	45 (14.4%)	15 (10.6%)	30 (17.5%)	
Active treatment	NA	ND	6 (3.5%)	
Depression[d]	60 (19.2%)	13 (9.2%)	47 (27.5%)	<0.01*
Based on HADS	42 (13.4%)	13 (9.2%)	29 (17.0%)	
Active treatment	NA	ND	18 (10.5%)	
Diabetes mellitus	NA	ND	63 (36.8%)	NA
Type 1	NA	ND	2 (1.2%)	
Type 2	NA	ND	60 (35.1%)	
Glucocorticoid-induced	NA	ND	1 (0.6%)	

Data are presented as mean (±standard deviation (SD)) or number (%). Abbreviations: COPD = Chronic Obstructive Pulmonary Disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease [1]; FEV_1=forced expiratory volume in 1 s; FVC = forced vital capacity; mMRC = modified Medical Research Council [35]; HRQoL = Health-related quality of life; CRQ = Chronic Respiratory Questionnaire [36]; HADS = Hospital Anxiety and Depression Scale [37]; NA = not applicable; ND = not documented.

*Significantly different ($p < 0.05$) between the COPE-II and COPE-III populations.

[a]Body mass index, COPD GOLD classification score, FEV_1 (%), and HADS score were missing for one patient (0.32%).

[b]MRC dyspnea scores (range 1 to 5) as used in COPE-II [32] were converted to mMRC scores (range 0 to 4).

[c]Patients with a cardiovascular disease could be diagnosed with IHD, CHF, anomalies in cardiac action potentials, myocardial infarction, and/or arrhythmia.

[d]All patients were diagnosed with anxiety and/or depression based on HADS scores (≥11) [32–34]. COPE-III patients could also have a clinical diagnosis if actively treated for anxiety and/or depression at the time of inclusion [33,34].

Table 3. Changes in health outcomes after 12 months of follow-up compared to baseline.

	Combined group ($n = 313$)	COPE-II ($n = 142$)	COPE-III ($n = 171$)	p-value
COPD exacerbations				
Frequency (patient/year)	2 (1–4)	3 (1–5)	1 (0–4)	<0.01*
Days (patient/year)	22 (4–51)	32 (11–67.5)	13 (0–39)	<0.01*
Duration in days (exacerbation/patient/year)	8 (3–13.5)	10.7 (6–14.5)	6.5 (0–11)	<0.01*
All-cause hospitalizations	86 (27.5%)	26 (18.3%)	60 (35.1%)	<0.01*
Frequency (patient/year)	0 (0–1)	0 (0–0)	0 (0–1)	<0.01*
Days (patient/year)	0 (0–3.5)	0 (0–0)	0 (0–6)	<0.01*
Duration in days (hospitalization/patient/year)	0 (0–3)	0 (0–0)	0 (0–4.7)	<0.01*
Medication				
Self-reported courses of Prednisolone	1 (0–3)	2 (1–4)	1 (0–3)	<0.01*
Self-reported courses of antibiotics	1 (0–3)	1 (0–3)	0 (0–2)	<0.01*
mMRC dyspnea score[a,b]	0.07 (±1.6)	−0.05 (±1.24)	0.17 (±0.87)	0.10
HRQoL domains (CRQ)[b]				
Emotional functioning	0.13 (±0.98)	0.15 (±0.97)	0.11 (±0.99)	0.79
Mastery	0.25 (±0.94)	0.27 (±0.94)	0.25 (±0.95)	0.73
Dyspnea	0 (±1.07)	0.16 (±1.04)	−0.14 (±1.08)	0.02*
Fatigue	0.07 (±1.14)	0.12 (±1.33)	0.03 (±0.94)	0.54
HADS domains[b]				
Anxiety	−0.84 (±3.08)	−0.66 (±2.84)	−0.99 (±3.27)	0.36
Depression	−0.49 (±2.65)	−0.55 (±2.63)	−0.44 (±2.68)	0.73

Data are presented in median (interquartile range (IQR)), mean (±SD) or number (%). Abbreviations: COPD = Chronic Obstructive Pulmonary Disease; ND = not documented; mMRC = modified Medical Research Council [35]; HRQoL = Health-related quality of life; CRQ = Chronic Respiratory Questionnaire [36]; HADS = Hospital Anxiety and Depression Scale [37]. *Significantly different ($p < 0.05$) between the COPE-II and COPE-III populations.

[a]MRC dyspnea scores (range 1 to 5) as used in COPE-II [32] were converted to mMRC dyspnea scores (range 0 to 4).

[b]Presented mMRC, CRQ, and HADS data are the 12-month follow-up scores minus the baseline scores. Positive scores indicate worsening of mMRC and HADS, and improvement of CRQ. mMRC, CRQ, and HADS scores were missing for 32 (10.2%), 28 (9.0%), and 30 (9.6%) patients, respectively.

Table 4. Primary and secondary outcomes.

	Combined group ($n = 313$)	COPE-II ($n = 142$)	COPE-III ($n = 171$)	p-value
Primary outcomes				
COPD exacerbation-free days (patient/year)	342 (307–361)	330 (290–352)	351 (320–365)	<0.01*
Days with no more symptoms than usual (patient/year)	285 (212–330)	274 (183–324)	293 (227–337)	0.06
Secondary outcome				
Combined COPD exacerbation and comorbid flare-up-free days (patient/year)	NA	ND	350 (309–365)	NA

Data are presented in median (IQR). Abbreviations: COPD = Chronic Obstructive Pulmonary Disease; NA = not applicable; ND = not documented. *Significantly different ($p < 0.05$) between the COPE-II and COPE-III populations.

Table 5. Associations of the number of COPD exacerbation-free days, days with no more symptoms than usual, and combined free days of COPD exacerbations and comorbid flare-ups with patient characteristics (negative binomial regression analyzes).

Dependent variable	Independent variables	IRR (95% CI)	p-value
Number of COPD exacerbation-free days (patient/year) ($n = 313$)	Self-treatment intervention[a]	1.04 (0.99–1.10)	0.12
	Having no comorbidity[b]	0.94 (0.88–0.99)	0.03*
	CRQ fatigue domain	1.03 (1.01–1.05)	0.02*
	CRQ mastery domain	1.03 (1.00–1.06)	0.04*
Number of days with no more symptoms than usual (patient/year) ($n = 313$)	Self-treatment intervention[a]	1.04 (0.94–1.16)	0.44
	CRQ fatigue domain	1.05 (1.00–1.10)	0.04*
	CRQ mastery domain	1.06 (1.00–1.12)	0.04*
Number of combined COPD exacerbation and comorbid flare-up-free days[c] (patient/year) ($n = 171$)	Self-treatment intervention[a]	1.01 (0.95–1.08)	0.76
	mMRC	0.95 (0.92–0.98)	<0.01*
Sensitivity analyzes (including data of only those patients who completed the entire 12-month follow-up of symptoms diary data)			
Number of COPD exacerbation-free days (patient/year) ($n = 173$)	Self-treatment intervention[a]	1.04 (0.98–1.11)	0.24
	Having no comorbidity[b]	0.94 (0.87–1.00)	0.05
	CRQ fatigue domain	1.02 (0.99–1.06)	0.12
	CRQ mastery domain	1.04 (1.00–1.07)	0.03*
Number of days with no more symptoms than usual (patient/year) ($n = 173$)	Self-treatment intervention[a]	1.02 (0.88–1.18)	0.83
	CRQ fatigue domain	1.07 (1.00–1.15)	0.07
	CRQ mastery domain	1.10 (1.02–1.19)	0.02*
Number of combined COPD exacerbation and comorbid flare-up-free days[c] (patient/year) ($n = 75$)	Self-treatment intervention[a]	1.00 (0.91–1.10)	0.99
	mMRC	0.95 (0.91–0.99)	0.03*

Abbreviations: IRR = incidence rate ratio; CI = confidence interval; COPD = Chronic Obstructive Pulmonary Disease; CRQ = Chronic Respiratory Questionnaire; mMRC = modified Medical Research Council. *$p < 0.05$.
[a]Control group was set as reference.
[b]Having a comorbidity was set as reference.
[c]Data obtained with the included subsample of patients from the COPE-III study population [33].

Sensitivity analyzes including only patients who completed the 12-month follow-up resulted in comparable results (Table 5).

Health outcomes associated with COPD exacerbation-free days, days with no more symptoms than usual for all included patients, and the number of combined COPD exacerbation and comorbid flare-up-free days for the subsample of patients with comorbidities are presented in Table 6.

Being allocated to the self-treatment intervention and fewer self-reported courses of antibiotics were significantly associated with a higher number of COPD exacerbation-free days.

A better CRQ dyspnea score over the 12-month follow-up and fewer self-reported courses of antibiotics were significantly related to more days with no more symptoms than usual.

In the COPE-III population [33], fewer self-reported courses of antibiotics were significantly correlated with a higher number of combined COPD exacerbation and comorbid flare-up-free days.

Similar results were found in sensitivity analyzes including only patients who completed the 12-month follow-up (Table 6).

Discussion

Our results showed that better baseline CRQ fatigue and mastery scores were associated with a higher number of days free of COPD exacerbations and deteriorated symptoms. As in line with our hypothesis, associations with patient characteristics and health outcomes are stronger for days with no more symptoms than usual compared to COPD exacerbation-free days. Moreover, experiencing less dyspnea after 12-month follow-up was correlated to more days with no more symptoms than usual, but no relation with COPD exacerbation-free days was found. In the subsample of COPD patients with comorbidities, more combined free days of COPD exacerbations and comorbid flare-ups were associated with less baseline dyspnea severity and fewer courses of antibiotics.

We found better mastering of COPD and less fatigue at baseline, suggesting better HRQoL, to be related to more COPD exacerbation-free days and days with no more symptoms than usual. These findings are in line with those of Boer et al., who found the same association with COPD exacerbation-free weeks [31]. The association may be explained by the fact that patients with better HRQoL are

Table 6. Associations of the number of COPD exacerbation-free days, days with no more symptoms than usual, and combined free days of COPD exacerbations and comorbid flare-ups with health outcomes (negative binomial regression analyzes).

Dependent variable	Independent variables	IRR (95% CI)	*p*-value
Number of COPD exacerbation-free days (patient/year) ($n = 313$)	Self-treatment intervention[a]	1.06 (1.01–1.11)	0.01*
	Number of courses antibiotics	0.95 (0.94–0.96)	<0.01*
Number of days with no more symptoms than usual (patient/year) ($n = 285$)	Self-treatment intervention[a]	1.09 (0.98–1.21)	0.13
	CRQ dyspnea domain[b]	1.07 (1.01–1.12)	0.02*
	Number of courses antibiotics	0.94 (0.91–0.96)	<0.01*
Number of combined COPD exacerbation and comorbid flare-up-free days[c] (patient/year) ($n = 171$)	Self-treatment intervention[a]	1.00 (0.95–1.06)	0.91
	Number of courses antibiotics	0.94 (0.93–0.95)	<0.01*
Sensitivity analyzes (including data of patients who completed the 12-month follow-up symptoms diary data)			
Number of COPD exacerbation-free days (patient/year) ($n = 173$)	Self-treatment intervention[a]	1.07 (1.01–1.13)	0.02*
	Number of courses antibiotics	0.95 (0.94–0.97)	<0.01*
Number of days with no more symptoms than usual (patient/year) ($n = 168$)	Self-treatment intervention[a]	1.07 (0.92–1.24)	0.41
	CRQ dyspnea domain[b]	1.09 (1.01–1.17)	0.02*
	Number of courses antibiotics	0.94 (0.91–0.97)	<0.01*
Number of combined COPD exacerbation and comorbid flare-up-free days[c] (patient/year) ($n = 75$)	Self-treatment intervention[a]	0.98 (0.91–1.06)	0.68
	Number of courses antibiotics	0.94 (0.93–0.96)	<0.01*

Abbreviations: IRR = incidence rate ratio; CI = confidence interval; COPD = Chronic Obstructive Pulmonary Disease; CRQ = Chronic Respiratory Questionnaire.
*$p < 0.05$.
[a]Control group was set as reference.
[b]The score measured after 12-month follow-up minus the baseline score.
[c]Data obtained with the included subsample of patients from the COPE-III study population [33].

likely to be adherent to their treatment, which could positively affect COPD exacerbation frequency and symptom burden [38–40]. Also, being aware of what COPD entails and the necessity of its treatments is crucial to accept and cope with the disease [41]. Mastering COPD optimizes disease management and emotional well-being and can result in reduced symptom burden, frequency, and duration of COPD exacerbations [25,41]. Moreover, experiencing fatigue is not only related to symptoms like dyspnea, anxiety, and depression, but to COPD exacerbation frequency as well [42–45].

In patients with comorbidities, having less severe baseline dyspnea turned out to be associated with more combined free days of COPD exacerbations and comorbid flare-ups. This is consistent with previous evidence as dyspnea cannot only trigger COPD exacerbations, but also feelings of anxiety and depression [16,21,26,46]. Our previous research suggests that severe baseline dyspnea is a predictor of delayed or no treatment of COPD exacerbations [47]. This implies prolonged COPD exacerbations that could elicit comorbid flare-ups [15–17], and thus reduce the number of days free of COPD exacerbations and comorbid flare-ups.

In line with previous evidence, we found that patients assigned to the self-treatment intervention had significantly more COPD exacerbation-free days compared to patients in the control group, indicating that using an exacerbation action plan may shorten COPD exacerbations [48,49]. Because exacerbation action plans direct patients only to start treatment in case of significantly increased symptoms, no difference in days with no more symptoms than usual between study groups was expected and detected. Our results showed that days free of COPD exacerbations and more symptoms than usual, but also free of combined COPD exacerbations and comorbid flare-ups were related to fewer self-reported courses of antibiotics. Treatment with antibiotics is initiated to shorten a COPD exacerbation with a bacterial infection [3,10,26], so the association with COPD exacerbation-free days was rather expected. Having shorter COPD exacerbations because of using antibiotics also lowers the chance of comorbid flare-ups and associated symptom burden [15–17]. This may explain the relation of antibiotic courses to days free of deteriorated symptoms and combined COPD exacerbations and comorbid flare-ups.

Remarkably, we found that COPD patients with comorbidities had more COPD exacerbation-free days compared to COPD patients without comorbidities, while comorbid flare-ups can trigger and prolong COPD exacerbations [16,18–21]. A possible explanation may be that the COPE-II study (including COPD patients without severe comorbidities) [32] was performed eight years before the COPE-III study (including COPD patients with comorbidities) [33]. Healthcare has improved over the years, and self-management has become more part of usual care [50]. Whereas COPD patients with comorbidities have a higher symptom burden relative to COPD patients without comorbidities [22], improved treatments over the years may have resulted in better symptom control in COPD patients in general, leading to more days with no more symptoms than usual. Unfortunately, we have not been able to adjust our analyzes for the "time of inclusion" or possible improved treatment over the years, because of the high correlation with the variable "having comorbidities" already been included in the models. Therefore, one should be cautious with the interpretation of these findings.

Boer et al. [31] discussed that exacerbation details may have been lost due to their data collection of COPD exacerbation-free time only every two weeks. This is the first study that used daily symptom diaries to assess not only days free of COPD exacerbations and more symptoms than usual, but also free of combined COPD exacerbations and comorbid flare-ups. Daily symptom scores provided detailed and accurate insight in patients' daily symptom fluctuations and frequency of COPD exacerbations and

comorbid flare-ups. Another strength is our heterogeneous study population, derived from two randomized controlled trials including COPD patients with and without comorbidities receiving a self-management intervention including an exacerbation action plan or usual care [32,33]. This makes our study population more typical for those patients with COPD treated in clinical practice.

However, this study also has limitations. Our imputation technique may have underestimated the number of COPD exacerbation days, and hence daily symptom burden and comorbid flare-ups. This may have resulted in an overestimation of days free of COPD exacerbations, more symptoms than usual, and combined COPD exacerbations and comorbid flare-ups and consequently overestimations of associations with patient characteristics and health outcomes. Nevertheless, sensitivity analyzes by including only 173 (55.3%) patients who completed the 12-month follow-up revealed comparable effect sizes (Tables 5 and 6). However, as could have been expected, fewer of these effect sizes were significant because of the significant lower number of patients included in the sub-analyzes. Another potential limitation is our previous mentioned inability to correct for "time of inclusion." Since both COPE studies only included frequently exacerbating COPD patients (i.e. at least three exacerbations or one respiratory-related hospitalization in the two years before inclusion) [32–34], a limitation is that we were not able to stratify our analyzes by exacerbation status in the pretrial period. This makes our results generalizable for those COPD patients who frequently exacerbate. In addition, we did not correct for the 2-by-2 factorial design that was used in the COPE-II study [32]. However, because no interactions were found between the two interventions in the COPE-II data (i.e. self-treatment of exacerbation and an exercise intervention) [32], we assumed that the underlying 2-by-2 factorial design has not influenced our results. A final limitation is that comorbidity-related symptom variations were only reported in the daily symptom diaries of the COPE-III population [33]. As a result, COPE-II patients could not register potential deteriorations of comorbidity-related symptoms. As the number of days with no more symptoms as usual were defined with only COPD-related symptoms in the COPE-II study, this may have led to an overestimation of the number of days with no more symptoms than usual in the COPE-II patients.

Healthcare professionals should be aware that in COPD patients, more time free of COPD exacerbations and deteriorated symptoms is related to experiencing less fatigue, better mastering of COPD, proper treatment of COPD exacerbations, and less severe dyspnea. A self-management intervention that includes self-treatment and uses an individualized positive health approach centralizing the period free of COPD exacerbations and deteriorated symptoms, may help stimulate patients to better cope with COPD exacerbations, comorbid-flare-ups, and activities of daily living. This may reduce daily symptom burden and improve quality of life. Future (qualitative) studies may be able to provide better clinical guidance in disease management if focusing on the period free of COPD exacerbations and deteriorated symptomsinstead of focusing on reducing the incidence and duration of COPD exacerbations and symptoms.

In summary, exploring the period patients are free of COPD exacerbations and deteriorated symptoms, revealed interesting related variables as fatigue and mastering of COPD. Associations with the number of days with no more symptoms were stronger than the associations with the number of COPD exacerbation-free days.

Data availability statement

Data that support the findings of this study are available upon reasonable request (corresponding author, A. Lenferink).

Declaration of interest

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ORCID

Tanja W. Effing http://orcid.org/0000-0003-1489-2030
Job van der Palen http://orcid.org/0000-0003-1071-6769
Jade Schrijver http://orcid.org/0000-0002-1190-0106
Paul van der Valk http://orcid.org/0000-0001-7987-0735
Anke Lenferink http://orcid.org/0000-0002-2276-5691

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