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Manuscript title

Treatable traits qualifying for non-pharmacological interventions in COPD patients upon first referral to a pulmonologist: the COPD *sTRAITosphere*

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Material and Methods

Study participants

All patients with a confirmed diagnosis of COPD, with a first-time referral between October 2014 and December 2018 to the outpatient respiratory department of Radboudumc, Nijmegen, and Bernhoven Hospital, Uden, both in The Netherlands, were deemed eligible for participation providing they had been free of an acute exacerbation for ≥3 months. 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 approved the study and considered that the study protocol did not fall within the remit of the Medical Research Involving Human Subjects Act (WMO). Due to the observational nature of the study and the provision of usual care, written informed consent was waived (ref: 2017/3597).

Study design

This is a multicenter, ambispective, observational study. In the prospective study, upon referral by a GP, patients were assessed in a standardized, comprehensive diagnostic care pathway. This diagnostic trajectory sets out to assess individual determinants of the burden of disease (TTs), and to reveal options to increase activation for self-management.(1, 2) This pathway consisted of two visits within exactly one week and another third visit four weeks later. On the first visit, patients had a consultation with both the pulmonologist and respiratory nurse and underwent a series of assessments. On the second visit, all the results were reviewed in a face-to-face discussion between the respiratory nurse and the pulmonologist and subsequently communicated with the patient in two separate sessions. The pulmonologist focused on the biomedical aspects, whereas the respiratory nurse concentrated on the psychosocial and behavioral aspects. Four weeks later a final

consultation took place with the respiratory nurse in which the individual care plan was established and any agreements were made with respect to non-pharmacological interventions. In the meantime, additional diagnostic tests, such as extra blood testing, lung volume measurements or imaging and/or consultation with another subspecialist such as cardiologist could be completed, should the medical condition give rise to this.

Health status assessment and determination of non-pharmacological treatable traits

During the consultations with the pulmonologist and respiratory nurse on day one, the patients' medical history was taken including living situation, employment status, sick leave due to COPD in past 12 months and smoking status. A detailed registration was done of pulmonary medication and non-pharmacological intervention(s) for COPD as set up by the GP in the past 12 months. Comorbidities were recorded by the pulmonologist: (1) on the basis of the patient history, (2) what had been registered already in the electronic medical record, (3) what had been written in the referral letter from the GP, or, (4) what actual medication was used. Assessments included spirometry and flow-volume curve measurements before and after bronchodilator use (Salbutamol 400 µg), based on the Global Lung Initiative (GLI) equations (3) with reversibility defined as FEV_1 increase of ≥12% and at least 200 mL improvement(4), arterial blood gas analysis (5) with type 1 respiratory failure defined as P_aO_2<8.0 kPa(6), peripheral blood analysis including eosinophil count. X-ray of the thorax and ECG were taken in patients with an age > 40 years. Between the first and the second visit, patients wore a move monitor for a week to objectify the level of physical activity.(7) To quantify patients perceived health status, that is, the individual burden of disease, the Clinical COPD Questionnaire (CCQ) was used.(8, 9) In addition, composite indices reflecting health status impairment in a multidimensional way were calculated, that is, the (CCQ-based) GOLD ABCD classification(6) , BODE index(10) and ADO

index(11). The following nine potential TTs qualifying for non-pharmacological interventions were appraised: current smoking, activity-related dyspnea (12), frequent acute exacerbations, defined as an acute worsening of respiratory symptoms that result in additional therapy, (≥2 exacerbations past 12 months or ≥1 hospitalization past 12 months)(6), poor nutritional status(13), severe fatigue(14), depressed mood(15), poor exercise capacity(7), physical inactivity(7), and, a low level of activation for self-management.(16)

Results

Table E1. Correlation matrix of the nine examined TTs

	Smoking	MRC	Exacerbations	BMI	CIS	BDI	6MWD	Steps/day	PAM
Smoking		0.07	0.04	0.28*	-0.03	-0.01	-0.11*	-0.08	-0.01
MRC			0.27*	0.03	0.39*	0.24*	-0.52*	-0.47*	-0.16*
Exacerbations				-0.07	0.15*	0.15*	-0.20*	-0.16*	-0.13
BMI					-0.01	-0.05	-0.17*	-0.13*	-0.14*
CIS						0.32*	-0.21*	-0.24*	0.26*
BDI							-0.12	-0.11	-0.22*
6MWD								0.53*	0.10
Steps/day									0.01
PAM									

*=P<0.05; MRC=Medical Research Council dyspnea scale; BMI=Body Mass Index; BDI=Beck Depression Inventory; CIS= Checklist Individual Strength-Fatigue; 6MWD=6-minute walking distance; PAM=Patient Activation Measure.

Table E2. General and COPD-specific patient characteristics of the validation sample

Attribute		**# patients with a valid registration**
Sociodemographic features:		
Age, years	64±9	584 (100%)
Female, %	45	584 (100%)
Partnered, %	72	547 (94%)
Pulmonary function:		
FEV_1% predicted	59±19	584 (100%)
FVC % predicted	93±18	584 (100%)
FEV_1/FVC ratio	0.48±0.12	584 (100%)
FEV_1 reversibility, % patients	34	584 (100%)
GOLD class I/II/III/IV, %	14/51/31/4	584 (100%)
Blood gas analysis:		
Hb, mmol/L	NA	
Hb<8.5 (male) or <7.5 (female), %	NA	
pH	7.42±0.29	565 (97%)
PaCO2, kPa	5.21±0.66	565 (97%)
PaCO2>6.5 kPa, %	3	565 (97%)
PaO2, kPa	NA	
PaO2<8.0 kPa, %	NA	
BIC, mmol/L	24.5±2.5	565 (97%)

Base Excess	0.15±1.99	565 (97%)
SaO2, %	NA	
Comorbidities:		
Charlson comorbidity index	3 (0-9)	364 (62%)
Cardiovascular, %	NA	
Metabolic, %	NA	
Musculoskeletal, %	NA	
Psychiatric, %	NA	
Others, %	NA	
Pulmonary medication:		
Short acting bronchodilator(s), %	NA	
Long acting bronchodilator(s), %	NA	
Inhalation steroids, %	NA	
Maintenance systemic steroids, %	NA	
Burden of disease:		
GOLD class (CCQ-based) A/B/C/D, %	12/35/7/47	473 (81%
CCQ total score, points	2.18±1.17	525 (90%)
CCQ symptom sub score, points	2.52±1.17	525 (90%)
CCQ functional limitation sub score, points	2.23±1.49	525 (90%)
CCQ mental sub score, points	1.35±1.41	525 (90%)
CCQ total score>1.0, %	79	525 (90%)
BODE index, points	2.8±1.8	434 (74%)
BODE quartile 1/2/3/4, %	50/34/11/5	434 (74%)
Non-pharmacological interventions in primary care past 12 months:		
Patients receiving physiotherapy, %	NA	
Patients receiving care from dietician, %	NA	
Patients receiving occupational therapy, %	NA	
Patients receiving care from psychologist, %	NA	
Treatable traits:		
Smoking status, current/ex/never, %	53/45/2	584 (100%)
Activity-based dyspnea, MRC I/II/III/IV/V, %	25/29/23/13/10	514 (88%)
Number of exacerbation past year, 0/1/≥2 or ≥1 hospitalization, %	52/23/25	461 (79%)
Nutritional status, BMI<21/BMI 21-25/BMI 25-30, BMI 30-35, BMI >35, %	18/29/33/14/6	584 (100%)
Fatigue, CIS-F score, points	37±13	563 (96%)
Depressed mood, BDI score, points	2.0±2.5	577 (99%)
Physical capacity, 6MWD (meter.); 6MWD %predicted	461±123; 67±15	584 (100%)

Habitual physical activity, steps/day	5523±3364	584 (100%)
Activation for self-management, PAM score, points; PAM level I/II/III/IV, %	NA	

Data are presented as n, %, n (%), mean±SD, 5^{th}, 50^{th} and 95^{th} percentiles. FEV_1=forced expiratory volume in 1 s; FVC=forced vital capacity; GOLD=Global Initiative on Obstructive Lung Disease; Hb=hemoglobin; p5=5th percentile, p50=50^{th} percentile, p95=95^{th} 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-minute walking distance; PAM=Patient Activation Measure.

Legend Figure E1:

Figure E1. Prevalence of the eight TTs from the validation sample.

Figure E2. Frequencies of the total number of TTS per patients from the validation sample.

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