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

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Abstract

Introduction

The present study assessed the prevalence of nine treatable traits (TTs) pinpointing non-pharmacological interventions in patients with COPD upon first referral to a pulmonologist, how these TTs co-occurred, and whether and to what extent the TTs increased the odds having a severely impaired health status.

Methods

Data were collected from a sample of 402 COPD patients. A second sample of 381 patients with COPD was used for validation. Nine TTs were assessed: current smoking status, activity-related dyspnea, frequent exacerbations <12 months, severe fatigue, depressed mood, poor physical capacity, low physical activity, poor nutritional status, and a low level of self-management activation. For each TT the odds ratio of having a severe health status impairment was calculated. Furthermore, a graphic representation was created, the COPD sTRAITosphere, to visualize TTs prevalence and odds ratio.

Results

On average 3.9±2.0 TTs per patient were observed. These TTs occurred relatively independently of each other and coexisted in 151 unique combinations. A significant positive correlation was found between the number of TTs and CCQ total score (r=0.58; $P<0.001$). Patients with severe fatigue (odds ratio, OR: 8.8), severe activity-related dyspnea (OR: 5.8) or depressed mood (OR: 4.2) had the highest likelihood of having a severely impaired health status. The validation sample corroborated these findings.

Conclusions

Upon first referral to a pulmonologist, COPD patients show multiple TTs indicating them to several non-pharmacological interventions. These TTs coexist in many different combinations, are relatively independent and increase the likelihood of having a severely impaired health status.

Introduction

Chronic Obstructive Pulmonary disease (COPD) is a highly prevalent and complex disease, with an extraordinary heterogeneity in its clinical presentation.(1) While COPD is defined by the presence of an incomplete reversible airflow limitation, numerous intra- and extrapulmonary manifestations have been identified, which may be variably and/or transiently present, all adding up to the individual burden of disease.(2) Therefore, a personalized approach is advocated.(3) Hence, relevant and modifiable pulmonary, extrapulmonary and behavioral/lifestyle features, the so-called treatable traits (TTs), need to be identified through a comprehensive assessment and subsequently be addressed in a patient-centered management plan.(4) This comprehensive assessment must go beyond lung function measurements as relevant extra-pulmonary and behavioral TTs cannot be captured solely with pulmonary function testing.(5) A broad assessment of TTs is common at the start of a comprehensive pulmonary rehabilitation program but is certainly not standard in primary and secondary care work settings.(6) Regrettably, pulmonary rehabilitation is still markedly underutilized as potent non-pharmacological intervention option and often considered only late in the patient's disease career.(7, 8) Moreover, a considerable proportion of patients with COPD, who are cared for by the general practitioner (GP) and/or pulmonologist show evidence of physical, emotional and/or social (treatable) traits, that require non-pharmacological interventions beyond respiratory drug treatment, even when they are just in a mild stage of disease.(9, 10)

In the Netherlands, GPs are the gatekeepers of the care system.(11) Therefore, COPD is primarily diagnosed by GPs and then treated according to the national guideline. According to the

Dutch Standard of Care, patients with COPD can be referred to a pulmonologist for a hospital-based outpatient consultation if the treatment response in primary care is unsatisfactory and their burden of disease persists.(12) Such an outpatient consultation follows international recommendations and is usually limited to taking patients medical history, physical examination, biomedical assessments, such as pulmonary function, blood testing, pulmonary imaging, and, simple questionnaires to assess symptom burden.(13) However, although GPs and pulmonologists do have a clear understanding of what the content and methodology of a comprehensive outpatient hospital-based assessment should comprise, they generally do not measure TTs beyond lung function.(14, 15) Aims of the present study were to assess in patients with COPD upon first referral to a pulmonologist: the prevalence of nine potentially clinically relevant TTs pinpointing non-pharmacological interventions, the combinations in which they occur and whether the presence of multiple TTs increases the odds having a severely impaired health status. We hypothesized that patients with COPD upon first referral to a pulmonologist would have multiple TTs indicative for non-pharmacological interventions, that these TTs arise in different combinations, and that their presence would increase the odds of having a severely impaired health status.

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 Research Ethics Committee of the Radboud University Medical Centre approved the study. 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 to identify the presence of TTs indicative for non-pharmacological interventions.(15, 16) These nine TTs were selected because evidence-based interventions exist for them. Table 1 provides an overview of the examined nine TTs, the measurement instruments used, the applied cut-off values and appropriate evidence-based possible interventions. To quantify patients' health status, the Clinical COPD Questionnaire (CCQ) was used.(17) The CCQ has been accepted as valid and reliable questionnaire to measure health status in clinical practice in COPD patients(18), and, has been endorsed also as short but comprehensive disease-specific health status questionnaire for the ABCD assessment tool used in the GOLD document.(13) Additional details on the content of the diagnostic care pathway is provided in the online data supplement.

Table 1. Examined treatable traits, measurement instruments, cut-off values applied and appropriate evidence-based non-pharmacological interventions

	Treatable trait	Measurement instrument	Cut-of value	Possible (combinations of) intervention(s)
1	Current smoking	Medical history	Positive on history	Simple advice, combination of behavioral treatment and pharmacotherapy(19)
2	Activity-related dyspnea(20)	Medical Research Council dyspnea scale	Grade ≥3	exercise training, pulmonary rehabilitation(21)
3	Frequent exacerbations(13)	Medical history	≥2 exacerbations or ≥1 hospitalization past year	Exacerbation action plan(22), pulmonary rehabilitation(21)
4	Poor nutritional status(23)	Body Mass Index	BMI<21 or BMI>30 kg/m²	Nutritional support(24), dietary counseling and calorie restriction plus resistance exercise training(25)

5	Severe fatigue(26)	Checklist Individual Strength-Fatigue	≥36 points	Pulmonary rehabilitation(21)
6	Depressed mood(27)	Beck Depression Inventory	≥4 points	Cognitive behavioral therapy(28), pulmonary rehabilitation(21)
7	Poor exercise capacity(29)	Six-minute walk test	<70% predicted	Exercise training, pulmonary rehabilitation(21)
8	Low habitual physical activity(29)	Move monitor	<5000 steps/day	Exercise training plus physical activity counseling(30)
9	Patient activation for self-management(31)	Patient Activation Measure	Level 1-2	Self-management program(32)

ANALYSES

Inspired by Divo et al. who developed the COPD *comorbidome*(33), we created the COPD *sTRAITosphere*. This is a graphical presentation of the combination of the prevalence of each TT (depicted with the size), and the TT's odds ratios (ORs) of having a severe health status impairment (CCQ total score>2.0 points). The combined presentation allows to read the clinical relevance of each TT at a glance. Data from a retrospective study on a convenient second sample of 584 patients with COPD was used to validate the initial COPD *sTRAITosphere*. These were also all patients referred for the first time to the outpatient respiratory department of Amphia Hospital, Breda, The Netherlands, consecutively between April 2013 and December 2018, and free of an acute exacerbation ≥3 months. In this independent sample, except activation for self-management, all other eight TTs were assessed using the exact same methodology as in the primary sample.

Statistical methods

Descriptive statistics were used to summarize the data as means (standard deviations), medians (ranges) or frequencies (proportions), as appropriate. The presence of the nine TTs was dichotomously determined in each participating patient. Subsequently, the prevalence of each TT

was determined by calculating the percentage of patients who met the pre-defined criteria (Table 1). With nine TTs a maximum number of 512 (2^9) unique combinations is possible. An individual sum score was calculated in patients with a valid registration of all nine TTs. The association between the nine TTs was assessed using Pearson's correlation coefficients. With nine TTs, this produces up to 36 ((9^2-9) *0.5) unique correlation coefficients. In these patients, the association between individual TT sum scores and FEV1%predicted as well as CCQ total score were also assessed using Pearson's correlation coefficients. Moreover, TT sum scores were related to the CCQ impairment classification, that is, mild impairment (CCQ total score 0-1 point), moderate impairment (1-2 points), severe impairment (2-3 points), or very severe impairment >3 points, applying one-way ANOVA. [22] To further elicit the clinical relevance of the number of TTs for health status, linear regression analysis was performed with CCQ total as response variable and FEV1%predicted or the total number of TTs as explanatory variables. Logistic regression assessed the OR of having a severely impaired health status (CCQ total score >2 points) per TT and for (very) severe degree of airflow limitation (GOLD III/IV). Both regression analyses were checked for possible confounding by age and sex. Should this be the case, the results were corrected for this. All statistical analyses were conducted using SPSS Version 22 (IBM Corp., Armonk, NY, USA). Significance levels were set to *P*<0.05.

Results

Patient characteristics

In total, 402 patients were included. General and COPD-specific patient characteristics including measures reflecting the burden of disease are summarized in Table 2. More patients (48%) had a moderate airway obstruction, closely followed (36%) by severe obstruction, severe hypoxemia was present in 16%, and a median of two comorbidities was found. The vast majority (80%) of the patients was symptomatic (GOLD group B or D). In the year preceding referral to secondary care, 109

patients (27%) had been referred to an allied healthcare professional, of which physiotherapy was

the most frequent (83 cases; 20%).

Table 2. General and COPD-specific patient characteristics.

Attribute		# patients with a valid registration
Sociodemographic features:		
Age, years	63±9	402 (100%)
Female, %	50	402 (100%)
Partnered, %	71	402 (100%)
Pulmonary function:		
FEV_1% predicted	55±18	402 (100%)
FVC % predicted	91±17	402 (100%)
FEV_1/FVC ratio	48±12	402 (100%)
FEV_1 reversibility, % patients	36	402 (100%)
GOLD class I/II/III/IV, %	9/48/36/7	402 (100%)
Blood gas analysis:		
Hb, mmol/L	8.9±0.9	182 (45%)
Hb<8.5 (male) or <7.5 (female), %	22/8	91/91 (45%)
pH	7.42±0.32	245 (61%)
$PaCO2$, kPa	5.15±0.66	245 (61%)
$PaCO2$>6.5 kPa, %	3	245 (61%)
$PaO2$, kPa	9.46±1.51	245 (61%)
$PaO2$<8.0 kPa, %	16	245 (61%)
BIC, mmol/L	24.7±2.7	245 (61%)
Base Excess	0.67±2.33	245 (61%)
$SaO2$, %	94±3	245 (61%)
Comorbidities:		
Number of comorbidities (0/1/2/3/4/5/6/7), %	19/30/22/15/9/2/1/1	402 (100%)
Cardiovascular, %	49	402 (100%)
Metabolic, %	11	402 (100%)
Musculoskeletal, %	17	402 (100%)
Psychiatric, %	13	402 (100%)
Others, %	51	402 (100%)
Pulmonary medication:		
Short acting bronchodilator(s), %	46	402 (100%)
Long acting bronchodilator(s), %	71	402 (100%)

Inhalation steroids, %	52	402 (100%)
Maintenance systemic steroids, %	1	402 (100%)
Burden of disease:		
GOLD class (CCQ-based) A/B/C/D, %	11/33/9/47	363 (90%)
CCQ total score, points	1.95±1.05	363 (90%)
CCQ symptom sub score, points	2.36±1.18	359 (89%)
CCQ functional limitation sub score, points	1.84±1.21	359 (89%)
CCQ mental sub score, points	1.28±1.44	359 (89%0
CCQ total score>1.0, %	80	363 (90%)
BODE index, points	2.8±1.6	333 (83%)
BODE quartile 1/2/3/4, %	28/54/12/6	333 (83%)
Non-pharmacological interventions in primary care past 12 months:		
Patients receiving physiotherapy, %	20	402 (100%)
Patients receiving care from dietician, %	10	402 (100%)
Patients receiving occupational therapy, %	1	402 (100%)
Patients receiving care from psychologist, %	4	402 (100%)
Treatable traits:		
Smoking status, current/ex/never, %	44/54/2	402 (100%)
Activity-based dyspnea, MRC I/II/III/IV/V, %	31/31/25/9/4	363 (90%)
Number of exacerbation past year, 0/1/≥2 or ≥1 hospitalization, %	52/18/30	379 (94%)
Nutritional status, BMI<21/BMI 21-25/BMI 25-30, BMI 30-35, BMI >35, %	20/31/28/16/5	392 (98%)
Fatigue, CIS-F score, points	39±12	362 (90%)
Depressed mood, BDI score, points	2.2±2.5	360 (90%)
Physical capacity, 6MWD (meter.); 6MWD %predicted	461±123; 71±18	382 (95%)
Habitual physical activity, steps/day	5465±3029	366 (91%)
Activation for self-management, PAM score, points; PAM level I/II/III/IV, %	52±10; 34/28/31/7	365 (91%)

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; Hb=hemoglobin; 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-minute walking distance; PAM=Patient Activation Measure.

Prevalence of treatable traits

Prevalence of the nine examined TTs is shown in Figure 1. The top-3 TTs consists of severe fatigue, poor activation for self-management and low habitual physical activity. From 279 patients (70%), data points on all nine TTs were available. Of these, Figure 2 shows the distribution of the 151 unique combinations of TTs (panel A), the frequencies of the number of TTs present per patient (panel B), a scatterplot of CCQ total score against the number of TTs present per patient (panel C) and a scatterplot of FEV1%predicted against the number of TTs present per patient (panel D). A mean of 3.9±2.0 TTs per patient was observed. A significant correlation coefficient was found between 21 (58%) of the TTs. However, the vast majority (44%) correlated only weakly (range 0.11-0.28). Another 14% correlated moderately (range 0.32-0.53). Strong correlations did not appear. In table E1 of the online data supplement, the correlation matrix of the TTs is provided. Of the 151 unique TTs combinations, 91 (60%) occurred only once, 30 (20%) twice (60 patients), 14 (9%) three times (42 patients), eight (5%) four times (32 patients), four (3%) five times (20 patients), two (1%) eight times (16 patients), one (<1%) seven times (7 patients), and, one (<1%) occurred 11 times (11 patients). The lower panel of Figure 2 shows the heterogeneity in the number and combinations of the nine TTs.

Treatable traits and health status

The relationship between number of TTs and impaired health status and FEV_1%predicted is graphically presented in the two upper panels of Figure 2. Significant correlation coefficients were found between the total number of TTs and FEV1%predicted (r= -0.29; P<0.001) and CCQ total score (r=0.58; P<0.001). Linear regression analysis produced the following regression equation: CCQ total score = 0.765+0.298*number of TTs (*P*<0.001). Correlation between CCQ total score and FEV_1%predicted amounted to only -0.19 (*P*<0.001). Regression analyses did not appear to require adjustment for age and sex. Mean total number of TTs summed up to 2.4±1.2, 3.4±1.6, 4.6±1.6 and 5.5±1.7 in patients with COPD with mild, moderate, severe or very severely impaired health status

respectively and differed significantly (P<0.001) between all four stages. In Figure 3A the COPD *sTRAITosphere* is presented. A severely impaired health status is at the very center of the *sTRAITosphere* and each TT and FEV1%predicted is presented as sphere. The size of the spheres is proportional to the prevalence of the TT and the distance to the center reflects the OR of having a severely impaired health status. The closer the TT is to the center, the higher the likelihood of having a severely impaired health status.

Validation sample

Data points on all eight TTs were available from 381 patients (65%) of the Amphia validation sample and were used to validate the COPD *sTRAITosphere*. The Patient Activation Measure (PAM) was not measured in the validation sample. The validation sample had similar characteristics compared to the initial COPD sample. In an online data supplement, general and COPD-specific patient characteristics of the validation sample (Table E2), the prevalence of the eight TTs (Figure E1), and the frequencies of the number of TTs present per patient (Figure E2) are provided. Again, patients with a depressed mood (OR: 5.6 (3.2; 9.9)), activity-related dyspnea (OR: 8.2 (5.4; 12.4)), or severe fatigue (OR: 8.3 (5.6; 12.5)) had the highest likelihood for having a severely impaired health status (Figure 3B).

Discussion

The present study setting out to determine the prevalence of nine treatable traits indicating non-pharmacological interventions of patients with COPD, with a first-time referral to an outpatient respiratory clinic shows three important findings. Firstly, patients exhibited on average four out of nine TTs qualifying for non-pharmacological treatment options. Secondly, the observed TTs appeared to be relatively independent of each other and emerged mostly in unique combinations, confirming the well-known phenotypical heterogeneity from the TTs perspective. Thirdly, the clinical relevance of the TTs was confirmed because a significant positive association was found between

the number of TTs and the impaired health status, and, except for smoking status all individual TTs increased the likelihood of having a severely impaired health status. Combining these findings suggests that the TTs examined in this study form a window of opportunity to ease symptoms and to better daily functioning of highly symptomatic patients with COPD. Moreover, a reduction of ≥1 TTs may already result in a clinically relevant improvement in health status.

Health status impairment

Eighty percent of the patients in the current study were highly symptomatic, which indeed justifies a referral by the GP to an outpatient consultation of the pulmonologist.(34) About 80% of the patients referred to secondary care had a significant COPD-related impaired daily functioning of whom nearly half was severely to very severely impaired, 44% of the patients were still smoking and 16% even presented with severe hypoxemia, indicating them for long-term oxygen therapy. This shows that patients were referred late in their disease career to specialized respiratory care. It can be argued that the high impact on health status might have been (partially) prevented should these TTs have been addressed earlier. Another 10% of the referred patients were hardly symptomatic and were classified as GOLD A which raises the question why these patients had been referred to a pulmonologist anyway. A plausible explanation for this is that there might have been doubts about the diagnosis by the GP and the reason for referral was to get a proper pulmonary diagnosis and/or to get clues and assistance with a view on improving the patient's health status. Indeed, setting the right diagnosis of COPD still seems difficult in primary care.(35) Empowering GPs in diagnosing COPD by ongoing training in interpreting spirometry might be a first solution here(36), and/ or implementing remote quality control systems.(37) Incidentally, this study shows that patients with only a GOLD class A do not exclude the presence of clinically relevant TTs. Only 22% had none TT, 23% one, 20% two, and 35% had ≥3 TTs.

The number and clinical relevance of TTs

To our knowledge, this is the first study reporting on the large prevalence and relative independency of TTs in patient referred for hospital-based outpatient consultation, which occurred mostly in unique combinations. Indeed, 60% of the identified 151 combinations of TTs occurred only once and the correlation between the number of TTs and FEV_1%predicted was poor. This TT approach nicely illustrates the known complexity and heterogeneity beyond the degree of airflow limitation.(2) This indicates the importance and opportunity to improve patients' health status should these TTs adequately be addressed in the clinical management. Results of the COPD *sTRAITosphere* suggests that fatigue, activity related dyspnea and depressed mood are the most outstanding TTs to better health status as patients with these TTs had the highest likelihood of having a severely impaired health status. These findings were confirmed in a second, independent sample of patients with COPD. With a mean of four TTs per patient and given that the minimal clinically important difference of the CCQ total score is between -0.5 and -0.3 points, it can be estimated from the regression equation that a clinically relevant improvement in health status can be obtained already when only one TT improves following treatment.(38) Indeed, positive effects of such an approach have been shown in a proof-of-concept study in COPD(39) and very recently also in patients with asthma.(40) The current findings emphasize the need for a comprehensive assessment in each individual patient with COPD early in the disease career, and, subsequently, a personalized COPD management program, including pharmacological and non-pharmacological treatment options. Such a comprehensive assessment is feasible to implement and does not require highly demanding recourses.(16) Seven out of nine TTs assessed in the present study can be appraised through readily available and validated questionnaires, which, these days, can be administered relatively easily and processed digitally. Only the assessment of physical capacity and physical activity requires additional efforts. Clinical decision making based on the presence or absence of a particular TT can be dichotomously determined by applying available validated cut-off values. With regard to choices

about exercise-based interventions, the recently introduced Dutch model for profiling patients with COPD for adequate referral to exercise-based care is available.(41)

Methodological considerations

Large observational studies such as ECLIPSE(42) and others(43), did provide important data on the complexity and heterogeneity of patients with COPD. However, these studies have used stringent inclusion criteria apparently limiting the generalizability of the findings of these studies.(44) The present observational clinical study specifically aimed to assess the presence TTs in non-selected COPD patients indicative for non-pharmacological interventions alongside drug therapy, who were referred for a routine outpatient consultation. The number of examined TTs in this study is certainly not inexhaustible. Other traits, deemed important, may also be relevant to consider in the phenotyping of patients with COPD.(45) We have chosen deliberately to use this set of TTs because for each of these TTs evidence-based non-pharmacological interventions are available (Table 1, last column) and because they are relatively easily to capture in a clinical routine. Obviously, the cross-sectional study design precludes a longitudinal follow-up of the TTs. However, TTs fluctuate over time, while the degree of airflow limitation may remain stable. For example, Peters and colleagues showed that the proportion of COPD patients with severe fatigue doubled during four years of usual care, while the FEV_1%predicted remained stable.(46)

Conclusions

Patients with COPD show a markedly impaired health status upon referral to a pulmonologist and present numerous TTs indicating them to non-pharmacological interventions. These TTs co-occur in various unique combinations, are relatively independent and increase the likelihood of having a severely impaired health status. Findings of this study stress the need for a comprehensive assessment and addressing these TTs early in the personalized clinical management.

Acknowledgements

Legend Figure 1:

Figure 1. Frequencies of the nine treatable traits. SM=self-management

Legend Figure 2:

Figure 2. The total number of TTs.

In panel A the 151 unique combinations of TTs are illustrated in relation to the total number of TTs per patient. Red represents the presence of a particular TT whereas green represents the absence. The blue lines mark the subgroups with a corresponding total number of TTs. In panel B are the frequencies of the number of TTs present per patient displayed. In panel C and panel D a scatterplot is presented of the total number of TTs and the CCQ total score and FEV1%predicted, respectively. FEV1%predicted=forced expiratory volume in one second expressed as percentage of the predicted value; CCQ=Clinical COPD Questionnaire; PAM=Patient Activation Measure; 6MWD=6-minte walking distance; TTs=Treatable traits.

Legend Figure 3:
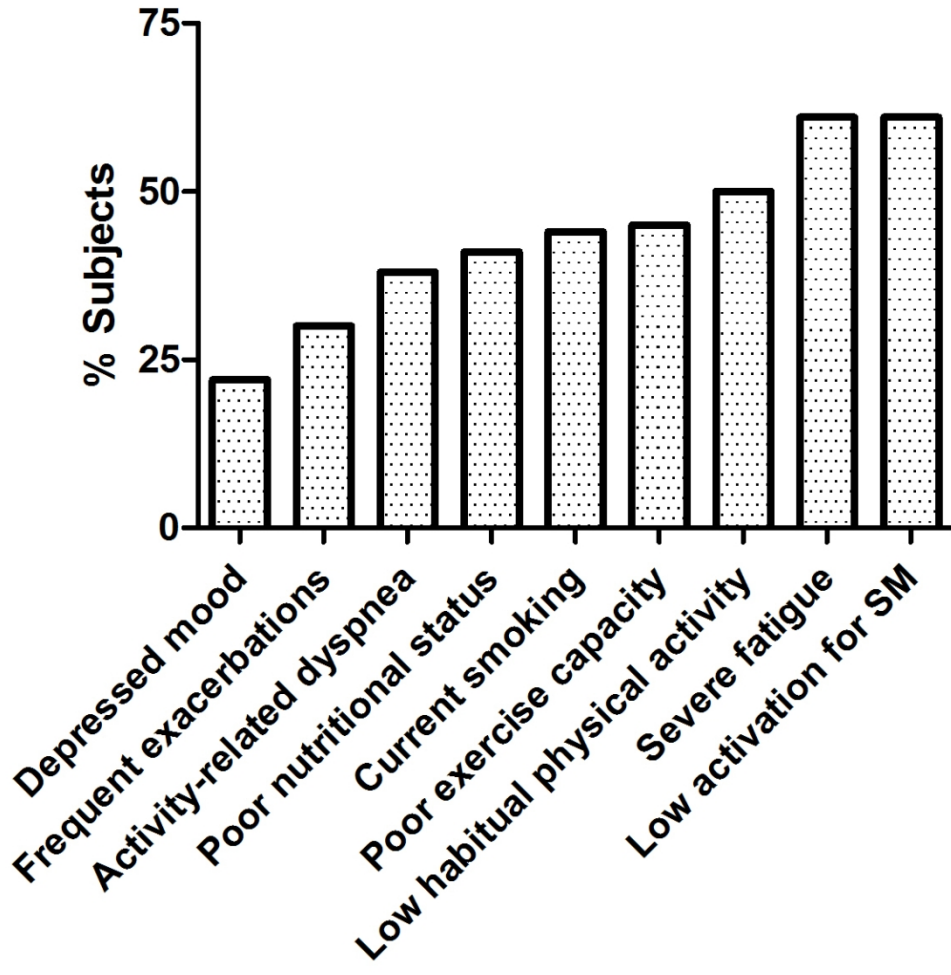
Figure 3A. The COPD *sTRAITosphere*. A severely impaired health status (CCQ total score >2 points) is at the very center of the *sTRAITosphere* and each TT is presented as sphere. The size of the spheres is proportional to the prevalence of the TT and the distance to the center reflects the OR of having a severely impaired health status. Figure 3B. Validation of the COPD *sTRAITosphere*.
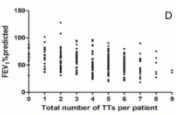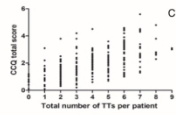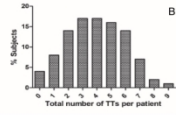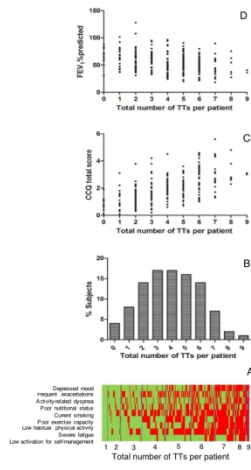
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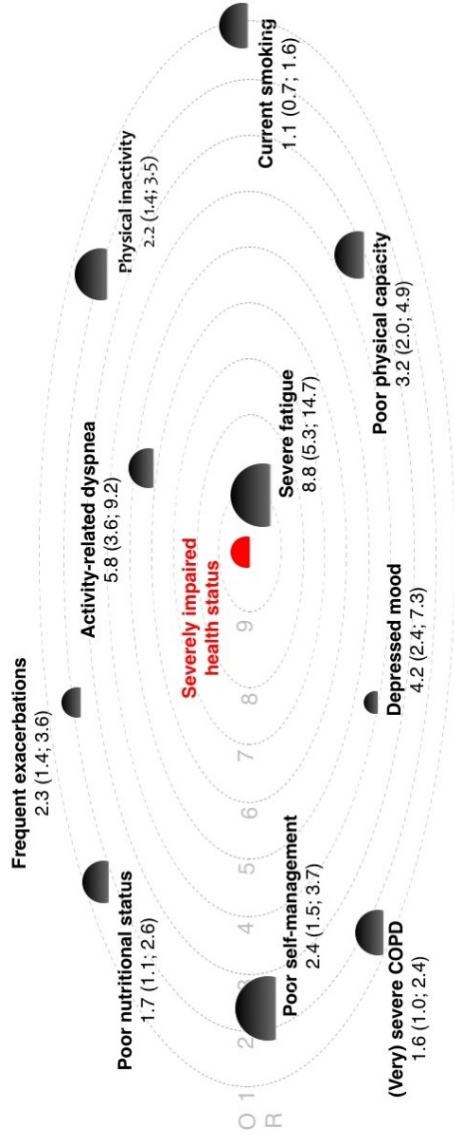
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Figure D: FEV₁ %predicted vs Total number of TTs per patient

Figure C: CCQ total score vs Total number of TTs per patient

Figure B: % Subjects vs Total number of TTs per patient

Figure A: Heat map of treatable traits (Depressed mood, Frequent exacerbations, Activity-related dyspnea, Poor nutritional status, Current smoking, Poor exercise capacity, Low habitual physical activity, Severe fatigue, Low activation for self-management) vs Total number of TTs per patient

A

Frequent exacerbations
2.3 (1.4; 3.6)

Physical inactivity
2.2 (1.4; 3.5)

Current smoking
1.1 (0.7; 1.6)

Activity-related dyspnea
5.8 (3.6; 9.2)

Severe fatigue
8.8 (5.3; 14.7)

Poor physical capacity
3.2 (2.0; 4.9)

**Severely impaired
health status**

Depressed mood
4.2 (2.4; 7.3)

Poor nutritional status
1.7 (1.1; 2.6)

Poor self-management
2.4 (1.5; 3.7)

(Very) severe COPD
1.6 (1.0; 2.4)

O 1 2 3 4 5 6 7 8 9
R

B

Frequent exacerbations
2.3 (1.5; 3.6)

Poor nutritional status
1.2 (0.8; 1.7)

Activity-related dyspnea
8.2 (5.4; 12.4)

Physical inactivity
2.5 (1.8; 3.5)

Severely impaired
health status

O 1 2 3 4 5 6 7 8 9
R

Current smoking
0.8 (0.6; 1.2)

Severe fatigue
8.3 (5.6-12.5)

Depressed mood
5.6 (3.2; 9.9)

(Very) severe COPD
1.4 (0.97; 2.0)
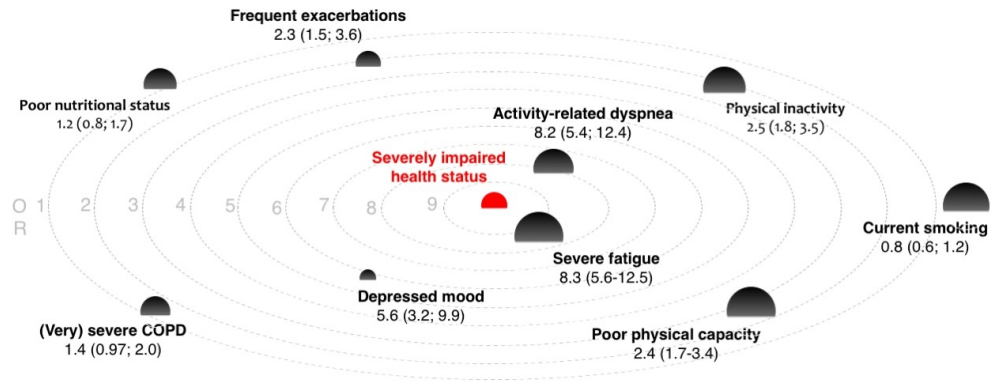
Poor physical capacity
2.4 (1.7-3.4)

Cover sheet Online Data Supplement

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, 5th, 50th and 95th 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=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-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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