MASTER THESIS

Exacerbation-free time to assess the impact of Chronic Obstructive Pulmonary Disease (COPD)

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ABSTRACT

Background: The course of chronic obstructive pulmonary disease (COPD) is characterised by periods of deterioration of respiratory symptoms, termed exacerbations. In these analyses, data of the COPE-II and COPE-III study were used, which both evaluated the effectiveness of self-management interventions including exacerbation action plans to reduce the number of COPD exacerbation days. The intervention of the COPE-III study was modified to address comorbidities in COPD patients. From the patients' perspective, it may be appropriate to look at the time they are free from COPD exacerbations to further explore if they derive benefit from using exacerbation action plans. We examined how COPD exacerbation-free time relates to baseline characteristics and health outcomes in COPD patients using exacerbation action plans. Also, whether the relations are different in COPD patients with no or non-severe comorbidities using COPD exacerbation action plans versus COPD patients with comorbidities using COPD and comorbidity-related exacerbation action plans.

Methods: Patients with severe comorbidities were excluded in the COPE-II study, while for inclusion in the COPE-III study patients had to be diagnosed with at least one comorbidity (cardiovascular diseases, diabetes mellitus, anxiety, depression). Patients were included in the current analyses if they participated in the self-treatment intervention and had completed at least 75% of their daily symptom diary throughout the 12 months of follow-up. The primary outcome was defined as the number of COPD exacerbation-free days per patient per year and calculated as the inverse of the number of COPD exacerbation days extracted from the daily symptom diaries. Associations of COPD exacerbation-free days with baseline characteristics and health outcomes were analysed.

Results: Data were analysed of 147 patients (COPE-II, n=64; COPE-III, n=83). A lower baseline modified Medical Research Council (mMRC) score (r_s=-0.183, p=0.027) and a better baseline Chronic Respiratory Questionnaire (CRQ) emotional functioning score (r_s=0.165, p=0.046) were associated with more COPD exacerbation-free days. Also, men (median=353) had more COPD exacerbation-free days than women (median=340, p<0.050) and non-smokers (median=352) versus smokers (median=336, p=0.005). More COPD exacerbation-free days were related to a lower mMRC score (r_s=-0.202, p=0.021) and better CRQ emotional functioning (r_s=0.257, p=0.003), mastery (r_s=0.172, p=0.049), dyspnoea (r_s=0.289, p=0.001), and fatigue (r_s=0.191, p=0.029) scores measured after 12 months of follow-up. The associations of COPD exacerbation-free days with baseline characteristics and health outcomes were largely similar between COPE-II and COPE-III patients. In COPE-II patients, more COPD exacerbation-free days were related to less feelings of anxiety (r_s=-0.288, p=0.027) and depression (r_s=-0.293, p=0.025) and in COPE-III patients it was related to less depression-related symptoms (r_s=-0.281, p=0.016) measured by the Hospital Anxiety and Depression Scale after 12 months of follow-up.

Conclusion: COPD exacerbation-free time is related to less dyspnoea severity and better HRQoL. COPD patients with comorbidities showed stronger associations of less dyspnoea severity, better emotional functioning and mastery, and fewer depression-related symptoms with more COPD exacerbation-free time than COPD patients with no or non-severe comorbidities.

INTRODUCTION

In 2020, chronic obstructive pulmonary disease (COPD) was ranked as the third leading cause of death, and approximately 11.8% of men and 8.5% of women suffered from COPD worldwide (1). COPD is a progressive lung condition characterised by persistent airflow obstruction and episodes of deterioration in respiratory symptoms (2), such as increased dyspnoea, cough, and sputum production (1). Moreover, many COPD patients have been diagnosed with at least one comorbidity, such as cardiovascular, metabolic (e.g. diabetes mellitus (DM)), and/or psychological disorders, since comorbidities share common risk factors (e.g. increasing age and smoking) with COPD (3–6).

The episodes of deterioration in respiratory symptoms observed in COPD patients either with or without comorbidities are called exacerbations, which are defined as an acute worsening of the respiratory symptoms which persist for at least several consecutive days (7,8). COPD exacerbations differ both between and within COPD patients in terms of heterogeneity in frequency, severity, symptoms, and recovery time (9,10), which may be explained by a difference in the trigger of the COPD exacerbation (e.g. smoking, air pollution, viral infection (7)) or the severity of the COPD progression (11). Furthermore, COPD exacerbations lead to morbidity, mortality, hospitalisations, increased health care utilisation, augmented health care costs, reduced health-related quality of life (HRQoL), and declined lung function (8,12–15). COPD patients with comorbidities have an even higher risk of COPD exacerbations, hospitalisations, mortality, and increased health care costs (3–6,16,17), since COPD exacerbations may also be triggered by comorbidity-related exacerbations and symptoms (e.g. dyspnoea) can overlap (18–20). To illustrate, dyspnoea-, anxiety- and depression-related symptoms increase the risk of having and prolong a COPD exacerbation (20,21). COPD exacerbations require additional treatment in addition to daily treatment to minimise the negative impact (22), for instance by a course of prednisolone and/or antibiotics or hospitalisation including non-invasive ventilatory support dependent on the severity of the COPD exacerbation (7,14,23).

Self-management interventions are designed to shorten the duration of COPD exacerbations by early symptom recognition and prompt self-treatment, but not to prevent the occurrence of COPD exacerbations (24). Self-management refers to “an individual’s ability to detect and manage symptoms, treatment, physical and psychosocial consequences, and lifestyle changes inherent in living with a chronic condition” (25). In general, self-management interventions facilitate both the acquisition of health behaviour knowledge and its implementation, by fostering the self-management skills of problem-solving, decision-making, resource utilisation, formation of patient-provider partnerships, and action planning (26–28). Self-management interventions can be generic or disease-specific approaches to manage chronic diseases, whereas COPD exacerbation action plans are disease-specific. Action plans are considered as an intrinsic part of COPD self-management and they support COPD patients either with or without comorbidities to respond to symptom deterioration early in the course of a COPD or comorbidity-related exacerbation, and thereby make appropriate decisions regarding their self-treatment (28–30). Self-management interventions including COPD exacerbation action plans are associated with

reduced duration of COPD exacerbations and hospitalisations, as well as improved HRQoL in COPD patients without comorbidities (31,32). In COPD patients with comorbidities, the self-management interventions result in shortened COPD exacerbations (24,33), less risk of having respiratory-related hospitalisations (33), decreased frequency of hospitalisations (34), diminished utilisation of healthcare services, and improved HRQoL (35).

Studies into the effect of self-management interventions including COPD exacerbation action plans often assess COPD exacerbation duration as an outcome measure (24,32,33). From the patients' perspective, it may be more appropriate to look at the period they are free from COPD exacerbations (i.e. COPD exacerbation-free time) instead of looking at the period they are suffering from them to reflect the impact of COPD (36). COPD exacerbation-free time can be used to further investigate whether patients derive benefit from using COPD self-management exacerbation action plans (37,38). Boer et al. (36) showed that more COPD exacerbation-free weeks are related to better HRQoL. In addition, they investigated the associations between COPD exacerbation-free weeks and several baseline characteristics and found that current smokers have fewer COPD exacerbation-free weeks than non-smokers (36).

Although COPD exacerbation-free time seems valuable in assessing the burden of COPD, more research is needed to explore the COPD exacerbation-free time in COPD patients with and without comorbidities using exacerbation action plans (36). Therefore, the current study aims to explore how COPD exacerbation-free time relates to baseline characteristics and health outcomes in COPD patients using exacerbation action plans. Secondly, to investigate whether COPD exacerbation-free time relates differently to baseline characteristics and health outcomes in COPD patients with no or non-severe comorbidities using COPD exacerbation action plans versus COPD patients with comorbidities using COPD and comorbidity-related exacerbation action plans. Based on the study of Boer et al. (36), the hypothesis is that COPD exacerbation-free time is only moderately correlated to baseline characteristics (e.g. age, smoking status, COPD severity) and health outcomes (e.g. HRQoL, hospitalisations). Additionally, we expect stronger correlations between COPD exacerbation-free time and baseline characteristics as dyspnoea-, anxiety-, and depression-related symptoms in COPD patients with comorbidities compared to COPD patients with no or non-severe comorbidities because these symptoms may be more severe in COPD patients with comorbidities, and can trigger and prolong COPD exacerbations (6,20,21).

METHODS

Study design

Secondary analyses were performed on extracted data from two randomised controlled trials (the COPE-II (31) and COPE-III (33) study) that were previously conducted at the Department of Pulmonary Medicine of Medisch Spectrum Twente Hospital, Enschede, The Netherlands. In both COPE studies, the effectiveness of self-management interventions including COPD exacerbation action plans in COPD

patients was evaluated and compared with control groups (COPE-II: self-management programme without self-treatment; COPE-III: usual care) during a 12 month follow-up period (31,33). In addition, the intervention of the COPE-III study was modified to address frequently occurring comorbidities (cardiovascular diseases (CVD), DM, anxiety, depression) in COPD patients.
In the present analyses, data of both the COPE-II and COPE-III study were combined leading to a mixed population of COPD patients with and without comorbidities.

Population

The patients included in the current analyses all participated either in the COPE-II or the COPE-III study. In the COPE-II study, patients were recruited from November 2004 through July 2006 from the outpatient department of Pulmonary Medicine of Medisch Spectrum Twente Hospital, Enschede, The Netherlands. Recruitment for the COPE-III study took place from the outpatient departments of respiratory medicine of two hospitals in the Netherlands (Medisch Spectrum Twente, Enschede; Canisius-Wilhelmina Ziekenhuis, Nijmegen) and three in Australia (Repatriation General Hospital, Adelaide; Royal Adelaide Hospital, Adelaide; Flinders Medical Centre, Adelaide) between 2012 and 2015. Most in- and exclusion criteria of the COPE-II and COPE-III studies were comparable, but whereas patients with severe comorbidities were excluded from the COPE-II study (31), for inclusion in the COPE-II study patients were required to have at least one, severe or non-severe, comorbidity (CVD, DM, anxiety, and/or depression) (33,39). In- and exclusion criteria of both COPE studies are published elsewhere (31,39).
The patients were included in the current analyses when they were assigned to the self-treatment intervention group including exacerbation action plans of either the COPE-II or COPE-III study. Patients were excluded from analyses if less than 75% of their daily symptom diaries had been completed during the 12 months of follow-up, after missing diary data of fewer than four consecutive days had been imputed using a predefined algorithm (see appendix A).
All patients gave written informed consent and were able to understand and read Dutch and/or English.

Self-treatment intervention

Patients in the COPE-II (31) and COPE-III (33,39) self-treatment intervention groups received two group and two individual self-management training sessions by a case manager (respiratory nurse). The sessions intended to train the patients in self-treatment of exacerbations, but also to promote optimal use of specified disease self-management behaviour patterns by increasing their knowledge, confronting them with the consequences of specific behaviours, and providing them with tools to deal with their diseases (31,39). During the training sessions, patients described their individual COPD symptom levels in a stable health state on a “What are my ‘usual’ symptoms” card (see appendix B). COPE-III patients’ symptoms of the individual diagnosed comorbidities were also described on this card (33,39).

Subsequently, patients received their tailored written COPD exacerbation action plan from the case manager and were trained in early recognition of COPD exacerbations using their "What are my 'usual' symptoms" card and daily symptom diary (see appendix C). In both COPE studies, patients were educated to complete daily diaries, in which they had to report whether their major COPD symptoms (breathlessness, sputum production, sputum colour) and minor COPD symptoms (cough, wheeze, running nose, sore throat, fever (>38.5 °C)) were normal, slightly increased, or clearly increased compared to their usual symptoms in the last 24 hours (31,33,39). Moreover, COPE-III patients' individual diagnosed comorbidities were assessed in the diaries and they received tailored exacerbation action plans for these comorbidities. Patients learned when to start self-treatment of exacerbations according to their written action plan (see appendix D). When a patient experienced significantly increased COPD symptoms for at least two symptom diary questions two days in a row, the action plan guided the patient to start a prednisolone course, and a change in sputum colour was the indicator to start an antibiotics course as well.

Completed diaries, also including information regarding the use of additional medications, were returned at the end of each month. Patients were called to provide feedback on their diary use, and to adjust symptom levels on the "What are my 'usual' symptoms" card if necessary (39).

Detailed methods of the COPE-II and COPE-III study have previously been published elsewhere (31,33,39).

Outcomes

The primary outcome COPD exacerbation-free time was defined as the number of COPD exacerbation-free days per patient per year. The daily diaries were used to establish whether a COPD exacerbation had occurred. The start of a COPD exacerbation was determined as "a significant negative change in two major symptoms or one major and one minor symptom from baseline, for at least two consecutive days" (31,33). The recovery was defined as "the first day of: 1) three successive days that the patient has returned to his normal health state (see figure 1.A); 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 (see figure 1.B)" (31,33). Based on these definitions the number of COPD exacerbation days per patient per year was determined. In these analyses, the number of COPD exacerbation-free days per patient per year was defined as the inverse of the number of COPD exacerbation days per patient per year, i.e. the number of days without a COPD exacerbation.

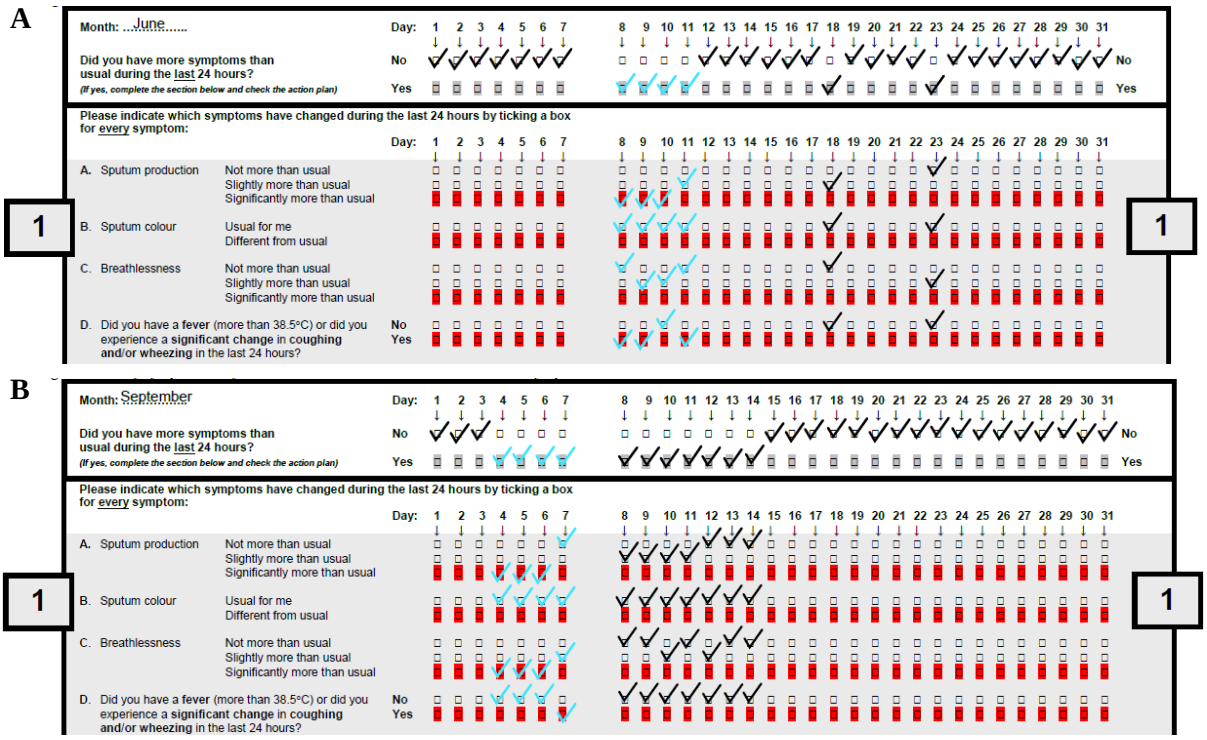

Figure 1: Two examples of COPD exacerbations according to the daily symptom diary. A) The patient experienced one COPD exacerbation of four days in June (see blue). In this example, the patient is recovered from the COPD exacerbation at day 12, the first day of three successive days that the patient has returned to his normal health state. On day 18 and 23 there is a slightly increase of a major symptom, but these days are classified as COPD exacerbation-free days because they do not meet the definition of a COPD exacerbation. B) The patient experienced one COPD exacerbation of four days in September (see blue). In this example, the patient is recovered from the COPD exacerbation, according to the definition that the patient continuously reported no or only a slight increase in symptoms compared to baseline, with no fever or change in sputum colour for seven consecutive days. The seven consecutive days with no or a slightly increase of symptoms are classified as COPD exacerbation-free days.

The baseline characteristics of the patients were: age, gender, smoking status, body mass index (BMI), COPD severity, forced expiratory volume in 1 s (FEV_1) in litres (l), ratio FEV_1 to forced vital capacity (FEV_1/FVC), dyspnoea severity, comorbidities (CVD, DM, anxiety, depression), HRQoL, and anxiety- and depression-related symptoms. In addition, the following health outcomes measured after 12 months of follow-up were included: dyspnoea severity, HRQoL, anxiety- and depression-related symptoms, medication use, hospitalisations, action plan adherence, COPD exacerbation frequency, and duration of COPD exacerbations. In the COPE-III study, the modified Medical Research Council (mMRC) dyspnoea scale (score range from 0 to 4) was performed to allocate the dyspnoea severity, in contrast to the COPE-II study where the MRC with a score range from 1 to 5 was used. In the present analyses, the dyspnoea data of the COPE-II patients were converted to the mMRC scale by subtracting 1 from all scores, so that all patients were scored similarly. The outcome measures are described in Table 1.

Table 1: Description of outcome measures.

Outcome measure	Description
COPD severity	The Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification was used to classify the severity of COPD, where GOLD I represents mild COPD (FEV_1 ≥80% predicted) and GOLD IV represents very severe COPD (FEV_1 <30% predicted) (1).
Dyspnoea severity	The mMRC is a questionnaire about perceived breathlessness that ranges with scores from 0 ('I only get breathless with strenuous exercise') to 4 ('I am too breathless to leave the house') (40).
HRQoL	Chronic Respiratory Questionnaire (CRQ) measures an individual's HRQoL by a 20-item questionnaire with four subdomains: dyspnoea (five items), fatigue (four items), emotional functioning (seven items), and mastery (four items). Patients rate their experience of the items on a seven-point scale, ranging from 1 (maximum impairment) to 7 (no impairment) (41). A higher CRQ score representing better HRQoL.
Anxiety and depression symptoms	Hospital Anxiety and Depression Scale (HADS) produces a score of 0 to 21 for anxiety- and depression-related symptoms, separately. A higher score indicating more anxiety- and/or depression-related symptoms and a score of 11 or higher suggesting a suspected anxiety or depression disorder (42).
Medication use	Medication use was defined as the number of self-initiated medication courses of both prednisolone and antibiotics separately during the 12 months follow-up period.
Hospitalisations	The number of all-cause hospitalisation days per patient was calculated by summing up all hospitalisation days throughout the 12 months of follow-up.
Action plan adherence	The action plan adherence was determined based on both the self-reported COPD exacerbation data and the self-initiated prednisolone courses. Four categories of patient adherence to COPD action plans were defined: 'optimal treatment', 'sub-optimal treatment', 'significant delay or no treatment', and 'treatment outside the actual exacerbation period' (43) (see appendix E). Patients were only assigned to a category if they had experienced ≥1 COPD exacerbation according to the symptom scores reported in their daily diary and/or reported ≥1 self-initiated course of prednisolone for the self-treatment of a COPD exacerbation. Detailed methods of classification to the adherence categories are published elsewhere (43).
COPD exacerbation frequency	The COPD exacerbation frequency per patient over the 12 month of follow-up was determined by summing up the number of COPD exacerbations, based on the daily diaries (31,33).
Duration of COPD exacerbations	The mean duration (in days) of the COPD exacerbations per patient during the 12 month follow-up was calculated by dividing the number of COPD exacerbation days per patient by the number of COPD exacerbations per patient (31,33).

Abbreviations: COPD=Chronic Obstructive Pulmonary Disease; mMRC=modified Medical Research Council; HRQoL=Health-Related Quality of Life.

Data analysis

Two comparable data sets were merged to create one pooled dataset. The data of baseline characteristics and health outcomes measured after 12 months of follow-up of both the COPE-II and COPE-III study were used. All statistical analyses were conducted on an intention-to-treat principle and included all available data of the participating patients. The statistical analyses were performed on the pooled data set, and the COPE-II and COPE-III data, separately. IBM SPSS Statistics 26 (version 26.0.0.1) software was used for all analyses with $p<0.05$ considered to be statistically significant.

Missing diary data

In both COPE studies, incomplete diary data were first compared with hospital admission data, and then patients were contacted by phone to fill gaps on missing diary days (31,33). If the diary data was still incomplete a predefined algorithm was used, in case of fewer than four consecutive missing days (see appendix A) (31,33). The algorithm combined the last observation carried forward and the next observation carried backward to the missing value.

In the current analyses, if four or more consecutive days were missing, the missing days were proportionally imputed to be able to determine the number of COPD exacerbation days per patient per year. For example, if the patient experienced 25 COPD exacerbation days over 300 days of follow-up, this was considered 30 COPD exacerbation days over 365 days. These data were imputed to enable the calculation of the number of COPD exacerbation-free days per patient per year. This imputation technique has only been used in patients of whom at least 75% of diary data during the 12 months of follow-up was known, otherwise, patients were excluded from further analyses.

Statistical analysis

The normality of the data was assessed visually, using a histogram and P-P plot. Differences in baseline characteristics and health outcomes between COPE-II and COPE-III patients were analysed by Mann-Whitney U tests. The associations of the number of COPD exacerbation-free days with baseline characteristics and health outcomes were examined using the two-tailed Spearman's rank correlation coefficient (r_s). The r_s ranges from -1 to 1, within this range (-)0.70 to (-)1.00, (-)0.30 to (-)0.69, and 0.00 to (-)0.29 represent a strong, moderate, and none to weak association, respectively (44).

The between-group differences in COPD exacerbation-free days for gender and smoking status were examined using a Mann-Whitney U test. The variable smoking status was divided into three groups (current smoker, ex-smoker, and never smoker), in which the group 'never smoker' consisted of one patient. For statistical purposes, the groups 'ex-smoker' and 'never smoker' were merged into the group 'non-smoker' (during 12 month of follow-up). The differences in COPD exacerbation-free days between the four action plan adherence categories were analysed by the Kruskal-Wallis test and post hoc analyses by Mann-Whitney U tests. Because of the increased risk of a type I error when performing multiple statistical tests, the Bonferroni-Holm correction was used (45). Since the action plan guided the patients to immediately initiate a prednisolone course at the onset of a COPD exacerbation, only patients in the 'optimal treatment' group optimally adhered to the action plan. Therefore, we also recoded the four action plan adherence categories into the groups: 'optimal adherence' and 'sub-optimal/non-adherence'. The 'optimal treatment' category was recoded as 'optimal adherence', whereas the 'sub-optimal treatment', 'significant delay or no treatment', and 'the treatment outside the actual exacerbation period' categories were merged into the 'sub-optimal/non-adherence' category. A Mann-Whitney U test was used to analyse the between-group difference.

Sensitivity analyses were conducted by including diary data without imputation of more than four consecutive missing days.

RESULTS

Patients

Of the 172 patients in the two studies, 147 (85.5%) completed at least 75% of the daily diaries throughout 12 months of follow-up, and after missing diary data of less than four consecutive days had been imputed (see Figure 2). The daily diaries (including imputation of <4 successive missing days) were fully completed by 52 (81.3%) COPE-II patients and 45 (54.2%) COPE-III patients. COPE-II and COPE-III patients who had incomplete diaries had an average of 40.4 (±19.3) and 26.3 (±25.1) missing diary days of more than four consecutive days, respectively.

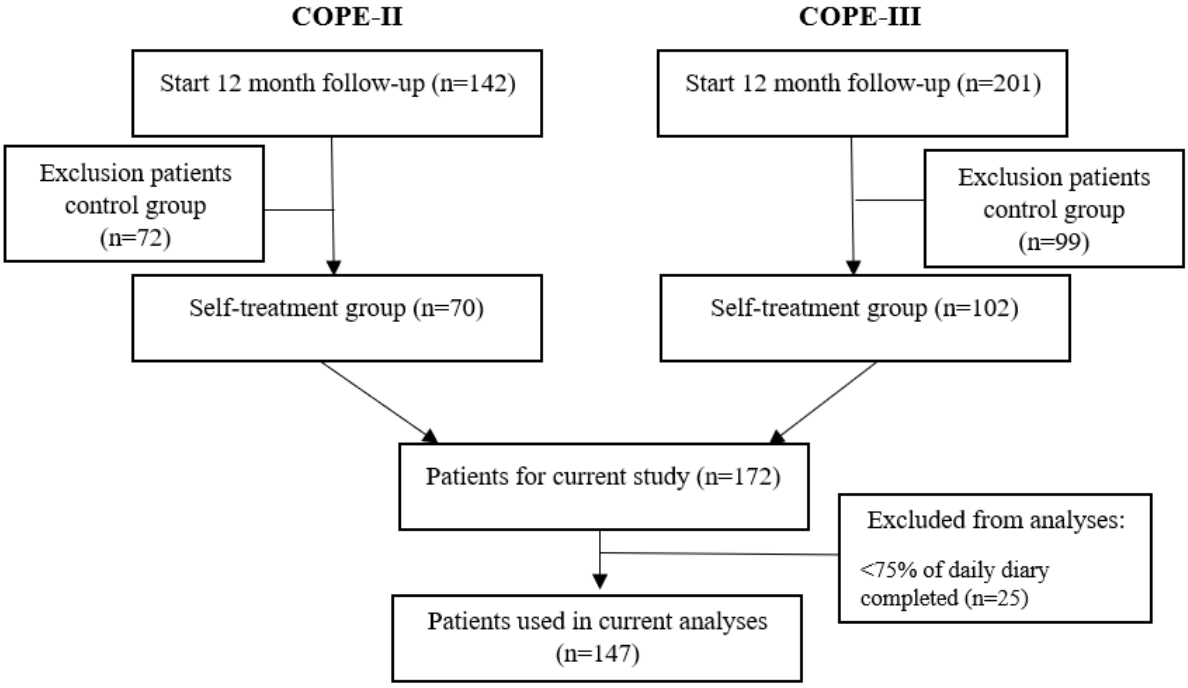

Figure 1: Flowchart of patient enrolment.

Table 2 shows the patients' baseline characteristics for the pooled dataset (Total) and separately for each COPE study. COPE-II patients were younger, had a lower mMRC score, a higher CRQ mastery score, a higher CRQ fatigue score, and a lower HADS anxiety and depression score than COPE-III patients at baseline. A total of 37 (25.2%) patients suffered from two or more comorbidities. COPE-III patients (mean=1.53±0.69) were diagnosed with significantly more comorbidities compared to COPE-II patients (mean=0.38±0.52, $p<0.001$).

Table 2: Baseline characteristics of patients.

	Total (n=147)	COPE-II (n=64)	COPE-III (n=83)	p-value
Age (SD)	66.2 (±7.65)	63.5 (±7.72)	68.3 (±8.79)	0.001*
Male (%)	94 (64.0%)	37 (57.8%)	57 (68.7%)	
Current smoker (%)	35 (23.8%)	19 (29.7%)	16 (19.3%)	
BMI (SD)	28.7 (±6.27)	27.5 (±5.06)	29.6 (±6.94)	0.086
GOLD score				
I (%)	4 (2.7%)	4 (6.4%)	0 (0.0%)	
II (%)	75 (51.4%)	26 (41.3%)	49 (59.0%)	
III (%)	55 (37.7%)	25 (39.7%)	30 (36.1%)	
IV (%)	12 (8.2%)	8 (12.7%)	4 (4.8%)	
FEV_1 (l) (SD)	1.43 (±0.54)	1.43 (±0.58)	1.44 (±0.51)	0.972
FEV_1/FVC (SD)	46.9 (±13.2)	45.0 (±12.7)	48.3 (±13.5)	0.105
mMRC (SD)	1.78 (±1.10)	1.34 (±1.09)	2.11 (±0.99)	<0.001*
CRQ emotions (SD)	4.83 (±1.14)	4.97 (±1.04)	4.72 (±1.20)	0.275
CRQ mastery (SD)	5.09 (±1.11)	5.36 (±1.04)	4.88 (±1.13)	0.008*
CRQ dyspnoea (SD)	4.43 (±1.37)	4.62 (±1.44)	4.28 (±1.31)	0.139
CRQ fatigue (SD)	4.04 (±1.17)	4.32 (±1.17)	3.82 (±1.12)	0.010*
HADS anxiety (SD)	5.87 (±4.06)	4.52 (±3.25)	6.92 (±4.32)	0.001*
HADS depression (SD)	5.65 (±3.91)	4.39 (±3.51)	6.63 (±3.94)	<0.001*
Comorbidities				
CVD (%)	65 (44.2%)	15 (23.4%)	50 (60.2%)	
Anxiety (%)	24 (16.3%)	5 (7.8%)	19 (22.9%)	
Depression (%)	31 (21.1%)	4 (6.3%)	27 (32.5%)	
DM (%)	30 (20.4%)	0 (0.0%)	30 (36.1%)	

Data are presented as mean (standard deviation (SD)) or number (%). Abbreviations: BMI=Body Mass Index; GOLD=Global Initiative for Chronic Obstructive Lung Disease; FEV_1=forced expiratory volume in 1 s; FVC=forced vital capacity; mMRC=modified Medical Research Council; CRQ=Chronic Respiratory Questionnaire; HADS=Hospital Anxiety and Depression Scale; CVD=cardiovascular disease; DM=Diabetes Mellitus. The p-value represents the comparison between COPE-II and COPE-III patients. *p<0.05. The GOLD score was missing for one COPE-II patient. COPE-II patients were assigned to have an anxiety or depression disorder if their HADS score was 11 or higher (31), while COPE-III patients were diagnosed using the HADS score (≥11) and/or whether they were treated for an anxiety or depression disorder at inclusion (39). Patients with CVD could be diagnosed with ischemic heart disease, congestive heart failure, anomalies in cardiac action potentials, myocardial infarction, and/or arrhythmia. Additionally, patients diagnosed with DM could have either type 1 DM, type 2 DM, or steroid-induced DM.

The patients' health outcomes are presented in Table 3. The health outcomes differed significantly between COPE-II and COPE-III patients. Fascinatingly, COPE-II patients had a lower mMRC score, a higher score on the four CRQ domains, and a lower HADS anxiety and depression score relative to COPE-III patients measured after 12 months of follow-up. As mentioned, patients were only assigned to an action plan adherence category, if they had experienced ≥1 COPD exacerbation according to the symptom scores reported in their daily diary and/or reported ≥1 self-initiated course of prednisolone (43). In total, 127 (86.4%) patients were assigned to an adherence category, of whom 58 (90.6%) COPE-II and 69 (83.1%) COPE-III patients.

Table 3: Data of patients' health outcomes at 12 months of follow-up.

	Total (n=147)	COPE-II (n=64)	COPE-III (n=83)	p-value
Number of COPD exacerbation-free days (SD, IQR)	330 (±50.1), 347 (319-363)	323 (±40.8), 334 (299-355)	336 (±55.9), 356 (332-365)	<0.001*
COPD exacerbation frequency (IQR)	2.0 (1.0-4.0)	3.0 (1.0-5.8)	1.0 (0-3.0)	0.001*
Duration of COPD exacerbation (in days) (IQR)	6.8 (2.0-11.3)	8.1 (6.0-13.9)	4.4 (0-9.0)	<0.001*
Medication-use prednisolone (IQR)	2.0 (0-4.0)	2.0 (1.0-4.8)	1.0 (0-3.0)	0.005*
Medication-use antibiotics (IQR)	1.0 (0-3.0)	2.0 (1.0-3.8)	0 (0-2.0)	0.002*
All cause hospitalisation days (SD)	4.0 (±10.03)	2.5 (±8.3)	5.2 (±11.1)	0.028*
Action plan adherence				
Optimal treatment (%)	32 (25.2%)	14 (24.1%)	18 (26.1%)	
Sub-optimal treatment (%)	15 (11.8%)	10 (17.2%)	5 (7.3%)	
Significant delay or no treatment (%)	39 (30.7%)	22 (37.9%)	17 (24.6%)	
Treatment outside the actual exacerbation period (%)	41 (32.3%)	12 (20.7%)	29 (42.0%)	
mMRC (SD)	1.89 (±1.14)	1.22 (±1.11)	2.41 (±0.86)	<0.001*
CRQ emotions (SD)	4.98 (±1.25)	5.38 (±1.16)	4.66 (±1.23)	0.001*
CRQ mastery (SD)	5.43 (±1.15)	5.84 (1.04)	5.10 (±1.14)	<0.001*
CRQ dyspnoea (SD)	4.36 (±1.49)	4.82 (±1.45)	3.99 (±1.42)	0.002*
CRQ fatigue (SD)	4.14 (±1.25)	4.61 (±1.25)	3.76 (±1.13)	<0.001*
HADS anxiety (SD)	4.96 (±3.96)	3.61 (±3.48)	6.05 (±4.01)	<0.001*
HADS depression (SD)	4.95 (±3.85)	3.39 (±3.23)	6.21 (±3.88)	<0.001*

Data are presented in mean (SD), median (interquartile range (IQR)), or number (%). Abbreviations: COPD=Chronic Obstructive Pulmonary Disease; mMRC=modified Medical Research Council; CRQ=Chronic Respiratory Questionnaire; HADS=Hospital Anxiety and Depression Scale. The p-value represents the comparison between COPE-II and COPE-III patients. *p<0.05. The mMRC questionnaire was completed by 58 (90.6%) COPE-II and 73 (88.0%) COPE-III patients and the CRQ and HADS questionnaires by 59 (92.2%) COPE-II and 73 (88.0%) COPE-III patients.

Baseline characteristics and health outcomes in relation to the number of COPD exacerbation-free days per patient per year

COPD patients showed no to weak correlations (r_s=0.00-0.29) between the number of COPD exacerbation-free days and baseline characteristics (see Total, Table 4). A lower baseline mMRC score (r_s=-0.183, p=0.027), a higher baseline CRQ emotional functioning score (r_s=0.165, p=0.046), and having more comorbidities (r_s=0.213, p=0.009) were significantly associated with a higher number of COPD exacerbation-free days.

In addition, Table 4 distinguishes how the number of COPD exacerbation-free days is correlated to baseline characteristics in COPE-II and COPE-III patients. COPE-III patients showed that a lower baseline mMRC score (r_s=-0.386, p<0.001), better baseline emotional functioning (r_s=0.279, p=0.011) and mastery (r_s=0.299, p=0.006), and less depression-related symptoms at baseline (r_s=-0.252, p=0.022) were significantly related to more COPD exacerbation-free days, whereas these relations were not significant in COPE-II patients.

Table 4: Spearman's rank correlation coefficients (r_s) of the number of COPD exacerbation-free days per patient per year with baseline characteristics.

	The number of COPD exacerbation-free days per patient per year					
	Total (n=147)		COPE-II (n=64)		COPE-III (n=83)	
	r_s	p-value	r_s	p-value	r_s	p-value
COPD exacerbations (complete dataset with imputations)						
Age	0.131	0.113	0.117	0.359	0.041	0.714
BMI	0.127	0.126	0.051	0.693	0.078	0.483
GOLD score	-0.145	0.082	-0.150	0.241	-0.093	0.402
FEV_1 (l)	0.079	0.341	0.191	0.130	0.009	0.936
FEV_1/FVC	0.123	0.139	0.157	0.236	0.034	0.763
mMRC	-0.183	0.027*	-0.226	0.073	-0.368	<0.001*
CRQ emotions	0.165	0.046*	0.080	0.528	0.279	0.011*
CRQ mastery	0.134	0.106	0.099	0.438	0.299	0.006*
CRQ dyspnoea	0.083	0.315	0.019	0.879	0.196	0.075
CRQ fatigue	0.079	0.342	0.037	0.772	0.209	0.058
HADS anxiety	0.008	0.924	-0.010	0.940	-0.126	0.256
HADS depression	-0.066	0.428	-0.058	0.648	-0.252	0.022*
Number of comorbidities	0.213	0.009*	0.014	0.913	0.022	0.847
COPD exacerbations (dataset with only imputations <4 consecutive missing days)						
Age	0.122	0.142	0.157	0.215	0.033	0.770
BMI	0.177	0.033*	0.081	0.529	0.181	0.102
GOLD score	-0.110	0.187	-0.124	0.334	-0.068	0.543
FEV_1 (l)	0.066	0.425	0.135	0.287	0.030	0.787
FEV_1/FVC	0.086	0.300	0.130	0.307	0.022	0.847
mMRC	-0.112	0.176	-0.128	0.312	-0.222	0.043*
CRQ emotions	0.181	0.028*	0.122	0.338	0.260	0.018*
CRQ mastery	0.139	0.094	0.118	0.354	0.253	0.021*
CRQ dyspnoea	0.060	0.472	0.012	0.927	0.135	0.225
CRQ fatigue	0.057	0.491	0.016	0.900	0.143	0.199
HADS anxiety	-0.021	0.803	0.011	0.929	-0.129	0.244
HADS depression	-0.097	0.244	-0.102	0.423	-0.226	0.040*
Number of comorbidities	0.130	0.117	0.080	0.530	-0.034	0.761

Abbreviations: COPD=Chronic Obstructive Pulmonary Disease; BMI=Body Mass Index; GOLD=Global Initiative for Chronic Obstructive Lung Disease; FEV_1=forced expiratory volume in 1 s; FVC=forced vital capacity; mMRC=modified Medical Research Council; CRQ=Chronic Respiratory Questionnaire; HADS=Hospital Anxiety and Depression Scale. *p<0.05

The total study population of COPD patients demonstrated significant correlations between the number of COPD exacerbation-free days and health outcomes, except for the anxiety and depression domain of the HADS (see Table 5). Strong associations were found of a higher number of COPD exacerbation-free days with less frequent COPD exacerbations (r_s=-0.857, p<0.001), shorter COPD exacerbations (r_s=-0.867, p<0.001), and fewer prednisolone (r_s=-0.816, p<0.001) and antibiotics courses (r_s=-0.805, p<0.001). More interestingly are the significant relations found between more COPD exacerbation-free days and fewer hospitalisation days (r_s=-0.241, p=0.003), a lower mMRC score (r_s=-0.202, p=0.021) and better scores on the CRQ emotional functioning (r_s=0.257, p=0.003), mastery (r_s=0.172, p=0.049), dyspnoea (r_s=0.289, p=0.001), and fatigue domain (r_s=0.191, p=0.029) measured after 12 months of follow-up.

COPE-II and COPE-III patients show similar correlations. But whereas COPE-II patients showed that a higher number of COPD exacerbation-free days is significantly associated with fewer anxiety-related symptoms (r_s=-0.288, p=0.027) measured after 12 months of follow-up, this relationship is not significant in COPE-III patients (r_s=-0.154, p=0.192).

Sensitivity analyses including data with only imputations of less than four consecutive missing days resulted in comparable correlations. Two patients showed extremely few COPD exacerbation-free days (<55 days), indicating a potential chronic worsening of symptoms. Excluding these two patients resulted in similar outcomes. The significant correlations are presented visually in appendix G, figures 8-24.

Table 5: Spearman's rank correlation coefficients (r_s) of the number of COPD exacerbation-free days per patient per year with health outcomes measured after 12 months of follow-up.

	The number of COPD exacerbation-free days per patient per year					
	Total (n=147)		**COPE-II (n=64)**		**COPE-III (n=83)**	
	r_s	**p-value**	**r_s**	**p-value**	**r_s**	**p-value**
COPD exacerbations (complete dataset with imputations)						
COPD exacerbation frequency	-0.857	<0.001*	-0.799	<0.001*	-0.891	<0.001*
Duration of COPD exacerbation	-0.867	<0.001*	-0.745	<0.001*	-0.917	<0.001*
Medication-use prednisolone	-0.816	<0.001*	-0.667	<0.001*	-0.895	<0.001*
Medication-use antibiotics	-0.805	<0.001*	-0.668	<0.001*	-0.856	<0.001*
All cause hospitalisation days	-0.241	0.003*	-0.295	0.018*	-0.327	0.001*
mMRC	-0.202	0.021*	-0.393	0.002*	-0.472	<0.001*
CRQ emotions	0.257	0.003*	0.411	0.001*	0.338	0.003*
CRQ mastery	0.172	0.049*	0.276	0.034*	0.292	0.012*
CRQ dyspnoea	0.289	0.001*	0.384	0.003*	0.389	0.001*
CRQ fatigue	0.191	0.029*	0.362	0.005*	0.258	0.028*
HADS anxiety	-0.100	0.253	-0.288	0.027*	-0.154	0.192
HADS depression	-0.151	0.085	-0.293	0.025*	-0.281	0.016*
COPD exacerbations (dataset with only						

imputations <4 consecutive missing days)						
COPD exacerbation frequency	-0.697	<0.001*	-0.699	<0.001*	-0.667	<0.001*
Duration of COPD exacerbation	-0.735	<0.001*	-0.699	<0.001*	-0.721	<0.001*
Medication-use prednisolone	-0.668	<0.001*	-0.580	<0.001*	-0.692	<0.001*
Medication-use antibiotics	-0.660	<0.001*	-0.548	<0.001*	-0.698	<0.001*
All cause hospitalisation days	-0.277	0.001*	-0.289	0.021*	-0.354	0.001*
mMRC	-0.233	0.007*	-0.334	0.010*	-0.479	<0.001*
CRQ emotions	0.255	0.003*	0.372	0.009*	0.311	0.007*
CRQ mastery	0.179	0.040*	0.221	0.092	0.297	0.011*
CRQ dyspnoea	0.296	0.001*	0.337	0.009*	0.395	0.001*
CRQ fatigue	0.178	0.041*	0.286	0.028*	0.216	0.067
HADS anxiety	-0.143	0.101	-0.266	0.041*	-0.201	0.088
HADS depression	-0.174	0.046*	-0.256	<0.050*	-0.283	0.015*

Abbreviations: COPD=Chronic Obstructive Pulmonary Disease; CRQ=Chronic Respiratory Questionnaire; HADS=Hospital Anxiety and Depression Scale. *p<0.05

Differences in the number of COPD exacerbation-free days for gender, smoking status, and action plan adherence

The total group of COPD patients showed a significant between-group difference in COPD exacerbation-free days for gender, smoking status, and action plan adherence (see Table 6). Men (median=353) presented a significantly higher number of COPD exacerbation-free days per patient per year than women (median=340, p<0.050). Also, patients who quit smoking or never smoked (median=352) had more COPD exacerbation-free days compared to current smokers (median=336, p=0.005). Additionally, the number of COPD exacerbation-free days differed significantly between the four action plan adherence categories (p<0.001). Further analyses revealed that patients categorised as 'optimal treatment' (median=338) had a significantly higher number of COPD exacerbation-free days relative to patients categorised as 'significant delay or no treatment' (median=302, p=0.016) (see appendix F, Table 7). Furthermore, patients in the 'treatment outside the actual exacerbation period' category (median=360) had significantly more COPD exacerbation-free days per patient per year than patients in the 'optimal treatment' (median=338, p<0.001), 'sub-optimal treatment' (median=333, p<0.001), and 'significant delay or no treatment' (median=302, p<0.001) categories. No significant between-group difference was found in patients' adherence to action plans recoded in an 'optimal adherence' and 'sub-optimal/non-adherence' category (see appendix F, Table 8).

Distinguishing between COPE-II and COPE-III patients, the results demonstrated in the COPE-II population a significant difference in COPD exacerbation-free days for men versus women, smoker compared to non-smokers, and between the four action plan adherence categories, while in the COPE-III population COPD exacerbation-free days only differed between the four action plan adherence categories. COPE-II patients in the 'treatment outside the actual exacerbation period' group (median=351) had a significantly higher number of COPD exacerbation-free days compared to patients

in the 'significant delay or no treatment' group (median=291, p=0.004). This contrasts with COPE-III patients, where patients categorised as 'treatment outside the actual exacerbation period' (median=365) had significantly more COPD exacerbation-free days than patients categorised as 'optimal treatment' (median=339, p<0.001), 'sub-optimal treatment' (median=332, p=0.012) and 'significant delay or no treatment' (median=311, p<0.001). Only COPE-III patients demonstrated a significant difference in the number of COPD exacerbation-free days between the two recoded action plan adherence categories, where patients in the 'sub-optimal/non-adherence' group (median=356) had more COPD exacerbation-free days compared to patients in the 'optimal adherence' group (median=339, p=0.040) (see appendix F, Table 8).

Sensitivity analyses including data with only imputations of less than four consecutive missing days showed similar results.

Table 6: Results from Mann-Whitney U and Kruskal-Wallis analyses for between-group differences in the number of COPD exacerbation-free days per patient per year.

	Total (n=147)		**COPE-II (n=64)**		**COPE-III (n=83)**	
	Median (IQR)	**p-value**	**Median (IQR)**	**p-value**	**Median (IQR)**	**p-value**
COPD exacerbations (complete dataset with imputations ≥4 consecutive days)						
Gender		<0.050*		0.036*		0.467
Male	353 (329-365)		342 (321-358)		357 (333-365)	
Female	340 (303-356)		321 (285-346)		348 (331-365)	
Smoking		0.005*		0.008*		0.307
Current smoker	336 (291-355)		314 (259-346)		351 (310-364)	
Non-smoker	352 (324-365)		339 (320-358)		357 (333-365)	
Action plan adherence		<0.001*		0.010*		<0.001*
Optimal	338 (316-349)		331 (313-345)		339 (314-354)	
Sub-optimal	333 (320-352)		334 (317-352)		332 (325-359)	
Significant delay or no treatment	302 (252-340)		291 (250-341)		311 (241-344)	
Treatment outside the actual exacerbation period	360 (349-365)		351 (330-359)		365 (356-365)	
COPD exacerbations (dataset only with imputations <4 consecutive days)						
Gender		0.037*		0.030*		0.413
Male	346 (303-361)		338 (303-357)		353 (303-364)	
Female	321 (291-350)		317 (271-343)		339 (304-356)	
Smoking		0.007*		0.015*		0.246
Current smoker	318 (275-350)		300 (245-346)		341 (296-356)	
Non-smoker	343 (303-361)		334 (300-357)		347 (304-364)	
Action plan adherence		<0.001*		0.032*		<0.001*
Optimal	331 (288-349)		331 (313-345)		324 (277-353)	
Sub-optimal	330 (310-352)		327 (307-352)		330 (306-359)	

Significant delay or no treatment	296 (245-340)	285 (245-341)	303 (238-336)
Treatment outside the actual exacerbation period	357 (334-365)	344 (302-359)	360 (344-365)

***p<0.05**

DISCUSSION

In these analyses, we explored how COPD exacerbation-free time relates to baseline characteristics and health outcomes in COPD patients with and without comorbidities using exacerbation action plans. Less baseline dyspnoea severity, better emotional functioning at baseline, having more comorbidities, being a man, and non-smoking were related to more COPD exacerbation-free days. Furthermore, more COPD exacerbation-free days were associated with less frequent and shorter COPD exacerbations, a lower number of both prednisolone and antibiotics courses, fewer hospitalisation days, less dyspnoea severity, and better HRQoL measured after 12 months of follow-up. COPD patients of whom adherence to the action plan was categorised as 'optimal treatment' had more COPD exacerbation-free days relative to patients categorised as 'significant delay or no treatment'. Also, patients in the 'treatment outside the actual exacerbation period' group had more COPD exacerbation-free days than patients in the 'optimal treatment', 'sub-optimal treatment', or 'significant delay or no treatment' group. The associations were largely similar for COPE-II versus COPE-III patients, except for the baseline dyspnoea severity, emotional functioning, mastery, depression-related symptoms, gender, and smoking status, and the anxiety-related symptoms measured after 12 months of follow-up. Finally, COPE-III patients showed more COPD exacerbation-free days in the recoded 'sub-optimal/non-adherence' category relative to the 'optimal adherence' category.

Before the analyses, we hypothesised that the number of COPD exacerbation-free days would be moderately correlated to baseline characteristics and health outcomes. The results were partly in line with the hypothesis, as we observed moderate (r_s=0.30-0.69) associations, but weak (r_s=0.00-0.29) and strong (r_s=0.70-1.00) associations as well. Firstly, we will focus on the baseline characteristics. COPD exacerbation-free time is quite a new outcome measure, with the consequence that only a few studies used it as an outcome measure. Our results seem consistent with previous evidence (36,46) that less baseline dyspnoea severity is correlated to fewer COPD exacerbations, and subsequently more COPD exacerbation-free days. This may be explained by the fact that COPD exacerbations become more frequent as the dyspnoea worsens (11). We also found that better emotional functioning at baseline measured with the CRQ is related to more COPD exacerbation-free days, suggesting that if the patient is satisfied in general and concerning his symptoms, a COPD exacerbation is less likely to be triggered. There is evidence that poor HRQoL measured with the St. George's Respiratory Questionnaire is associated with a higher COPD exacerbation frequency (47,48). However, to our knowledge, there are no data in the literature analysing the CRQ ability to predict COPD exacerbations. Remarkably, having more comorbidities is related to a higher number of COPD exacerbation-free days. Whereas COPD

patients with comorbidities may have experienced fewer COPD exacerbations, i.e. more COPD exacerbation-free days, this does not mean they have been free from exacerbations as they may well have suffered from comorbidity-related exacerbations. These comorbidity-related exacerbations may actually have been COPD exacerbations as the symptoms may overlap (49). This could have incorrectly resulted in more COPD exacerbation-free days. Furthermore, our results seem consistent with previous evidence that women develop more COPD exacerbations, so experience fewer COPD exacerbation-free days, than men (50). But male patients had, almost significantly ($p=0.052$), more comorbidities and better emotional functioning relative to female patients (see appendix F, Table 9), as underlined by Grabicki et al. (50). This may have affected the results since we performed univariate analysis and having more comorbidities and better emotional functioning seems to be related to more COPD exacerbation-free days. This observation shows that multivariate analysis is needed to determine whether the COPD exacerbation-free days actually differed between men and women. Additionally, patients who quit smoking or never smoked showed more COPD exacerbation-free days than current smokers, which is in line with previous research (14,36). The fact that smoking can trigger a COPD exacerbation can explain this finding (7). Moreover, this finding supports smoking cessation in the treatment of COPD (14).

As expected, a higher number of COPD exacerbation-free days is strongly correlated to less frequent and shorter COPD exacerbations since their calculations are linked. Moreover, the action plan guided the patients to start a prednisolone course in case of a COPD exacerbation and additionally an antibiotics course if the sputum colour changed (31,33), which explains the strong association between more COPD exacerbation-free days and less prednisolone and antibiotics courses. COPD exacerbations can lead to hospitalisations (7,8,13), and therefore it was expected to find that more COPD exacerbation-free days are correlated to fewer all-cause hospitalisation days. Furthermore, our results showed that patients having more COPD exacerbation-free days had less dyspnoea severity measured after 12 months of follow-up. Patients who suffered from COPD exacerbations may not have been returned to baseline dyspnoea severity, resulting in a higher mMRC score. Previous evidence suggested that COPD exacerbations reduce patients' HRQoL (8,12,14,36). Although the correlations were weak, our findings demonstrated that patients having more COPD exacerbation-free days had a better overall HRQoL measured with the CRQ, with better emotional functioning and mastery, and less dyspnoea-related symptoms and fatigue. CRQ scores were based on the patients' experiences two weeks before administration, which may have been influenced by whether or not the patient experienced a COPD exacerbation during these two weeks. Patients were taught when to start self-treatment of exacerbations via their action plan, and each patient was categorised based on their adherence to the action plan (43). Patients who started a prednisolone course on the day of or one day prior/after the onset of a COPD exacerbation showed a higher number of COPD exacerbation-free days than patients who initiated a prednisolone course later ($\geq$3 days after onset of a COPD exacerbation) or not at all. Previous evidence underlines this since prompt self-treatment guided by action plans has been shown to shorten COPD

exacerbations which implies more COPD exacerbation-free days (24,31–33). Remarkably, patients in the ‘treatment outside the actual exacerbation period’ group had more COPD exacerbation-free days than patients in the ‘optimal treatment’, ‘sub-optimal treatment’, or ‘significant delay or no treatment’ group. Half of the patients categorised as 'treatment outside the actual exacerbation period' started a prednisolone course more than three days before the onset of a COPD exacerbation (43). This may have prevented or shortened the impending COPD exacerbation, leading to a greater number of COPD exacerbation-free days. An alternative explanation may be that patients who started a prednisolone course after the COPD exacerbation recovery or without having an actual COPD exacerbation were treating overlapping symptoms from a comorbidity-related exacerbation (43,49).

In addition, we expected more strongly correlations between COPD exacerbation-free days and the baseline dyspnoea-, anxiety-, and depression-related symptoms in COPE-III versus COPE-II patients. COPE-II patients had no or non-severe comorbidities and only used COPD exacerbation action plans (31), while COPE-III patients had at least one, severe or non-severe, comorbidity and used both COPD and tailored comorbidity exacerbation action plans (33,39). As expected, less baseline dyspnoea severity is more strongly associated with more COPD exacerbation-free days in COPD patients with comorbidities relative to COPD patients with no or non-severe comorbidities. This can be explained by the fact that COPD patients with comorbidities had more severe dyspnoea compared to COPD patients with no or non-severe comorbidities, more severe dyspnoea contributes to more COPD exacerbations end thus less COPD exacerbation-free days (20). We did not expect to find that better emotional functioning and mastery at baseline is related to more COPD exacerbation-free days in COPD patients with comorbidities, and not in COPD patients with no or non-severe comorbidities. COPD patients with comorbidities had a lower CRQ emotional functioning score and significantly lower CRQ mastery score in comparison to COPD patients with no or non-severe comorbidities, indicating a lower HRQoL, as underlined by Koskela et al. (51). The lower HRQoL might be associated with less COPD exacerbation-free days (47,48). To continue, we found that COPD patients with comorbidities with less depression-related symptoms at baseline had more COPD exacerbation-free days, while COPD patients with no or non-severe comorbidities did not show this relation. Depression-related symptoms can trigger a COPD exacerbation (21), which may explain this difference since COPD patients with comorbidities suffered from significantly more baseline depression-related symptoms measured with the HADS compared to COPD patients with no or non-severe comorbidities. Also against our expectation are the different correlations of gender and smoking status with COPD exacerbation-free days we found between COPD patients with no or non-severe comorbidities versus COPD patients with comorbidities. Only in COPD patients with no or non-severe comorbidities, men showed more COPD exacerbation-free days compared to women, which may be explained by the fact that male patients had more comorbidities than women (see appendix F, Table 9). According to our results, having more comorbidities is related to a higher number of COPD exacerbation-free days. Again, multivariate analysis should rule out if there was a difference in COPD exacerbation-free days between men and women. In addition, COPD patients

with no or non-severe comorbidities who smoked had less COPD exacerbation-free days than non-smokers. Smoking is a risk factor for both COPD and comorbidity-related exacerbations (6,17), so COPD patients with comorbidities who smoked may have experienced comorbidity-related exacerbations instead of COPD exacerbations resulting in a small difference in the number of COPD exacerbation-free days between smokers and non-smokers.

COPD patients with no or non-severe comorbidities showed that more COPD exacerbation-free days are associated with fewer anxiety- and depression-related symptoms measured after 12 months of follow-up, while COPD patients with comorbidities only showed that more COPD exacerbation-free days is related to less depression-related symptoms. In the population of COPD patients with comorbidities, COPD patients diagnosed with anxiety and/or depression received tailored action plans about how to cope with feelings of anxiety and/or depression, these feeling may have been caused by COPD exacerbations. Adherence to the action plan may have ensured that feelings of anxiety and depression due to COPD exacerbations were reduced, weakening the correlations between COPD exacerbation-free days and anxiety- and depression-related symptoms. In general, our findings are consistent with previous literature that patients who suffered from COPD exacerbations have higher HADS scores indicating more anxiety- and depression-related symptoms (52,53). In other words, COPD exacerbations can trigger feelings of anxiety and depression. The HADS score was based on what the patient experienced in the four weeks before administration, which may have been influenced by whether or not the patient experienced a COPD exacerbation during these four weeks.

Strength and limitations

A strength of this analyses is the large and heterogeneous study sample, derived from two randomised controlled trials including COPD patients with and without comorbidities. In addition, a variety of different outcome measures could be included in the analyses, so that a broad picture could be formed about how COPD exacerbation-free time is related to baseline characteristics and health outcomes. Boer et al. (36) indicated that a timeframe of two weeks may not be detailed enough for the measurement of COPD exacerbation-free time, so another strength of the present analyses is basing COPD exacerbation data on daily symptom diaries.

However, this study has also limitations. Firstly, the COPD exacerbation data is based on what patients themselves experienced as a COPD exacerbation. This may have resulted in variation between the patients, as patients may have experienced the same increase of symptoms differently. Secondly, our approach and interpretation of missing diary data may have influenced the results. We assumed that if a patient experienced several COPD exacerbation-free days during a period (<365 days) this is proportional to the number of COPD exacerbation-free days over 365 days since prior COPD exacerbations are an important predictor of future COPD exacerbations (47,48). Although, it is an important predictor does not necessarily mean it is always the case. But sensitivity analyses revealed comparable results indicating that our imputation approach did not or slightly influenced the results.

Furthermore, patients were excluded if less than 75% of their dairy data was known. The exclusion of patients can also be seen as a limitation since valuable information may have been lost. Nonetheless, most of the excluded patients had more than 150 missing diary days, which outweighed the value of retaining the patients and imputing their missing diary data. A last limitation of the present study is that we performed only univariate analyses. However, various parameters might influence the number of COPD exacerbation-free days. To our knowledge, how COPD exacerbation-free time is related to all the included baseline characteristics and health outcomes has not been described before. This and the fact that univariate analyses acts as a precursor to multivariate analyses and is necessary for understanding the multivariate analyses (54), has made us decide to perform only univariate analyses in this study.

Implications for future research

Future studies should execute multivariate analyses and use larger study populations to explore COPD exacerbation-free time. In addition, in the current analyses, we only focussed on COPD exacerbation-free time, while COPD patients with comorbidities also may have suffered from comorbidity-related exacerbations throughout the 12 months of follow-up. We recommend that future studies should focus on how overall exacerbation-free time is related to baseline characteristics and health outcomes in COPD patients using exacerbation action plans, but in COPD patients receiving usual care as well. Also, the patients participated in a self-treatment intervention including exacerbation action plans, which might have affected how the number of COPD exacerbation-free days progresses over the year since there may be a learning effect. It would be interesting to investigate how the number of COPD exacerbation-free days is distributed over the year from start to end of the intervention, but also whether there is a difference in the number of COPD exacerbation-free days between the four seasons.

CONCLUSION

In conclusion, COPD exacerbation-free time is not only related to dyspnoea severity and HRQoL but to anxiety- and depression-related symptoms as well. We also observed that current smokers had less COPD exacerbation-free time relative to patients who quit smoking or never smoked. In addition, our results encourage prompt self-treatment of COPD exacerbations, instead of delayed or no self-treatment at all to have more COPD exacerbation-free time. In COPD patients with comorbidities, less dyspnoea severity, better emotional functioning and mastery, and fewer depression-related symptoms at baseline are more strongly related to more COPD exacerbation-free time than in COPD patients with no or non-severe comorbidities. In clinical practice, health care providers should be aware that if the patient functions emotionally fine and is well in control of his symptoms this could be associated with more COPD exacerbation-free time. Additionally, that COPD exacerbations may trigger feelings of anxiety and depression, and negatively affects the patients' dyspnoea severity and overall HRQoL.

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APPENDIX

Appendix A. Predefined algorithm missing data of <4 consecutive days

If there were fewer than four consecutive days of missing COPD symptom scores, these were manually completed using a predefined algorithm that combined the last observation carried forward and next observation carried backward to the missing value:

One missing COPD symptom score:

- Mean of three scores before the missing score

Two consecutive missing COPD symptom scores:

- First missing score: mean of three scores before the missing score
- Second missing score: mean of three scores after the last missing score

Three consecutive missing COPD symptom scores:

- First two missing scores: mean of three scores before the first missing scores
- Third missing score: mean of three scores after the last missing scores

Missing hospital admission day: maximalisation of COPD symptom scores for the missing score.

Figure 3: Predefined algorithm missing COPD symptom scores and hospital admission days (33).

Appendix B. 'What are my "usual" symptoms' card

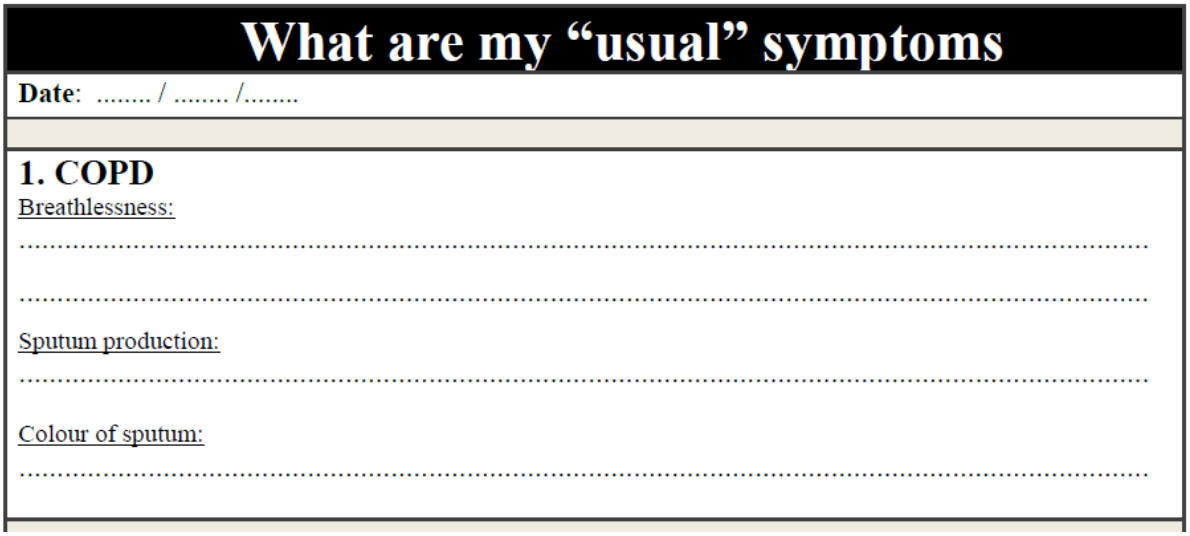

Figure 4: 'What are my "usual" symptoms' card for the COPD symptoms (33).

Appendix C. Daily symptom diary of COPD symptoms

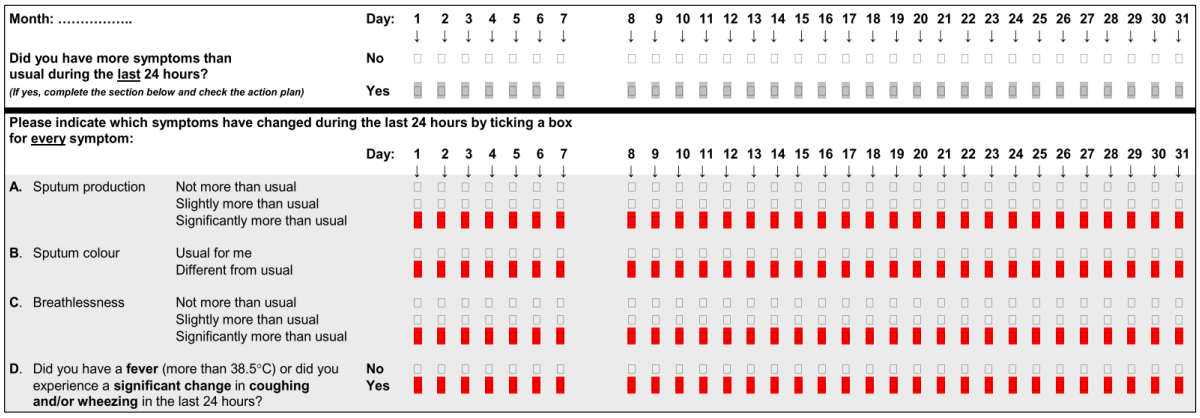

Figure 5: Daily symptom diary for COPD (33).

Appendix D. Patient-tailored action plan for COPD

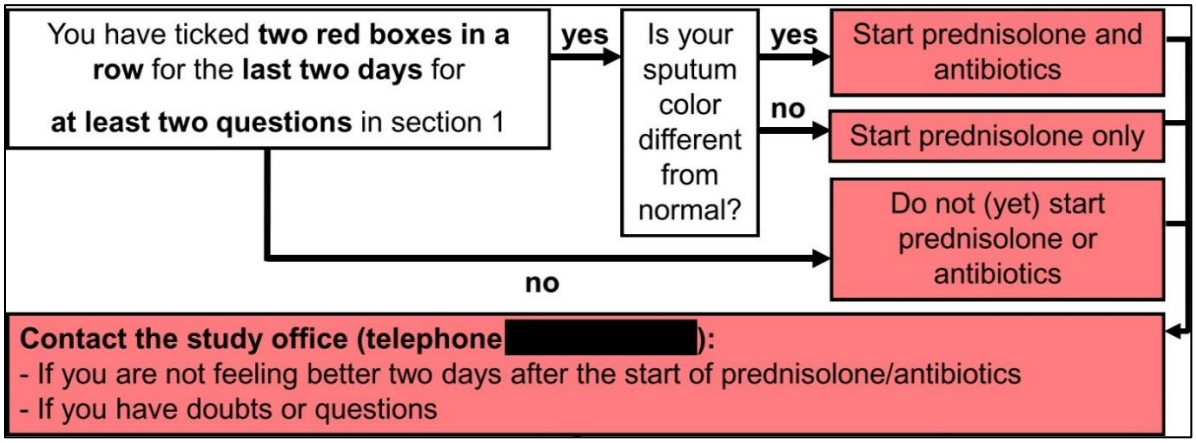

Figure 6: Patient-tailored exacerbation action plan for the self-treatment of a COPD exacerbation (33).

Appendix E. Action plan adherence categories

Optimal treatment	Prednisolone course initiated at the day of exacerbation onset
	Prednisolone course initiated 1 day prior to onset of exacerbation
	Prednisolone course initiated 1 day after onset of exacerbation
Sub optimal treatment	Prednisolone course initiated 2 days prior to onset of exacerbation
	Prednisolone course initiated 2 days after onset of exacerbation
	No prednisolone course initiated, exacerbation duration ≥1 and ≤3 days
Significant delay or no treatment	No prednisolone course initiated, exacerbation duration ≥4 days
	Prednisolone course initiated ≥3 days after onset of exacerbation, but before exacerbation recovery
Treatment outside the actual exacerbation period	Prednisolone course initiated, but no actual exacerbation
	Prednisolone course initiated ≥3 days prior to onset of exacerbation
	Prednisolone course initiated after exacerbation recovery

Figure 7: Categories of action plan adherence. Classification of self-treatment actions into patient adherence to COPD exacerbation action plans based on the time difference between the self-initiation a prednisolone course and the onset of the COPD exacerbation (43).

Appendix F. Supplementary tables results

Table 7: Results from Mann-Whitney U analyses for between-group differences of the number of COPD exacerbation-free days per patient per year in action plan adherence.

	Total (n=127)		COPE-II (n=58)		COPE-III (n=69)	
	Median (IQR)	p-value	Median (IQR)	p-value	Median (IQR)	p-value
COPD exacerbations (complete dataset with imputations)						
Optimal	338 (316-349)	0.828	331 (313-345)	0.558	339 (314-354)	0.766
Sub-optimal	333 (320-352)		334 (317-352)		332 (325-359)	
Optimal	338 (316-349)	0.016*	331 (313-345)	0.112	339 (314-354)	0.083
Significant delay or no treatment	302 (252-340)		291 (250-341)		311 (241-344)	
Optimal	338 (316-349)	<0.001*	331 (313-345)	0.037	339 (314-354)	<0.001*
Treatment outside the actual exacerbation period	360 (349-365)		351 (330-359)		365 (356-365)	
Sub-optimal	333 (320-352)	0.028	334 (317-352)	0.100	332 (325-359)	0.108
Significant delay or no treatment	302 (252-340)		291 (250-341)		311 (241-344)	
Sub-optimal	333 (320-352)	<0.001*	334 (317-352)	0.075	332 (325-359)	0.012*
Treatment outside the actual exacerbation period	360 (349-365)		351 (330-359)		365 (356-365)	
Significant delay or no treatment	302 (252-340)	<0.001*	291 (250-341)	0.004*	311 (241-344)	<0.001*
Treatment outside the actual exacerbation period	360 (349-365)		351 (330-359)		365 (356-365)	
COPD exacerbations (dataset with only imputations <4 consecutive missing days)						
Optimal	331 (288-349)	0.568	331 (313-345)	0.860	324 (277-353)	0.332
Sub-optimal	330 (310-352)		327 (307-352)		330 (306-359)	
Optimal	331 (288-349)	0.026	331 (313-345)	0.060	324 (277-353)	0.262
Significant delay or no treatment	296 (245-340)		285 (245-341)		303 (238-336)	
Optimal	331 (288-349)	<0.001*	331 (313-345)	0.280	324 (277-353)	<0.001*
Treatment outside the actual exacerbation period	357 (334-365)		344 (302-359)		360 (344-365)	
Sub-optimal	330 (310-352)	0.018	327 (307-352)	0.077	330 (306-359)	0.117
Significant delay or no treatment	296 (245-340)		285 (245-341)		303 (238-336)	
Sub-optimal	330 (310-352)	0.007*	327 (307-352)	0.356	330 (306-359)	0.080
Treatment outside the actual exacerbation period	357 (334-365)		344 (302-359)		360 (344-365)	
Significant delay or no treatment	296 (245-340)	<0.001*	285 (245-341)	0.009	303 (238-336)	<0.001*
Treatment outside the actual exacerbation period	357 (334-365)		344 (302-359)		360 (344-365)	

p-value according to Bonferroni-Holm correction = α/(K-i+1), whereas α is 0.05, K is the number of performed tests (6 in this case), and i indicates the i-th ordered p-value (45).

Table 8: Results from Mann-Whitney U analyses for between-group differences of the number of COPD exacerbation-free days per patient per year in action plan adherence. Action plan adherence is divided in two groups. The 'optimal treatment' group is renamed as 'optimal adherence' group. The 'sub-optimal treatment', 'significant delay or no treatment', and 'treatment outside the actual exacerbation period' groups are merged into the 'sub-optimal/non-adherence' group.

	Total (n=127)		COPE-II (n=58)		COPE-III (n=69)	
	Median (IQR)	p-value	Median (IQR)	p-value	Median (IQR)	p-value
COPD exacerbations (complete dataset with imputations)						
Optimal adherence	338 (316-349)	0.174	331 (313-345)	0.978	339 (314-354)	0.040*
Sub-optimal/non-adherence	342 (308-359)		332 (288-352)		356 (326-365)	
COPD exacerbations (dataset only with imputations <4 consecutive days)						
Optimal adherence	331 (288-349)	0.315	331 (313-345)	0.537	324 (277-353)	0.056
Sub-optimal/non-adherence	334 (295-357)		319 (282-352)		347 (316-362)	

The 'optimal adherence' category consisted of 32 (25.3%), 14 (24.1%), 18 (26.1%) patients in the total COPD population, COPE-II patients, and COPE-III patients, respectively. The 'sub-optimal/non-adherence' category consisted of 95 (74.8%), 44 (75.9%), 51 (73.9 %) in the total COPD population, COPE-II patients, and COPE-III patients. *p<0.05

Table 9: Results from Mann-Whitney U analyses for gender differences in baseline characteristics.

	Total (n=147)			COPE-II (n=64)			COPE-III (n=83)		
	Male	Female	p-value	Male	Female	p-value	Male	Female	p-value
Age	67.6 (±8.5)	63.6 (±8.4)	0.009*	64.8 (±7.8)	61.6 (±7.5)	0.088	69.6 (±8.6)	65.6 (±8.9)	0.136
BMI	28.3 (±6.0)	29.3 (±6.7)	0.505	27.5 (±5.0)	27.4 (±5.3)	0.883	28.9 (±6.6)	31.2 (±7.6)	0.172
GOLD	2.6 (±0.7)	2.4 (±0.7)	0.114	2.6 (±0.8)	2.5 (±0.9)	0.599	2.5 (±0.6)	2.3 (±0.5)	0.060
FEV_1 (l)	1.5 (±0.6)	1.2 (±0.4)	0.003*	1.6 (±0.6)	1.2 (±0.5)	0.017*	1.5 (±0.5)	1.3 (±0.4)	0.079
FEV_1/FVC	44.2 (±12.0)	51.7 (±14.1)	0.003*	42.3 (±10.6)	48.6 (±14.7)	0.104	45.4 (±12.7)	54.7 (±13.0)	0.005*
mMRC	1.7 (±1.1)	1.9 (±1.1)	0.241	1.2 (±1.1)	1.5 (±1.0)	0.127	2.1 (±1.0)	2.3 (±1.0)	0.269
Comorb	1.1 (±1.0)	0.8 (±1.0)	0.052	0.4 (±0.5)	0.1 (±0.3)	0.048*	1.7 (±0.8)	1.7 (±0.8)	0.869
CRQ dyspnoea	4.5 (±1.3)	4.4 (±1.5)	0.776	4.9 (±1.2)	4.3 (±1.6)	0.088	4.2 (±1.3)	4.5 (±1.4)	0.227
CRQ emotions	5.0 (±1.1)	4.6 (±1.1)	0.035*	5.1 (±0.9)	4.8 (±1.2)	0.173	4.9 (±1.3)	4.4 (±1.0)	0.096
CRQ fatigue	4.1 (±1.2)	3.9 (±1.2)	0.196	4.5 (±1.0)	4.1 (±1.4)	0.152	3.9 (±1.2)	3.7 (±0.9)	0.558
CRQ mastery	5.1 (±1.2)	5.2 (±1.0)	0.633	5.4 (±1.0)	5.3 (±1.1)	0.571	4.8 (±1.2)	5.0 (±1.0)	0.425
HADS anxiety	5.7 (±4.2)	6.1 (±3.9)	0.538	4.2 (±3.0)	5.0 (±3.6)	0.477	6.7 (±4.5)	7.4 (±3.9)	0.643
HADS depression	5.6 (±4.0)	5.8 (±3.9)	0.675	4.2 (±3.8)	4.6 (±3.1)	0.385	6.5 (±3.8)	7.0 (±4.3)	0.715

Data is presented in mean (SD). Abbreviations: Comorb=number of comorbidities; CRQ=Chronic Respiratory Questionnaire; HADS=Hospital Anxiety and Depression Scale. *p<0.005

Appendix G. Supplementary figures results

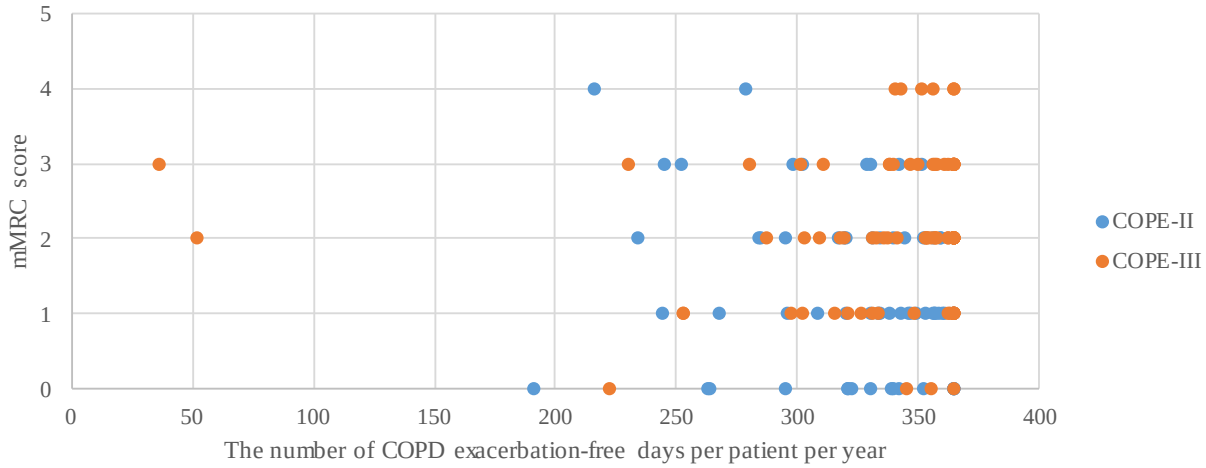

Figure 8: Scatter plot of the number of COPD exacerbation-free days per patient per year against the baseline mMRC score. Each dot represents one patient (n = 147). All dots together represent the mixed population of both COPD patients with and without comorbidities.

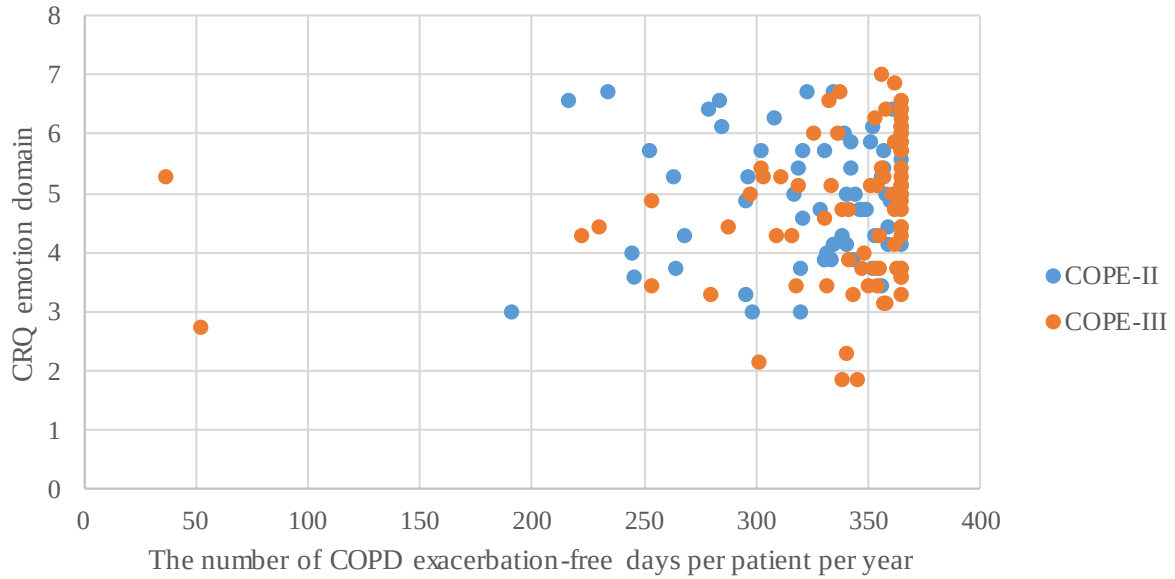

Figure 9: Scatter plot of the number of COPD exacerbation-free days per patient per year against the baseline CRQ emotion domain. Each dot represents one patient (n = 147). All dots together represent the mixed population of both COPD patients with and without comorbidities.

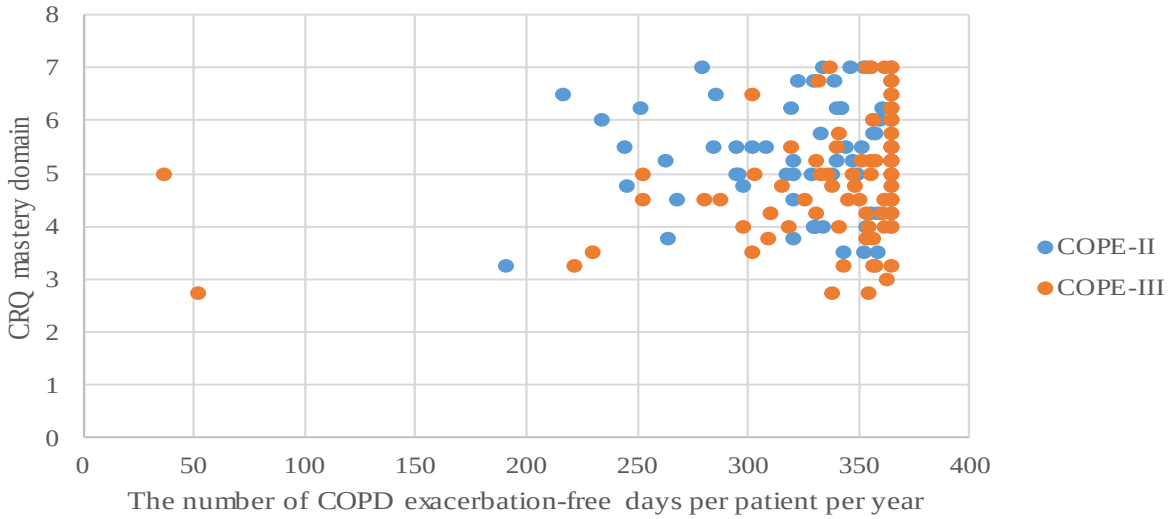

Figure 10: Scatter plot of the number of COPD exacerbation-free days per patient per year against the baseline CRQ mastery domain. Each dot represents one patient (n = 147). All dots together represent the mixed population of both COPD patients with and without comorbidities.

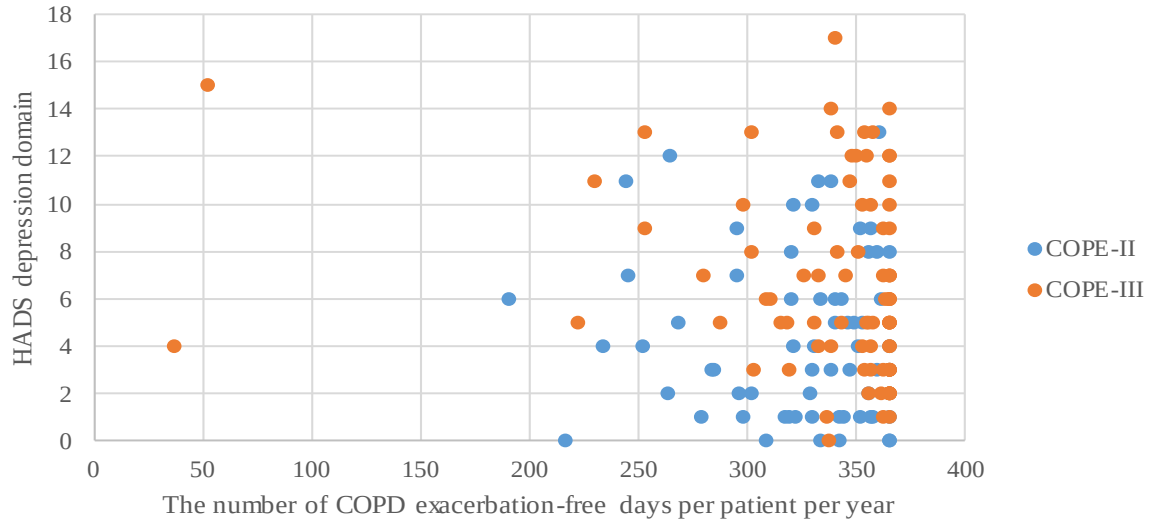

Figure 11: Scatter plot of the number of COPD exacerbation-free days per patient per year against the baseline HADS depression domain. Each dot represents one patient (n = 147). All dots together represent the mixed population of both COPD patients with and without comorbidities.

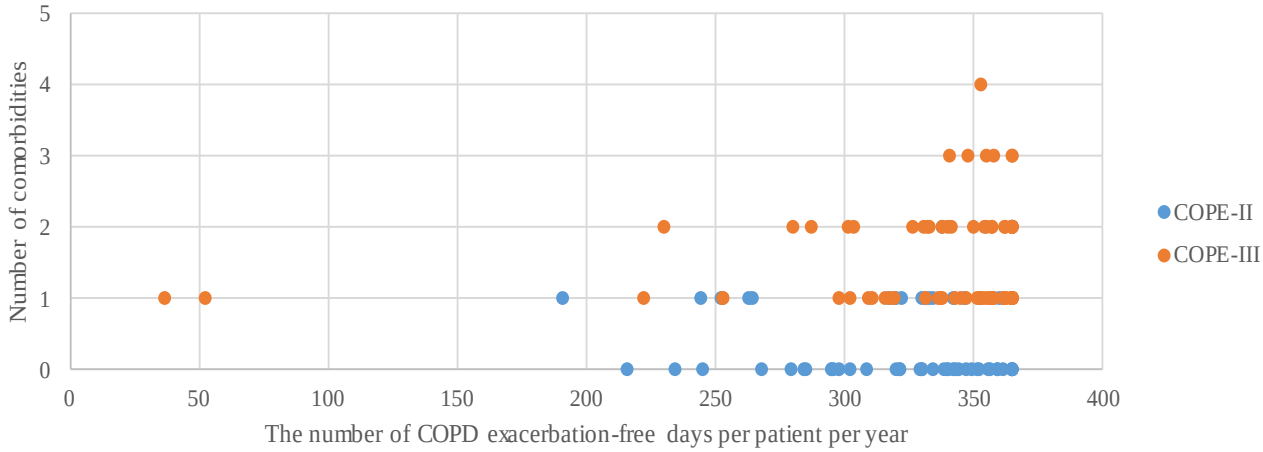

Figure 12: Scatter plot of the number of COPD exacerbation-free days per patient per year against the number of comorbidities. Each dot represents one patient (n = 147). All dots together represent the mixed population of both COPD patients with and without comorbidities.

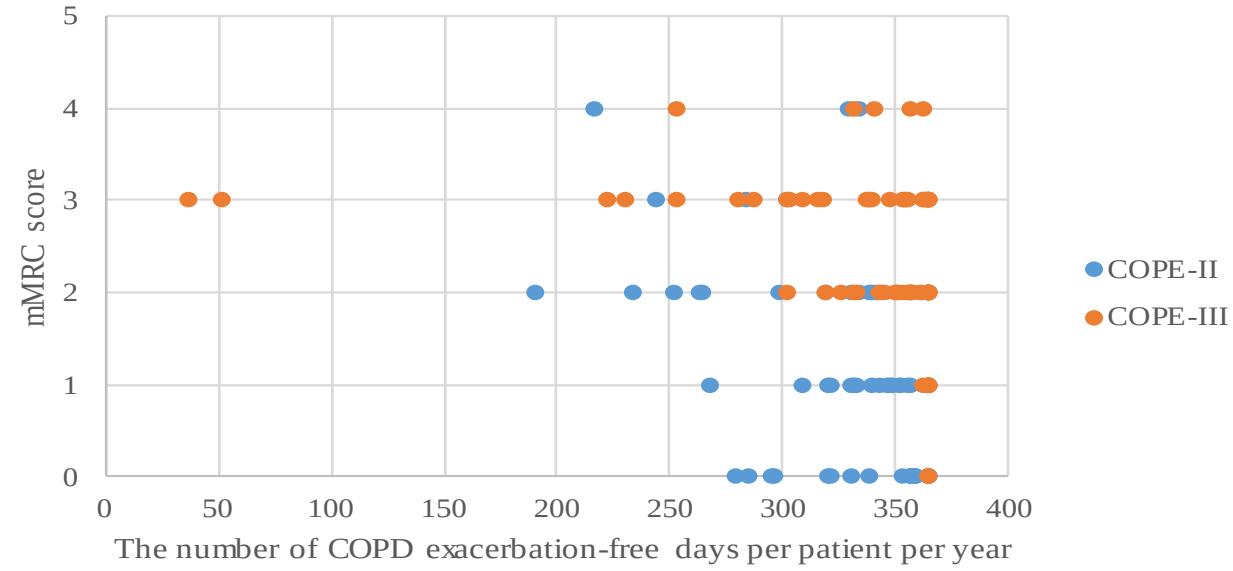

Figure 13: Scatter plot of the number of COPD exacerbation-free days per patient per year against the mMRC score measured at 12 months follow-up. Each dot represents one patient (n = 147). All dots together represent the mixed population of both COPD patients with and without comorbidities.

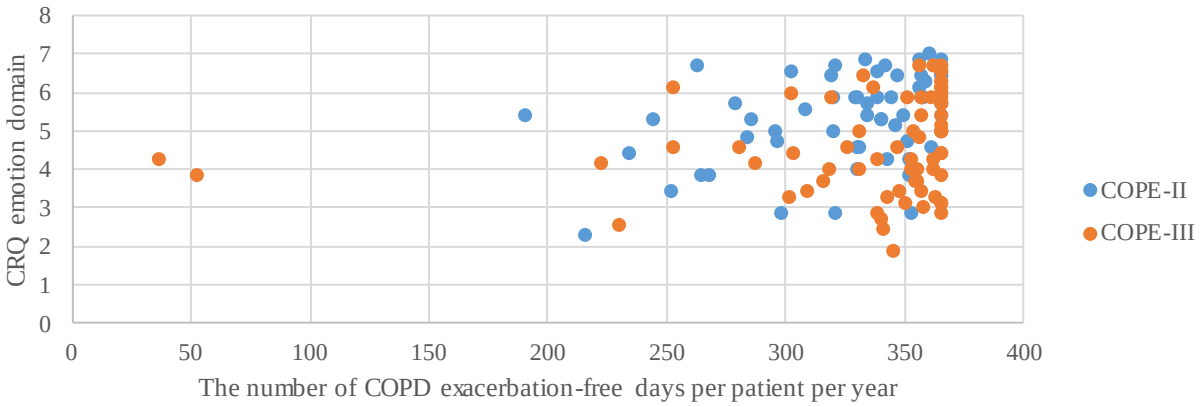

Figure 14: Scatter plot of the number of COPD exacerbation-free days per patient per year against the CRQ emotional functioning domain measured at 12 months follow-up. Each dot represents one patient (n = 147). All dots together represent the mixed population of both COPD patients with and without comorbidities.

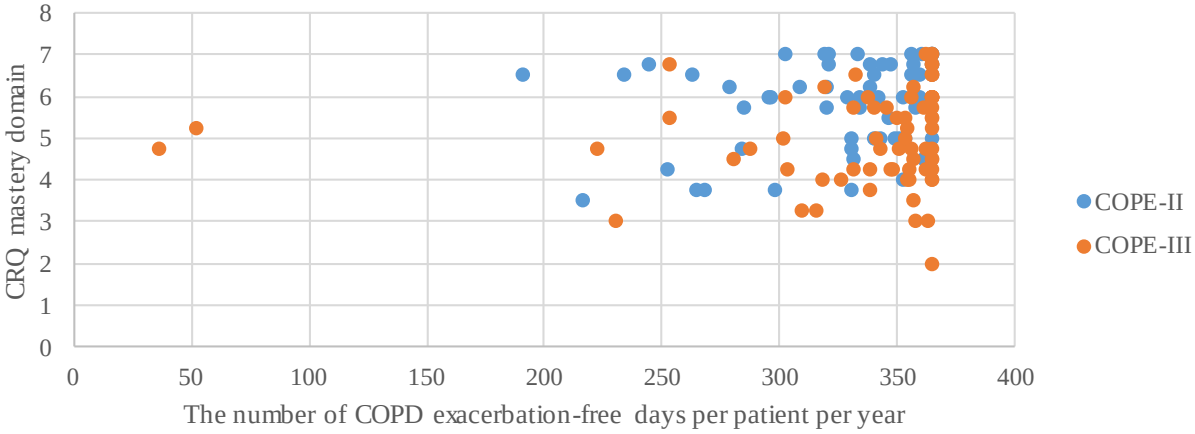

Figure 15: Scatter plot of the number of COPD exacerbation-free days per patient per year against the CRQ mastery domain measured at 12 months follow-up. Each dot represents one patient (n = 147). All dots together represent the mixed population of both COPD patients with and without comorbidities.

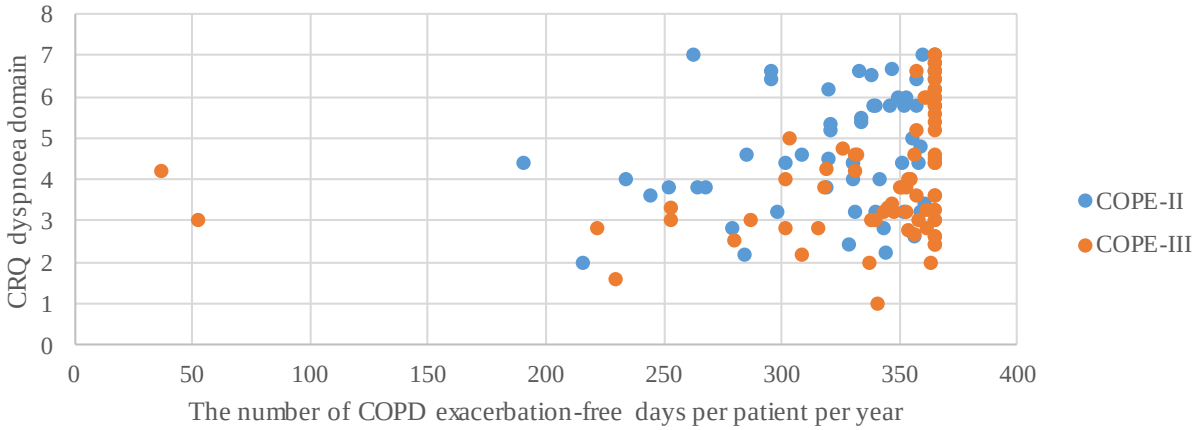

Figure 16: Scatter plot of the number of COPD exacerbation-free days per patient per year against the CRQ dyspnoea domain measured at 12 months follow-up. Each dot represents one patient (n = 147). All dots together represent the mixed population of both COPD patients with and without comorbidities.

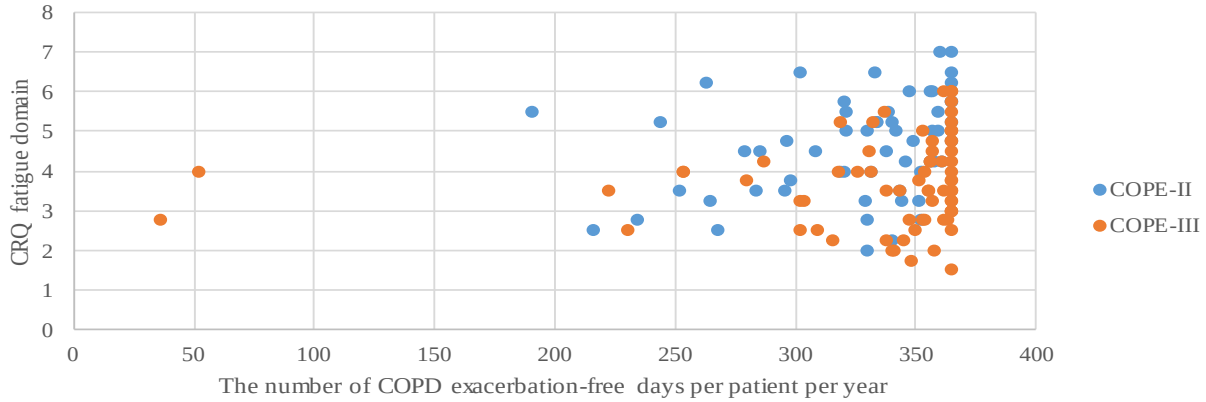

Figure 17: Scatter plot of the number of COPD exacerbation-free days per patient per year against the CRQ fatigue domain measured at 12 months follow-up. Each dot represents one patient (n = 147). All dots together represent the mixed population of both COPD patients with and without comorbidities.

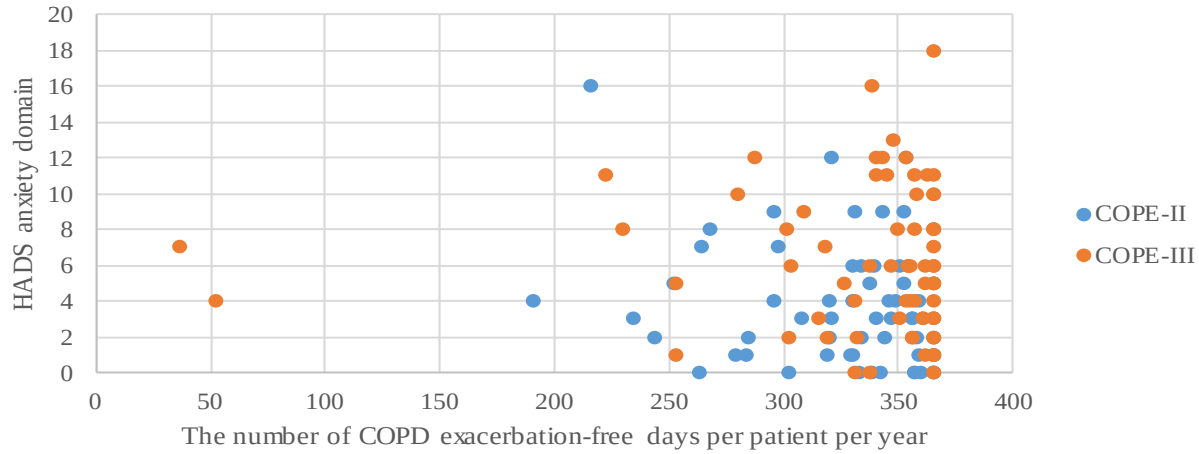

Figure 18: Scatter plot of the number of COPD exacerbation-free days per patient per year against the HADS anxiety domain measured at 12 months follow-up. Each dot represents one patient (n = 147). All dots together represent the mixed population of both COPD patients with and without comorbidities.

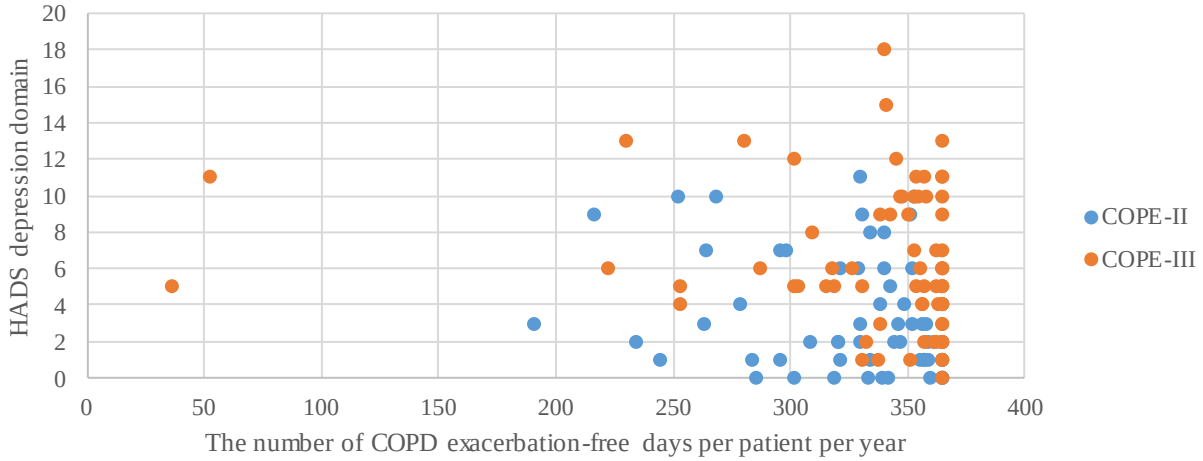

Figure 19: Scatter plot of the number of COPD exacerbation-free days per patient per year against the HADS depression domain measured at 12 months follow-up. Each dot represents one patient (n = 147). All dots together represent the mixed population of both COPD patients with and without comorbidities.

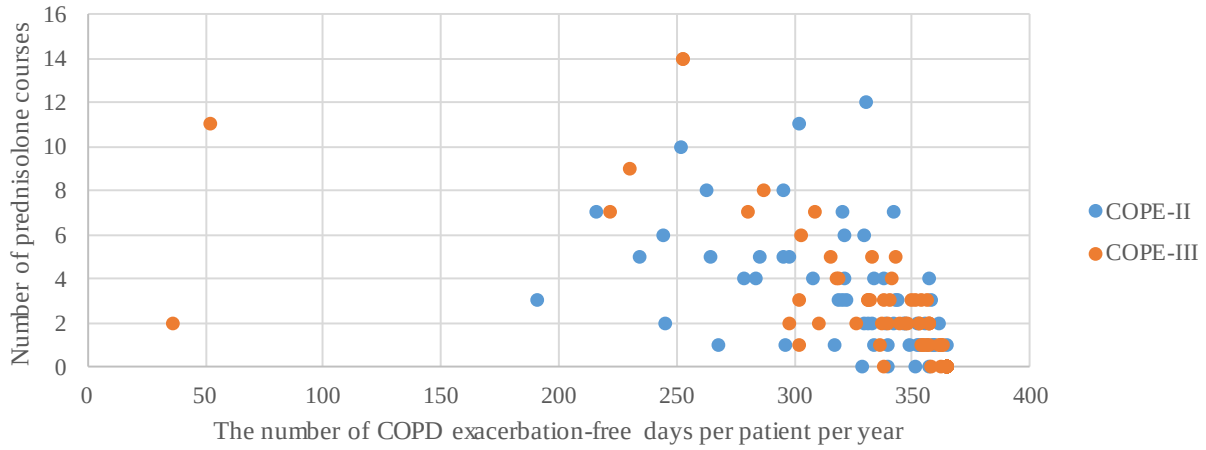

Figure 20: Scatter plot of the number of COPD exacerbation-free days per patient per year against the number of prednisolone courses. Each dot represents one patient (n = 147). All dots together represent the mixed population of both COPD patients with and without comorbidities.

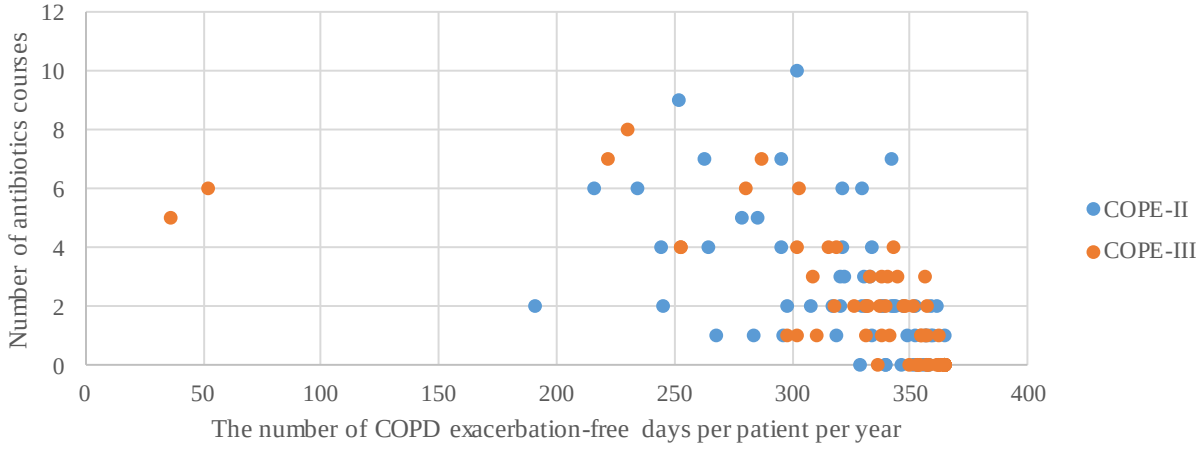

Figure 21: Scatter plot of the number of COPD exacerbation-free days per patient per year against the number of antibiotics courses. Each dot represents one patient (n = 147). All dots together represent the mixed population of both COPD patients with and without comorbidities.

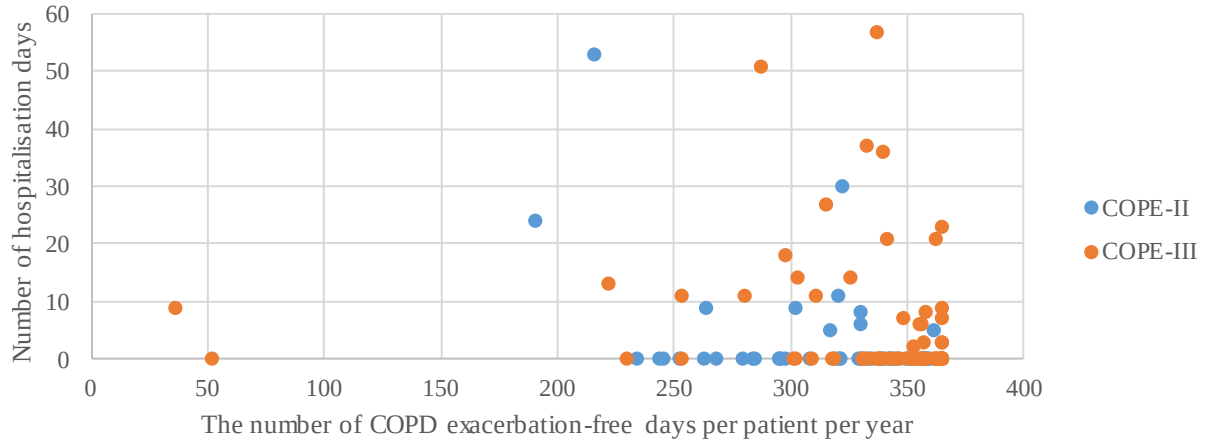

Figure 22: Scatter plot of the number of COPD exacerbation-free days per patient per year against the number of all-cause hospitalisation days. Each dot represents one patient (n = 147). All dots together represent the mixed population of both COPD patients with and without comorbidities.

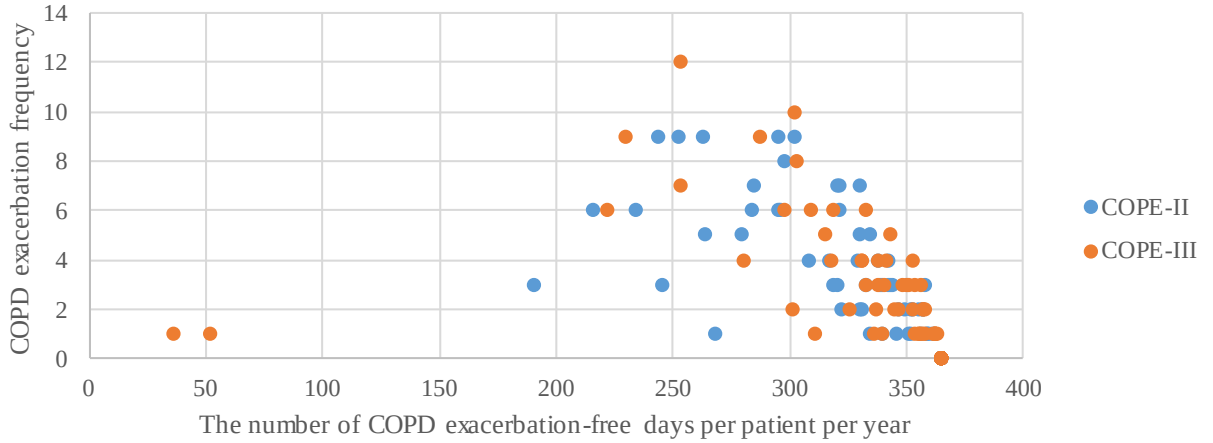

Figure 23: Scatter plot of the number of COPD exacerbation-free days per patient per year against the number of COPD exacerbations. Each dot represents one patient (n = 147). All dots together represent the mixed population of both COPD patients with and without comorbidities.

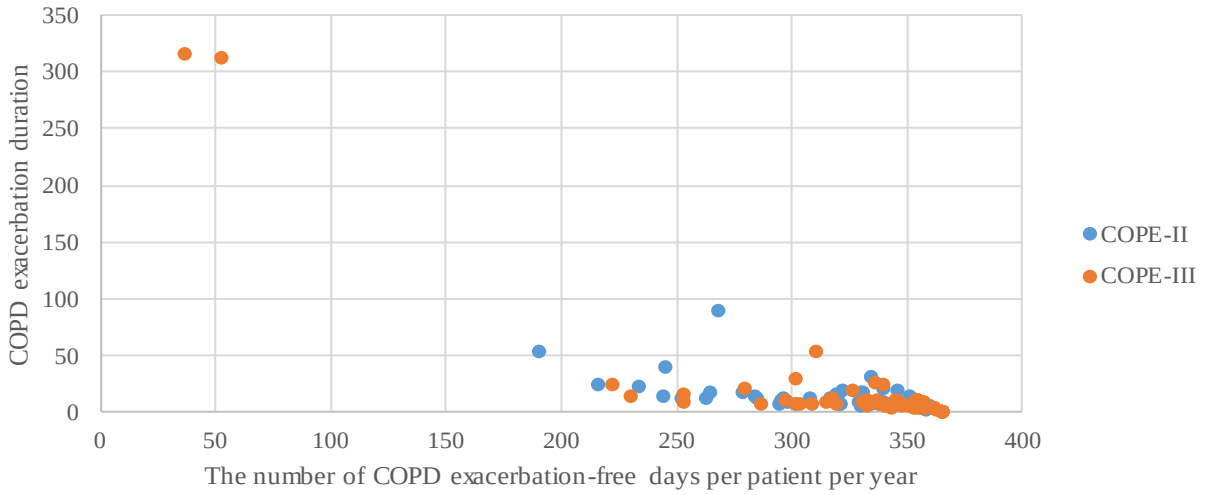

Figure 24: Scatter plot of the number of COPD exacerbation-free days per patient per year against the COPD exacerbation duration. Each dot represents one patient (n = 147). All dots together represent the mixed population of both COPD patients with and without comorbidities.