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Clinical Trial Paper

The clinical effectiveness of the COPDnet integrated care model

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A B S T R A C T

Rationale: Integrated care models have the potential to improve outcomes for patients with COPD. We therefore designed the COPDnet integrated care model and implemented it in two hospitals and affiliated primary care regions in the Netherlands. The COPDnet model consists of a comprehensive diagnostic trajectory ran in secondary care followed by a non-pharmacological intervention program of both monodisciplinary and multidisciplinary components.
Objective: To assess the clinical effectiveness of the COPDnet integrated care model on health status change in patients with COPD.
Methods: A total of 402 patients with COPD were offered care according to the COPDnet model. At baseline and between 7- and 9-months later health status was measured with the Clinical COPD Questionnaire (CCQ). Primary analysis was carried out for the sample at large. In addition, subgroup analyses were performed after stratification for the type of non-pharmacological intervention where patients had been referred to.
Results: The CCQ total score improved statistically significantly from 1.94 ± 1.04 to 1.73 ± 0.96 ($P < 0.01$) in the 154 patients with valid follow-up measurements. Subgroup analyses revealed significant improvements in the patients receiving pulmonary rehabilitation only. No change in health status was found in patients receiving pharmacotherapy only, carried out self-treatment or who participated in mono-disciplinary primary care offered by allied healthcare professionals.
Conclusions: An improved health status was found in patients with COPD who received care according to the COPDnet integrated care model. Subgroups participating in an interdisciplinary pulmonary rehabilitation program predominantly accounted for this effect.

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a highly prevalent, complex and heterogenous disease, with a huge impact for both the individual patient as for society [1]. Given this complicated nature of COPD, it is perhaps not surprising that COPD patients' global satisfaction with current management is only moderate [2]. In addition, many patients with COPD perceive a high symptom burden which restricts their daily activities [3]. Real-world care for patients with COPD, in which effective non-pharmacological interventions are markedly underutilized [4] show dissatisfactory results on health status over time [5]. Cumulatively, the results from the abovementioned studies suggest that there is substantive room for improvement in the effectiveness of the current clinical management of patients with COPD. To achieve such an improvement, a more widespread application of the principles of integrated care has been advocated [6]. Integrated care refers to a patient-centered, holistic approach in which the right care is provided at the right moment by the right caregiver [7]. In integrated care a multidimensional biopsychosocial model is pivotal instead of an unidimensional biomedical approach [8]. Indeed, integrated care models of at least three months duration hold the promise to improve disease-specific quality of life and exercise tolerance up to 12 months of follow-up and demonstrated a reduction in respiratory-related hospital admissions and hospital days per person in patients with COPD [9]. However, integrated care models appear, as yet, only limited to use in current healthcare delivery pathways. For instance, pulmonary rehabilitation, a safe and effective integrated care model, still has a very low patient referral and uptake [10]. Limited deployment of integrated care models was confirmed also in a recently performed survey in five European union countries [11]. In that paper, the authors concluded that current COPD healthcare pathways are fragmented and care is not integrated properly between healthcare tiers. Moreover, the authors

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suggested that in order to succeed in providing integrated care, knowledge from controlled studies should be translated more into practical clinical solutions.

To move forward from there, we have developed an integrated care model, named COPDnet and implemented this care model in two hospitals and affiliated primary care regions [12]. Primary goal of the COPDnet model is to improve health status by offering patient-centered care, which is based on a comprehensive assessment of the patients' needs and preferences. [6] Within the COPDnet model, a strong emphasis is put on the application of non-pharmacological interventions. The added value of the COPDnet integrated care model is evaluated with a series of interrelated studies [13]. In the current study, we assessed whether and to what extent changes in health status occurred six months after patients enrolled in this COPDnet model. Primary analysis was carried out for the sample at large. In addition, subgroup analyses were performed after stratification for the type of non-pharmacological intervention where patients had been referred to.

2. Material and methods

2.1. Study design

This real-world study was designed as a prospective, multi-centre, observational clinical trial. Interim results have been presented at the 2019 European Respiratory Society annual congress [14].

2.2. Study subjects

All patients with a first-time referral to the outpatient respiratory department of Radboudumc, Nijmegen, and Bernhoven Hospital, Uden, both in the Netherlands, and a confirmed diagnosis of COPD [1] were deemed eligible for participation. Patients were excluded from this study if they had had an acute exacerbation in the three months prior to the referral, if they had any impairment considerably limiting life expectancy, if they had a cognitive impairment, or if they were unable to fill out questionnaires. Inclusion started from the moment the COPDnet model was implemented in both the hospital and affiliated primary care region. For Radboudumc this was as of October 2014, whereas Bernhoven started by April 2016. Based on the estimated number of patients needed to be included in this study, and, based on historical referral rates, it was foreseen that recruitment could be completed by September 2017. The study was conducted in accordance with European Union directive 2001/20/EC and the Declaration of Helsinki. The Research Ethics Committee of the Radboud University Medical Centre, and Bernhoven Hospital reviewed and approved the study and considered that the study protocol did not fall within the remit of the Medical Research Involving Human Subjects Act (WMO) (ref: 2017/3597).

2.3. Intervention

Upon referral by a general practitioner (GP), patients were assessed via a comprehensive diagnostic care pathway aiming: (1) to make a thorough analysis of overall health status, (2) to determine the individual burden of disease, and, (3) to increase activation for self-management. The details of content of this COPDnet diagnostic care pathway have been published elsewhere [12,15]. Briefly, this pathway consisted of two visits with exactly one week in between and a third visit three to six weeks later. During the first visit, assessments were performed to capture the overall health status which is considered to consist of four domains: physiological impairment, symptoms, functional limitation and quality of life [16]. To this end, biomedical measurements, i.e. pulmonary function, exercise capacity, and physical activity, were taken and subjective symptoms, perceived limitations and perceptions of quality of life were assessed using the Nijmegen Clinical Screening Instrument (NCSI) [16]. On the second visit, assessment results were shared with the patient. The pulmonologist focused on the biomedical aspects, including optimizing pharmacotherapy. The respiratory nurse concentrated on the psychosocial functioning such as mood and social conditions interfering with coping the disease, and, self-management behaviors like medication use, lifestyle factors and coping with exacerbations. In the latter, the NCSI method was used as an important tool to activate patients for self-management and to motivate them for behavioral change. Briefly, this method consists of three highly integrated components: (1) a detailed measurement of perceptions of health status, (2) a counseling intervention by the respiratory nurse that helps to identify individual treatment goals and to motivate patients to change their behavior, and, (3) an automated monitoring system that simply identifies patients with new problem in health status [17]. Also non-pharmacological intervention options complementary to the drug therapy were discussed based on the presence of treatable traits (TTs) indicative for specific interventions. These TTs included: self-reporting current smoking status, activity-related dyspnea (Medical Research Counsel Dyspnea grade $\geq$3) [18], frequent acute exacerbations; defined as an acute worsening of respiratory symptoms that result in additional therapy ($\geq$2 exacerbations past 12 months or $\geq$1 hospitalization past 12 months) [1], poor nutritional status (BMI<21 or BMI>30) [19], severe fatigue (Checklist Individual Strength-Fatigue>36) [20], depressed mood (Beck Depression Inventory$\geq$4) [21], poor exercise capacity (6-min walking distance <70% predicted) [22], physical inactivity (<5000 steps/day) [22], and a low level of activation for self-management (Patient Activation Measure Level 1–2) [23]. Patients were encouraged to be accompanied by a significant person as they progress through the diagnostic care pathway. During the second visit patients were asked to consider the intervention options and to discuss them with their loved ones. Three to six weeks later, a final consultation took place with the respiratory nurse on which the individual care plan was established and agreements were made on the basis of shared-decision making, with respect to non-pharmacological interventions [17,24]. Finally, patients were referred back to their GPs for further assistance in accomplishing the agreed goal(s) of their individual care plan. This is in accordance with the Dutch national health policy to substitute care from secondary to primary health care services as much as possible. Table 1 summarizes the hallmarks of the COPDnet model compared to usual care.

Because the provision of (components of) care according to the COPDnet model was innovative for both pulmonologists and respiratory nurses, a Quality Management System (QMS) was developed. This QMS included three education and training sessions lasting two hours each by experts, for example, in the interpretation of physical functioning on the basis of physical activity and capacity assessment [22] and the NCSI method [17], and during the first two years of working with the COPDnet model, periodical (quarterly) a case presentation and

Table 1
Hallmarks of the COPDnet model compared to usual care.

COPDnet	Usual care
Comprehensive, multidimensional biopsychosocial assessment of relevant physical and psychosocial treatable traits	Unidimensional biomedical assessment
Interdisciplinary assessment in secondary care with sufficient consultation time for healthcare professionals and patients	Monodisciplinary assessment in secondary care with relatively short consultation time
Individualized care plan on the basis of objectified treatable traits and shared-decision making between patient and healthcare professionals	Treatment advice by healthcare professional lacking clear commitment of the patient
Focus on empowerment for self-management by pulmonologist and respiratory nurse during assessment	Limited explicit use of patient empowerment for self-management
Extensive use of various non-pharmacological interventions	Non-pharmacological interventions are markedly underutilized

discussion supervised by an expert in the understanding of integral health status. These discussions involved learning to estimate the individual burden of disease, identifying relevant TTs, reflections on conversation aimed at increasing patient activation for self-management, and, referral to the appropriate non-pharmacological interventions.

2.4. COPDnet non-pharmacological interventions

Based on the severity of the health status impairment, the number and type of TTs, patient preferences, and with the help of intervention allocation decision trees, shared-decisions were made between patient and pulmonologist/respiratory nurse with respect to treatment components as part of an individual care plan. Details of this complex process have been described elsewhere [12]. Applied referral criteria for non-pharmacological interventions regarding exercise-based care used in the COPDnet model were recently published [25]. Non-pharmacological intervention options added to a (optimized) drug therapy comprised of: (1) none; not applying an intervention, (2) self-treatment; interventions carried out by patients themselves, most frequently comprising attempting to quit smoking, lose weight or become more physically active, (3) referral to allied health care professionals (AHCPs), that is, a dietician, an occupational therapist or a physiotherapist in primary care, or, (4) referral to a tertiary pulmonary rehabilitation assessment with the possibility to follow an inpatient or outpatient rehabilitation program. Primary care AHCPs participated on the basis of their pre-existing experience with the treatment of pulmonary patients and provided care according to current (inter)national standards and guidelines. These therapists had all followed a post-graduate course on the treatment of patients with COPD accredited by their respective national professional organizations, participated in a local network of therapists, and had received two additional four-hour training sessions in providing care according to the COPDnet model [12]. Patients referred for pulmonary rehabilitation first underwent an extensive three days assessment. Based on the outcomes of this assessment, that is, the number and complexity of TTs, a choice was made for outpatient or more extensive inpatient pulmonary rehabilitation. The greater the total number of TTs or the complexity thereof, the more often the extensive inpatient program was applied. Both programs were customized to the patients' needs and could contain group sessions as well as individual therapy sessions in accordance with current guidelines [26]. Potential disciplines include: creative therapist, dietician, physiotherapist, psychologist, psychomotor therapist, pulmonologist, respiratory nurse, and social worker. The only difference between the outpatient and inpatient rehabilitation was the total volume. The outpatient program lasted 8 weeks on three days per week, while the inpatient program lasted 10 weeks on five days per week. The pulmonary rehabilitation programs were provided as part of regular care by an experienced multidisciplinary rehabilitation team of Radboudumc, location Dekkerswald.

2.5. Outcomes

The primary outcome was the change in health status, measured with the Clinical COPD Questionnaire (CCQ) from baseline to its measurement approximately six months after the final consultation with the respiratory nurse during of the diagnostic trajectory. Among available measurement instruments to capture health status in patients with COPD we selected the CCQ because it is one of the two measurement instruments recommended by the GOLD guideline [1], but has a slight advantage over the COPD Assessment Test (CAT) based on patient preference. [27] A follow-up period of six months was chosen, assuming that this would be sufficient to elicit any effect from non-pharmacological interventions [26]. Due to some random variation in the exact timing of this final consultation, and in the momentum at which patients completed follow-up questionnaires, the post-intervention measurement was typically obtained between 7 and 9 months after baseline assessment. The CCQ is a self-administrated questionnaire of which reliability and validity has been verified in patients with COPD [28]. The minimal clinically important difference (MCID) of the CCQ total score was recently re-established to range between −0.50 and −0.19 points [29]. For the follow-up measurements, patients were sent an e-mail, with a weblink, inviting them to fill out the CCQ. Additional questionnaires were simultaneously sent for evaluation of the secondary outcome measures. These secondary outcome measures included the NCSI [30], physical activity measured with the Marshall Questionnaire [31], and a question regarding healthcare utilisation in the past six months. The NCSI measures eight subdomains of health status covering three domains: (1) symptoms (three subdomains), (2) functional impairment (two subdomains), and (3) quality of life (three subdomains) [30].

2.6. Sample size

Using G-power with an a priori *t*-test based on the difference between two dependent means, we calculated that a sample of 199 patients would be required to detect a decrease of 0.2 points on the CCQ. The value of 0.2 points corresponds to the lower border of the MCID for improvement of the CCQ, and reflects a small effect size with a significance of 5% and a power of 80%. We chose to power the study to enable the detection of a small effect because of the absence of any data on the possible effect size of the COPDnet model at the outset of this study. Anticipating a dropout rate of 25% would mean that a total of 250 patients needed to be included. At the time this number of patients was included (September 2017), it became, however, obvious that the proportion of patients lost to follow-up was about twice the number anticipated. Therefore, we decided to extend the study period with another 15 months allowing to include more patients but also to stay within the practical constraints of the time lines of the study.

2.7. Statistical analysis

Descriptive statistics were used to summarize the data as means (standard deviations), medians (ranges) or frequencies (proportions), as appropriate. To remain consistent with the main outcome of this study we chose to base the GOLD ABCD classification on the CCQ [32]. The pre to post change in CCQ total score, the NCSI subscales and Marshall questionnaire for the sample at large was tested applying a two-tailed Paired-Samples T-test. Subgroups were defined, based on the actual applied non-pharmacological interventions where patients were referred to, that is, (1) pharmacotherapy only, (2) self-treatment, (3) AHCP in primary care, (4) outpatient pulmonary rehabilitation, or, (5) inpatient pulmonary rehabilitation. Between subgroups differences were tested with a one-way ANOVA and a post-hoc Tukey test. Due to the absence of definition of the MCID for the NCSI domains. Analysis and interpretation of any change in NCSI domains was omitted from the subgroup analysis due to the lack of a definition of the MCID. All statistical analyses were conducted using SPSS Version 25 (IBM Corp., Armonk, NY, USA). Significance levels were set to $P < 0.05$.

3. Results

3.1. Patient characteristics

A total of 402 patients with COPD were enrolled in this study. As of the study closing date per January 2019, valid follow-up measurements were available from 154 patients (38%). In Table 2, general and COPD-specific patient characteristics are provided from patients with and without follow-up measurement. No baseline characteristic was statistically significantly different between these two groups.

Follow-up measurements of primary and secondary outcomes were not obtained in 248 patients (62%) due to the following reasons:

Table 2
General and COPD-specific patient characteristics.

Attribute	Patients with follow-up CCQ (n = 154)	Patients without follow-up CCQ (n = 248)
Sociodemographic features:		
Age, years	63 ± 8	63 ± 9
p5, p50, p95	50, 64, 78	46, 63, 79
Female, %	49	51
Partnered, %	78	66
Employed, %	31	28
Pulmonary function:		
FEV_1% predicted p5, p50, p95	54 ± 19 25, 52, 86	55 ± 17 28, 54, 85
FVC % predicted	92 ± 17	91 ± 18
FEV_1/FVC ratio	47 ± 13	48 ± 12
GOLD class I/II/III/IV, %	7/47/38/8	10/49/35/6
Comorbidities:		
Number of comorbidities (0/1/2/3/4/5/6/7), % p5, p50, p95	17/35/22/15/7/3/2/0 0, 1, 5	21/27/22/16/10/2/1/1 0, 2, 4
Health status:		
GOLD class (CCQ-based) A/B/C/D, %	9/34/8/50	13/33/9/45
CCQ total score, points p5, p50, p95	1.94 ± 1.04 0.5, 1.8, 4.2	1.96 ± 1.06 0.5/1.9/3.9
CCQ symptom sub score, points	2.31 ± 1.19	2.39 ± 1.19
CCQ functional limitation sub score, points	1.86 ± 1.15	1.82 ± 1.25
CCQ mental sub score, points	1.31 ± 1.49	1.26 ± 1.40
Treatable traits:		
Smoking status, current/ex/never, %	42/56/2	46/52/2
Activity-based dyspnea, MRC I/II/III/IV/V, %	31/33/25/8/3	31/31/24/9/5
Number of exacerbation past year, 0/1/≥2 or ≥1 hospitalization, %	46/19/35	56/17/27
Nutritional status, BMI<21/BMI 21–25/BMI 25–30/BMI 30–35/BMI >35, %	17/30/35/16/2	21/33/23/15/8
Fatigue, CIS–F score, points p5, p50, p95	38 ± 12 14, 38, 56	39 ± 12 15, 41, 56
Depressed mood, BDI score, points p5, p50, p95	2.2 ± 2.5 0, 1.0, 9.0	2.1 ± 2.7 0, 1.0, 7.4
Physical capacity, 6MWD (mtr.); 6MWD %predicted p5, p50, p95	461 ± 115; 71 ± 17 270, 477, 638; 41, 72, 98	461 ± 127; 71 ± 18 240, 475, 629; 39, 72, 97
Habitual physical activity, steps/day p5, p50, p95	5233 ± 2653 1438, 4848, 9554	5615 ± 3248 997, 5327, 11,964
Activation for self-management, PAM score, points; PAM level I/II/III/IV, %	53 ± 12; 34/26/30/10	52 ± 10; 34/29/32/5

Data are presented as n, %, n (%), mean ± SD, 5th, 50th and 95th percentiles. FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; GOLD = Global Initiative on Obstructive Lung Disease; p5 = 5th percentile, p50 = 50th percentile, p95 = 95th percentile; CCQ=Clinical COPD Questionnaire; MRC = Medical Research Council dyspnea scale; BMI=Body Mass Index; BDI=Beck Depression Inventory; CIS= Checklist Individual Strength-Fatigue; 6MWD = 6-min walking distance; PAM=Patient Activation Measure.

1. Follow-up measurements turned out not to have been automatically generated by the ICT system (n = 72, 18%)
2. Patients did not receive or could not open the sent email due to difficulties using the ICT system. In these cases, the email appeared to have ended up in the spam folder and was therefore unnoticed by the patient, or, the patient experienced difficulties logging in because of the strong security of the ICT system (n = 15, 4%)
3. Patients died before the follow-up measurement was taken (n = 3, <1%)
4. Patients did not return the follow-up measurement for unknown reasons (n = 158, 39%)

3.2. Primary outcome

In the patients with follow-up measurements the CCQ total score improved statistically significantly from 1.94 ± 1.04 to 1.73 ± 0.96 ($P < 0.01$). Fig. 1 shows the average decrease of 0.20 ± 0.84 points which is at the threshold of clinical relevance. Applying a MCID range of the CCQ total score between −0.50 and −0.19 points at the individual level, 33–48% of the COPD patients had a clinically relevant better health status, 25–52% of them had not changed, and in another 14–27% health status had deteriorated. No significant correlation was found between the number of comorbidities and the CCQ total score measured at baseline. Furthermore, the number of comorbidities did not correlate with the change in CCQ total score.

3.3. Secondary outcomes

Significantly better scores were found in the NCSI subscale health-related quality of life (5.2 ± 2.0 versus 4.5 ± 2.0; $P < 0.01$), subjective complaints (11.3 ± 4.9 versus 10.4 ± 4.5; $P < 0.05$) and fatigue (38.7 ± 12.1 versus 35.6 ± 11.5; $P < 0.01$). Furthermore, the Marshall score improved statistically significantly from 2.7 ± 2.4 to 3.3 ± 2.5 (P < 0.01). Seventeen patients (11%) moved from a 'insufficient active'

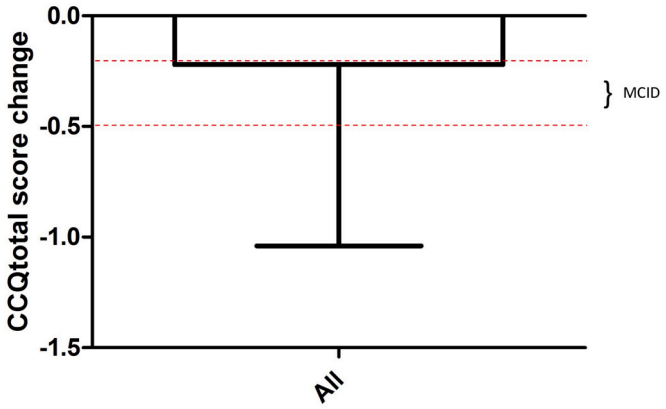

Fig. 1. Average decrease (=improvement) in CCQ total score of the 154 patients with a follow-up measurement. Legend: CCQ= Clinical COPD Questionnaire; MCID = Minimal Clinically Important Difference.

Table 3
Baseline characteristics after stratification for non-pharmacological intervention.

Attribute	Pharmacotherapy only	Self-treatment	AHCPs in primary care	Outpatient pulmonary rehab	Inpatient pulmonary rehab	*P*-value
	(n = 39; 11%)	(n = 61; 17%)	(n = 218; 61%)	(n = 20; 6%)	(n = 19; 5%)	
Sociodemogra-phic features:						
Age, years	62 ± 11	63 ± 7	65 ± 9	60 ± 8	60 ± 9	$P < 0.05$
p5, p50, p95	45, 62, 81	51, 63, 76	50, 65, 80	42, 60, 70	39, 60, 71	
Female, %	41	44	55	40	53	$P = 0.28$
Partnered, %	59	74	71	85	63	$P = 0.28$
Employed, %	39	30	24	35	37	$P = 0.24$
Pulmonary function:						
FEV_1% predicted p5, p50, p95	69 ± 19[c,d,e] 29, 69, 99	60 ± 17[c,e] 31, 58, 90	52 ± 17[a,b,e] 26, 51, 83	53 ± 15[a] 27, 55, 79	40 ± 13[a,b,c] 19, 39, 63	$P < 0.001$
FVC % predicted	98 ± 20[e]	93 ± 17[e]	91 ± 18[e]	91 ± 15	79 ± 19[a,b,c,]	$P < 0.01$
FEV_1/FVC ratio	55 ± 12[c,d,e]	52 ± 12[c,e]	46 ± 12[a,b]	46 ± 11[a]	41 ± 12[a,b]	$P < 0.001$
GOLD class I/II/III/IV, %	36/50/8/6	12/54/31/3	6/47/40/7	0/65/30/5	0/26/53/21	$P < 0.001$
Comorbidities:						
Number of comorbidities (0/1/2/3/4/5/6/7), %	36/18/23/13/0/0/0/3	15/38/13/23/7/2/1/1	17/31/26/12/9/3/2	15/40/10/20/5/5/5	16/21/26/21/16/0/0	$P = 0.77$
p5, p50, p95	0, 1, 4	0, 1, 5	0, 2, 4	0, 1, 6	0, 2, 6	
Health status:						
GOLD class (CCQ-based) A/B/C/D, %	47/31/3/19	25/32/8/36	5/35/10/50	5/40/0/55	0/17/0/83	$P < 0.001$
CCQ total score, points	1.39 ± 1.07[c,e]	1.65 ± 1.07[e]	2.06 ± 0.98[a,e]	1.96 ± 0.83[e]	3.13 ± 1.25[a,b,c,d]	$P < 0.001$
p5, p50, p95	0.1, 1.1, 4.0	0.4/1.3/4.3	0.7/1.9/3.9	0.4/1.9/4.1	1.5/2.7/4.2	
CCQ symptom sub score, points	1.67 ± 1.15[c,e]	2.14 ± 1.21[e]	2.46 ± 1.16[a]	2.38 ± 1.08	3.13 ± 1.50[a,b]	$P < 0.001$
CCQ functional limitation sub score, points	1.00 ± 0.99[c,e]	1.52 ± 1.27[e]	2.00 ± 1.14[a,e]	1.80 ± 0.78[e]	3.29 ± 1.20[a,b,c,d]	$P < 0.001$
CCQ mental sub score, points	0.66 ± 1.42[e]	0.92 ± 1.15[e]	1.38 ± 1.43[e]	1.42 ± 1.24[e]	2.82 ± 2.04[a,b,c,d]	$P < 0.001$
Treatable traits:						
Smoking status, current/ex/never, %	36/61/3	49/51/0	36/62/2	50/50/0	47/53/0	$P < 0.001$
Activity-based dyspnea, MRC I/II/III/IV/V, %	49/30/12/3/6	31/43/20/2/4	27/28/28/12/6	35/25/40/0/0	17/35/18/18/12	$P < 0.05$
Number of exacerbation past year, 0/1/≥2 or ≥1 hospitalization, %	68/8/24	73/13/15	48/22/30	50/15/35	17/11/72	$P < 0.001$
Nutritional status, BMI<21/BMI 21–25/BMI 25–30/BMI 30–35/BMI >35, %	12/48/32/8/0	12/35/25/19/9	21/30/27/16/6	20/25/45/10/0	31/29/29/11/0	$P < 0.001$
Fatigue, CIS–F score, points	29 ± 14[b,c,d,e]	38 ± 12[a,e]	40 ± 11[a]	38 ± 11[a]	47±9[a,b]	$P < 0.001$
p5, p50, p95	9, 27, 54	14, 39, 56	19, 41, 56	14, 40, 55	31, 50, 55	
Depressed mood, BDI score, points	2.1 ± 3.5[e]	1.3 ± 1.9[e]	2.1 ± 2.5[e]	2.6 ± 2.7[e]	5.3 ± 3.5[a,b,c,d]	$P < 0.001$
p5, p50, p95	0, 1.0, 11.7	0, 1.0, 5.75	0, 1, 7.5	0, 2, 8.0	0, 5, 11.0	
Physical capacity, 6MWD (mtr.); 6MWD % predicted	507 ± 130[c,e]; 77 ± 16[e]	492 ± 130[c,e]; 77 ± 21[c,e]	438 ± 121[a,b]; 69 ± 17[b]	495 ± 68; 74 ± 10[e]	401 ± 108[a,b]; 59 ± 15[a,b,d]	$P < 0.001$; $P < 0.001$
p5, p50, p95	269, 525, 702; 39, 77, 100	355, 483, 629; 57, 75, 103	209, 450, 621; 34, 70, 96	367, 505, 613; 56, 77, 94	175, 420, 538; 27, 60, 83	
Habitual physical activity, steps/day	6548 ± 4306	5910 ± 2340	5072 ± 2816	5406 ± 2235	5198 ± 2063	$P = 0.08$
p5, p50, p95	575, 6250, 14,073	2062, 6035, 9728	927, 4663, 10,239	2045, 5114, 10,791	1771, 5381, 7566	
Activation for self-management, PAM score, points; PAM level I/II/III/IV, %	53 ± 10; 29/26/36/9	52 ± 10; 44/27/24/5	52 ± 11; 33/30/29/8	54 ± 8; 25/30/40/5	48 ± 9; 44/19/37/0	$P = 0.60$; $P = 0.82$
Total number of treatable traits	2.3 ± 2.0[c,e]	3.3 ± 1.8[c,e]	4.2 ± 2.0[a,b,e]	4.0 ± 1.5[e]	6.0 ± 2.0[a,b,c,d]	$P < 0.001$

AHCP = allied healthcare professional; p5 = 5th percentile, p50 = 50th percentile, p95 = 95th percentile; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; GOLD = Global Initiative on Obstructive Lung Disease; CCQ=Clinical COPD Questionnaire; MRC = Medical Research Council dyspnea scale; BMI=Body Mass Index; CIS= Checklist Individual Strength-Fatigue; BDI=Beck Depression Inventory; 6MWD = six-minute walking distance; PAM=Patient Activation Measure; Statistically significantly different from pharmacotherapy only[a], Self-treatment[b], AHCPs in primary care[c], outpatient pulmonary rehabilitation[d], inpatient pulmonary rehabilitation.[e].

status to a 'sufficient active' status using this questionnaire.

3.4. Subgroup analysis

Table 3 lists the baseline characteristics of the patients stratified for the intervention to which they had been referred. The bulk of patients (n = 218; 61%) was referred to one or two AHCPs in primary care. Of these 218 patients, 68% were referred to a physiotherapist, 24% to an occupational therapist, and 20% to a dietician. Statistically significant between subgroup differences were found in most of the baseline characteristics, as well as in the total number of TTs. Fig. 2 shows the CCQ total score responses of the subgroups. CCQ change also differed statistically significantly between subgroups ($P < 0.01$). Post-hoc analysis revealed significant differences only between the two subgroups receiving pulmonary rehabilitation, either outpatient or inpatient based, and the subgroup referred for treatment to an AHCP in primary care ($P < 0.05$). In both the pulmonary rehabilitation groups the CCQ change exceeded the conservative upper limit of the MCID of −0.50 points.

4. Discussion

This real-world clinical study demonstrates that in COPD patients who received care according to the COPDnet integrated care model, a statistically significantly improved health status was found in a period of 7–9 months after the baseline assessment. On average, this improvement was only on the edge of clinical relevance. Subgroup analysis based on stratification for intervention, however, revealed marked between group differences in responses. Patients who received pulmonary rehabilitation, either outpatient or inpatient based, showed the greatest improvement in health status.

4.1. Interpreting outcome

To the best of the authors' knowledge this is the first study of its kind on the effectiveness of an integrated care model for patients with COPD with a first-time referral to secondary care. These patients were in accordance with the Dutch Standard of Care for COPD referred to

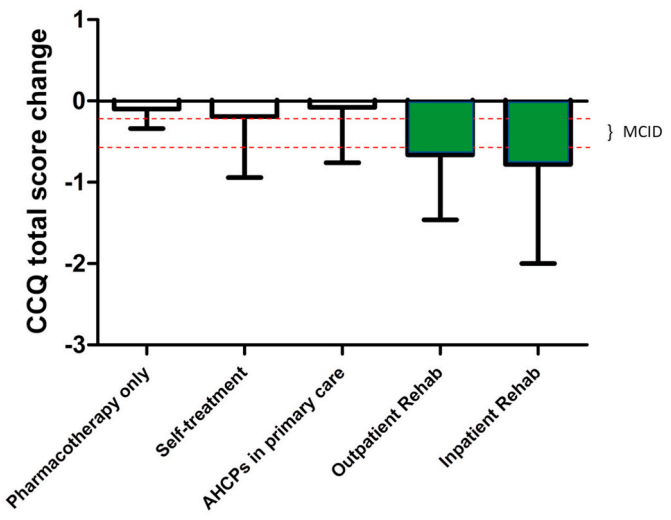

Fig. 2. Mean improvement (decrease) in CCQ total score per subgroup based on the actual intervention allocation.
Legend: CCQ=Clinical COPD Questionnaire; AHCP = Allied Healthcare Professional; MCID = Minimal Clinically Important Difference.

secondary care mainly because of persistent complaints while in a so-called 'stable state of disease' which could apparently not or insufficiently be alleviated by management in primary care [33]. To put the results of the COPDnet integrated care model into perspective, we searched for data on the outcome of usual care in patients with COPD. In particular we looked for sources reporting on the effects of usual care in patients referred to secondary care. Surprisingly, however, these data are not available. It appeared that longitudinal data on the dynamics of health status of usual care are not systematically analysed and reported in the Netherlands, for example for quality management purposes, and, a national registry on COPD is lacking. Alternatively, we searched for empirical data from published studies to which we could mirror the results from the current study and found in this respect three useful studies. The Randomized Clinical Trial on Effectiveness of integrated COPD management in primary care (RECODE) was a large cluster randomized provider targeted trial including 1086 patients with COPD [34]. In RECODE, GPs, practice nurses and specialized physiotherapists received a two-day training course on incorporating integrated disease management in primary care practice. Efforts were also made to create a network platform for team members. In this context, patients were offered personalized care taking the individual needs as starting point. Main outcome of this study was also the change in CCQ total score. There, no significant change ($P = 0.80$) was found between the intervention group and usual care group [35]. Also in the within groups analyses no differences were seen. The RECODE authors considered that the absence of effect could be attributed to the primary care provider targeted intervention, and, the little room for improvement in the already well-developed Dutch healthcare system. The outcomes of our study do express, however, that it is feasible to obtain an improvement in health status and in some patients even in a striking improvement, and puts another perspective on the authors' considerations. Indeed, a marked difference in the applied methodology between the RECODE and our study is the patient targeted focus rather than focus on the healthcare provider. Another clear difference is the inclusion of secondary care expertise both in the diagnostic trajectory and the intervention part of the COPDnet integrated care model, and in some patients even the use of expertise from a tertiary care pulmonary rehabilitation specialized centre. Indeed, aligning of expertise between GPs and pulmonologists may largely improve the diagnoses and management of patients with chronic respiratory disorders [36]. A recent Dutch, real-world care, observational study reported the effects of usual care of 207 COPD patients from primary care and secondary care combined whom were followed for one year. This study showed no change in CCQ after six months (delta CCQ total 0.00 points) and 12 months (delta CCQ total 0.02 points) follow-up [37]. Finally, data from the Rainbow study, a six year observational single-site study in 201 patients with mild to moderate airflow obstruction carried out in Belgium, showed an annual CCQ total score worsening of 0.05 points [38]. Collectively, it appears from these three studies that usual care in patients with COPD result in no change or even a small deterioration of health status in a one-year period. Such a conclusion would favour the results from the current study on the outcomes of care according to COPDnet integrated care model.

4.2. Clinical relevance of the findings

The observed improvement of 0.2 ± 0.84 points of the CCQ total score is statistically significant, looks better than usual care but may on average still be interpreted as small [37]. Yet, clear between subgroup differences emerged when patients were differentiated by the intervention to which they had been referred to. The most pronounced improvement was seen in patients referred to inpatient pulmonary rehabilitation. This improvement corresponds to the large effects of a similar pulmonary rehabilitation program deployed in another region in the Netherlands [39]. It could be argued that these patients perhaps had the largest room for improvement. Indeed, patients referred to inpatient pulmonary rehabilitation had a significantly worse health status compared to all other subgroups. It must be noticed however that these patients were also the most complex patients with on average 6.0 ± 2.0 TTs for which extensive pulmonary rehabilitation may be the appropriate intervention [40]. Also, in patients receiving outpatient pulmonary rehabilitation a positive effect was observed exceeding the conservative upper limit of the MCID. By contrast, monodisciplinary non-pharmacological interventions provided in primary care, by far the most frequently applied intervention in the current study, and, given by well-trained AHCPs, resulted in an only trivial improvement on the CCQ. A likely explanation for this finding may be that a monodisciplinary approach, addressing only one or limited number of TTs, is insufficiently effective in patients with a complex health disorder to achieve improvement in overall health status. Noteworthy, there were hardly any differences in pulmonary function impairment, health status and the total number of TTs between patients referred to outpatient pulmonary rehabilitation and monodisciplinary non-pharmacological interventions delivered in primary care. Such complex patients may be better off with an interdisciplinary approach [26]. What have resulted in the choice for outpatient pulmonary rehabilitation or monodisciplinary treatment in primary care cannot be determined from this study, but certainly is relevant to know for further development of the COPDnet model. What might have played a role is the wish to comply with current Dutch health care policy, that is, to provide care to patients with chronic conditions as much as possible in primary care close to the patient's living environment. From the patient perspective, preferences might have affected intervention choices. Making shared-decisions between patient and healthcare professional is at the heart of the COPDnet model. Regardless of the cause, the results of this study give reason to address this aspect in the further development of the COPDnet model.

Finally, we believe that the results of this study are generalizable to other countries even if their care system does not completely equal the Dutch system. Medical specialist care is a common part of the care to pulmonary patients across nations. This is exactly what this study related to and for which an important signal is given which intervention (s) influence the achievement of a desired treatment result.

4.3. Methodological considerations

The findings of the current study were interpreted with caution for the significant number (62%) of missing follow-up measurements.

Generally, significant loss to follow-up may violate the internal validity of studies due to attrition bias and loss of statistical power. However, missing follow-up data appeared to have occurred completely at random in the present study. No significant differences were found between the baseline characteristics of the patients with and without follow-up measurements. In a study on the effect of missing values on outcomes of cohort studies, it was nicely demonstrated that no important bias was found with loss to follow-up measurements up to 60%, if data were 'missing completely at random' or 'missing at random' [41]. Furthermore, the number of missing values in the current study is actually smaller than it may seem at first sight. In 87 patients (22%) the lost to follow-up was due to ICT malfunction either on the sender's side or on the recipient's side. These 87 patients could not have responded at all. So, if we assume a total of 315 patients (402 minus 87) where a follow-up measurement could have been obtained, the percentage lost to follow-up is de facto reduced to 51%. Future studies in which online questionnaires are administered must thoroughly test the digital platform in advance and check for reliability. Due to the unforeseen large number of patients lost to follow-up, which became obvious during the interim analysis, we decided to extent the inclusion period. Nevertheless, we did not attain the calculated number of 199 patients with a valid pre- and postintervention measurement from the power calculation. Apparently, however, the actual power to detect a change in CCQ total score outweighed the assumptions from the power calculation, as the observed change in CCQ total score was already significant in a sample of 154 patients. This above expected result prevented the occurrence of a type II statistical error, it avoided a false negative conclusion on the significance of the measured change in CCQ total score, and it favours the clinical effectiveness of the COPDnet model. Therefore, we are confident that our results reflect a clear signal and have not been significantly impacted by responder selection bias.

Because we considered this study mainly as a proof of concept of the COPDnet model, we opted for an observational design. Obviously, the absence of control group precluded a more robust conclusion regarding the (cost)effectiveness, hence the external validity, of this first study on the value of the COPDnet model. We deliberately decided, however, not to use a randomized controlled study design because of the risk of contamination. We argued that it would be difficult for pulmonologists and respiratory nurses from the same clinic to practice an integrated approach in some patients and not in others. It might have resulted in an effect dilution resulting in a type II statistical error.

For the required follow-up research into the added clinical value of the COPDnet model with a controlled study design, we recommend using a multiple interrupted time series (mITS) design. ITS analysis is the strongest quasi-experimental design to evaluate the longitudinal effects of complex interventions, through regression modelling, when randomization is not an option [42,43].

5. Conclusion

This first observational study on the clinical effectiveness of the COPDnet integrated care model showed that a statistically significant improvement in health status was obtained. This gain in health status was found predominantly in patients who received pulmonary rehabilitation.

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CRediT authorship contribution statement

E.H. Koolen: Investigation, Formal analysis, Data curation, Writing - original draft. **B. van den Borst:** Writing - original draft. **M. de Man:** Resources, Writing - review & editing. **J.C. Antons:** Resources, Writing - review & editing. **B. Robberts:** Resources, Writing - review & editing. **P. N.R. Dekhuijzen:** Conceptualization, Writing - review & editing, Funding acquisition. **J.H. Vercoulen:** Methodology, Writing - review & editing. **M. van den Heuvel:** Writing - review & editing. **M.A. Spruit:** Writing - original draft. **P.J. van der Wees:** Methodology, Writing - review & editing, Writing - review & editing. **A.J. van 't Hul:** Conceptualization.

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Appendix A. Supplementary data

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