Noortje Koolen

The COPDnet integrated care model

a newly developed and effective care pathway for patients with Chronic Obstructive Pulmonary Disease

The COPDnet integrated care model

a newly developed and effective care pathway
for patients with Chronic Obstructive Pulmonary Disease

Eleonore Huberta Koolen

ISBN: 978-94-6423-483-1

Cover design & lay-out: Wendy Schoneveld || www.wenziD.nl
Printed by:

The research described in this thesis was performed at the departments of Pulmonary Diseases and IQ Healthcare. These departments are part of the Radboud Institute for Health Sciences (RIHS), one of the approved research institutes of the Radboud University Medical Center.

Financial support by PICASSO Zorgoptimalisatie

The COPDnet integrated care model

a newly developed and effective care pathway
for patients with Chronic Obstructive Pulmonary Disease

Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. dr. J.H.J.M. van Krieken,
volgens besluit van het college voor promoties
in het openbaar te verdedigen op

woensdag 17 november 2021
om 10.30 uur precies

door

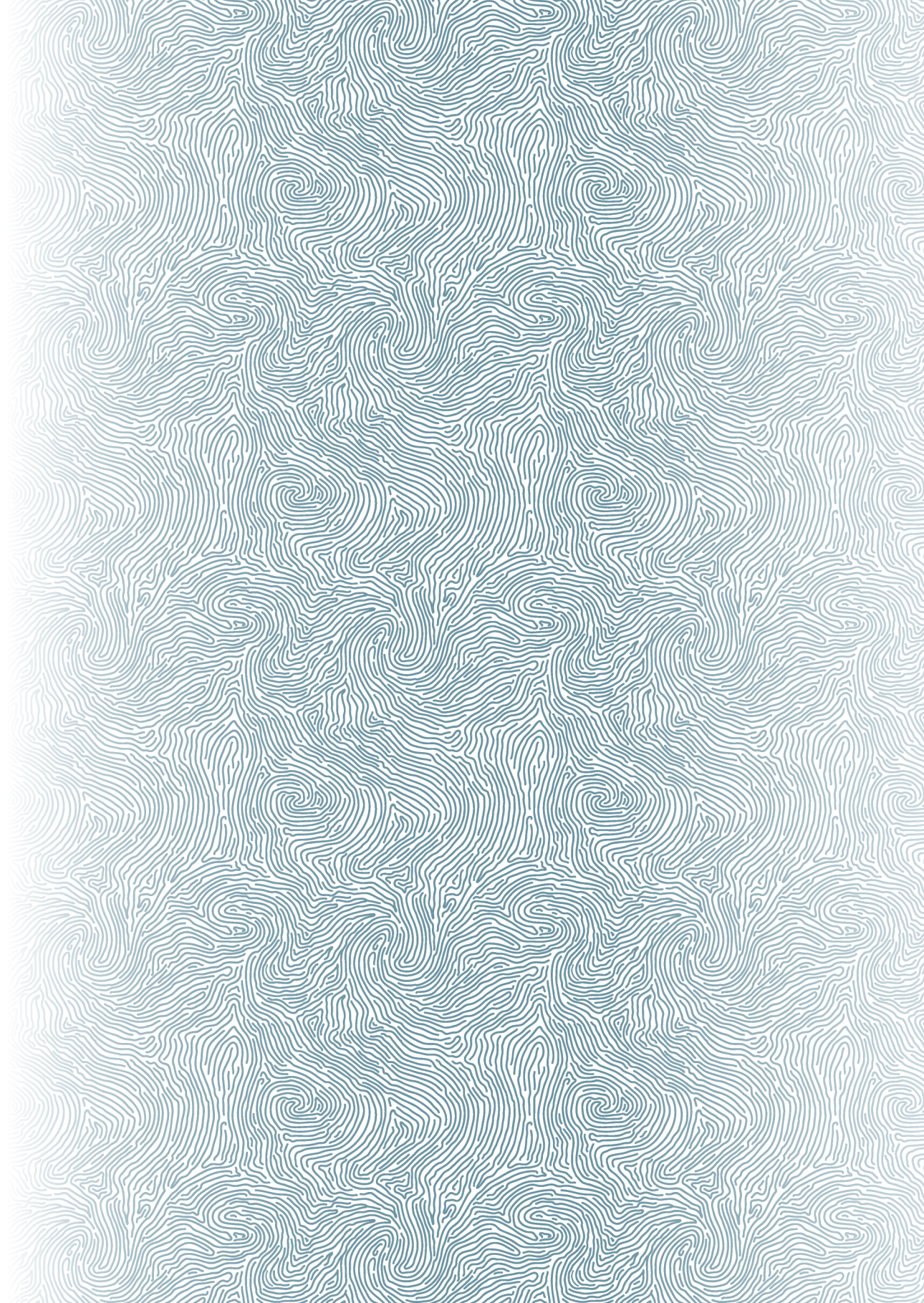
Eleonore Huberta Koolen
geboren op 25 maart 1989
te Geldrop

Promotoren:
Prof. dr. M.M. van den Heuvel
Prof. dr. P.J. van der Wees

Copromotor:
Dr. A.J. van ‘t Hul

Manuscriptcommissie:
Prof. dr. B.R. Bloem
Prof. dr. J.W.M. Muris (Maastricht UMC)
Prof. dr. H.A.M. Kerstjens (UMC Groningen)

Contents



GENERAL INTRODUCTION

INTRODUCTION

Epidemiology

In 2019, Chronic Obstructive Pulmonary Disease (COPD) was the third leading cause of death worldwide.[1] In the Netherlands, nearly 585.000 people had COPD in 2019, more than 6700 people died from the disease in 2019 and it leads to approximately 912 million euro healthcare expenditures in 2017.[2] Moreover, the impact of COPD places an inordinate burden on healthcare resources given the significant direct and indirect costs of care.[3] Projections on the future suggest a further rise in the prevalence of COPD patients, especially of patients with severe or very severe disease.[4] Based on demographic developments only, the absolute number of people with COPD is expected to increase by 36% in the period 2015-2040 in the Netherlands.[2]

Chronic Obstructive Pulmonary Disease

COPD is defined as "a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases and influenced by host factors including abnormal lung development".[5] Based on this definition, the diagnosis of COPD is still considered a predominantly respiratory disease, as the severity of the airflow limitation is still a core component.

Complex and heterogenous disease

Fortunately, our understanding of COPD has changed in the last decades and it is therefore considered as a complex and heterogeneous condition with a variety of intrapulmonary manifestations and several extrapulmonary features and comorbidities.[6-10] The term 'complex' means that COPD has a number of intrapulmonary and extrapulmonary components whose dynamic interactions along time are not linear, whereas 'heterogeneous' indicates that not all of these components are present in all patients at any given time.[11] It is therefore important not only to evaluate the physiological aspects of the obstructive lung disease, but to obtain a more comprehensive analysis of the health status in patients with COPD.[12-16] Whereas the severity of COPD is defined by the pathophysiological impairment (airway obstruction), the burden of disease is based on the perceived health problems by the individual patient.[17]

Complex organization of care

Besides the fact that COPD is considered a complex and heterogeneous disease, the organization of this COPD care is also complexly organized. COPD patients may receive their care within a primary, secondary or tertiary care setting and, in addition, many different professionals may be involved simultaneously or alternately. A recent study

by De Klein et al. showed that not all COPD patients seem to be managed at the most appropriate level of care, indicating that this does not mean that the most complex COPD patients in the Netherlands are treated in higher echelons and vice versa.[18] Furthermore, the results of this study imply that a detailed comprehensive analysis of the health status is necessary, not only to gain a better understanding of the level of care a COPD patient needs, but also to support healthcare professionals in optimizing and tailoring chronic COPD care.[18]

Given the great challenges of providing good care for people with COPD, as outlined above, it is perhaps not surprising that studies on the outcomes of "real life" care are dissatisfying and show room for improvement.[19-24] This disappointing insight is at odds with the current view on healthcare which assumes that it is important to establish a care process that maximizes outcomes in relation to the efforts and costs made.[25] This concept, the so-called value-based healthcare, described by M.E. Porter, arose from the fact that obtaining high value for patients should be the main goal of healthcare, in which value is defined as "the health outcomes achieved per dollar spent".[25] The principles of value-based healthcare could be relevant and applicable for chronic conditions, given the increasing number of patients and the increasing costs that will be incurred.

Integrated care

Better outcomes of care in patients with chronic conditions may be expected from implemented integrated disease management programs in healthcare settings[26-28], including COPD patients.[29-31] According to the definition of integrated disease management by Peytremann-Bridevaux and Burnand[32], such programs should address simultaneously both the content of care (individualized, patient-centred holistic approach), as well as, the organization of care (integrated medical care among healthcare professionals and across healthcare sectors).[33] However, a recently conducted study in five countries of the European Union, including the Netherlands, concluded that integrated care models are currently only used to a limited extent in care pathways, i.e. COPD patients' care pathways are fragmented and care is not properly integrated.[34]

The COPDnet integrated care model

In order to bridge the gap between current and desired care, in which the principles of integrated care are applied, we have started to develop a evidence-based comprehensive care model for COPD patients with moderate or severe burden of disease who are referred to secondary care. We named it the COPDnet integrated care model. The assumption was made that this particular group of patients had such a burden of disease that they could be good candidates for an integrated care approach.

During the designing process of the COPDnet model we could build on a recently developed and implemented innovative diagnostic pathway for patients with obstructive lung disease. This diagnostic pathway was successfully implemented in two outpatient respiratory clinics in the Netherlands, that is, Amphia Hospital in Breda and Franciscus Gasthuis & Vlietland in Rotterdam. Because an integrated approach should not be limited to diagnostics, we have added a subsequent intervention program. Therefore, we adopted in this intervention program an already available center-based pulmonary rehabilitation program. In addition, we developed and implemented a modular program for non-pharmacological treatment options provided in primary care.

Objectives of this thesis

Given the importance of improving the care for patients with COPD with moderate or severe burden of disease who are referred to secondary care, the overall aim of the research on which this thesis is based is to develop an integrated healthcare model in order to improve healthcare outcomes. More specifically, the following five research questions and one objective are addressed in this thesis:

1. What are the components for an integrated care model developed for COPD patients with moderate or severe burden of disease (**Chapter 2**)?
2. To describe the methodology in a study protocol as to how the added value of the COPDnet model was evaluated (**Chapter 3**)
3. What is the clinical applicability of a novel concept to better understand physical functioning in patients with COPD (**Chapter 4**)?
4. What is the prevalence of nine potentially clinically relevant treatable traits in patients with COPD being referred to secondary care (**Chapter 5**)?
5. What is the clinical effectiveness of one of the non-pharmacological primary care intervention options of the COPDnet integrated care model, specifically home-based occupational therapy (**Chapter 6**)?
6. What is the clinical effectiveness of the COPDnet integrated care model (**Chapter 7**)?

OUTLINE OF THIS THESIS

Chapter 2 and **Chapter 3** address the development and study protocol of a new integrated disease management pathway in patients with COPD, named the COPDnet integrated care model. **Chapter 2** reports the development of this new COPDnet integrated care model for COPD patients with moderate or severe burden of disease, who are referred to secondary care. **Chapter 3** describes the study protocol in order to evaluate this newly developed COPDnet model.

Chapter 4 and **Chapter 5** address the complexity and heterogeneity of the COPD disease in patients who have been referred to secondary care for the first time. In order to better understand physical functioning in COPD patients, **Chapter 4** describes the development of a pragmatic clinical quadrant concept in which COPD patients could be subdivided along axes of what they physically "can do" (physical capacity), and what they actually "do do" (physical activity), in their daily lives. **Chapter 5** reports on the prevalence of nine potentially clinically relevant treatable traits in COPD patients being referred upon first time referral to a pulmonologist in secondary care.

Chapter 6 reports the clinical effectiveness of home-based monodisciplinary occupational therapy in primary care in patients with COPD, who were enrolled in the COPDnet integrated care model.
Chapter 7 describes the clinical effectiveness of the COPDnet integrated care model on health status change in patients with COPD.
Finally, in **Chapter 8**, the preceding chapters are discussed in the light of previous research and future perspectives.

REFERENCES

1. World Health Organization (WHO). The top 10 causes of death. Available from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death. Accessed April 05, 2021.

2. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). COPD. Available from: https://www.volksgezondheidenzorg.info/onderwerp/copd. Accessed April 05, 2021. Dutch

3. Wouters EF. Economic analysis of the Confronting COPD survey: an overview of results. *Respiratory Medicine.* 2003;97 Suppl C:S3-14.

4. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. *Lancet.* 2007;370(9589):765-773.

5. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease - 2020 Report. Available from: https://goldcopd.org/wp-content/uploads/2019/12/GOLD-2020-FINAL-ver1.2-03Dec19_WMV.pdf. Published 2020. Accessed April 05, 2021.

6. Agusti A, Calverley PM, Celli B, et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. *Respiratory Research.* 2010;11:122.

7. Wouters EFM, Wouters B, Augustin IML, Houben-Wilke S, Vanfleteren L, Franssen FME. Personalised pulmonary rehabilitation in COPD. *European Respiratory Review : an official journal of the European Respiratory Society.* 2018;27(147).

8. Vanfleteren LE, Spruit MA, Groenen M, et al. Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine.* 2013;187(7):728-735.

9. Vanfleteren L, Spruit MA, Wouters EFM, Franssen FME. Management of chronic obstructive pulmonary disease beyond the lungs. *The Lancet Respiratory Medicine.* 2016;4(11):911-924.

10. Miller J, Edwards LD, Agusti A, et al. Comorbidity, systemic inflammation and outcomes in the ECLIPSE cohort. *Respiratory Medicine.* 2013;107(9):1376-1384.

11. Agusti A, Bel E, Thomas M, et al. Treatable traits: toward precision medicine of chronic airway diseases. *The European Respiratory Journal.* 2016;47(2):410-419.

12. Agusti A, Sin DD. Biomarkers in COPD. *Clinics in chest medicine.* 2014;35(1):131-141.

13. Jones PW, Agusti AG. Outcomes and markers in the assessment of chronic obstructive pulmonary disease. *The European Respiratory Journal.* 2006;27(4):822-832.

14. Papaioannou AI, Loukides S, Gourgoulianis KI, Kostikas K. Global assessment of the COPD patient: time to look beyond FEV1? *Respiratory Medicine.* 2009;103(5):650-660.

15. Tsiligianni I, Kocks J, Tzanakis N, Siafakas N, van der Molen T. Factors that influence disease-specific quality of life or health status in patients with COPD: a review and meta-analysis of Pearson correlations. *Primary Care Respiratory Journal : journal of the General Practice Airways Group.* 2011;20(3):257-268.

16. Zuwallack RL, Nici L. Modifying the course of chronic obstructive pulmonary disease: looking beyond the FEV1. *COPD.* 2012;9(6):637-648.

17. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. *JAMA.* 1995;273(1):59-65.

18. de Klein MM, Peters JB, van 't Hul AJ, et al. Comparing health status between patients with COPD in primary, secondary and tertiary care. *NPJ Primary Care Respiratory Medicine.* 2020;30(1):39.

19. Ellingsen J, Johansson G, Larsson K, et al. Impact of Comorbidities and Commonly Used Drugs on Mortality in COPD - Real-World Data from a Primary Care Setting. *International Journal of Chronic Obstructive Pulmonary Disease.* 2020;15:235-245.

20. Worth H, Buhl R, Criee CP, Kardos P, Mailander C, Vogelmeier C. The 'real-life' COPD patient in Germany: The DACCORD study. *Respiratory Medicine.* 2016;111:64-71.

21. Buhl R, Criee CP, Kardos P, et al. A year in the life of German patients with COPD: the DACCORD observational study. *International Journal of Chronic Obstructive Pulmonary Disease.* 2016;11:1639-1646.

22. Haughney J, Gruffydd-Jones K, Roberts J, Lee AJ, Hardwell A, McGarvey L. The distribution of COPD in UK general practice using the new GOLD classification. *The European Respiratory Journal.* 2014;43(4):993-1002.

23. Ke X, Marvel J, Yu TC, et al. Impact of lung function on exacerbations, health care utilization, and costs among patients with COPD. *International Journal of Chronic Obstructive Pulmonary Disease.* 2016;11:1689-1703.

24. Price D, West D, Brusselle G, et al. Management of COPD in the UK primary-care setting: an analysis of real-life prescribing patterns. *International Journal of Chronic Obstructive Pulmonary Disease.* 2014;9:889-904.

25. Porter ME. What is value in health care? *The New England Journal of Medicine.* 2010;363(26):2477-2481.

26. Ofman JJ, Badamgarav E, Henning JM, et al. Does disease management improve clinical and economic outcomes in patients with chronic diseases? A systematic review. *The American Journal of Medicine.* 2004;117(3):182-192.

27. Fuchs S, Henschke C, Blumel M, Busse R. Disease management programs for type 2 diabetes in Germany: a systematic literature review evaluating effectiveness. *Deutsches Arzteblatt International.* 2014;111(26):453-463.

28. de Bruin SR, Heijink R, Lemmens LC, Struijs JN, Baan CA. Impact of disease management programs on healthcare expenditures for patients with diabetes, depression, heart failure or chronic obstructive pulmonary disease: a systematic review of the literature. *Health Policy.* 2011;101(2):105-121.

29. Lemmens KM, Lemmens LC, Boom JH, et al. Chronic care management for patients with COPD: a critical review of available evidence. *Journal of Evaluation in Clinical Practice.* 2013;19(5):734-752.

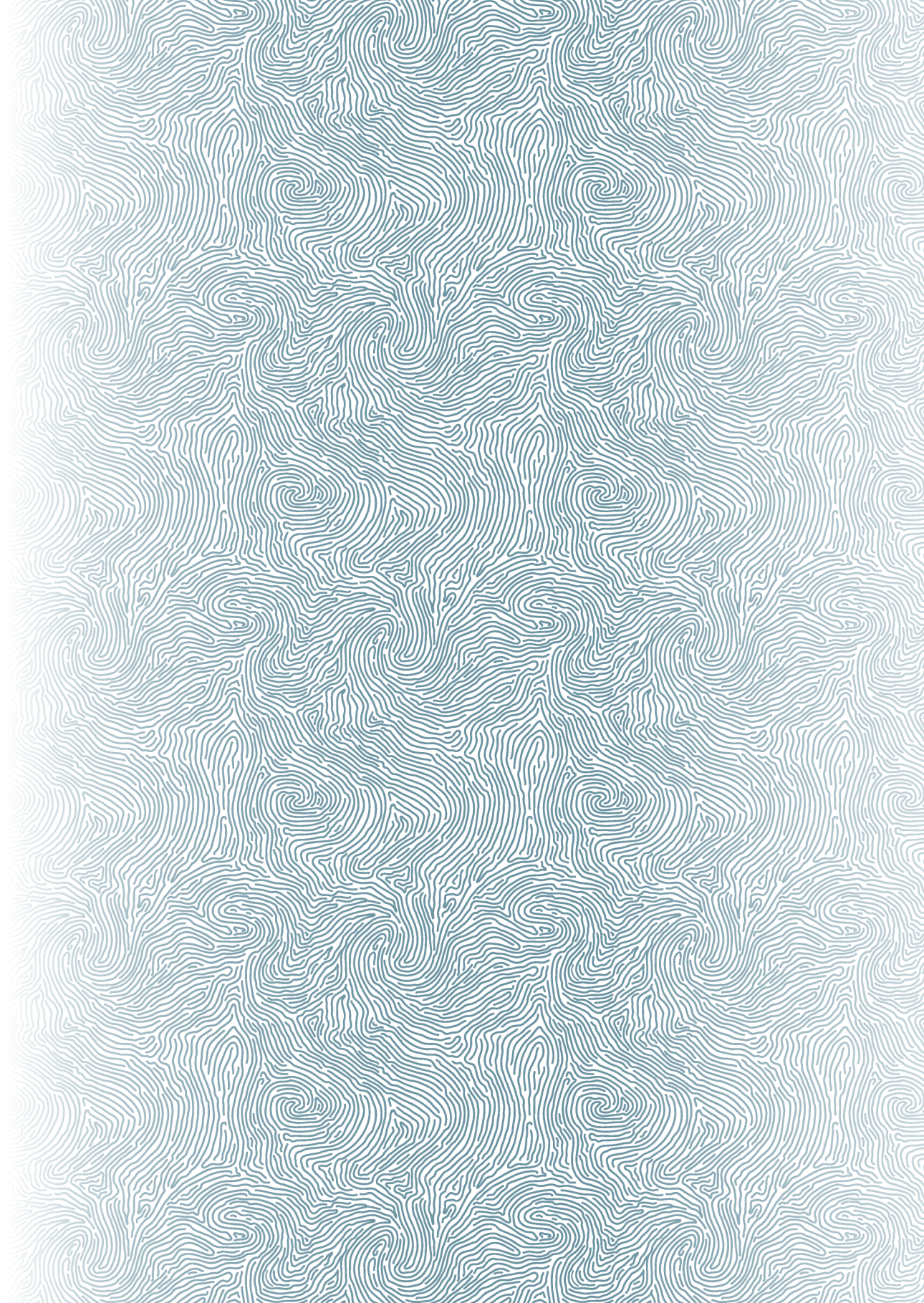
30. Lemmens KM, Nieboer AP, Huijsman R. A systematic review of integrated use of disease-management interventions in asthma and COPD. *Respiratory Medicine.* 2009;103(5):670-691.

31. Lemmens KM, Nieboer AP, Rutten-Van Molken MP, et al. Application of a theoretical model to evaluate COPD disease management. *BMC Health Services Research.* 2010;10:81.

32. Peytremann-Bridevaux I, Burnand B. Disease management: a proposal for a new definition. *International Journal of Integrated Care.* 2009;9:e16.

33. Nici L, ZuWallack R, American Thoracic Society Subcommittee on Integrated Care of the CP. An official American Thoracic Society workshop report: the Integrated Care of The COPD Patient. *Proceedings of the American Thoracic Society.* 2012;9(1):9-18.

34. Kayyali R, Odeh B, Frerichs I, et al. COPD care delivery pathways in five European Union countries: mapping and health care professionals' perceptions. *International Journal of Chronic Obstructive Pulmonary Disease.* 2016;11:2831-2838.



The COPDnet integrated care model

E.H. Koolen
P.J. van der Wees
G.P. Westert
P.N.R. Dekhuijzen
Y.F. Heijdra
A.J. van 't Hul

International Journal of Chronic Obstructive Pulmonary Disease 2018 Jul 19;13:2225-2235

ABSTRACT

INTRODUCTION

This research project sets out to design an integrated disease management model for patients with Chronic Obstructive Pulmonary Disease (COPD) who were referred to a secondary care setting, and who qualified for pharmacological and non-pharmacological intervention options.

THEORY AND METHODS

The integrated disease management model was designed according to the guidelines of the European Pathway Association (EPA) and the content founded on the Chronic Care Model (CCM), principles of integrated disease management, and knowledge of Quality Management Systems (QMS).

RESULTS

An integrated disease management model was created and comprises (1) a diagnostic trajectory in a secondary care setting, (2) a non-medical intervention programme in a primary care setting and, (3) a pulmonary rehabilitation service in a tertiary care setting. The model also includes a QMS, and regional agreements about exacerbation management and palliative care.

DISCUSSION

In the next phase of the project the COPDnet model will be implemented in at least two different regions, in order to assess the added value of the entire model and its components, in terms of feasibility, health status benefits and costs of care.

CONCLUSION

Based on recent theories and models, a new integrated disease management model was developed for COPD patients, named COPDnet. Once the model is stable, it will be evaluated for its feasibility, health status benefits, and costs.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a highly prevalent disease and often puts a high burden of disease on those affected, even when they are in a relatively stable phase of their disease or only have mild to moderate airway obstruction.[1] Moreover, the impact of COPD places an inordinate burden on healthcare resources given the significant direct and indirect costs of care.[2] Projections on the future suggest a further rise in the prevalence of COPD patients, especially of patients with severe or very severe disease.[3]

Given this high prevalence, the expected rise, and the significant impact on the individual and on society, it is important to establish a care process that maximizes outcomes in relation to the efforts and costs made.[4]

Surprisingly, little scientific data is available on the outcome of 'real life' care in these patients in the chronic phase of their illness, that is to say, outcomes of care outside the remit of treatment of exacerbations.[5] The first publications on the outcomes of 'real life' chronic care in COPD are available and suggest room for improvement for the organisation of care, as well as for the content of care and for the cost-effectiveness of care.[6-9]

Better outcomes of care for patients with chronic conditions, like type 2 diabetes, are to be expected from the widespread use of integrated disease management programmes.[10] This also counts for patients with COPD.[11] According to the definition of integrated disease management by Peytremann-Bridevaux et al, such programmes should address simultaneously both the content of care as well as the organisation of care.[12] That is to say, to provide: 1) a patient-centred, holistic care based on the patient's individual needs, captured through a thorough assessment in 2) a synchronized manner with coordination of services and therapies across healthcare settings and healthcare providers.[13]

The most recent systematic review confirmed the evidence for the efficacy of integrated disease management interventions in people with COPD of at least three months duration on 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.[14] However, when taking a closer look at the studies, it appeared that only five out of the twenty-six included studies described an integrated disease management program within a combination of primary and secondary healthcare settings.[15-19] In addition, interventions were either directed towards the content of care[15,16,19] or the organisation of care[17,18] but never addressed them together.

A recent publication on the effects of the German disease management program for COPD, predominantly directed at primary care, also lends support to the effectiveness of an integrated approach for COPD.[20]

Finally, our impression is that integrated care models are, as yet, only in limited use in our present care delivery pathways. This was confirmed in a recently performed survey in five European union countries, including the Netherlands. In this paper the authors concluded that COPD healthcare pathways are fragmented and care is not integrated properly. In order to succeed in providing integrated chronic disease management care, knowledge from controlled studies should be translated into practical applications.[21]

This paper describes the results of a research project, which was set out to design an integrated disease management model for patients with COPD, named the COPDnet integrated care model. This model may serve as a blueprint for the establishment of regular care for COPD patients across all healthcare settings, and it will address both the content, as well as the organisational aspects of care. The COPDnet integrated care model was specifically designed for patients with moderate or severe burden of disease, whom according to the Dutch Standard of Care for COPD meet the criteria for care in a primary, secondary or a tertiary care setting, and qualify for both pharmacological and non-pharmacological intervention options.[22]

DESCRIPTION OF THE CARE PRACTICE

Description of the development process

The COPDnet integrated care model was designed according to the guidelines of the European Pathway Association (EPA) in which seven phases are distinguished: (1) a screening phase, (2) a project management phase, (3) a diagnostic phase (baseline measurements, mapping existing pathways), (4) a design and plan phase (development of care pathway), (5) an implementation phase, (6) an evaluation phase, (7) a continuous follow-up phase (making it clinical routine and on-going review).[23] We designed this model because it seemed particularly applicable to in-hospital, primary care and cross-boundary projects. In phase two and three an analysis and baseline measurements were carried out and we found that the process of care at that time did not sufficiently comply with the principles of integrated disease management care. During the course of phase 4, the designing process, general practitioners (GPs), respiratory nurses, pulmonologists, representatives of the Dutch Lung Foundation, and medical advisors of health insurance companies externally reviewed the COPDnet integrated care model.

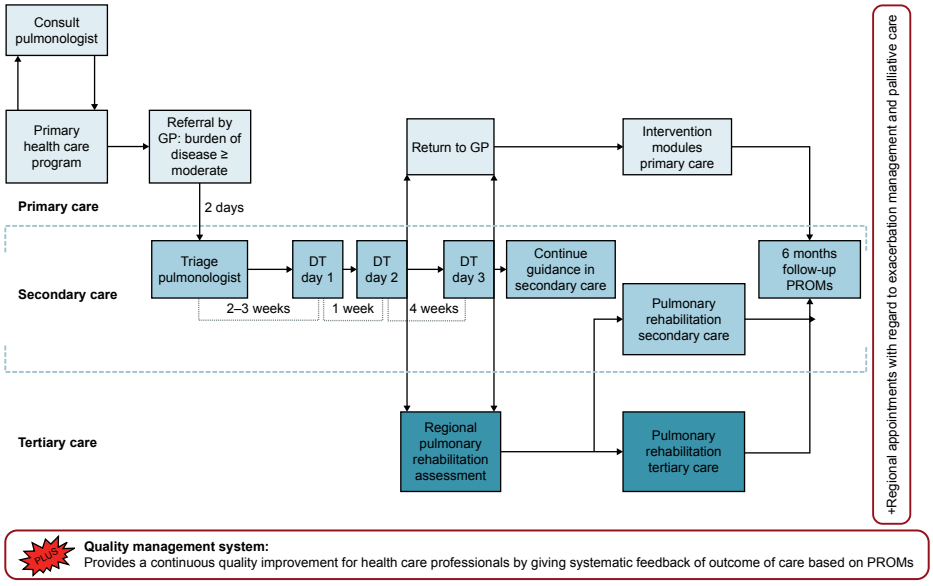


Figure 1. The COPDnet integrated care model
Legend: GP=General Practitioner; DT=Diagnostic Trajectory; PROMs=Patient Reported Outcome Measurements

The content of the COPDnet model

The definition of chronic disease management was used as a starting point for the development of the COPDnet integrated care model.[12] In order to operationalize this definition in the designing process, we have used the Chronic Care Model (CCM) as a guideline.[24] The CCM sets out to transform the daily care for patients with chronic illnesses from acute and reactive to proactive, planned, and population-based.[25] Moreover, application of the principles of the CCM in the context of COPD has shown added value and highlighted the need for implementing multiple components of the CCM to prevent complications and improve outcomes in patients with COPD.[26] Therefore, four elements of the health care system, as identified in the CCM, were used in our COPDnet integrated care model: (1) self-management support, (2) decision support, (3) delivery system design and (4) clinical information systems. The CCM is not an explanatory theory, yet the model is more like a flexible evidence-based guideline.[27] We have added specific diagnostic procedures to our model in order to better address the complexity and heterogeneity of COPD and thereby to provide the best personalised treatment of a given patient.[28]

Figure 1 represents a graphical overview of all the elements of the COPDnet integrated care model, that is, (1) a diagnostic trajectory carried out in a secondary care setting, (2) a non-medical intervention programme in a primary care setting and (3) a pulmonary

rehabilitation service in a tertiary care setting. The model also includes a Quality Management System (QMS) and a set of regional network agreements about exacerbation management and palliative care. The COPDnet model uses the diagnostic trajectory of which one of the authors (AvtH) was co-creator and is based on The Delphi Panel Study.[29] Novelties in this diagnostic trajectory are a measurement of dynamic hyperinflation, objectivation of physical activity with a move monitor, and a systematic evaluation of the burden of disease measured with the Nijmegen Clinical Screening Instrument (NCSI). The identification of comorbidities is explicitly part of the diagnostic workup in the COPDnet model and is acted upon if and when this is deemed appropriate by the pulmonologist.[30] Details regarding the content of the diagnostic trajectory are published elsewhere.[31]
Below we describe in detail how the four CCM components have been integrated in the COPDnet model:

Self-management support

More and more the reinforcement of self-management skills is found to be an important aspect in the care of patients with a chronic health condition. An effective self-management strategy should include the initiation of behavioural change, be tailored individually, take the patient's perspective into account, and it should be adapted to the course of the patient's disease and co-morbidities.[32] Recently, international consensus has been reached regarding a conceptual definition of what a COPD self-management intervention should comprise.[33] Subsequently, we have included the following strategies for self-management support in our COPDnet model: (1) Patient Activation Measurement (PAM) and Motivational Interviewing, (2) Capabilities Opportunities Motivation-Behaviour model (COM-B model), (3) shared decision making, and (4) an individual care plan.

Patient Activation Measurement and Motivational interviewing

An understanding of the level of activation for self-management, defined as "patients' knowledge, skills and self-efficacy regarding self-management" is important because it gives clues as to how self-management may be improved by the individual patient.[34] The level of activation for self-management can be determined with the PAM.[34,35] In the COPDnet integrated care model we use the shortened 13-item version of the PAM.[34] This measures patients' activation levels for self-management and classifies patients into four different levels: (1) believing in the importance of their own role, (2) having the confidence and knowledge required to take action, (3) actually taking action to maintain and improve health, and (4) staying the course even under stress. With the outcome of the PAM, the stages of change in health behaviour can be monitored.[36] Based on these outcomes healthcare professionals apply motivational interviewing techniques to improve patients' self-management skills. Motivational interviewing is a

communication technique, which focuses on helping patients to change their behaviour, by exploring their personal perspectives as well as their perceived barriers.[37]

Capabilities Opportunities Motivation-Behaviour model

The COM-B model is a theoretical model, which suggests that there are three ways in which human behaviour (B) results from the interaction between: psychological capabilities (C), social and environmental opportunities (O), and motivation (M). This model helps to identify which dimension in this COM-B model should be addressed to encourage behavioural change in patients.[38]

Shared decision-making

Shared decision making is used in our COPDnet model. Although the principles of shared decision-making are well documented, we have described a comprehensive practical approach to patient centred care. Achieving shared decision making relies on a good relationship in the clinical encounter so that information is shared and patients are supported to deliberate and express their preferences and views during the decision making process.[39] Shared decision making is based on introducing a choice (choice talk), describing options (option talk), and helping patients to explore preferences and to make informed decisions (decision talk).[39] In our COPDnet model the choice talk takes place during day one, the option talk during day two and the decision talk during day three of the diagnostic trajectory.

Individual care plan

Based on the various talks between the healthcare professionals and the patient, the patient is asked to construct an individual care plan - including the patient's personal objective(s) - between visit two and three. During visit three, this individual care plan will be further explored with the respiratory nurse and developed into informed preferences regarding treatment options.

Decision support

Guidelines on decision making

Based on state-of-the-art insights, practical guidelines on decision making were introduced in our model for: (1) Additional diagnostics, (2) Classification of the burden of disease, and (3) Choices between care settings for personalized interventions.

Additional diagnostic tests

The COPDnet diagnostic trajectory is designed to provide an optimal diagnosis with minimal measurements, as adequately as possible. The model creates an overview of the individual traits of each patient. In some patients, a further understanding of the pathophysiology is necessary in order to come to a proper diagnosis or to set an

appropriate indication for the best interventions. For these patients, additional diagnostics may be required after day one of the diagnostic trajectory. In patients in which exercise training is offered as intervention, a cardiopulmonary exercise test is carried out. The performance on a maximal exercise test is used to set individual training parameters.[40] Further diagnostic tests may be requested, see Table 1.

Classification of burden of disease

The diagnostic trajectory of the COPDnet model aims to provide a classification of the burden of disease on the patient. Subsequently, this classification is used for the allocation of patients to the appropriate care setting which means, either a referral back to a primary care setting or a referral to a tertiary care setting for a pulmonary rehabilitation assessment.

Whereas the severity of COPD is defined by the pathophysiological impairment (airway obstruction), the burden of disease is based on the perceived health problems by the individual patient.[41] This allows for tailoring treatment to the patient, based on a comprehensive assessment of the individual causes of the burden of disease. The severity of the burden of disease is classified into: mild, moderate or severe, see Table 2.

Table 1. Additional diagnostics

Additional diagnostics	Aim	Indication
Measurement of static lung volumes	To determine the presence of restrictive pulmonary function impairment	- FVC < 80% of the predicted value
CO diffusion capacity	To determine whether or not CO diffusion is limited	- Persisting doubts about the diagnosis asthma or COPD - Suspected ILD - Discrepancy between spirometric values and desaturation during the 6MWD
Histamine provocation test	To determine the presence and severity of bronchial hyperreactivity	- Doubts about the diagnosis of asthma or COPD - To set up or adjust medication in case of asthma
Cardiopulmonary exercise test	To determine maximal exercise capacity and cause of exercise limitation	- Steps per day < 5000 or VMU < 0.210 and 6MWD < 70% of predicted value, and the patient is willing to participate in an exercise training program
CT thorax	Imaging of the thorax	- Doubts about the presence of malignancy or ILD
Referral to cardiologist or ENT-specialist	To determine the diagnosis and treatment of relevant comorbidity	- Suspicion of relevant cardiac or ENT comorbidity

Abbreviations: FVC = Forced Vital Capacity; CO diffusion = Carbon Monoxide diffusion; COPD = Chronic Obstructive Pulmonary Disease; ILD = Interstitial Lung Disease; 6MWD = 6-Minute Walk Distance; VMU = Vector Magnitude Units; ENT = Ear Nose Throat

Table 2. Classification of burden of disease

Mild	Moderate	Severe
- Exacerbations: none in the last year	- Exacerbations: 1 in the last year	- Exacerbations: ≥ 2 in the last year or 1 hospitalization due to exacerbation COPD
- Comorbidities: none or do not contribute to the burden of disease	- Comorbidities: present and contribute moderately to the burden of disease	- Comorbidities: present and contribute markedly to the burden of disease
- MRC = 0 – 1	- MRC = 1 – 2	- MRC = 3 – 5
- BMI > 21 or < 30	- BMI < 21 or 30 – 35	- BMI < 21 or > 35
- 6MWD ≥ 500 meter	- 6MWD = 400 – 500 meter	- 6MWD < 400 meter
- PAL ≥ 1.7	- PAL = 1.4 – 1.7	- PAL < 1.4
- CCQ < 2.0	- CCQ = 2 – 3	- CCQ > 3.0
- NCSI = normal or mildly disturbed	- NCSI = moderately disturbed	- NCSI = severely disturbed
- No or mild disturbance of the social participation (work, family, hobbies, sports, and so on)	- Moderate disturbance of the social participation (work, family, hobbies, sports, and so on)	- Severe disturbance of the social participation (work, family, hobbies, sports, and so on)

Note: PAL was measured with the MoveMonitor
Abbreviations: MRC = Medical Research Council; BMI = Body Mass Index; 6MWD = 6-Minute Walk Distance; PAL = Physical Activity Level; CCQ = Clinical COPD Questionnaire; NCSI = Nijmegen Clinical Screening Instrument

Choices with respect to the indices of, and cut-off values for the burden of disease in our model are partially based on the existing literature and partially on expert-opinion based on such thresholds, for instance to classify the 6-minute walking distance.

Choices between care settings for personalized interventions

During the diagnostic trajectory in a secondary care setting: (1) the medical diagnosis is confirmed, (2) classification of the burden of disease is made, and (3) the number and complexity of individual traits are determined. The classification of the burden of disease leads to the next phase, that is, referral to a primary, secondary or tertiary care setting for tailor-made interventions. An important aim of the COPDnet model is the provision of appropriate care of patients as close as possible to their home environment, that is, preferably in a primary care setting and, only if necessary, in a secondary or tertiary care setting.

In principle, patients with mild or moderate burden of disease are (re)referred to a primary care setting and, according to their individual care plan, will be offered one or more non-medical intervention module(s) provided by allied health care professionals. In order to enable referral of the right patients to the appropriate non-medical intervention module(s), a guideline on decision making was developed for the allocation of COPD patients to modules provided by dieticians, occupational therapists and physiotherapists, see Figure 2.

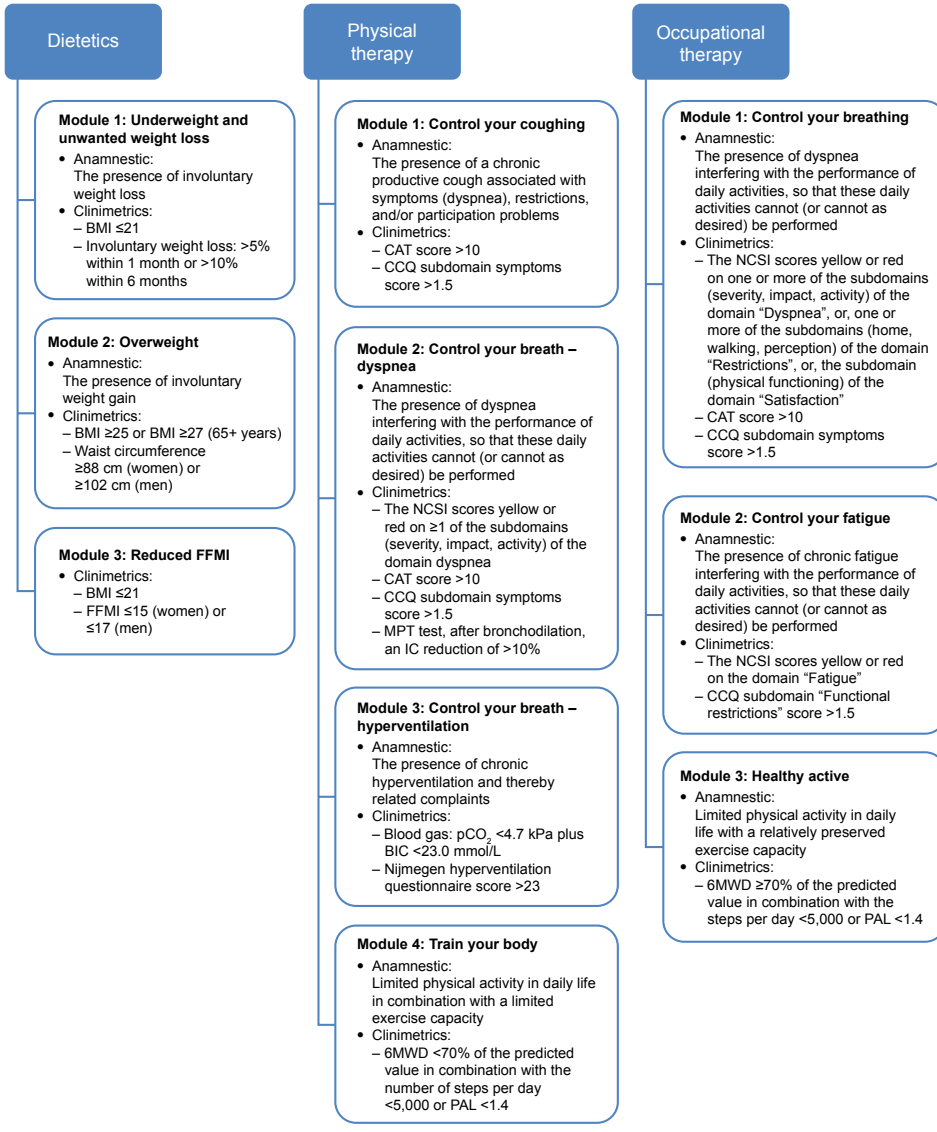


Figure 2. Guideline on decision making for non-medical intervention modules in a primary care setting.
Note: PAL was measured with the MoveMonitor
Abbreviations: BMI = Body Mass Index; FFMI = Fat-Free Mass Index; CAT = COPD Assessment Test; CCQ = Clinical COPD Questionnaire; NCSI = Nijmegen Clinical Screening Instrument; MPT = Manually Paced Tachypnea; IC = Inspiratory Capacity; pCO_2 = Partial pressure of carbon dioxide; kPa = Kilopascal; BIC = Blood Isotope Clearance; 6MWD = 6-Minute Walk Distance; PAL = Physical Activity Level

Patients with a severe burden of disease may be referred to a pulmonary rehabilitation setting, where an additional pre-rehabilitation assessment is carried out and the indication for pulmonary rehabilitation is re-established. Again, personal goals are set and the components of the rehabilitation programme are determined, which means that either an in- or an outpatient-based rehabilitation programme is indicated.[42]

In the case of such an indication, patients continue under supervision for some time in a secondary care setting by the pulmonologist and/or respiratory nurse. Typically, this applies to patients who were not on the appropriate inhalation medication yet, as recommended by current guidelines. Also, when more time is required to reach an agreement with the patient on the individual care plan.

Multilevel outcome measurement

Most importantly, we deliberately set out to include a systematic registration of the outcome of care at multiple levels in the COPDnet model, using Patient Reported Outcome Measurements (PROMs): (1) NCSI, (2) Clinical COPD Questionnaire (CCQ), and (3) 13-PAM. Data from The NCSI and CCQ are collected on Day 1 of the diagnostic trajectory and on six months follow-up. The outcomes of The 13-PAM are also collected on Day 1 of the diagnostic trajectory, on the last day of the diagnostic trajectory (Day two or three), and also on six months follow-up.

Nijmegen Clinical Screening Instrument

The NCSI enables the clinician to obtain a valid, reliable, and detailed picture of a patient's health status by measuring multiple sub-domains covering the following four domains; physiological functioning, symptoms, functional impairment, and quality of life.[43] In combination with the automated monitoring system of the Patient Profile Chart, the NCSI can easily be used in routine care as a guide to patient-tailored treatment.[43] The Patient Profile Chart offers a visual and therefore easily interpretable picture of the integral health status of an individual patient for the pulmonologist, respiratory nurse, and the patient.[44]

Clinical COPD Questionnaire

The CCQ is a self-administered 10-item questionnaire specially developed to measure clinical control in patients with COPD. Data support the validity, reliability and responsiveness of this questionnaire.[45]

13-Patient Activation Measurement

The 13-PAM is a valid and reliable 13-item Guttman-like scale and assesses the level of activation for self-management.[34,35]

Delivery system design

Cohesive, transmural model

The COPDnet model also aims to improve the transmural, organisational aspects of care. In order to do this we operationalized the following in our model: (1) standardisation of (electronic) referral procedures for the GP to a secondary care setting, (2) proactive management of the patient's expectations by the GP, (3) preparation of patients for the setting of goals after the diagnostic trajectory (information provided by an information flyer), (4) standardisation of reporting by the pulmonologist and respiratory nurse, and (5) agreements as to what information is provided to allied healthcare providers when referring a patient for an intervention module.

Lastly, every three months consultation takes place between representatives of healthcare providers from primary and secondary care settings and between representatives of secondary care and the regional tertiary care rehabilitation centre to discuss organisational aspects of care.

Quality Management System

Based on knowledge of quality management models, and in collaboration with the participating healthcare professionals, we developed a QMS primarily focused on the diagnostic trajectory in secondary care settings. The QMS aims to provide a continuous quality improvement for pulmonary specialists and respiratory nurse specialists, participating in the COPDnet integrated care model, by giving systematic feedback on outcomes of care based on PROMs. The COPDnet QMS includes: (1) Case presentation and discussion, (2) audit, and (3) education and training.

Case presentation and discussion

Every three months, one to two case histories are presented by the pulmonologist and respiratory nurse, and then discussed with a psychologist and an independent chairman.[46] Discussions may cover the interpretation of health status measurements, interviewing techniques, decisions on additional diagnostic tests and classification of the burden of disease, or choices with regard to the individual care plan. Mirroring the COPDnet guidelines, decision making is an important element in this process.

Audit

Audits are regularly performed between healthcare professionals from different hospitals working with the COPDnet model to evaluate and to discuss the aspects of the organization of the care process.[47] Sharing experiences between users are thought to be helpful to further optimize the model.

Education and training
Education and training sessions are offered depending on the specific needs indicated by the healthcare professionals. The topics of the education and training may vary, but they are always related to the COPDnet model.

Exacerbation management and palliative care
In the COPDnet model regional action plans with regard to exacerbation management and palliative care were agreed.[48,49]

Clinical information systems

Electronic Health Record
An Electronic Health Record (EHR) is used to register key administrative and clinical data of patients during the diagnostic trajectory of the COPDnet model. Relevant clinical parameters for evaluation of the individual health status at baseline, as well as the change of health status over time, systematically registered in the EHR. The data may be used to support the clinical decision-making process at the individual level, and may also be used in aggregated (anonymised) data, at the population level for quality purposes, as well as for scientific research purposes. Also important features with regard to the care process are periodically analysed.

Electronic communication platform
To facilitate digital communication between healthcare professionals and the patient in the COPDnet model a patient portal is used, for instance to exchange information or to enable the administration of questionnaires at home at regular intervals. This portal is considered an important digital add-on contributing to the effectiveness of the care model, but also to the perceived quality of care by patients.

DISCUSSION

With the current project we wish to present an evidence-based comprehensive integrated disease management model for patients with COPD patients with moderate or severe burden of disease, who, according to the Dutch Standards of Care for COPD, meet the criteria for shared care between primary and secondary care settings.[22]

The idea behind this project arose from the awareness of the poor and fragmented use of the principles of integrated care in COPD patients in real life care in the various healthcare settings.[21] This is not in keeping with the scientific evidence of the added value of an integrated approach, in terms of improving the quality and the efficiency of care and reducing healthcare costs.[50] In addition, the first observational studies on

the outcome of 'real life' COPD care, recently carried out in Germany, demonstrated extensive room for improvement.[6-9] More studies on the outcome of 'real life' COPD care are expected in due time.[51-53] Last but not least, the poor outcome observations are in line with a recently performed survey in five European union countries, including the Netherlands, in which the authors concluded that COPD healthcare pathways are fragmented and care is not integrated properly.[21]

We assume that the availability of a scientifically documented care pathway, based on principles of integrated disease management and founded on the CCM, may facilitate the wider use of the principles of integrated disease management care in real life clinical practice and that it will boost the clinical effectiveness of care in COPD patients. Evidence in support or this assumption is the outcome of a study on the effects of the introduction of a QMS targeting patients treated on an outpatient base in hospitals in Denmark. In this study, it was found that with the implementation of a nationwide registration, the care provided was more in line with principles of integrated care.[53]

Although the added value of our model has to be empirically determined, we believe that it has a strong basis. During the development of our integrated disease management pathway we used a robust and scientifically based method, that is, the seven-phase model of the EPA.[23] With this method, several other care pathways have been successfully developed and implemented, including a pathway for acutely ill patients with COPD who were in need of hospitalization.[54-57] In the seven-phase model, co-creation in the designing process is acknowledged to be crucial in establishing a supported innovative care model.[58] Therefore, early on in the designing process, we consulted different stakeholders, both with respect to their opinions regarding the care process, as well as to their views on the content of the integrated disease management pathway.

Notably, the content of our model addresses disease specific aspects based on knowledge regarding its complexity and heterogeneity.[1] But it also includes features relating to the more general needs of patients with a chronic condition. Inspiration for the latter we found in the CCM.[24] The assumption of the CCM is that better outcomes of care in patients with chronic conditions, such as COPD, are to be expected as a result of the productive interaction between proactive healthcare professionals and an activated patient. To enable and support this productive interaction, several features of the healthcare system should be reconsidered and improved by united efforts. These improvements concern self-management strategies, decision support, delivery system design and clinical information systems.[26] In our COPDnet model, all these four elements are explicitly addressed. With the incorporation of the systematic measurement on outcomes (using PROMs) of the integrated care pathway, as a basis

for the QMS, we supported the creation of a continuously learning organisation. This will enable us to keep on introducing new improvements to our COPDnet model.

Despite our positive expectations with regard to the added value of our care pathway, we acknowledge some challenges in its use. Care according to the COPDnet model starts at the moment a patient with COPD is referred from primary care (GP) to secondary care (pulmonologist) because of persistent burden of disease. Hence, proper working of the COPDnet model presupposes timely and adequate medical diagnosis and a correct determination of the burden of disease by the GP. Under- or misdiagnosis of COPD and a wrong estimate of the burden of disease in primary care would result in absent, late or improper referrals to secondary care and challenges the proper application of the COPDnet model. In addition, during the diagnostic workup of the pulmonologist, the medical diagnosis is verified and adjusted if indicated.

Our COPDnet model strongly relies on the reinforcement of self-management strategies and seeks to initiate behavioural change in patients.[33,59] However, much is still unclear in this domain and requires further development.[60] Also, our model requires a change in attitude on the part of the healthcare professionals. The one-dimensional medical perspective is abandoned to make way for a multi-dimensional biopsychosocial approach to patients, which is not an easy task for healthcare providers.[61,62] Furthermore, our COPDnet model also relies on an adequate interaction between healthcare professionals working in different settings within the healthcare system, which are, primary, secondary and tertiary care settings. This means that although communications can be easily digitally supported, in real life communication appears to be not as easy as that.[63-65]

Finally, although our integrated disease management pathway has been established in a scientific manner and the content is in line with current insights, we acknowledge that the COPDnet model is complex. Significant investments may be needed to use the full model. These investments must focus on clear agreements on effective communications between healthcare professionals in order to facilitate the transfer of patients across the COPDnet model. In addition, education and training of healthcare professionals in the use of the different components will be required and are therefore integrated in the QMS. Further studies on the feasibility, health status benefits and costs of the model will provide answers as to the added value of the COPDnet model.

CONCLUSION

A new integrated disease management pathway in patients with COPD, named COPDnet, has been designed according to current knowledge on important disease specific aspects as well as on insights regarding effective care in patients with a chronic condition. The model provides for the application of principles of a learning organization, through a continuous evaluation of the results. This in turn may lead to future adaptations of the model. Once the model is stable, it will be evaluated for its feasibility, health status benefits, and costs of care.

REFERENCES

1. Agusti A, Calverley PM, Celli B, et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. *Respiratory research.* 2010;11:122.

2. Wouters EF. Economic analysis of the Confronting COPD survey: an overview of results. *Respiratory medicine.* 2003;97 Suppl C:S3-14.

3. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. *Lancet.* 2007;370(9589):765-773.

4. Porter ME. What is value in health care? *The New England journal of medicine.* 2010;363(26):2477-2481.

5. Porter ME, Larsson S, Lee TH. Standardizing Patient Outcomes Measurement. *The New England journal of medicine.* 2016;374(6):504-506.

6. Worth H, Buhl R, Criee CP, Kardos P, Mailander C, Vogelmeier C. The 'real-life' COPD patient in Germany: The DACCORD study. *Respiratory medicine.* 2016;111:64-71.

7. Buhl R, Criee CP, Kardos P, et al. A year in the life of German patients with COPD: the DACCORD observational study. *International Journal of Chronic Obstructive Pulmonary Disease.* 2016;11:1639-1646.

8. Haughney J, Gruffydd-Jones K, Roberts J, Lee AJ, Hardwell A, McGarvey L. The distribution of COPD in UK general practice using the new GOLD classification. *The European Respiratory Journal.* 2014;43(4):993-1002.

9. Ke X, Marvel J, Yu TC, et al. Impact of lung function on exacerbations, health care utilization, and costs among patients with COPD. *International Journal of Chronic Obstructive Pulmonary Disease.* 2016;11:1689-1703.

10. Fuchs S, Henschke C, Blumel M, Busse R. Disease management programs for type 2 diabetes in Germany: a systematic literature review evaluating effectiveness. *Deutsches Arzteblatt International.* 2014;111(26):453-463.

11. Lemmens KM, Nieboer AP, Huijsman R. A systematic review of integrated use of disease-management interventions in asthma and COPD. *Respiratory medicine.* 2009;103(5):670-691.

12. Peytremann-Bridevaux I, Burnand B. Disease management: a proposal for a new definition. *International Journal of Integrated Care.* 2009;9:e16.

13. Nici L, ZuWallack R. American Thoracic Society Subcommittee on Integrated Care of the CP. An official American Thoracic Society workshop report: the Integrated Care of The COPD Patient. *Proceedings of the American Thoracic Society.* 2012;9(1):9-18.

14. Kruis AL, Smidt N, Assendelft WJ, et al. Integrated disease management interventions for patients with chronic obstructive pulmonary disease. *The Cochrane database of systematic reviews.* 2013;10:CD009437.

15. Mendes de Oliveira JC, Studart Leitão Filho FS, Malosa Sampaio LM, et al. Outpatient vs. home-based pulmonary rehabilitation in COPD: a randomized controlled trial. *Multidisciplinary Respiratory Medicine.* 2010;5(6):401-408.

16. Rea H, McAuley S, Stewart A, Lamont C, Roseman P, Didsbury P. A chronic disease management programme can reduce days in hospital for patients with chronic obstructive pulmonary disease. *Internal medicine journal.* 2004;34(11):608-614.

17. Smith BJ, Appleton SL, Bennett PW, et al. The effect of a respiratory home nurse intervention in patients with chronic obstructive pulmonary disease (COPD). *Australian and New Zealand journal of medicine.* 1999;29(5):718-725.

18. Sridhar M, Taylor R, Dawson S, Roberts NJ, Partridge MR. A nurse led intermediate care package in patients who have been hospitalised with an acute exacerbation of chronic obstructive pulmonary disease. *Thorax.* 2008;63(3):194-200.

19. Strijbos JH, Postma DS, van Altena R, Gimeno F, Koeter GH. A comparison between an outpatient hospital-based pulmonary rehabilitation program and a home-care pulmonary rehabilitation program in patients with COPD. A follow-up of 18 months. *Chest.* 1996;109(2):366-372.

20. Achelrod D, Welte T, Schreyogg J, Stargardt T. Costs and outcomes of the German disease management programme (DMP) for chronic obstructive pulmonary disease (COPD)-A large population-based cohort study. *Health policy.* 2016;120(9):1029-1039.

21. Kayyali R, Odeh B, Frerichs I, et al. COPD care delivery pathways in five European Union countries: mapping and health care professionals' perceptions. *International Journal of Chronic Obstructive Pulmonary Disease.* 2016;11:2831-2838.

22. Long Alliantie Nederland (LAN) [Lung Alliance Netherlands]. Zorgstandaard COPD [Care Standard COPD]; 2016. Available from: http:// www.longalliantie.nl/zorgstandaard-copd. Accessed: March 16, 2018. Dutch.

23. Vanhaecht K, Van Gerven E, Deneckere S, et al. 7-fasenmodel voor de ontwikkeling, implementatie, evaluatie en continue opvolging van zorgpaden. *Tijdschrift voor Geneeskunde.* 2011;10:8.

24. Wagner EH, Austin BT, Von Korff M. Improving outcomes in chronic illness. *Managed care quarterly.* 1996;4(2):12-25.

25. Coleman K, Austin BT, Brach C, Wagner EH. Evidence on the Chronic Care Model in the new millennium. *Health affairs.* 2009;28(1):75-85.

26. Adams SG, Smith PK, Allan PF, Anzueto A, Pugh JA, Cornell JE. Systematic review of the chronic care model in chronic obstructive pulmonary disease prevention and management. *Archives of internal medicine.* 2007;167(6):551-561.

27. Wagner EH, Austin BT, Davis C, Hindmarsh M, Schaefer J, Bonomi A. Improving chronic illness care: translating evidence into action. *Health affairs.* 2001;20(6):64-78.

28. Agusti A, MacNee W. The COPD control panel: towards personalised medicine in COPD. *Thorax.* 2013;68(7):687-690.

29. van den Akker EF, Van 't Hul AJ, Birnie E, Chavannes NH, Rutten-van Molken MP, In 't Veen JC. Comprehensive Diagnostic Assessment of Health Status of Patients with Asthma or COPD: A Delphi Panel Study among Dutch Experts. *COPD.* 2016:1-10.

30. Hillas G, Perlikos F, Tsiligianni I, Tzanakis N. Managing comorbidities in COPD. *International Journal of Chronic Obstructive Pulmonary Disease.* 2015;10:95-109.

31. van den Akker EF, van 't Hul AJ, Chavannes NH, et al. Development of an integral assessment approach of health status in patients with obstructive airway diseases: the CORONA study. *International Journal of Chronic Obstructive Pulmonary Disease.* 2015;10:2413-2422.

32. Effing TW, Bourbeau J, Vercoulen J, et al. Self-management programmes for COPD: moving forward. *Chronic respiratory disease.* 2012;9(1):27-35.

33. Effing TW, Vercoulen JH, Bourbeau J, et al. Definition of a COPD self-management intervention: International Expert Group consensus. *The European respiratory journal.* 2016;48(1):46-54.

34. Hibbard JH, Mahoney ER, Stockard J, Tusler M. Development and testing of a short form of the patient activation measure. *Health services research.* 2005;40(6 Pt 1):1918-1930.

35. Hibbard JH, Stockard J, Mahoney ER, Tusler M. Development of the Patient Activation Measure (PAM): conceptualizing and measuring activation in patients and consumers. *Health services research.* 2004;39(4 Pt 1):1005-1026.

36. Prochaska JO, DiClemente CC. Stages of change in the modification of problem behaviors. *Progress in behavior modification.* 1992;28:183-218.

37. Elwyn G, Dehlendorf C, Epstein RM, Marrin K, White J, Frosch DL. Shared decision making and motivational interviewing: achieving patient-centered care across the spectrum of health care problems. *Annals of family medicine.* 2014;12(3):270-275.

38. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implementation science : IS.* 2011;6:42.

39. Elwyn G, Frosch D, Thomson R, et al. Shared decision making: a model for clinical practice. *Journal of general internal medicine.* 2012;27(10):1361-1367.

40. Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *American journal of respiratory and critical care medicine.* 2013;188(8):e13-64.

41. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. *JAMA.* 1995;273(1):59-65.

42. van Ranst D, Otten H, Meijer JW, van 't Hul AJ. Outcome of pulmonary rehabilitation in COPD patients with severely impaired health status. *International Journal of Chronic Obstructive Pulmonary Disease.* 2011;6:647-657.

43. Peters JB, Daudey L, Heijdra YF, Molema J, Dekhuijzen PN, Vercoulen JH. Development of a battery of instruments for detailed measurement of health status in patients with COPD in routine care: the Nijmegen Clinical Screening Instrument. *Quality of life research: an international journal of quality of life aspects of treatment, care and rehabilitation.* 2009;18(7):901-912.

44. Vercoulen JH. A simple method to enable patient-tailored treatment and to motivate the patient to change behaviour. *Chronic respiratory disease.* 2012;9(4):259-268.

45. van der Molen T, Willemse BW, Schokker S, ten Hacken NH, Postma DS, Juniper EF. Development, validity and responsiveness of the Clinical COPD Questionnaire. *Health and quality of life outcomes.* 2003;1:13.

46. Kruis AL, Soljak M, Chavannes NH, Elkin SL. COPD Multidisciplinary Team Meetings in the United Kingdom: Health Care Professionals' Perceptions of Aims and Structure. *COPD.* 2016;13(5):639-641.

47. Ivers N, Jamtvedt G, Flottorp S, et al. Audit and feedback: effects on professional practice and healthcare outcomes. *The Cochrane database of systematic reviews.* 2012(6):CD000259.

48. Reticker AL, Nici L, ZuWallack R. Pulmonary rehabilitation and palliative care in COPD: Two sides of the same coin? *Chronic respiratory disease.* 2012;9(2):107-116.

49. Trappenburg JC, Monninkhof EM, Bourbeau J, et al. Effect of an action plan with ongoing support by a case manager on exacerbation-related outcome in patients with COPD: a multicentre randomised controlled trial. *Thorax.* 2011;66(11):977-984.

50. Kruis AL, Smidt N, Assendelft WJ, et al. Cochrane corner: is integrated disease management for patients with COPD effective? *Thorax.* 2014;69(11):1053-1055.

51. Kardos P, Vogelmeier C, Buhl R, Criee CP, Worth H. The Prospective Non-Interventional DACCORD Study in the National COPD Registry in Germany: design and methods. *BMC pulmonary medicine.* 2015;15:2.

52. Bourbeau J, Tan WC, Benedetti A, et al. Canadian Cohort Obstructive Lung Disease (CanCOLD): Fulfilling the need for longitudinal observational studies in COPD. *COPD.* 2014;11(2):125-132.

53. Tottenborg SS, Thomsen RW, Nielsen H, Johnsen SP, Frausing Hansen E, Lange P. Improving quality of care among COPD outpatients in Denmark 2008-2011. *The clinical respiratory journal.* 2013;7(4):319-327.

54. Panella M, Marchisio S, Brambilla R, Vanhaecht K, Di Stanislao F. A cluster randomized trial to assess the effect of clinical pathways for patients with stroke: results of the clinical pathways for effective and appropriate care study. *BMC medicine.* 2012;10:71.

55. Panella M, Marchisio S, Demarchi ML, Manzoli L, Di Stanislao F. Reduced in-hospital mortality for heart failure with clinical pathways: the results of a cluster randomised controlled trial. *Quality & safety in health care.* 2009;18(5):369-373.

56. Vanhaecht K, Sermeus W, Peers J, et al. The impact of care pathways for patients with proximal femur fracture: rationale and design of a cluster-randomized controlled trial. *BMC health services research.* 2012;12:124.

57. Vanhaecht K, Sermeus W, Peers J, et al. The impact of care pathways for exacerbation of Chronic Obstructive Pulmonary Disease: rationale and design of a cluster randomized controlled trial. *Trials.* 2010;11:111.

58. Grol R, Grol R. *Improving patient care : the implementation of change in health care.* 2nd ed. Chichester, UK ; Hoboken, NJ, USA: Wiley Blackwell, BMJ/Books; 2013.

59. Jonkman NH, Schuurmans MJ, Jaarsma T, Shortridge-Baggett LM, Hoes AW, Trappenburg JC. Self-management interventions: Proposal and validation of a new operational definition. *Journal of clinical epidemiology.* 2016;80:34-42.

60. Kaptein AA, Fischer MJ, Scharloo M. Self-management in patients with COPD: theoretical context, content, outcomes, and integration into clinical care. *International Journal of Chronic Obstructive Pulmonary Disease.* 2014;9:907-917.

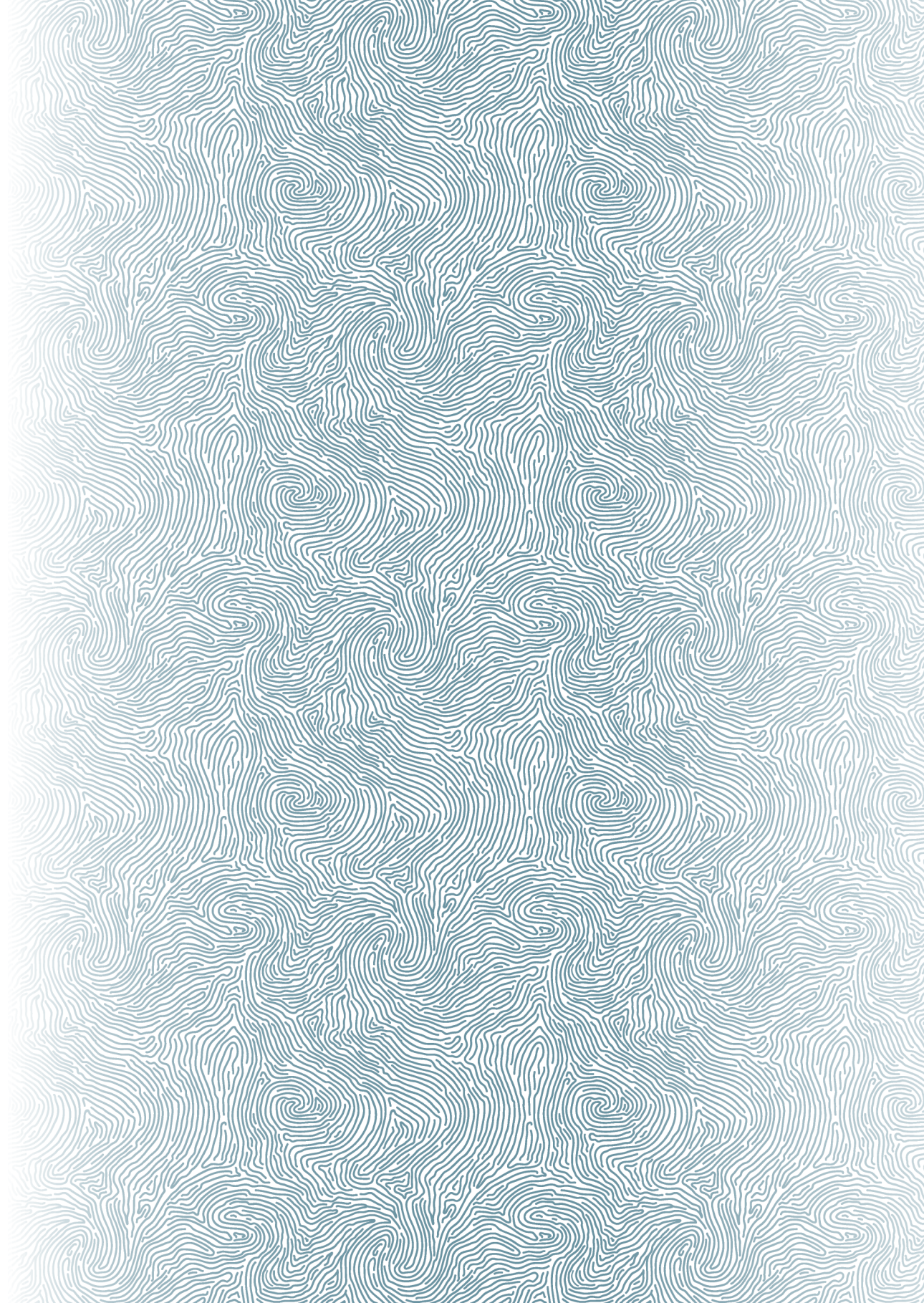
61. Young HM, Apps LD, Harrison SL, Johnson-Warrington VL, Hudson N, Singh SJ. Important, misunderstood, and challenging: a qualitative study of nurses' and allied health professionals' perceptions of implementing self-management for patients with COPD. *International Journal of Chronic Obstructive Pulmonary Disease.* 2015;10:1043-1052.

62. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. *Lancet.* 2003;362(9391):1225-1230.

63. Sampson R, Barbour R, Wilson P. Email communication at the medical primary-secondary care interface: a qualitative exploration. *The British journal of general practice : the journal of the Royal College of General Practitioners.* 2016;66(648):e467-473.

64. Sampson R, Barbour R, Wilson P. The relationship between GPs and hospital consultants and the implications for patient care: a qualitative study. *BMC family practice.* 2016;17:45.

65. Sheu L, Fung K, Mourad M, Ranji S, Wu E. We need to talk: Primary care provider communication at discharge in the era of a shared electronic medical record. *Journal of hospital medicine.* 2015;10(5):307-310.



Evaluation of the COPDnet integrated care model in patients with chronic obstructive lung diseases: the study protocol

E.H. Koolen
P.J. van der Wees
G.P. Westert
P.N.R. Dekhuijzen
Y.F. Heijdra
A.J. van 't Hul

International Journal of Chronic Obstructive Pulmonary Disease 2018 Jul 19;13:2237-2244

ABSTRACT

BACKGROUND

Projections on the future suggest a further rise in the prevalence of patients with Chronic Obstructive Pulmonary Disease (COPD), morbidity, mortality, and health-care costs worldwide. Given the substantial impact on the individual and on society, it is important to establish a care process that maximizes outcomes in relation to the efforts and costs made. In an attempt to bridge this gap we set out to develop an evidence-based model of integrated care for patients with COPD, named the COPDnet integrated care model.

PURPOSE

The current study protocol sets out: 1) to evaluate the feasibility of employing the COPDnet model in present real life care within the context of the Dutch healthcare system, 2) to explore the potential health status benefits, and 3) to analyse the costs of care of this model.

PATIENTS AND METHODS

In this prospective study, feasibility and health status changes will be evaluated with an experimental before and after study design. The costs of the diagnostic trajectory will be calculated according to a standard economic healthcare evaluation approach. Furthermore, the feasibility and cost of care studies will comprise both quantitative and qualitative data collection. For the studies on the feasibility and change in health status, all new patients qualifying for shared care by primary and secondary care professionals according to the Dutch Standard of Care for COPD, and, patients referred by their GPs to one of the COPDnet hospitals will be included. To evaluate the feasibility and costs of care, semi-structured interviews will be held with patients, hospital personnel, healthcare professionals in the affiliated primary care region, and hospital and primary care group managers.

CONCLUSION

The COPDnet integrated care model for COPD patients has been designed according to current insights regarding effective care for patients with a chronic condition in general and for patients with COPD in particular. It will be evaluated for its feasibility, potential health status benefits, and the costs of care of the diagnostic trajectory in secondary care.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is defined as a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation.[1] Moreover, COPD is a complex and heterogeneous disease with highly variable clinical manifestations.[2,3] Even when COPD patients are in a relatively stable phase of their disease or only have mild to moderate airway obstruction, COPD often puts a significant burden of disease on those affected.[2] The impact of COPD also places a high burden on healthcare resources, given the significant direct and indirect costs of care.[4] Projections on the future suggest a further rise in the prevalence of patients with COPD, morbidity, mortality, and health-care costs worldwide.[5]

Given the substantial impact on the individual and on society, it is important to establish a care process that maximizes outcomes in relation to the efforts and costs made.[6] There is evidence to suggest that COPD disease management programmes, providing integrated holistic care in an integrated care process, have the potential to better both health outcomes as well as costs compared to single-dimensional medical approaches.[7] A recent review shows that better outcomes may be achieved with an integrated disease management programme of at least three months duration with a follow-up ranging from 3 to 24 months on disease-specific quality of life and exercise capacity, and, also, a reduction in respiratory related hospital admissions and hospital days per person.[8] The clinical impression is, however, that integrated care models are, as yet, only in limited use in our present care delivery pathways. This was confirmed in a recently performed survey in five European union countries, including the Netherlands. In this paper the authors concluded that COPD healthcare pathways are fragmented and care is not integrated properly.[9]

In an attempt to bridge this gap we set out to develop an evidence-based model of integrated care for patients with COPD, named the COPDnet integrated care model.[10] The COPDnet integrated care model has the ambition to innovate, simultaneously, both the content of care, i.e. applying a holistic approach, as well as the organisation of care, i.e. providing coherent, integrated care within the Dutch healthcare system. The use of such a model holds a promise to generate better outcomes of care for patients with COPD, as well as an overall reduction in the health-care costs.[11]
As we acknowledge it is a challenge to implement this highly complex COPDnet integrated care model[12], the current study protocol sets out: 1) to evaluate the feasibility of employing the COPDnet model in present day real life care within the context of the Dutch healthcare system, 2) to explore the potential health status benefits from the patients perspective, and 3) to analyse the costs of care of this model.

Objectives of the study protocol

To realize the objectives of the current research project a series of interrelated studies will be conducted with the following aims:

- To evaluate the feasibility of the implementation of the COPDnet integrated care model
- To evaluate changes in health status over time in COPD patients who were offered care according to the COPDnet integrated care model
- To evaluate the costs of care of the diagnostic trajectory in secondary care, as a component of the COPDnet integrated care model

The objective of this article is to present the rationale and the different methods of this prospective study.

Intervention

The COPDnet integrated care model describes a transparent and highly standardized outpatient care process. Figure 1 represents a graphical overview of all elements of the COPDnet integrated care model, that is, a diagnostic trajectory carried out in secondary care, a non-medical intervention programme provided in primary care, and a pulmonary rehabilitation service in tertiary care. The model also includes a QMS based on Patient Reported Outcome Measurements (PROMs), and regional appointments pertaining to exacerbation management and palliative care. Principles of the model include: 1) an individual care plan based on an assessment of the individual determinants of the burden of disease, 2) which is carried out closely to the natural habitat of the patient, and, 3) looks for opportunities to initiate behavioural change, i.e. reinforcement of patients' self-management capabilities. Full details of the COPDnet integrated care model can be found in a recently published article by Koolen et al.[10]

METHODS AND ANALYSIS

Study setting and design

The series of studies of this research project will be carried out in three hospitals and their affiliated primary care region, that is, the outpatient clinic of the Department of pulmonary diseases of Radboudumc (Nijmegen), Bernhoven Hospital (Uden), and Canisius Wilhelmina Hospital (Nijmegen).

In this prospective study, feasibility and health status changes will be evaluated with an experimental before and after study design. The costs of the diagnostic trajectory will be calculated according to a standard economic healthcare evaluation approach. Furthermore, the feasibility and cost of care studies will comprise both quantitative and qualitative data collection and analyses.

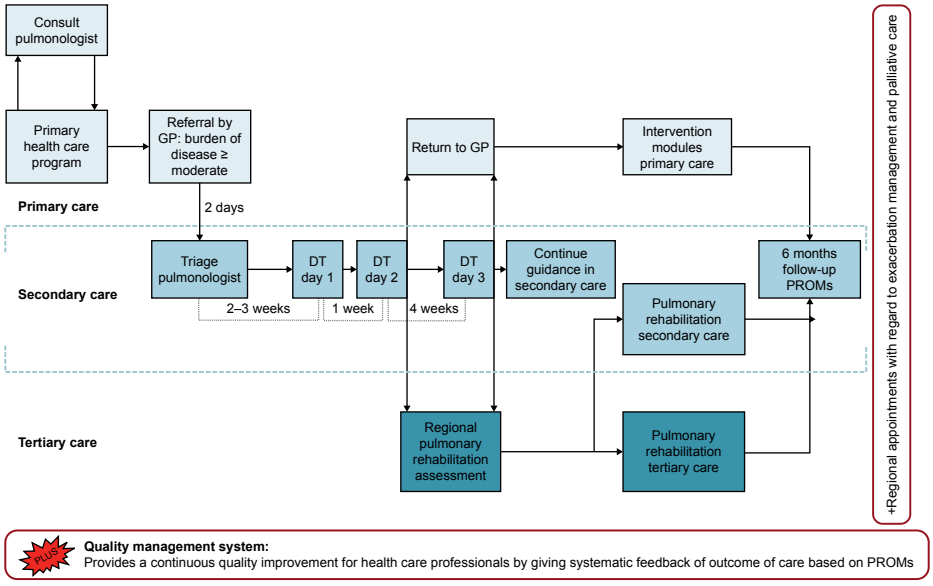


Figure 1. The COPDnet integrated care model
Legend: GP=General Practitioner; DT=Diagnostic Trajectory; PROMs=Patient Reported Outcome Measurements

Study population

Patients

For the studies on the feasibility of the implementation of this COPDnet integrated care model and of the change in health status, patients will be included based on the following two criteria:

- New patients qualifying for shared care by primary and secondary care professionals according to the Dutch Standard of Care for COPD[13], and,
- Patients referred by their GPs to the outpatient clinic of Radboudumc, Bernhoven Hospital, or Canisius Wilhelmina Hospital.

Patients will be excluded if:

- The patient is unable to complete questionnaires because of cognitive impairment
- The patient is unable to speak or understand the Dutch language.

Healthcare professionals

To evaluate the feasibility and costs of care, the following healthcare professionals, providing care according to the COPDnet integrated care protocol, will be included in these studies:

- Primary care: GP's, nurse practitioners, physiotherapists, dieticians, occupational therapists, primary care group managers

- Secondary care: pulmonary specialists, respiratory nurse specialists, pulmonary function technicians, medical secretaries, staff of the clinometric department and hospital care group managers

Outcomes

Feasibility

The feasibility of implementing the COPDnet integrated care model will be evaluated from three different perspectives, that is, patient perspective, healthcare perspective, and organisational perspective, applying both quantitative and qualitative methods.

Quantitative evaluation

The following questionnaires will be used for the evaluation of the patient outcomes: the Consumer Quality Index (CQi) Asthma and COPD[14], and the Patients Assessment Chronic Illness Care (PACIC).[15] To evaluate the healthcare professional perspective: the Assessment of Chronic Illness Care (ACIC)[16], the Clinician Support for Patient Activation Measure (CS-PAM)[17], and the Assessment of Primary Care Recourses and Supports for Chronic Disease Self-Management (PRCS).[18] And finally, for the evaluation of the organisational perspective: the Care Process Self Evaluation Tool (CPSET) will be applied.[19]

Qualitative evaluation

First of all, two authors (EHK and AJvtH), will develop semi-structured interview guides, which should enhance the feasibility of using the COPDnet model in contemporary healthcare within the context of the Dutch healthcare system. The semi-structured interview guides will be tailored specifically to patients, hospital personnel, healthcare professionals in the affiliated primary care region, and hospital and primary care group managers.

The patients will be selected based on purposive sampling from the three COPDnet hospitals. We will seek a varied sample of patients based on age, sex and burden of disease. The respiratory nurse specialists will invite these patients for participation in one of the interviews after they have completed the full trajectory of the COPDnet integrated care model. EHK will invite the professionals by telephone or e-mail. All participants will receive written information about the purpose and procedure of the interviews and they will be asked to confirm their participation by e-mail or telephone. Moreover, EHK will use the interview guides to conduct the semi-structured interviews, either by telephone or face-to-face, after obtaining written informed consent.

Analysis of the patient perspective-, healthcare professional perspective-, and organisational perspective questionnaires, patient health records and the semi-

structured interviews, will be carried out between 12 and 36 months after the implementation of the COPDnet model in the three participating hospitals

Health status

An analysis will be made of the potential improvements in health status through measuring changes in health status in patients enrolled in the COPDnet model, using widely accepted and validated PROMs. Primary outcome measure will be the Clinical COPD Questionnaire (CCQ). The results of the health status of enrolled patients at baseline, and at 6 months after the diagnostic trajectory in the COPDnet hospitals, will be compared.[20] The CCQ is a self-administrated questionnaire and the psychometric properties are well documented.[20] In addition to the primary outcomes, the following secondary outcome measurements will be systematically registered in the COPDnet hospitals: The Patient Activation Measure (PAM)[21,22], the Nijmegen Clinical Screening Instrument (NCSI)[23,24], and physical activity measured with the Marshall Questionnaire.[25] All data will be collected at baseline during the first visit at the hospital, at discharge after completion of the diagnostic trajectory of the COPDnet model and, finally, after 6 months follow-up. Also, patient characteristics and the following health status characteristics will be registered at baseline: the medication prescribed in primary care, comorbidities, smoking behaviour, pulmonary function, blood gas analysis, six-minute walking distance (6MWD), physical activity measured with an activity monitor, medical diagnosis, and the classification of the burden of disease.

Costs of care

Costs of care will be analysed on the basis of completed and registered care activities performed during the diagnostic trajectory in the participating hospitals of the COPDnet model, complying with the principles of Time-Driven Activity-Based Costing (TDABC) in value-based healthcare.[26] TDABC requires the estimation of two parameters: the costs per time required to supply resources to the activities, and the time required to perform activities in service deliveries.[26] We will use the seven-step approach to the application of the TDABC in our healthcare setting.[27] By using the TDABC model we will be able to understand the cost of care delivery and control costs.[28] We will develop TDABC models for all COPDnet hospitals, in which direct costs as well as indirect costs for delivering the diagnostic trajectory are taken into account.

Cost mapping will be performed on: 1) Calculation of the total (internal) costs of the COPDnet model on the basis of factual delivery of care activities and time spent to carry out these activities, and 2) Comparing the (internal) costs of the diagnostic trajectory with the reimbursement fees of the health insurance companies. Data source for cost mapping is the Hospital Information System (HIS) of the participating hospitals. TDABC models have been using different methods, with respect to the time required

to perform activities which may result in different costs of patient care.[28] Therefore, our TDABC models will be developed on the basis of three methods. First of all, we will evaluate the direct and indirect (non-) patient-related time through an objective measurement of time. Therefore we will measure the time of each step in the diagnostic trajectory by using a stopwatch. Secondly, we will evaluate the direct and indirect (non-) patient-related time subjectively, by interviewing all the participating healthcare professionals. Thirdly, we will interview the hospital care group managers, so that they may estimate the invested time of each step in the diagnostic trajectory in the secondary care setting. Differences and similarities between these three approaches will be evaluated.

Finally, we will compare the TDABC models with the average costs of usual care, which was provided before the introduction of the COPDnet model, based on health care records.

Qualitative evaluation

EHK and AJvtH will also develop the semi-structured interview guides for the participating healthcare professionals and hospital care group managers, in which the focus will be on an estimate of the time the professionals have to invest to meet the requirements of the COPDnet model. All the participating healthcare professionals and hospital care group managers from the three COPDnet hospitals, who work according to the model, will be invited. EHK will invite the professionals by telephone or e-mail and if they want to participate they will receive written information about the purpose and procedure of the interview. EHK will use the interview guides to conduct the semi-structured interviews, either by telephone or face-to-face, after obtaining written informed consent.

Sample size

Feasibility

On each location semi-structured interviews will be held with patients, clinicians and managers. We anticipate on including five patients on each location – dependent on data saturation. Also, on each location, two pulmonary specialists, two respiratory nurses, and, of each discipline, two allied healthcare professionals will be invited to participate in the interviews. The to be interviewed pulmonary specialists and respiratory nurse specialists include all healthcare professionals actually providing care following the COPDnet model in the three participating hospitals. Finally, a convenient sample of hospital and primary care group managers will be interviewed on what working with the COPDnet model means from an organizational perspective and how this affects feasibility.

Health status

The sample size for the secondary objective is estimated using G-power with an a priori t-test, based on an estimated difference between two dependent means. A total of 199 patients are required to detect a small effect size of 0.2 on the CCQ, with a significance of 5% and a power of 80%. However, anticipating a dropout rate of 25%, we will include 250 patients.

Costs of care

To evaluate the time invested, semi-structured interviews will be held with two pulmonary specialists, two respiratory nurses, one pulmonary function technician, one medical secretary, and one hospital care group manager, on each location.

Recruitment

All patients, qualifying for shared care in primary and secondary care settings (according to the Dutch Standard of Care for COPD[13]) and who are referred by their GP to secondary care, will be automatically enrolled into the COPDnet model, either in the outpatient clinic of the Radboudumc (Nijmegen), in the Bernhoven Hospital (Uden), or in the Canisius Wilhelmina Hospital (Nijmegen). Within these three hospitals, the COPDnet integrated care model has been accepted as the new standard care pathway for all new patients with COPD. All patients will be examined according to the new standard patient care pathway in one of the COPDnet hospitals mentioned above. Furthermore, patients will not be exposed to extra questionnaires, tests or site visits. Only a minority of the purposively selected patients (10-15/200=5-8%), and all of the participating COPDnet healthcare professionals, will be asked to participate, voluntarily, in a semi-structured interview. Therefore, patients and healthcare professionals in this study will not be exposed to any additional health-related risk. Patients will be informed about the study by way of a patient information form. All patients receiving usual care, according to the COPDnet model, will be included in these studies, and will be excluded only when they say they are unwilling to participate.

Data management

All study data will be handled confidentially. The handling of the personal data will be fully compliant with the Dutch Personal Data Protection Act (de Wet Bescherming Persoonsgegevens). Study data will be kept for 15 years.

Statistical analysis

Quantitative analysis

Descriptive statistics, including means, standard deviation, frequencies, medians, and interquartile ranges will be used to summarize our collected data. Handling missing data will be carried out according to the guidelines of the different questionnaires.

To evaluate the feasibility of the COPDnet model, a two-tailed paired sample t-test or Wilcoxon signed rank test will be used to analyse the differences between the several measurement instruments at baseline and after implementation of the COPDnet model. To evaluate the potential health status benefits by testing the differences between baseline PROMS and follow-up PROMS, a two-tailed paired sample t-test or the Wilcoxon signed rank test will also be used. A priori, a two-sided level of significance will be set at $p \leq 0.05$. For data analysis SPSS V.22.0 will be used.

The economic evaluation of the cost of care of the COPDnet model, based on the different TDABC models, will be analyzed with appropriate descriptive statistics, and will be displayed graphically.

Qualitative analysis

To evaluate the feasibility and the costs of care, all semi-structured interviews of the COPDnet model will be audio-taped after obtaining the respondent's permission. Subsequently, the audio tapes will be transcribed verbatim, and entered into Atlas.ti qualitative software for analysis. We will use qualitative content analysis with a directed approach.[29] We will conduct a thematic analysis of the implementation of the COPDnet model. Results from the qualitative analysis will be triangulated with results from the quantitative analyses to identify concordant and disparate results across the data sources.

Ethics and dissemination

The Research Ethics Committee of the Radboud University Medical Center has passed a positive judgment on the study. The Committee considered that the study protocol doesn't fall within the remit of the Medical Research Involving Human Subjects Act (WMO) (ref: 2017/3597). Patients, healthcare professionals, and organisational managers will be asked to sign an Informed Consent form before participating in a semi-structured interview. This project will be conducted according to the Declaration of Helsinki and the Agreement on Medical Treatment Act (In Dutch: Wet op de Geneeskundige Behandelingsovereenkomst or WGBO).

DISCUSSION

This study protocol focuses on the challenge to implement the COPDnet integrated care model into three hospitals and affiliated primary care regions. It will evaluate the feasibility of integrating the COPDnet model into actual care within the context of the Dutch healthcare system. It will evaluate the potential health status benefits from the patient's perspective, and it will evaluate the direct and indirect costs, on the basis of

TDABC models, of the diagnostic trajectory as a component of the COPDnet model. This study protocol has strengths and limitations, which will be discussed below.

Strenghts

A major strength of this study protocol is that we evaluate Dutch real life care, derived from the care delivered by the implemented COPDnet integrated care models. Although the number of real life studies on COPD is growing[30], little scientific data is available on the outcome of real life COPD care outside the remit of treatment or exacerbations.[31] The first publications on the outcome of this real life COPD care suggest room for improvement on the organisation of care, the content of care, and the cost-effectiveness of care.[9,32-35]

This study will generate knowledge about the COPDnet model, which is founded on the principles of the CCM. The aim of the CCM is to transform daily care for patients with chronic illnesses from acute and reactive, to proactive, planned, and population-based.[36] The use of the principles of the CCM in the context of COPD holds the promise to generate better outcomes of care.[11]

Furthermore, this study protocol describes a multi-site study. The COPDnet model will be implemented in three hospitals, each with a different character, and, subsequently, in different allied primary care regions. Although the COPDnet integrated care model was designed for the Dutch healthcare system, it is deemed applicable, mutatis mutandis, in every country that sets out to apply an integrated approach in an integrated healthcare chain. We based the development of the COPDnet model on evidence and frameworks available in the international literature. We think that our model is applicable in other healthcare systems, when tailored to national and local context.

Finally, this study protocol will provide a multi-perspective evaluation of the COPDnet model. Our COPDnet model is an integrated care model, and its evaluation is an integral part of it. Our analysis will focus on patient perspective, healthcare professional perspective, and organizational perspective, in primary and in secondary care settings.

Limitations

This study protocol has two limitations. First, this study protocol lacks a controlled design. This means that we have to be careful with the conclusions we draw from our study and we can apply the recommendations only to the local geographic context of our three COPDnet hospitals and primary care regions. However, randomized controlled trials may have a high internal validity, whereas real life studies have high generalizability.[30] Nevertheless, we consider the current study as a proof of concept

of the deployment of the COPDnet model, that is of the feasibility of working with the model, rather than a study on its effectiveness. Second, we have developed the current COPDnet model as it stands, but we are aware of its fragility. After the diagnostic trajectory in a secondary care setting, patients may be referred for further guidance and intervention to either a primary care setting or to a form of pulmonary rehabilitation in secondary or tertiary care settings. Referrals are based on the assessment of the burden of disease and actual individual traits. For this purpose, guidelines on decision making were developed. Even so, uptake, completion, and quality of the delivered intervention(s) can only be partly controlled for. As a result, changes in health status over time may be difficult to interpret.

Clinical consequences

This study protocol will provide prime insights with respect to feasibility, health status benefits, and cost of care of the diagnostic trajectory of the COPDnet integrated care model in three hospitals and their affiliated primary care regions. It is anticipated, that adjustments of the current model are to be made. Subsequently, a follow-up study may be performed with a controlled design, to evaluate the clinical (cost)-effectiveness of the model.

CONCLUSION

The COPDnet integrated care model for patients with COPD has been designed according to current insights regarding effective care for patients with a chronic condition in general and for patients with COPD in particular. It will be evaluated for its feasibility, potential health status benefits, and the costs of care of the diagnostic trajectory in secondary care.

REFERENCES

1. The Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. Available from: http://goldcopd.org/gold-reports-2017/. Accessed March 29, 2018.

2. Agusti A, Calverley PM, Celli B, et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. *Respiratory research.* 2010;11:122.

3. Vestbo J, Agusti A, Wouters EF, et al. Should we view chronic obstructive pulmonary disease differently after ECLIPSE? A clinical perspective from the study team. *American journal of respiratory and critical care medicine.* 2014;189(9):1022-1030.

4. Wouters EF. Economic analysis of the Confronting COPD survey: an overview of results. *Respiratory medicine.* 2003;97 Suppl C:S3-14.

5. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. *Lancet.* 2007;370(9589):765-773.

6. Porter ME. What is value in health care? *The New England journal of medicine.* 2010;363(26):2477-2481.

7. Boland MR, Tsiachristas A, Kruis AL, Chavannes NH, Rutten-van Molken MP. The health economic impact of disease management programs for COPD: a systematic literature review and meta-analysis. *BMC pulmonary medicine.* 2013;13:40.

8. Kruis AL, Smidt N, Assendelft WJ, et al. Integrated disease management interventions for patients with chronic obstructive pulmonary disease. *The Cochrane database of systematic reviews.* 2013;10:CD009437.

9. Kayyali R, Odeh B, Frerichs I, et al. COPD care delivery pathways in five European Union countries: mapping and health care professionals' perceptions. *International Journal of Chronic Obstructive Pulmonary Disease.* 2016;11:2831-2838.

10. Koolen EH, van der Wees PJ, Westert GP, Dekhuijzen R, Heijdra YF, van 't Hul AJ. The COPDnet integrated care model. *International Journal of Chronic Obstructive Pulmonary Disease.* 2018;13:2225-2235.

11. Adams SG, Smith PK, Allan PF, Anzueto A, Pugh JA, Cornell JE. Systematic review of the chronic care model in chronic obstructive pulmonary disease prevention and management. *Archives of internal medicine.* 2007;167(6):551-561.

12. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. *Lancet.* 2003;362(9391):1225-1230.

13. Long Alliantie Nederland LAN. Zorgstandaard COPD [Care Standard COPD]. 2016. Available from: http://www.longalliantie.nl/zorgstandaard-copd. Accessed March 29, 2018. Dutch.

14. Doorontwikkeling CQ-index Astma en COPD: validatie van een verkorte vragenlijst voor het meten van de kwaliteit van astma/COPD-zorg vanuit het perspectief van patiënten [Further development CQ-index Asthma and COPD, Validation of a shortened questionnaire for measuring the quality of asthma / COPD care from the perspective of patients]. Available from: https://www.nivel.nl/sites/default/files/bestanden/CQ-index%20Astma%20en%20COPD%202014.pdf. Accessed March 29, 2018. Dutch.

15. Wensing M, van Lieshout J, Jung HP, Hermsen J, Rosemann T. The Patients Assessment Chronic Illness Care (PACIC) questionnaire in The Netherlands: a validation study in rural general practice. *BMC health services research.* 2008;8:182.

16. Bonomi AE, Wagner EH, Glasgow RE, VonKorff M. Assessment of chronic illness care (ACIC): a practical tool to measure quality improvement. *Health services research.* 2002;37(3):791-820.

17. Hibbard JH, Collins PA, Mahoney E, Baker LH. The development and testing of a measure assessing clinician beliefs about patient self-management. *Health Expectations: an international journal of public participation in health care and health policy.* 2010;13(1):65-72.

18. Brownson CA, Miller D, Crespo R, et al. A quality improvement tool to assess self-management support in primary care. *Joint Commission journal on quality and patient safety.* 2007;33(7):408-416.

19. Vanhaecht K, De Witte K, Depreitere R, et al. Development and validation of a care process self-evaluation tool. *Health services management research.* 2007;20(3):189-202.

20. van der Molen T, Willemse BW, Schokker S, ten Hacken NH, Postma DS, Juniper EF. Development, validity and responsiveness of the Clinical COPD Questionnaire. *Health and quality of life outcomes.* 2003;1:13.

21. Hibbard JH, Mahoney ER, Stockard J, Tusler M. Development and testing of a short form of the patient activation measure. *Health services research.* 2005;40(6 Pt 1):1918-1930.

22. Hibbard JH, Stockard J, Mahoney ER, Tusler M. Development of the Patient Activation Measure (PAM): conceptualizing and measuring activation in patients and consumers. *Health services research.* 2004;39(4 Pt 1):1005-1026.

23. Peters JB, Daudey L, Heijdra YF, Molema J, Dekhuijzen PN, Vercoulen JH. Development of a battery of instruments for detailed measurement of health status in patients with COPD in routine care: the Nijmegen Clinical Screening Instrument. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2009;18(7):901-912.

24. Vercoulen JH. A simple method to enable patient-tailored treatment and to motivate the patient to change behaviour. *Chronic respiratory disease.* 2012;9(4):259-268.

25. Marshall AL, Smith BJ, Bauman AE, Kaur S. Reliability and validity of a brief physical activity assessment for use by family doctors. *British journal of sports medicine.* 2005;39(5):294-297; discussion 294-297.

26. Kaplan RS, Anderson SR. Time-driven activity-based costing. *Harvard Business Review.* 2004;82(11):131-138, 150.

27. Kaplan RS, Porter ME. How to solve the cost crisis in health care. *Harvard Business Review.* 2011;89(9):46-52, 54, 56-61 passim.

28. Keel G, Savage C, Rafiq M, Mazzocato P. Time-driven activity-based costing in health care: A systematic review of the literature. *Health policy.* 2017.

29. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. *Qualitative health research.* 2005;15(9):1277-1288.

30. Saturni S, Bellini F, Braido F, et al. Randomized Controlled Trials and real life studies. Approaches and methodologies: a clinical point of view. *Pulmonary Pharmacology & Therapeutics.* 2014;27(2):129-138.

31. Porter ME, Larsson S, Lee TH. Standardizing Patient Outcomes Measurement. *The New England journal of medicine.* 2016;374(6):504-506.

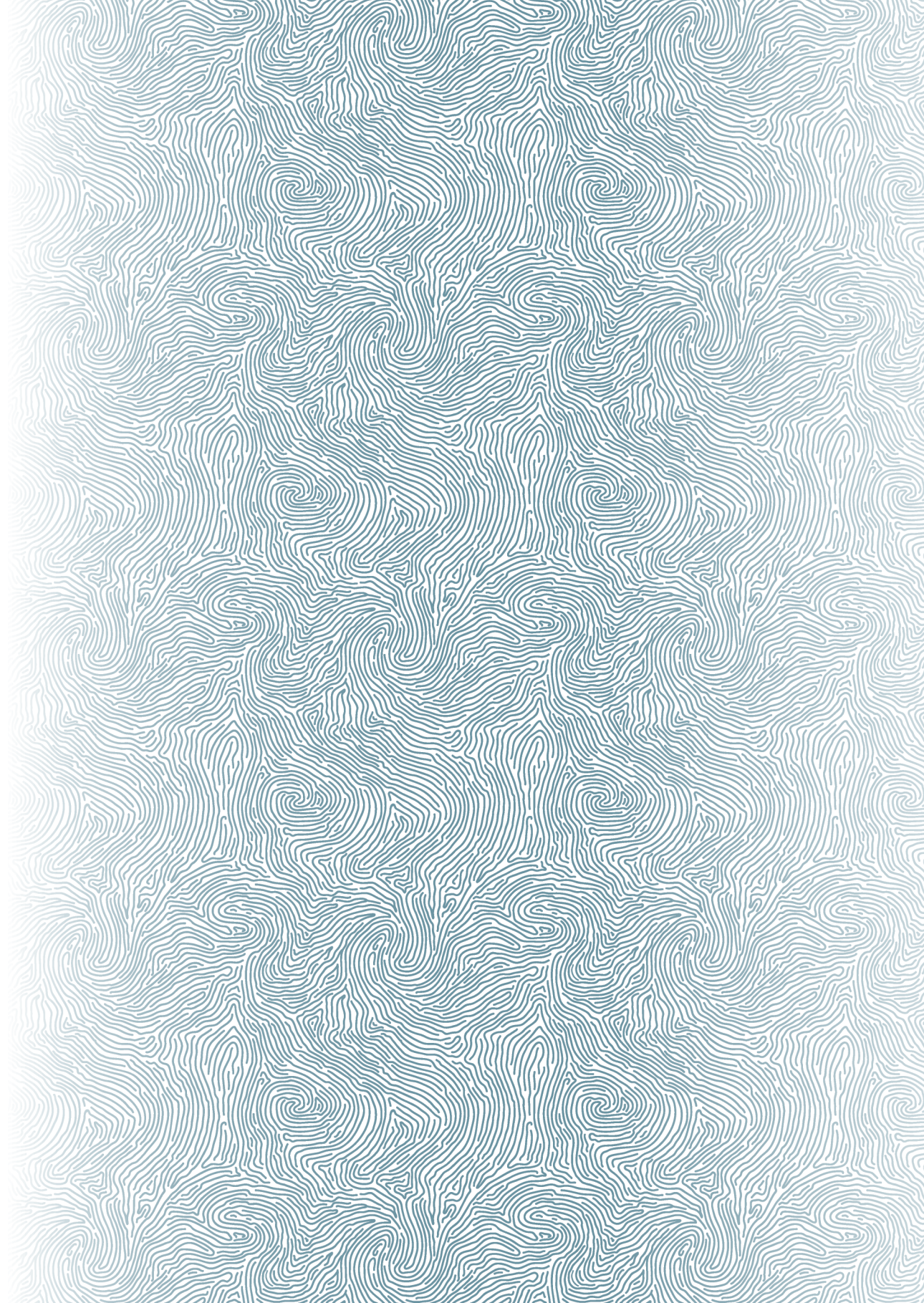
32. Worth H, Buhl R, Criee CP, Kardos P, Mailander C, Vogelmeier C. The 'real-life' COPD patient in Germany: The DACCORD study. *Respiratory medicine.* 2016;111:64-71.

33. Buhl R, Criee CP, Kardos P, et al. A year in the life of German patients with COPD: the DACCORD observational study. *International Journal of Chronic Obstructive Pulmonary Disease.* 2016;11:1639-1646.

34. Haughney J, Gruffydd-Jones K, Roberts J, Lee AJ, Hardwell A, McGarvey L. The distribution of COPD in UK general practice using the new GOLD classification. *The European respiratory journal.* 2014;43(4):993-1002.

35. Ke X, Marvel J, Yu TC, et al. Impact of lung function on exacerbations, health care utilization, and costs among patients with COPD. *International Journal of Chronic Obstructive Pulmonary Disease.* 2016;11:1689-1703.

36. Coleman K, Austin BT, Brach C, Wagner EH. Evidence on the Chronic Care Model in the new millennium. *Health affairs.* 2009;28(1):75-85.



“Can do” versus “do do”
A Novel Concept to Better Understand Physical Functioning in Patients with Chronic Obstructive Pulmonary Disease

E.H. Koolen
H.W. van Hees
R.C. van Lummel
P.N.R. Dekhuijzen
R.S. Djamin
M.A. Spruit
A.J. van ’t Hul

Journal of Clinical Medicine. 2019 Mar 11;8(3):340

ABSTRACT

BACKGROUND

Physical capacity (PC) and physical activity (PA) represent associated but separate domains of physical function. It remains unknown whether this framework may support a better understanding of the impaired physical function in patients with chronic obstructive pulmonary disease (COPD). The current study had two aims: (1) to determine the distribution of patients with COPD over the PC-PA quadrants, and (2) to explore whether differences exist in clinical characteristics between these quadrants.

METHODS

In this retrospective study, PC was measured using the six-minute walk distance (6MWD), and PA was assessed with an accelerometer. Moreover, patients' clinical characteristics were obtained. Patients were divided into the following quadrants: (I) low PC (6MWD <70% predicted), low PA, using a step-defined inactivity index (<5000 steps/day, "can't do, don't do" quadrant); (II) preserved PC, low PA ("can do, don't do" quadrant); (III) low PC, preserved PA ("can't do, do do" quadrant); and (IV) preserved PC, preserved PA ("can do, do do" quadrant).

RESULTS

The distribution of the 662 COPD patients over the quadrants was as follows: "can't do, don't do": 34%; "can do, don't do": 14%; "can't do, do do": 21%; and "can do, do do": 31%. Statistically significant differences between quadrants were found for all clinical characteristics, except for educational levels.

CONCLUSIONS

This study proves the applicability of the PC-PA quadrant concept in COPD. This concept serves as a pragmatic clinical tool, that may be useful in the understanding of the impaired physical functioning in COPD patients and therefore, may improve the selection of appropriate interventions to improve physical function.

INTRODUCTION

Impaired physical capacity (PC) and low-level daily physical activity (PA) are common features in people with chronic obstructive pulmonary disease (COPD).[1] PC refers to the ability to perform physical activities and is generally quantified by exercise tests.[2] Daily PA may be defined as any bodily movement produced by skeletal muscles that results in energy expenditure beyond that of the resting state.[3] These days, the measurement of PA is performed with activity monitors rather than with questionnaires.[4]

Over the last decade, an increasing number of studies have shown the clinical relevance of low-level daily PA in COPD patients, as it is associated with poor health status, increased healthcare utilization, and higher mortality risk. Moreover, these associations are independent of the degree of airway obstruction.[1] Therefore, improving PA is considered to be pivotal to the comprehensive management of COPD patients.[5]

Exercise training is a common intervention used to improve physical function in COPD patients, either as a single intervention or as part of pulmonary rehabilitation.[6] Despite the significant positive impact of such interventions on PC[7-10], the improvements in PA are disappointingly incongruous[11,12] and seem to point to some discrepancies between changes in PC levels ("can do") and changes in habitual PA levels ("do do").[13] These counterintuitive observations may, however, be less surprising given the identification of multiple determinants of PA in patients with COPD of which PC is an important determinant, but not the only one.[14] The need for further research in this field has been acknowledged both by the American Thoracic Society and the European Respiratory Society.[1,15]

Recently, a conceptual framework was published in which PC and PA were viewed as associated but separate domains of physical function in the elderly, enabling individually tailored interventions.[16] We used this framework as a starting point for the development of a PC-PA quadrant concept, in which COPD patients could be subdivided along axes of what they physically "can do" (PC), as in an exercise test, and what they actually "do do" (PA), in their daily lives.

The hypothesis of the present study is that using this PC-PA quadrant concept enables identification of subgroups of COPD patients with different clinical characteristics that may contribute to the explanation of the discrepancy between their PC and PA. The current study sets out to (1) determine the distribution of COPD patients over the proposed PC-PA quadrant concept, and (2) explore whether, and to what extent, differences exist in clinical characteristics between the patients subdivided into mutually exclusive PC-PA quadrants.

EXPERIMENTAL SECTION

Study Design and Participants

In this retrospective study, participants were patients over 40 years of age, with relatively stable COPD[5], who underwent a comprehensive health status assessment as part of the usual COPD care in Amphia Hospital in Breda and Radboud University Medical Centre in Nijmegen (both in The Netherlands) between April 2013 and June 2017. According to the Dutch Standard of Care for COPD, general practitioners referred these patients to pulmonologists in a secondary care setting because the patients had persistent respiratory symptoms and/or limited activities of daily living and an unsatisfactory response to the medical treatment offered in primary care. Patients with a COPD exacerbation in the previous three months were excluded, as exacerbation-related symptoms and physical inactivity could have still been present during this period.[17-19] The Medical Ethical Committee of the Radboudumc approved this retrospective study, and because the participants were subjected to usual care (ref: 2016–2603), they considered that it did not fall within the remit of the Medical Research Involving Human Subjects Act (WMO). Therefore, the de-identified and pre-existing data of 662 patients were used for analyses.

Assessments

In all patients, a standardized, comprehensive health status assessment was completed, as described elsewhere.[20] PC and PA were the two main outcomes. PC was measured with a six-minute walk test (6MWT) and expressed as a percentage of the predicted value[21] using the reference equation of Troosters et al.[22]. As peak oxygen uptake during a 6MWT was comparable with values obtained during a symptom-limited cardiopulmonary exercise test, it seems fair to conclude that the 6MWT can be considered a test of PC.[23] In addition, the 6MWT had the advantage of being a self-paced exercise test and allowed for the inclusion of patients into this study who exhibited extremely low exercise tolerance.[21] PA was objectively assessed with either an uniaxial accelerometer (Digiwalker SW-200; Yamax Corporation, Tokyo, Japan[24]) or a triaxial accelerometer (DynaPort MoveMonitor, McRoberts, The Hague, The Netherlands) for seven consecutive days, and it is expressed as the average number of steps per day measured over at least four valid days[25]. In addition, various patient and health status characteristics were systematically registered. These characteristics included the following: age (years); gender (male/female); Body Mass Index (BMI, body weight in kg divided by height in squared meters, kg/m²); waist circumference (cm; male ≥94 cm or female ≥80 cm are at risk for cardiovascular comorbidity)[26]; Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification (I–IV and A–D)[5]; pulmonary function (spirometry and flow-volume curve, using the Global Lung Initiative (GLI) equations)[27]; number of patients with frequent COPD exacerbations,

defined as an acute worsening of respiratory symptoms that result in additional therapy[5], in the last 12 months (infrequent: <2 exacerbations per year/frequent: ≥2 exacerbations per year); smoking status (current/former-never); partner (yes/no); employment status (yes/no); and educational level according to Verhage's classification (low/intermediate/high)[28]. Table 1: provides an overview of the health status questionnaires that were used.

Table 1. Overview questionnaires.

Questionnaire	Quantifies	Range	Interpretation
Charlson Comorbidity Index (CCI)[29]	Predict one-year mortality based on the presence of comorbidities	0–46	Higher scores indicate a higher mortality risk
Medical Research Council (MRC) dyspnea scale[30]	The degree of activity-related breathlessness	1–5	Higher scores indicate higher impact of dyspnea
Checklist Individual Strength fatigue domain (CIS)[31]	The degree of general fatigue	8–56	Higher scores indicate more fatigue
COPD Assessment Test (CAT)[32,33]	Burden of disease	0–40	Higher scores indicate higher burden of disease
COPD Clinical Questionnaire (CCQ)[34,35]	Burden of disease	0–6	Higher scores indicate higher burden of disease
Marshall Questionnaire[36]	Self-reported PA	0–8	Higher scores indicate higher level of self-reported PA

Statistical Analysis

Descriptive statistics were used to summarize the data as medians (ranges) or frequencies (proportions), as appropriate. The patients were divided into mutually exclusive categories using the quadrant concept on the basis of their PC and PA: (I) low PC (6MWD <70% of the predicted value[21]) and low PA (using a step-defined inactivity index <5000 steps per day[37,38], "can't do, don't do" quadrant); (II) preserved PC, low PA ("can do, don't do" quadrant); (III) low PC, preserved PA ("can't do, do do" quadrant); (IV) preserved PC and preserved PA ("can do, do do" quadrant). In the absence of a validated minimum value for PC that would interfere with the normal ability to perform daily tasks, the PC threshold was calculated. By putting two standard deviations below the mean value of the non-COPD subjects, we knew that only about 2.5% of the non-COPD subjects had such abnormally low 6 min walk distances. The mean 6MWD in non-COPD control subjects (631 m) was set as 100% of the predicted value[22], and one standard deviation (93 m) matched 15% of the predicted value[22]. Therefore, the mean (100%) minus twice the standard deviation resulted in an arbitrary, but statistically

reasonable cut off of 70% of the predicted value for PC. Furthermore, the threshold of a low PA was defined as <5000 steps per day. The continued use of <5000 steps per day as a step-defined sedentary lifestyle index for adults is appropriate for researchers and practitioners and for communicating with the general public[38] and has also been validated for COPD patients[37]. Differences between quadrants were tested with non-parametric tests, because the number of patients in the quadrants was not equal. Therefore, Kruskal–Wallis or Chi-square tests were used, including post-hoc analysis, as appropriate. The Pearson's correlation coefficient was used to evaluate the association between PC and PA, and *p*-values below 0.05 were considered statistically significant. All statistical analyses were conducted using SPSS Version 22 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 662 elderly patients with COPD were available for analyses. The majority were men (55%) who had a mild to very severe degree of airflow limitation and had a marked heterogeneity in their health status scores (Table 2). In brief, 53% of the COPD patients had a high symptom burden based on a CCQ score of ≥1.9 points and 50% based on a CAT score of ≥18 points.[35] Moreover, functional exercise performance (mean 6MWD: 68% predicted) and the level of physical activity (median steps per day: 5112) were abnormally low. There were no statistically significant differences between subgroups measured with the Digiwalker SW-200 or the Dynaport MoveMonitor with respect to PA (5328 ± 3664 versus 5700 ± 2897 steps per day; $p = 0.146$), PC (6MWD: 67 ± 15 versus 67 ± 15% predicted; $p = 0.876$), age (64 ± 10 versus 64 ± 9 years; $p = 0.974$), or the degree of airflow limitation (FEV1: 59 ± 20 *versus* 58 ± 18% predicted; $p = 0.667$).

The distribution of patients over the PC-PA quadrants was as follows: (I) "can't do, don't do": 34%, (II) "can do, don't do": 14%, (III) "can't do, do do": 21%, and (IV) "can do, do do": 31% (Figure 1). The Pearson's correlation coefficient between PC and PA was 0.4 ($p < 0.001$). Statistically significant differences between PC-PA quadrants were found for all the characteristics, except for the educational levels (Table 2).

DISCUSSION

The main findings from this study are (1) the proposed PC-PA quadrant concept enables subdivision of patients with COPD into four exclusive subgroups with distinctive PC-PA values, and (2) these PC-PA-based quadrants are considerably different in multiple clinical characteristics.

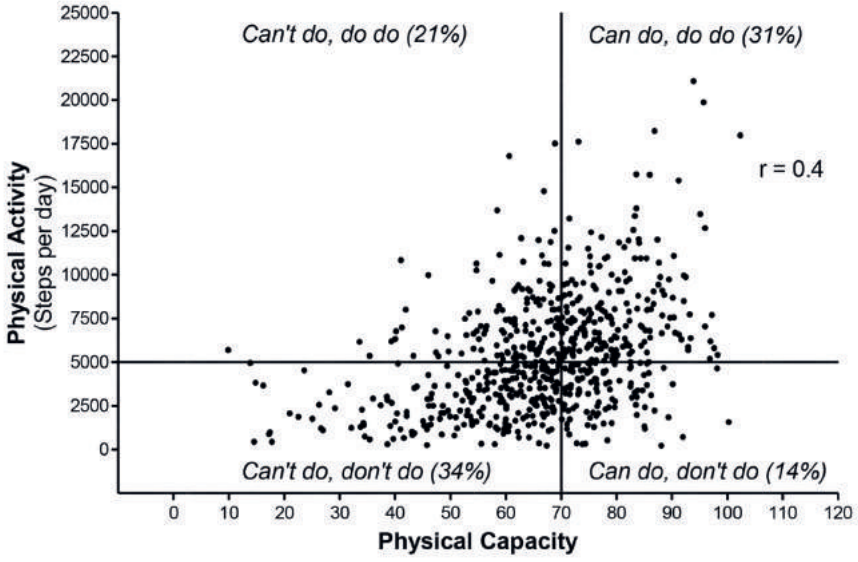


Figure 1. Graphical overview of the physical capacity-physical activity quadrant concept.
Note: Sample: n = 662 COPD patients
Abbreviations: 6MWD = Six-Minute Walk Distance; *r* = Pearson's correlation coefficient.

PC and PA showed a low but significant correlation ($r = 0.4$; $p < 0.001$), which is in line with earlier studies and confirms that PC is just one determinant of PA.[14,16] Psychosocial and behavioral aspects are equally important for understanding and targeting low-level daily PA in individual patients.[39] The PC-PA quadrant concept enables identification of subgroups of COPD patients with definable treatable traits and may be useful in the stratification of appropriate non-pharmacological interventions aiming to improve physical function in future studies (i.e., pulmonary rehabilitation and PA coaching), as was suggested earlier in an editorial by Singh.[40]

The patients in the "can't do, don't do" quadrant were mostly the patients with the highest disease burden, on the basis of the degree of pulmonary function impairment, comorbidities, exacerbation frequency, and symptom load, factors that are, not surprisingly, associated with the largest impact on overall health status. Because of the multiple and complex treatable traits in this subgroup, it identifies them as suitable candidates for a comprehensive pulmonary rehabilitation program.[9] To improve PA, it is suggested that the traditional approach to pulmonary rehabilitation with supervised high-intensity exercise training as the cornerstone may have little transfer-effect on an increase in PA.[41] Adaptations of such programs to turn improved PC into more active lifestyles seems feasible and results in higher PA.[42]

Table 2. Characteristics.

Attribute	Total Sample N = 662	"Can't do, don't do" N = 223; 34%	"Can do, don't do" N = 96; 14%	"Can't do, do do" N = 140; 21%	"Can do, do do" N = 203; 31%	Sig.
Age [a], years	63 (41–87)	67 (42–86) [†,‡]	67 (46–87) [†,‡]	59 (41–83)	62 (41–82)	<0.001
Female [b], %	45	41	49	40	52	<0.05
BMI [a], kg/m²	25.3 (14.1–51.6)	25.6 (14.1–51.6) [*,†]	27.6 (18.7–47.1) [†,‡]	23.6 (15.5–36.6)[‡]	25.1 (16.5-40.4)	<0.001
High WC [b], %	78	76 [*]	90[†]	70	80	<0.01
GOLD I/II/III/IV [b], %	14/51/31/4	9/43/41/8 [*,‡]	16/58/25/1	11/55/30/4	20/53/25/2	<0.001
GOLD A/B/C/D [b], %	13/34/8/46	3/27/7/62 [*,†,‡]	12/51/9/28	12/37/11/41	23/30/7/40	<0.001
FEV1 % pred. [a]	56 (14–116)	51 (14–111) [*,†,‡]	61 (28–109)	56 (21–07)	60 (23–116)	<0.001
FVC % pred. [a]	93 (42–151)	89 (42–135) [*,‡]	94 (50–150)	91 (54–131)[‡]	97 (49–151)	<0.001
FEV1/FVC ratio [a]	0.48 (0.2–0.7)	0.45 (0.2–0.7) [*,‡]	0.51 (0.2–0.7)	0.48 (0.2–0.7)	0.51 (0.2–0.7)	<0.001
CCI [a], points	3 (0–9)	3 (0–9) [‡]	3 (0–7) [‡]	2 (0–6)	2 (0–6)	<0.01
Frequent exacerbator. [b], %	26	35 [*]	10 [†]	26	23	<0.001
Current smokers [b], %	47	55 [‡]	48	54 [‡]	35	<0.001
Partnered [b], %	71	64 [‡]	69	76	77	<0.05
Employed [b], %	32	17 [†,‡]	28	43	44	<0.001
Low/Intermediate/High Educational level [b], %	16/65/18	15/64/21	18/68/14	14/66/20	19/64/17	0.289
CAT [a], points	18 (0–40)	21 (1–40) [†,‡]	18 (2–37) [‡]	17 (0–37)	14 (1–35)	<0.001
MRC dyspnoea scale [a]	2 (0–5)	3 (0–5) [*,†,‡]	2 (0–5) [‡]	2 (0–5) [‡]	2 (0–5)	<0.001
CIS Fatigue [a], points	37 (8–56)	43 (8–56) [†,‡]	36 (13–56) [‡]	36 (8–56)	33 (8–56)	<0.001
CCQ [a], points	2.0 (0.1–5.8)	2.7 (0.2–5.8) [*,†,‡]	2.0 (0.3–4.8)	1.8 (0.1–5.1) [‡]	1.5 (0.1–4.7)	<0.001
Marshall Quest. [b] ≥4 points, %	45	31 [‡]	33 [‡]	45	64	<0.01
6MWD [a], m	440 (76–805)	351 (100–558) [*,†,‡]	485 (317–660) [†,‡]	423 (76–550) [‡]	512 (339–805)	<0.001
6MWD% pred [a]	68 (10–102)	58 (15–70) [*,‡]	76 (70–100) [†]	63 (10–70) [‡]	79 (70–102)	<0.001
Steps per day [a]	5112 (333–21191)	2838 (345–4998) [†,‡]	3355 (333–4961) [†,‡]	7035 (5016–17621)	7556 (5000–21191)	<0.001

Abbreviations: BMI = Body Mass Index; High WC = High Waist Circumferences (Male >94 cm, Female >80 cm); GOLD = Global Initiative for Chronic Obstructive Lung Disease; FEV1% pred. = Forced Expiratory Volume in one second percentage predicted; FVC% pred. = Forced Vital Capacity percentage predicted; CCI = Charlson Comorbidity Index; CAT = COPD Assessment Test; MRC dyspnoea scale = Medical Research Council dyspnoea scale; CIS = Checklist Individual Strength; CCQ = COPD Clinical Questionnaire; 6MWD = Six-Minute Walking Distance; 6MWD% pred = Six-Minute Walking Distance percentage predicted.
Note: Missing sample data per category = *n* (%): Waist circumferences = 42 (6); GOLD (A-D)=116 (18); CCI = 328 (58); Exacerbations <12 months = 123 (19); Current smoking status = 23 (3); Partner = 37 (6); Employment = 47 (7); Educational level = 55(8); CAT = 138 (21); CCQ total = 62(9); MRC dyspnoea scale = 70 (11); Marshall questionnaire = 464 (70); CIS = 21 (3) [a]: Continuous variable: Median (Range) [b]: Categorical variable: Proportion (%) *: $p < 0.05$ versus "can do, don't do" †: $p < 0.05$ versus "can't do, do do" ‡: $p < 0.05$ versus "can do, do do".

The patients in the "can do, don't do" quadrant only showed a trivial difference in PC compared to those in the "can do, do do" quadrant.[21] By contrast, the statistically significant difference in PA of 4201 (56%) fewer steps per day is huge and exceeds the assumed threshold of clinical relevance in PA for COPD patients by four times.[43] In the "can do, don't do" quadrant, patients potentially have the ability to be active, but they "just" don't do it. Although exercise training on top of promoting PA resulted in improved exercise capacity in patients with mild to moderate COPD, it did not translate into statistically significant enhanced daily PA.[44] Targeting behavioral change in order to increase PA could be the more appropriate management strategy in this subgroup but certainly will not be an easy task.[45] To address behavioral change at the individual level, all personal barriers and enablers that may hinder or facilitate PA engagement must be considered in future studies.[46] Also, observations of the "can do, don't do" quadrant showed the highest BMI and the largest percentage of patients with a high waist circumference as compared to the other quadrants. Weight reducing measures may be important to improve PA and might also positively affect the risk of obesity related comorbidities.[47] Then again, a lack of PA may also have caused the high BMI which may improve by becoming physically more active.[48] Finally, a remarkable finding in this "can do, don't do" quadrant is the relatively low proportion of patients with frequent exacerbations, especially compared with the "can't do, don't do" quadrant (10% versus 35%). An earlier study showed a relationship between PA and exacerbation risk[49], which suggests that especially the combination of a low PC and low PA may predispose patients to repeated exacerbations.

In the "can't do, do do" quadrant, the median number of steps per day was 4197 (148%) higher than that of the "can't do, don't do" quadrant. However, despite the fact that the allocation criterion for PC was the same for these quadrants, the difference in 6MWD of 72 m, although not statistically significant, exceeds the threshold of clinical relevance. This unanticipated difference in PC between these two quadrants might, at least to some extent, be accountable for the marked difference in PA. Other clinical characteristics that may explain the higher PA in this subgroup are the younger age, the possibly related larger proportion of patients with a job, and the greater proportion of patients with a partner. The latter observation seems to be consistent with the finding that social support and objective indices of support by spouses, friends, or work colleagues are important enablers for improving PA levels generally[50], but also in COPD patients[39]. Furthermore, it is imperative to understand all the perceived psychosocial barriers and enablers of engagement in PA[39]. Therefore, further qualitative research into psychosocial barriers and enablers in this population is required to eventually develop interventions aimed at reducing perceived barriers while optimizing enablers. Finally, the patients in the "can do, do do" quadrant, both with preserved PC and PA, were actually the patients with the best overall outcomes. Obviously, there were

reasons to refer these patients to pulmonologists, indicating the presence of clinically relevant symptoms and/or functional limitations. Within this quadrant, treatment interventions should not be primarily focused on the level of PC or PA, but on other treatable traits regarding their burden of disease, such as self-management support, medication adherence, or cognitive behavioral therapy. Taking the individual traits into account applies to this quadrant, and to the other three quadrants, in order to provide the best personalized care.[51]

This study has several strengths. A large, real-life sample of COPD patients was recruited, who were referred by their general practitioner to the pulmonologist. This supports the external validity and generalizability of the findings in this study. Interestingly, high symptom burden[35], physical inactivity, and physical deconditioning were identified in a significant proportion of patients. This raises the question as to why this group of patients was referred to the pulmonologist at an apparently random stage. Also, an important point is that patients were comprehensively assessed, allowing for comparison between the quadrants using multiple patient characteristics. There are also some methodological considerations. Obviously, a change in PC and/or PA cut off points will redistribute the patients, especially in patients close to the cut points. The aim of the present study was, however, not to determine the clinically relevant thresholds of PC and PA precisely, but rather to demonstrate proof of the PC-PA concept in COPD patients.

FUTURE STUDIES AND CONCLUSIONS

This study provides proof of the PC-PA quadrant concept in COPD patients. Using this concept, it turned out to be possible to subdivide patients into exclusive quadrants with distinctive PC-PA relations. Obviously, future studies have to determine the extent to which PC-PA quadrants are useful in optimizing personalized medicine of patients with COPD, and their role in helping to better understand the association between low PA and/or PC and hospitalization risk. For current clinical practice, the PC-PA quadrant concept may already serve as a pragmatic clinical tool, which may be useful in the interpretation of the physical functioning of patients with COPD.

REFERENCES

1. Watz H, Pitta F, Rochester CL, et al. An official European Respiratory Society statement on physical activity in COPD. *The European Respiratory Journal.* 2014;44(6):1521-1537.

2. Puente-Maestu L, Palange P, Casaburi R, et al. Use of exercise testing in the evaluation of interventional efficacy: an official ERS statement. *The European Respiratory Journal.* 2016;47(2):429-460.

3. World Health Organization (WHO). Global Strategy on Diet, Physical Activity and Health. Available from: http://www.who.int/dietphysicalactivity/pa/en/. Accessed February 03, 2019.

4. Sievi NA, Brack T, Brutsche MH, et al. Accelerometer- versus questionnaire-based assessment of physical activity and their changes over time in patients with COPD. *International Journal of Chronic Obstructive Pulmonary Disease.* 2017;12:1113-1118.

5. The Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. Available from: http://goldcopd.org/gold-reports-2017/. Accessed February 03, 2019.

6. Spruit MA, Wouters EFM. Organizational aspects of pulmonary rehabilitation in chronic respiratory diseases. *Respirology.* 2019;24(9):838-843.

7. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *The Cochrane database of systematic reviews.* 2015(2):CD003793.

8. Augustin IML, Wouters EFM, Houben-Wilke S, et al. Comprehensive Lung Function Assessment Does not Allow to Infer Response to Pulmonary Rehabilitation in Patients with COPD. *Journal of Clinical Medicine.* 2018;8(1).

9. Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *American Journal of Respiratory and Critical Care Medicine.* 2013;188(8):e13-64.

10. Spruit MA, Augustin IM, Vanfleteren LE, et al. Differential response to pulmonary rehabilitation in COPD: multidimensional profiling. *The European Respiratory Journal.* 2015;46(6):1625-1635.

11. Cindy Ng LW, Mackney J, Jenkins S, Hill K. Does exercise training change physical activity in people with COPD? A systematic review and meta-analysis. *Chronic Respiratory Disease.* 2012;9(1):17-26.

12. Spruit MA, Pitta F, McAuley E, ZuWallack RL, Nici L. Pulmonary Rehabilitation and Physical Activity in Patients with Chronic Obstructive Pulmonary Disease. *American Journal of Respiratory and Critical Care Medicine.* 2015;192(8):924-933.

13. Bootsma-van der Wiel A, Gussekloo J, de Craen AJM, et al. Disability in the oldest old: „Can do" or „do do"? *Journal of the American Geriatrics Society.* 2001;49(7):909-914.

14. Gimeno-Santos E, Frei A, Steurer-Stey C, et al. Determinants and outcomes of physical activity in patients with COPD: a systematic review. *Thorax.* 2014;69(8):731-739.

15. Celli BR, Decramer M, Wedzicha JA, et al. An official American Thoracic Society/European Respiratory Society statement: research questions in COPD. *The European Respiratory Journal.* 2015;45(4):879-905.

16. van Lummel RC, Walgaard S, Pijnappels M, et al. Physical Performance and Physical Activity in Older Adults: Associated but Separate Domains of Physical Function in Old Age. *PloS one.* 2015;10(12):e0144048.

17. Pitta F, Troosters T, Probst VS, Spruit MA, Decramer M, Gosselink R. Physical activity and hospitalization for exacerbation of COPD. *Chest.* 2006;129(3):536-544.

18. Spruit MA, Gosselink R, Troosters T, et al. Muscle force during an acute exacerbation in hospitalised patients with COPD and its relationship with CXCL8 and IGF-I. *Thorax.* 2003;58(9):752-756.

19. Alahmari AD, Kowlessar BS, Patel AR, et al. Physical activity and exercise capacity in patients with moderate COPD exacerbations. *The European Respiratory Journal.* 2016;48(2):340-349.

20. van den Akker EF, van ,t Hul AJ, Chavannes NH, et al. Development of an integral assessment approach of health status in patients with obstructive airway diseases: the CORONA study. *International Journal of Chronic Obstructive Pulmonary Disease.* 2015;10:2413-2422.

21. Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *The European Respiratory Journal.* 2014;44(6):1428-1446.

22. Troosters T, Gosselink R, Decramer M. Six minute walking distance in healthy elderly subjects. *The European Respiratory Journal.* 1999;14(2):270-274.

23. Singh SJ, Puhan MA, Andrianopoulos V, et al. An official systematic review of the European Respiratory Society/American Thoracic Society: measurement properties of field walking tests in chronic respiratory disease. *The European Respiratory Journal.* 2014;44(6):1447-1478.

24. Le Masurier GC, Lee SM, Tudor-Locke C. Motion sensor accuracy under controlled and free-living conditions. *Medicine and Science in Sports and Exercise.* 2004;36(5):905-910.

25. Van Remoortel H, Raste Y, Louvaris Z, et al. Validity of six activity monitors in chronic obstructive pulmonary disease: a comparison with indirect calorimetry. *PloS one.* 2012;7(6):e39198.

26. Pouliot MC, Despres JP, Lemieux S, et al. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. *The American Journal of Cardiology.* 1994;73(7):460-468.

27. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *The European Respiratory Journal.* 2012;40(6):1324-1343.

28. Verhage F. Intelligence and Age in a Dutch Sample. *Human Development.* 1965;8(4):238-245.

29. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of Chronic Diseases.* 1987;40(5):373-383.

30. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. *Chest.* 1988;93(3):580-586.

31. Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. *Journal of Psychosomatic Research.* 1994;38(5):383-392.

32. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. *The European Respiratory Journal.* 2009;34(3):648-654.

33. Smid DE, Franssen FME, Houben-Wilke S, et al. Responsiveness and MCID Estimates for CAT, CCQ, and HADS in Patients With COPD Undergoing Pulmonary Rehabilitation: A Prospective Analysis. *Journal of the American Medical Directors Association.* 2017;18(1):53-58.

34. van der Molen T, Willemse BW, Schokker S, ten Hacken NH, Postma DS, Juniper EF. Development, validity and responsiveness of the Clinical COPD Questionnaire. *Health and Quality of Life Outcomes.* 2003;1:13.

35. Smid DE, Franssen FME, Gonik M, et al. Redefining Cut-Points for High Symptom Burden of the Global Initiative for Chronic Obstructive Lung Disease Classification in 18,577 Patients With Chronic Obstructive Pulmonary Disease. *Journal of the American Medical Directors Association.* 2017;18(12):1097 e1011-1097 e1024.

36. Marshall AL, Smith BJ, Bauman AE, Kaur S. Reliability and validity of a brief physical activity assessment for use by family doctors. *British Journal of Sports Medicine.* 2005;39(5):294-297; discussion 294-297.

37. Depew ZS, Novotny PJ, Benzo RP. How many steps are enough to avoid severe physical inactivity in patients with chronic obstructive pulmonary disease? *Respirology.* 2012;17(6):1026-1027.

38. Tudor-Locke C, Craig CL, Thyfault JP, Spence JC. A step-defined sedentary lifestyle index: <5000 steps/day. *Applied Physiology, Nutrition and Metabolism.* 2013;38(2):100-114.

39. Thorpe O, Johnston K, Kumar S. Barriers and enablers to physical activity participation in patients with COPD: a systematic review. *Journal of Cardiopulmonary Rehabilitation and Prevention.* 2012;32(6):359-369.

40. Singh S. Physical activity and pulmonary rehabilitation - A competing agenda? *Chronic Respiratory Disease.* 2014;11(4):187-189.

41. Langer D, Demeyer H. Interventions to modify physical activity in patients with COPD: where do we go from here? *The European Respiratory Journal.* 2016;48(1):14-17.

42. Cruz J, Brooks D, Marques A. Walk2Bactive: A randomised controlled trial of a physical activity-focused behavioural intervention beyond pulmonary rehabilitation in chronic obstructive pulmonary disease. *Chronic Respiratory Disease.* 2016;13(1):57-66.

43. Demeyer H, Burtin C, Hornikx M, et al. The Minimal Important Difference in Physical Activity in Patients with COPD. *PloS one.* 2016;11(4):e0154587.

44. Fastenau A, Van Schayck O, Winkens B, Gosselink R, Muris J. Effectiveness of a physical exercise training programme COPD in primary care: A randomized controlled trial. *European Respiratory Journal.* 2015;46(suppl 59).

45. Larson JL, Covey MK, Kapella MC, Alex CG, McAuley E. Self-efficacy enhancing intervention increases light physical activity in people with chronic obstructive pulmonary disease. *International Journal of Chronic Obstructive Pulmonary Disease.* 2014;9:1081-1090.

46. Kosteli MC, Heneghan NR, Roskell C, et al. Barriers and enablers of physical activity engagement for patients with COPD in primary care. *International Journal of Chronic Obstructive Pulmonary Disease.* 2017;12:1019-1031.

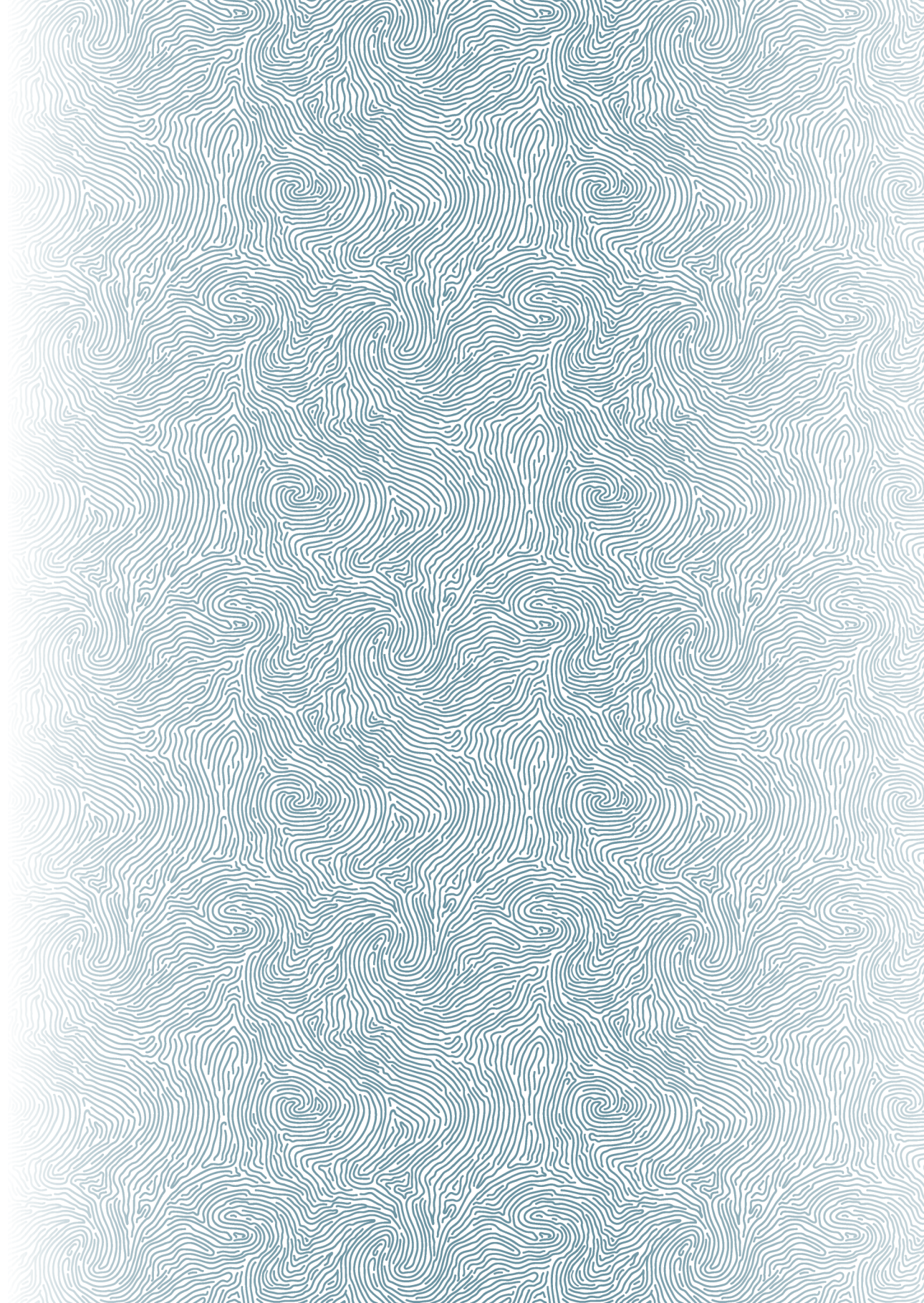
47. Watz H, Waschki B, Kirsten A, et al. The metabolic syndrome in patients with chronic bronchitis and COPD: frequency and associated consequences for systemic inflammation and physical inactivity. *Chest.* 2009;136(4):1039-1046.

48. Monteiro F, Camillo CA, Vitorasso R, et al. Obesity and Physical Activity in the Daily Life of Patients with COPD. *Lung.* 2012;190(4):403-410.

49. Garcia-Aymerich J, Farrero E, Felez MA, et al. Risk factors of readmission to hospital for a COPD exacerbation: a prospective study. *Thorax.* 2003;58(2):100-105.

50. Sherwood NE, Jeffery RW. The behavioral determinants of exercise: implications for physical activity interventions. *Annual Review of Nutrition.* 2000;20:21-44.

51. Agusti A, Bel E, Thomas M, et al. Treatable traits: toward precision medicine of chronic airway diseases. *The European Respiratory Journal.* 2016;47(2):410-419.



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

A.J. van 't Hul
E.H. Koolen
J.C. Antons
M. de Man
R.S. Djamin
J.C.C.M. in 't Veen
S.O. Simons
M.M. van den Heuvel
B. van den Borst
M.A. Spruit

ERJ Open Research. 2020 Nov 2;6(4):00438-2020

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 (OR) 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 (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.

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.

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]	MoveMonitor	<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]

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, and the results were corrected where this was the case. 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%).

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 (figure 2a), the frequencies of the number of TTs present per patient (figure 2b), a scatterplot of CCQ total score against the number of TTs present per patient (figure 2c) and a scatterplot of FEV1%predicted against the number of TTs present per patient (figure 2d). 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). Figure 2 shows the heterogeneity in the number and combinations of the nine TTs.

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%)

Table 2. Continued

Attribute		Patients with a valid registration
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%)

Note: Data are presented as %, n (%), mean±SD.
Abbreviations: FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; GOLD = Global Initiative on Obstructive Lung Disease; Hb = hemoglobin; CCQ = Clinical COPD Questionnaire; BODE: BMI, airflow obstruction, dyspnea, exercise capacity; MRC = Medical Research Council dyspnea scale; BMI = Body Mass Index; BDI = Beck Depression Inventory; CIS-F = Checklist Individual Strength-Fatigue; 6MWD = 6-minute walking distance; PAM = Patient Activation Measure.

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 x 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

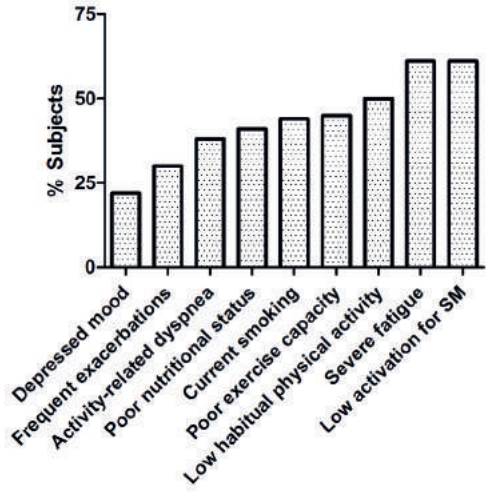


Figure 1. Frequencies of the nine treatable traits.
Abbreviations: SM = self-management

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).

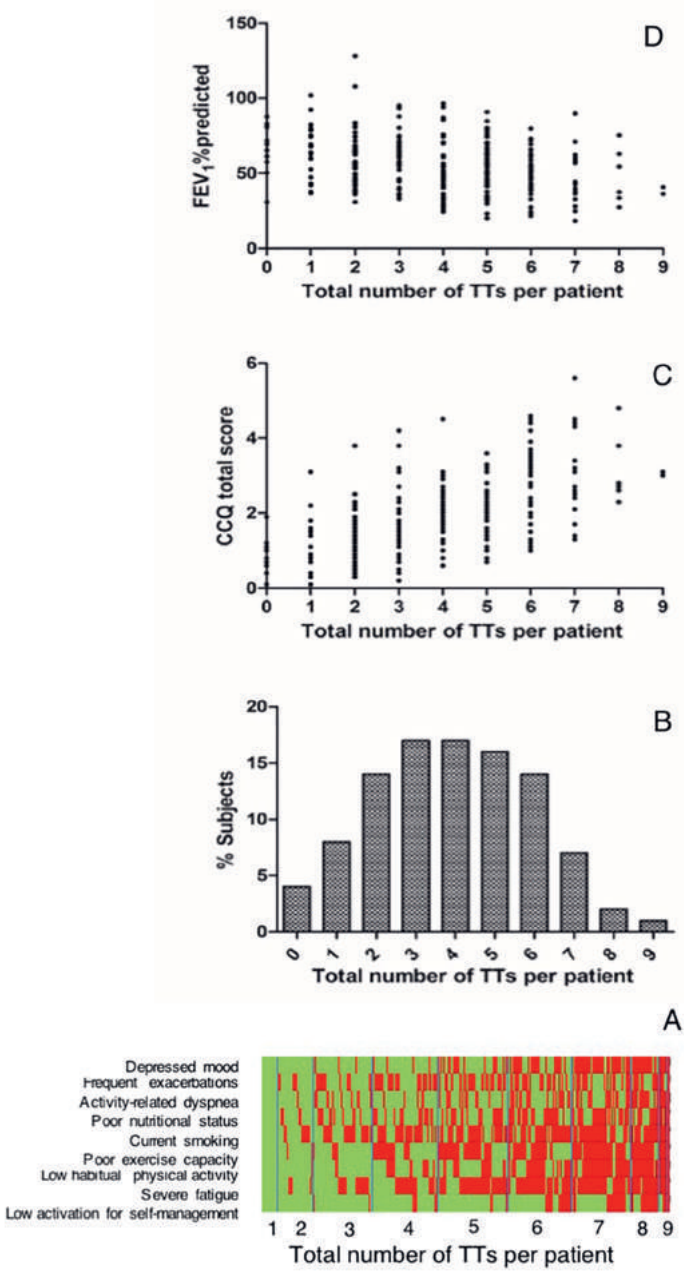


Figure 2. The total number of Treatable traits (TTs).
Note: In panel A the 151 unique combinations of TTs are illustrated in relation to the total number of TTs per patient. Red represents the presence of a particular TT whereas green represents the absence. The blue lines mark the subgroups with a corresponding 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 Clinical CCOPD Questionnaire (CCQ) total score and forced expiratory volume in 1 s (FEV1) % predicted, respectively.
Abbreviations: SM = self-management

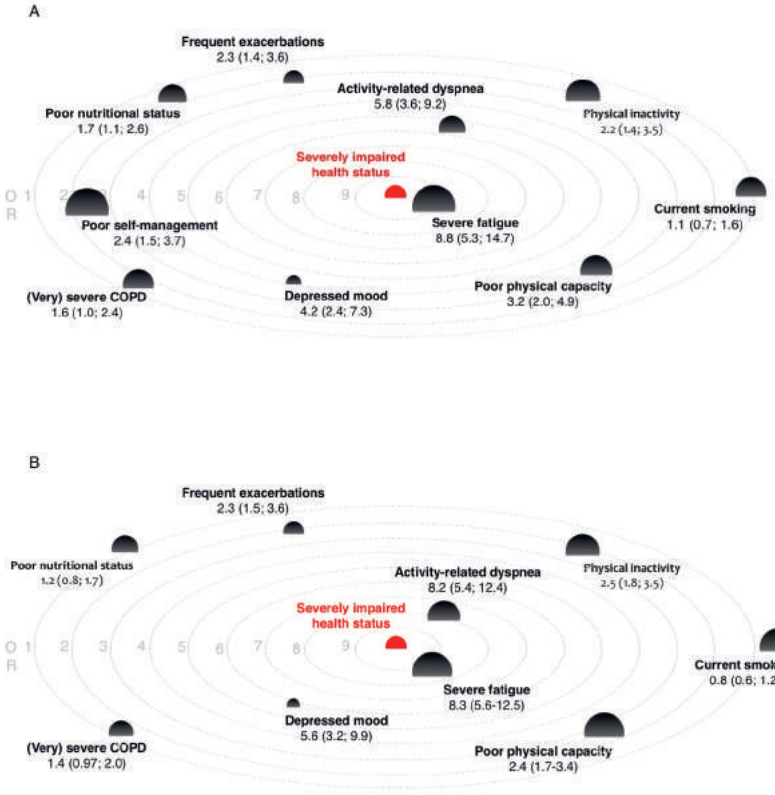


Figure 3a. The COPD sTRAITosphere. A severely impaired health status (Clinical COPD Questionnaire (CCQ) total score >2 points) is at the very center of the sTRAITosphere and each treatable trait (TT) is presented as sphere. The size of the spheres is proportional to the prevalence of the TT and the distance to the center reflects the OR of having a severely impaired health status.
Figure 3b. Validation of the COPD sTRAITosphere.

DISCUSSION

The present study setting out to determine the prevalence of nine TTs 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% had one, 20% had 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.

REFERENCES

1. Rabe KF, Watz H. Chronic obstructive pulmonary disease. *Lancet.* 2017;389(10082):1931-1940.

2. Houben-Wilke S, Augustin IM, Vercoulen JH, et al. COPD stands for complex obstructive pulmonary disease. *European Respiratory Review.* 2018;27(148).

3. Franssen FM, Alter P, Bar N, et al. Personalized medicine for patients with COPD: where are we? *International Journal of Chronic Obstructive Pulmonary Disease.* 2019;14:1465-1484.

4. Agusti A, Bafadhel M, Beasley R, et al. Precision medicine in airway diseases: moving to clinical practice. *European Respiratory Journal.* 2017;50(4).

5. Augustin IML, Spruit MA, Houben-Wilke S, et al. The respiratory physiome: Clustering based on a comprehensive lung function assessment in patients with COPD. *PloS One.* 2018;13(9):e0201593.

6. Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *American Journal of Respiratory Critical Care Medicine.* 2013;188(8):e13-64.

7. ZuWallack R, Hedges H. Primary care of the patient with chronic obstructive pulmonary disease-part 3: pulmonary rehabilitation and comprehensive care for the patient with chronic obstructive pulmonary disease. *American Journal of Medicine.* 2008;121(7 Suppl):S25-32.

8. Watson JS, Adab P, Jordan RE, Enocson A, Greenfield S. Referral of patients with chronic obstructive pulmonary disease to pulmonary rehabilitation: a qualitative study of barriers and enablers for primary healthcare practitioners. *British Journal of General Practice.* 2020.

9. Smid DE, Spruit MA, Houben-Wilke S, et al. Burden of COPD in patients treated in different care settings in the Netherlands. *Respiratory Medicine.* 2016;118:76-83.

10. Franssen FME, Smid DE, Deeg DJH, et al. The physical, mental, and social impact of COPD in a population-based sample: results from the Longitudinal Aging Study Amsterdam. *NPJ Primary Care Respiratory Medicine.* 2018;28(1):30.

11. van Kemenade YW. *Healthcare in Europe 2018*. Munich, EIT Health; 2018.

12. Long Alliantie Nederland (LAN) [Lung Alliance Netherlands]. Zorgstandaard COPD [Care Standard COPD]; 2016. Available from: http:// www.longalliantie.nl/zorgstandaard-copd. Accessed: May, 2020. Dutch.

13. The Global Strategy for the Diagnosis, Management, and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020 Available from: https://goldcopd.org/wp-content/uploads/2019/12/GOLD-2020-FINAL-ver1.2-03Dec19_WMV.pdf. Accessed May, 2020.

14. van den Akker EF, Van't Hul AJ, Birnie E, Chavannes NH, Rutten-van Molken MP, In't Veen JC. Comprehensive Diagnostic Assessment of Health Status of Patients with Asthma or COPD: A Delphi Panel Study among Dutch Experts. *COPD.* 2017;14(2):190-199.

15. van den Akker EF, van 't Hul AJ, Chavannes NH, et al. Development of an integral assessment approach of health status in patients with obstructive airway diseases: the CORONA study. *International Journal of Chronic Obstructive Pulmonary Disease.* 2015;10:2413-2422.

16. Koolen EH, van der Wees PJ, Westert GP, Dekhuijzen R, Heijdra YF, van 't Hul AJ. The COPDnet integrated care model. *International Journal of Chronic Obstructive Pulmonary Disease.* 2018;13:2225-2235.

17. van der Molen T, Willemse BW, Schokker S, ten Hacken NH, Postma DS, Juniper EF. Development, validity and responsiveness of the Clinical COPD Questionnaire. *Health and Quality of Life Outcomes.* 2003;1:13.

18. Tsiligianni IG, van der Molen T, Moraitaki D, et al. Assessing health status in COPD. A head-to-head comparison between the COPD assessment test (CAT) and the clinical COPD questionnaire (CCQ). *BMC Pulmonary Medicine.* 2012;12:20.

19. van Eerd EA, van der Meer RM, van Schayck OC, Kotz D. Smoking cessation for people with chronic obstructive pulmonary disease. *Cochrane Database Systematic Review.* 2016(8):CD010744.

20. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. *Chest.* 1988;93(3):580-586.

21. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Systematic Review.* 2015;2:CD003793.

22. Lenferink A, Brusse-Keizer M, van der Valk PD, et al. Self-management interventions including action plans for exacerbations versus usual care in patients with chronic obstructive pulmonary disease. *Cochrane Database Systematic Review.* 2017;8:CD011682.

23. World Health Organization (WHO). Obesity: preventing and managing the global epidemic. Report of a WHO consultation. Geneva, World Health Organization, 2000.

24. Collins PF, Stratton RJ, Elia M. Nutritional support in chronic obstructive pulmonary disease: a systematic review and meta-analysis. *American Journal of Clinical Nutrition.* 2012;95(6):1385-1395.

25. McDonald VM, Gibson PG, Scott HA, et al. Should we treat obesity in COPD? The effects of diet and resistance exercise training. *Respirology.* 2016;21(5):875-882.

26. Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. *Journal of Psychosomatic Research.* 1994;38(5):383-392.

27. Beck AT, Guth D, Steer RA, Ball R. Screening for major depression disorders in medical inpatients with the Beck Depression Inventory for Primary Care. *Behaviour Research and Therapy.* 1997;35(8):785-791.

28. Pollok J, van Agteren JE, Esterman AJ, Carson-Chahhoud KV. Psychological therapies for the treatment of depression in chronic obstructive pulmonary disease. *Cochrane Database Systematic Review.* 2019;3:CD012347.

29. Koolen EH, van Hees HW, van Lummel RC, et al. "Can do" versus "do do": A Novel Concept to Better Understand Physical Functioning in Patients with Chronic Obstructive Pulmonary Disease. *Journal of Clinical Medicine.* 2019;8(3).

30. Watz H, Pitta F, Rochester CL, et al. An official European Respiratory Society statement on physical activity in COPD. *European Respiratory Journal.* 2014;44(6):1521-1537.

31. Rademakers J, Nijman J, van der Hoek L, Heijmans M, Rijken M. Measuring patient activation in The Netherlands: translation and validation of the American short form Patient Activation Measure (PAM13). *BMC Public Health.* 2012;12:577.

32. Turner A, Anderson JK, Wallace LM, Bourne C. An evaluation of a self-management program for patients with long-term conditions. *Patient Education and Counseling.* 2015;98(2):213-219.

33. Divo M, Cote C, de Torres JP, et al. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory Critical Care Medicine.* 2012;186(2):155-161.

34. Agusti A. Simple versus complex COPD: implications for health-care management. *Lancet Respiratory Medicine.* 2016;4(2):e6-7.

35. Ragaišienė G, Kibarskytė R, Gauronskaitė R, et al. Diagnosing COPD in primary care: what has real life practice got to do with guidelines? *Multidisciplinary Respiratory Medicine.* 2019;14(1):28.

36. Graham BL, Steenbruggen I, Miller MR, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. *American Journal of Respiratory Critical Care Medicine.* 2019;200(8):e70-e88.

37. Burgos F, Disdier C, de Santamaria EL, et al. Telemedicine enhances quality of forced spirometry in primary care. *European Respiratory Journal.* 2012;39(6):1313-1318.

38. Smid DE, Franssen FM, Houben-Wilke S, et al. Responsiveness and MCID Estimates for CAT, CCQ, and HADS in Patients With COPD Undergoing Pulmonary Rehabilitation: A Prospective Analysis. *Journal of the American Medical Directors Association.* 2017;18(1):53-58.

39. McDonald VM, Higgins I, Wood LG, Gibson PG. Multidimensional assessment and tailored interventions for COPD: respiratory utopia or common sense? *Thorax.* 2013;68(7):691-694.

40. McDonald VM, Clark, V.L., Cordova-Rivera, L., Wark, P.A.B., Baines, K.J., Gibson, P.G. Targeting treatable traits in severe asthma: a randomised controlled trial. *European Respiratory Journal.* 2020;55.

41. Spruit MA, Van't Hul A, Vreeken HL, et al. Profiling of Patients with COPD for Adequate Referral to Exercise-Based Care: The Dutch Model. *Sports Medicine.* 2020;50(8):1421-1429.

42. Vestbo J, Anderson W, Coxson HO, et al. Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE). *European Respiratory Journal.* 2008;31(4):869-873.

43. Niewoehner DE. TORCH and UPLIFT: what has been learned from the COPD "mega-trials"? *COPD.* 2009;6(1):1-3.

44. Herland K, Akselsen JP, Skjonsberg OH, Bjermer L. How representative are clinical study patients with asthma or COPD for a larger "real life" population of patients with obstructive lung disease? *Respiratory Medicine.* 2005;99(1):11-19.

45. Agusti A, Bel E, Thomas M, et al. Treatable traits: toward precision medicine of chronic airway diseases. *European Respiratory Journal.* 2016;47(2):410-419.

46. Peters JB, Heijdra YF, Daudey L, et al. Course of normal and abnormal fatigue in patients with Chronic Obstructive Pulmonary Disease, and its relationship with domains of health status. *Patient Education and Counseling.* 2011;85(2):281-285.

SUPPLEMENTAL 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 treatable traits (TTs)

	Smoking	MRC	Exacer-bations	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-F						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									

Note: *=p < 0.05
Abbreviations: MRC = Medical Research Council dyspnea scale; BMI = Body Mass Index; BDI = Beck Depression Inventory; CIS-F = 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%)

Table E2. Continued

Attribute		Patients with a valid registration
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	

Note: Data are presented as %, n (%), mean±SD.
Abbreviations: FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; GOLD = Global Initiative on Obstructive Lung Disease; Hb = hemoglobin; CCQ = Clinical COPD Questionnaire; BODE: BMI, airflow obstruction, dyspnea, exercise capacity; MRC = Medical Research Council dyspnea scale; BMI = Body Mass Index; BDI = Beck Depression Inventory; CIS-F = Checklist Individual Strength-Fatigue; 6MWD = 6-minute walking distance; PAM = Patient Activation Measure.

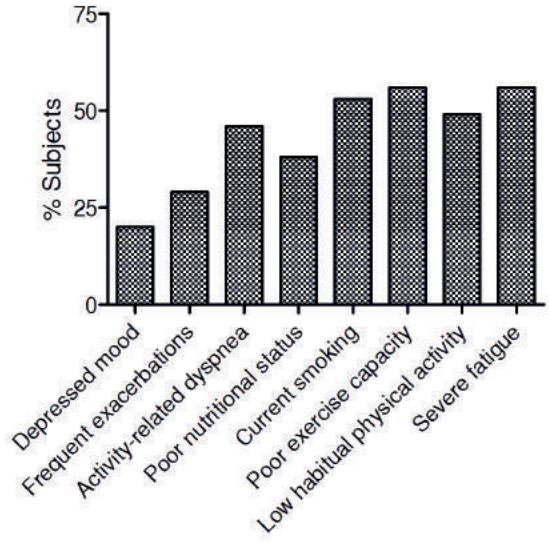


Figure E1. Prevalence of the eight treatable traits (TTs) from the validation sample.

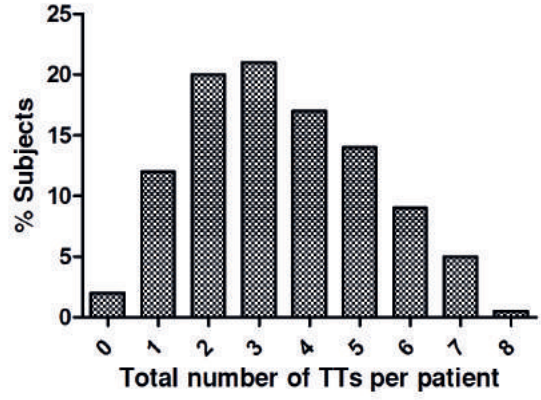


Figure E2. Frequencies of the total number of treatable traits (TTs) per patients from the validation sample.

REFERENCES

1. van den Akker EF, van 't Hul AJ, Chavannes NH, et al. Development of an integral assessment approach of health status in patients with obstructive airway diseases: the CORONA study. *International Journal of Chronic Obstructive Pulmonary Disease.* 2015;10:2413-2422.

2. Koolen EH, van der Wees PJ, Westert GP, Dekhuijzen R, Heijdra YF, van 't Hul AJ. The COPDnet integrated care model. *International Journal of Chronic Obstructive Pulmonary Disease.* 2018;13:2225-2235.

3. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *European Respiratory Journal.* 2012;40(6):1324-1343.

4. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *European Respiratory Journal.* 2005;26(5):948-968.

5. Dar K, Williams T, Aitken R, Woods KL, Fletcher S. Arterial versus capillary sampling for analysing blood gas pressures. *BMJ.* 1995;310(6971):24-25.

6. The Global Strategy for the Diagnosis, Management, and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020 Available from: https://goldcopd.org/wp-content/uploads/2019/12/GOLD-2020-FINAL-ver1.2-03Dec19_WMV.pdf. Accessed May, 2020.

7. Koolen EH, van Hees HW, van Lummel RC, et al. "Can do" versus "do do": A Novel Concept to Better Understand Physical Functioning in Patients with Chronic Obstructive Pulmonary Disease. *Journal of Clinical Medicine.* 2019;8(3).

8. van der Molen T, Willemse BW, Schokker S, ten Hacken NH, Postma DS, Juniper EF. Development, validity and responsiveness of the Clinical COPD Questionnaire. *Health and Quality of Life Outcomes.* 2003;1:13.

9. Smid DE, Franssen FME, Gonik M, et al. Redefining Cut-Points for High Symptom Burden of the Global Initiative for Chronic Obstructive Lung Disease Classification in 18,577 Patients With Chronic Obstructive Pulmonary Disease. *Journal of the American Medical Directors Association.* 2017;18(12):1097 e1011-1097 e1024.

10. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med.* 2004;350(10):1005-1012.

11. Puhan MA, Garcia-Aymerich J, Frey M, et al. Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated BODE index and the ADO index. *Lancet.* 2009;374(9691):704-711.

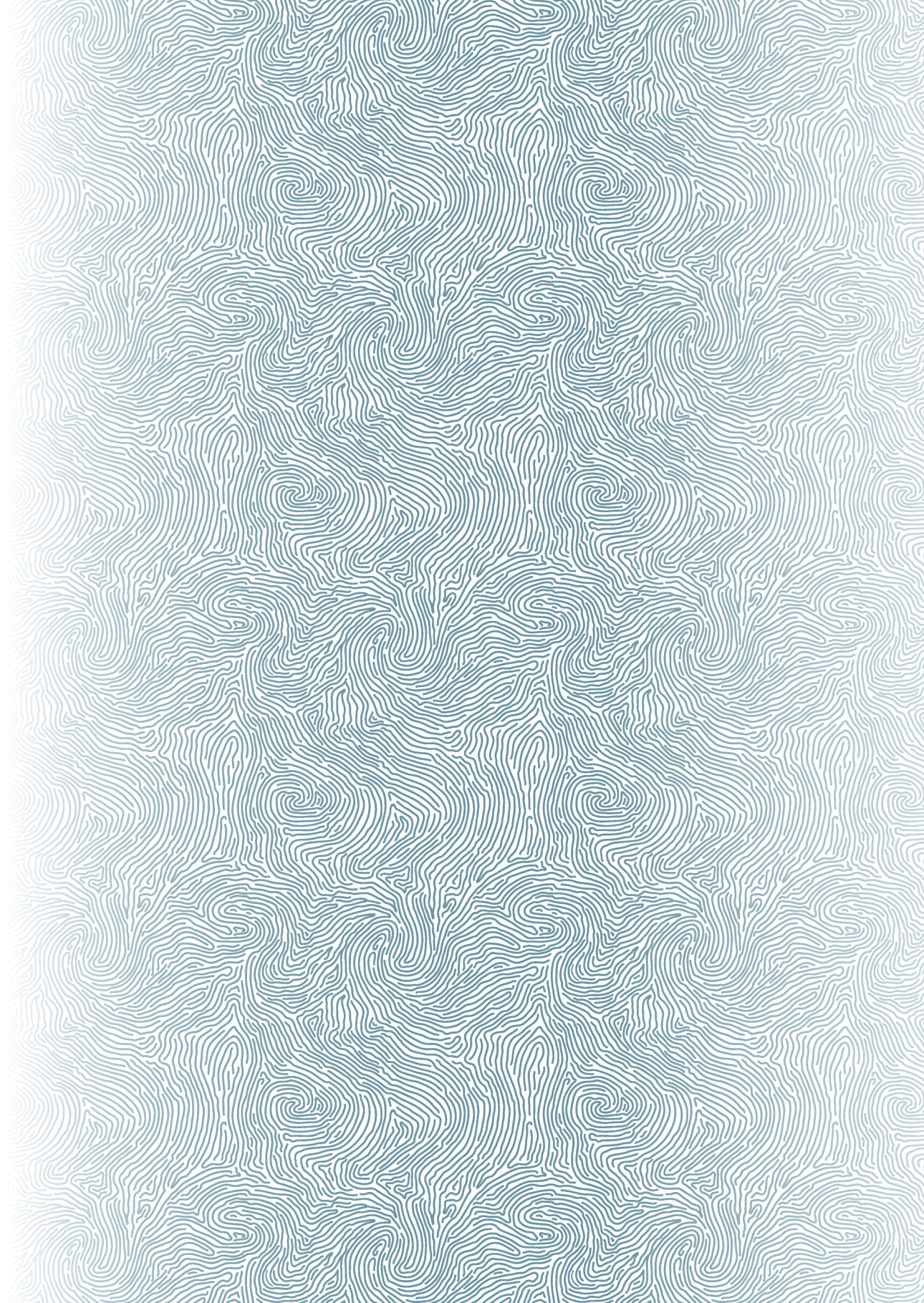
12. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. *Chest.* 1988;93(3):580-586.

13. World Health Organization (WHO). Obesity: preventing and managing the global epidemic. Report of a WHO consultation. Geneva, World Health Organization, 2000.

14. Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. *Journal of Psychosomatic Research.* 1994;38(5):383-392.

15. Beck AT, Guth D, Steer RA, Ball R. Screening for major depression disorders in medical inpatients with the Beck Depression Inventory for Primary Care. *Behaviour Research and Therapy.* 1997;35(8):785-791.

16. Rademakers J, Nijman J, van der Hoek L, Heijmans M, Rijken M. Measuring patient activation in The Netherlands: translation and validation of the American short form Patient Activation Measure (PAM13). *BMC Public Health.* 2012;12:577.



Effectiveness of home-based occupational therapy on COPM performance and satisfaction scores in patients with COPD

E.H. Koolen
M.A. Spruit
M. de Man
J.C. Antons
E. Nijhuis
N. Nakken
D.J.A. Janssen
A.J. van 't Hul

Canadian Journal of Occupational Therapy. 2020 Dec 23;8417420971124

ABSTRACT

BACKGROUND

Occupational therapy (OT) may be an important intervention in patients with COPD, but studies show conflicting results.

PURPOSE

To evaluate the effectiveness of home-based monodisciplinary OT in COPD patients

METHOD

We conducted an observational clinical study. Main outcomes were the mean differences in the Canadian Occupational Performance Measure (COPM) performance and satisfaction scores, pre-and post-intervention.

FINDINGS

Pre- and postintervention data were obtained from 41 patients. Statistically significant increases were observed in COPM performance (5.0±1.1 versus 6.9±0.9; $P<0.001$) and satisfaction (4.6±1.3 versus 6.9±1.0; $P<0.001$). The most frequently reported occupational performance problems were found in the domains of productivity (47%) and mobility (40%), fewer in self-care (10%) and the least in leisure (3%).

IMPLICATIONS

Home-based monodisciplinary OT can contribute significantly to the improvement of daily functioning of patients with COPD. OT should therefore be considered more often as part of the integrated management of these patients.

INTRODUCTION

Patients with chronic obstructive pulmonary disease (COPD) experience daily symptoms such as dyspnoea and fatigue, which may seriously hinder the performance of activities of daily living (ADLs).[1,2] The way these daily symptoms hamper engagement in meaningful occupations in patients with COPD may, at least in part, be due to the use of a relatively high proportion of peak oxygen uptake compared to healthy peers.[3] Therefore, occupational performance may be improved either by increasing patients' physical capacity, or by reducing the load of the ADLs, or by a combination thereof. Previously, it has been shown that lower-limb exercise training increases patients' physical capacity and performance and satisfaction scores for domestic function.[4] Furthermore, a systematic review and meta-analysis has shown that upper limb training, consisting of endurance and strength training, could significantly reduce dyspnoea in patients with chronic obstructive pulmonary disease.[5] Recently, following an interdisciplinary pulmonary rehabilitation program, including exercise training and occupational therapy (OT), patients were also found to use a significantly lower proportion of their peak aerobic capacity and ventilation to perform ADLs, which was accompanied by less dyspnea and fatigue.[6]

OT aims to support participation in daily life by increasing self-management, enabling the patient to engage in social roles that are meaningful to him/her, and to optimise activities in the domains of self-care, mobility, leisure, and productivity.[7] In patients with COPD, OT may focus on patient education, breathing coordination retraining and energy conservation techniques (ECTs) to reduce dyspnoea and/or fatigue.[8] OT addresses the hampered performance of meaningful occupations, experienced by patients with COPD, directly. In current clinical practice, however, occupational therapists are recommended merely as facultative members of pulmonary rehabilitation teams[9], and only about 30% of the pulmonary rehabilitation programs include OT.[10] There is some evidence that supports the added value of OT in patients with COPD. A single session of applying ECTs, which is one of the active ingredients of OT, has been shown to reduce the metabolic and symptom burden of domestic ADLs in a laboratory environment.[11,12] Several multidisciplinary pulmonary rehabilitation programs, which include OT, have resulted in statistically significant and clinically relevant improvements in problematic ADLs.[13,14] Clinical evidence for the contribution of OT, provided complementary to exercise training, to a decrease in dyspnoea and fatigue was found in a randomized controlled trial.[15] Furthermore, in a prospective, non-randomized parallel-group trial, OT, added to a multi-facetted pulmonary rehabilitation program, was found to result in an extra improvement in basic ADLs, compared to patients who did not receive OT.[16] Studies on the effects of monodisciplinary OT have conflicting results. A qualitative study found an improved perception of taking control of the disease and re-engagement in meaningful

occupations following an OT intervention.[8] Then again, a randomised controlled trial, comparing the effects of OT to usual care, did not show any improvement of occupational performance or satisfaction.[17] Therefore, the aim of the present study was to evaluate the effectiveness of home-based monodisciplinary OT in patients with COPD.

METHODS

Participants

Participants were patients with COPD, referred to a COPD-specialised occupational therapist in a primary care setting. Prior these patients completed a comprehensive diagnostic trajectory by a pulmonologist and specialized respiratory nurse, in the outpatient respiratory department of Bernhoven Hospital, Uden, The Netherlands, between February 2016 and January 2019.[18] The human-related research committee in the Nijmegen-Arnhem region approved the study and considered that it did not fall within the remit of the Medical Research Involving Human Subjects Act (WMO). Because the participants received usual care, obtaining written informed consent was deemed redundant for this study (ref: 2017-3597). Subsequently, the local Research Ethics Committee of Bernhoven Hospital approved the conductance of this study in their institution.

Study design

We conducted an observational clinical study into the effectiveness of home-based monodisciplinary OT in patients with COPD. The mean difference in pre- to post-intervention measurements of performance of problematic meaningful occupations and satisfaction with the performance, as measured with the Canadian Occupational Performance Measure (COPM), were the primary outcomes.[19]

Intervention

The COPDnet model

The OT content in this study is part of a recently developed comprehensive care model for patients with COPD: the COPDnet model.[18] This pragmatic integrated care model has been developed specifically for patients with COPD referred to a secondary care setting because of a persistent burden of disease, despite optimal management in primary care. Briefly, this model includes a comprehensive diagnostic and self-management activation trajectory in the outpatient pulmonary department, and sets out to identify relevant treatable traits.[20] The outcome results in an individual care plan, based on shared-goal setting and decision-making.[21] Referrals to further treatment depend on the extent of the individual burden of disease, the number and complexity of treatable traits, and patient's preferences. Subsequently, patients may be referred

for non-pharmacological interventions to an allied healthcare professional in a primary care setting, or be referred to a multidisciplinary pulmonary rehabilitation team. For allied healthcare professionals in primary care, i.e., for dieticians, physiotherapists and/or occupational therapists, specific evidence-based intervention modules were designed. The feasibility and added value of the full COPDnet model is currently under investigation.[22]

Occupational therapy

Monodisciplinary home-based OT is offered to patients, on the basis of the outcome of the COPDnet diagnostic trajectory, when breathlessness and/or fatigue have a negative effect on the performance of ADLs.[18] Patients solely received home-based OT and no other components of pulmonary rehabilitation. OT is provided with an individualized, patient-centred approach and emphasizes the enablement of optimal participation in everyday ADLs. Furthermore, OT was structured according to the Canadian Process Practice Framework (CPPF), containing eight steps.[23] These steps comprise: (1) (re) assessing the indication for OT (enter/initiate); (2) consultation on the content of the collaboration (set the stage); (3) problem analysis (assess/evaluate); (4) drawing up the plan of approach (agree on objectives and plan); (5) implement the plan of approach (implement the plan); (6) evaluate and, if necessary, adjust plan of action (monitor and modify); (7) evaluate the treatment outcomes (evaluate/outcome); and (8) termination of treatment (conclusion/exit). Based on the problem analysis (step 3) and the personal aims of the OT derived from the COPM, an individually tailored home-based intervention is offered which may differ in number and content of intervention components. OT intervention components may include: 1. Teaching and apply breathing techniques, that is, pursed-lip breathing, active expiration and the use of the 'blow as you go' principle, the use of paced-breathing during cyclic activities such as walking and stairclimbing, and the application of dyspnoea relieving positioning[24,25]; 2. The application of ECTs, including, a) using activity planning, adapting activities, that is, adjusting speed and/or intensity of activities (pacing activities) to the ventilatory capacity, b) deliberately interrupting activities (break-down of activities), c) prioritizing activities, d) optimizing day structure, and, e) creating balance in activities and resting; 3. Adapting the environment, such as making use of alternative equipment, or assistive devices, such as a walking aid, listening to music; 4. Coping with stress and time pressure while performing (problematic) meaningful occupations and 5. Patient education on the symptoms of breathlessness and fatigue.[26] OT was provided typically as a weekly one-hour session at the patients' home by a COPD-specialized occupational therapist with a maximum of 10 sessions (as 10 sessions are reimbursed from basic health care insurance in the Netherlands) in a two to four months period. This was typically six to eight sessions of one hour each per patient. These therapists had completed a general four-day course on OT in patients with COPD, and had received two additional four-hour training sessions in providing care according to the COPDnet model.[18]

Patient characteristics

The following patient characteristics were systematically registered by the pulmonologist and/or respiratory nurse in the Electronic Health Records: gender (female/male), age (in years), body mass index (BMI in kg/m^2), Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification (I-IV; A-D)[27], pulmonary function (spirometry and flow-volume curve, using the Global Lung Initiative (GLI) equations)[28], smoking status (current/former-never), partner (yes/no), employment status (yes/no), and the number of COPD exacerbations in the last 12 months. At baseline the following health status questionnaires were used. First of all, the COPD Clinical Questionnaire (CCQ) was completed, which is used as a measurement of overall health status (score range: 0-6).[29,30] The CCQ permits categorizing overall health status into mild (CCQ<1.0), moderate (CCQ 1-2), severe (CCQ 2-3, and very severe (CCQ>3) impairment.[29] Secondly, the Marshall questionnaire was registered as a measurement of self-reported level of physical activity in which a higher score indicates a higher level of self-reported physical activity (score range: 0-8).[31] And, last, the modified Medical Research Council (mMRC) dyspnea scale was used. This instrument evaluates the degree of activity-related breathlessness in which a higher score indicates a higher impact of dyspnea during activities (score range: 0-4).[32]

Outcome measurements

Primary and secondary outcomes were measured during the first session of the OT intervention and at completion, that is, the last session of the OT intervention.

Primary outcome

Canadian Occupational Performance Measure

The COPM is a semi-structured interview to identify and evaluate self-perceived problems in occupational performance areas.[19] During the interview, patients are invited to identify any occupations that they would like, or need, to do but finding it difficult to complete because of their respiratory condition. Patients then identify their five most important occupations and rate, first, their current level of performance and, second, their level of satisfaction with this current level of performance. Performance and satisfaction are rated per occupational performance problem on an ordinal scale ranging from 1-10 points, with higher scores indicating better performance and satisfaction. Reproducibility of the COPM has been shown in patients with COPD[33], and a change of two points has been revealed as the threshold for a clinically meaningful change.[34]

Secondary outcomes

Chronic Respiratory disease Questionnaire

The dyspnea dimension of the Chronic Respiratory disease Questionnaire (CRQ-Dyspnea) is used to measure perceived dyspnoea on a 7-point Likert-scale in the problem areas corresponding with the COPM occupations.[35] Higher scores indicate less breathlessness. A change of 0.5 points indicates a clinically meaningful change.[36]

Goal attainment scaling

Goal attainment scaling (GAS) is increasingly recognized as a validated method to evaluate personal treatment goals in healthcare.[37] Attainment scoring is done for each treatment goal by asking the patient on a 6-point scale to which degree their goal has been achieved: not at all (1), barely (2), somewhat (3), partially (4), largely (5) or completely (6). A treatment goal is considered achieved if the score is 5 or 6, a goal with a score of 3-4 is regarded as partially achieved.[38] GAS has good psychometric characteristics and is considered robust enough for use in practice.[39]

Power calculation

A power calculation using G-power version 3.1 applying an a priori paired t-test and assuming a significance of 0.05 and a power of 0.8, revealed that 15 patients would have to be included to detect a large effect size (0.8), 34 patients to detect a moderate effect size (0.5), and 199 patients to detect a small effect size (0.2).

Statistical analysis

Descriptive statistics, including means, standard deviation (SD), and frequencies, were used to summarize the collected data. Data were tested for normality. To evaluate differences in baseline characteristics between patients with and without follow-up measurement an independent sample t-test was applied, as appropriate. To assess the effectiveness of the OT intervention on primary and secondary outcome measures, a two-tailed paired sample t-test was used, to evaluate any differences between pre- and post- intervention values, as appropriate. Effect sizes were calculated based on the main outcome by taking the mean difference score between pre and post COPM measurements divided by the baseline standard deviation of the COPM scores. All patient-reported occupational performance problems measured with the COPM were classified into one of the four domains: Self-care, mobility, productivity and leisure, as previously defined by Annegarn et al.[1] Mobility-related occupational performance problems are usually part of the 'self-care' COPM domain.[34] However, mobility related occupational problems in COPD patients were expected to be highly prevalent.[1] The classification was carried out by two researchers (EK and AvtH) independently of each other. The two authors discussed their differences until agreement was reached. Finally, concurrent validity of the COPM scores for performance and satisfaction were evaluated

by calculation of Pearson's correlation coefficients with the CCQ total score, and, by conducting a one-way ANOVA to compare the baseline mean COPM scores between the four levels of health status impairment measured with the CCQ (mild/moderate/severe/very severe), including post-hoc analysis as appropriate. A priori, a two-sided level of significance was set at $P<0.05$. Statistical analyses were done using IBM SPSS 25 for Windows.

RESULTS

Patient characteristics

In the study period, a total of 84 COPD patients were referred to OT, of which 41 patients completed both baseline and follow-up measurements and therefore were available for analyses, see figure 1. No statistically significant differences were seen in baseline characteristics between the 41 patients with follow-up, and the 43 patients without follow-up measurements regarding age (63±7.3 versus 64±11.3; $p = 0.671$), FEV1 % pred. (50.5±16.6 versus 49.4±14.0; $p = 0.764$) and total score of the CCQ (2.1±0.9 versus 2.0±1.1; $p = 0.327$). Baseline characteristics of the 41 patients with follow-up measurements are shown in Table 1. These 41 patients reported a total of 156 occupational performance problems. Thirty-eight patients (93%) reported at least three problematic occupations. The majority of the baseline reported problematic occupations were found in the domains of productivity (47%) and mobility (40%), fewer in self-care (10%) and the least in leisure (3%). Table 2 presents the ten most reported baseline problematic occupations. Within these ten most reported occupations, six of the activities were in the domain of productivity, three in mobility, only one in self-care and none in leisure.

Baseline COPM scores for performance and satisfaction significantly correlated with the CCQ total score (r=-0.31, $p<0.05$ and r=-0.44, $p<0.01$). By contrast, no significant correlations were found between COPM scores and pulmonary function (FEV_1 % pred.). With an increase in the CCQ functional impairment level, statistically significantly lower COPM scores were found for satisfaction ($p<0.01$). See figure 2. A Bonferroni post-hoc test revealed that COPM scores for satisfaction were statistically significantly lower for the 'severe' ($p<0.05$) and 'very severe' ($p<0.05$) CCQ functional impairment levels compared to the 'mild' level.

Primary outcome

Statistically significant differences were found between pre- and post-OT intervention performance (5.0±1.1 versus 6.9±0.9; $p<0.001$) and satisfaction scores (4.6±1.3 versus 6.9±1.0; $p<0.001$). Figure 3 presents eight scatterplots of the individual pre- and post-

OT intervention performance and satisfaction COPM scores per domain. Figure 4 shows four vector diagrams of the individual pre-OT performance and satisfaction COPM scores combined with the individual post-OT performance and satisfaction COPM scores per domain. Effect sizes for COPM performance and satisfaction were 1.7 and 1.8, respectively, reflecting a large effect.[40]

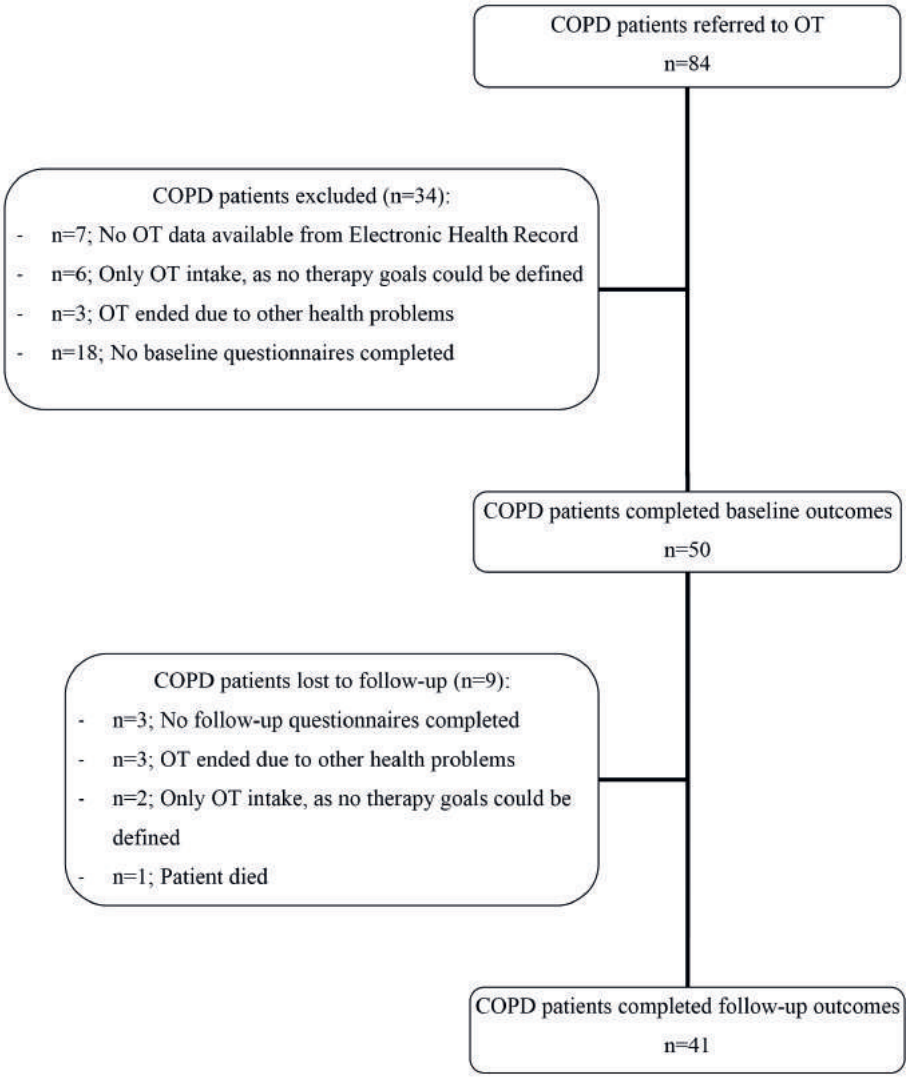


Figure 1. Flow chart study
Abbreviations: COPD = Chronic Obstructive Pulmonary Disease; OT = Occupational Therapy

Secondary outcomes

The scores on the CRQ dyspnoea dimension (n=38) revealed also a significant difference between pre- and post-intervention measurements (3.6±0.9 versus 5.1±0.8 points; p<0.001). A clinically meaningful improvement in CRQ dyspnoea dimension was

Table 1. Patient characteristics

	Patients (n=41)
Female, n (%)	24 (59)
Age (years), mean (SD)	63 (7.2)
BMI (kg/m2), mean (SD)	24.9 (4.3)
GOLD I/II/III/IV, n (%)	1 (2)/19 (46)/18 (44)/3 (7)
GOLD A/B/C/D, n (%) †	1 (3)/11 (29)/1 (3)/25 (66)
FEV1 (% predicted), mean (SD)	50.1 (16.4)
FVC (% predicted), mean (SD)	93.2 (17.3)
Current smokers, n (%)	9 (22)
Having a partner, n (%)	32 (78)
Employed, n (%)	14 (34)
Exacerbations, n (%) †	
- No exacerbation in previous year	15 (40)
- 1 exacerbation in previous year	8 (21)
- ≥ 2 exacerbations in previous year and/or 1 hospitalization	15 (40)
CCQ total, n (%) †	
- < 1 point	2 (5)
- 1-2 points	17 (45)
- 2-3 points	14 (37)
- > 3 points	5 (13)
Marshall questionnaire, n (%) †	
- < 4 points	23 (61)
- ≥ 4 points	15 (40)
mMRC, n (%) †	
- 0	8 (21)
- 1	16 (42)
- 2	10 (26)
- 3	4 (11)
- 4	0

† *n* = 38

Abbreviations: BMI = Body Mass Index; GOLD = Global Initiative for Chronic Obstructive Lung Disease; FEV1% pred. = Forced Expiratory Volume in one second percentage predicted; FVC% pred. = Forced Vital Capacity percentage predicted; CCQ = COPD Clinical Questionnaire; mMRC = modified Medical Research Council

observed in 84% (n=32) of the COPD patients. Furthermore, the GAS scores (n=29) resulted in the following percentages: The patient's treatment goal was 'somewhat' achieved in 3% (n=1) of the patients, 'partially' achieved in 34% (n=10) of the patients, in 21% (n=6) 'largely' and in 41% (n=12) 'completely' achieved.

Table 2. Top 10 reported problematic baseline occupations

	All patients (n=41)				
	Activity	**%**	**P (SD)**	**S (SD)**	**Domain**
1	Stair climbing	88	5.1 (1.4)	4.4 (1.8)	Mobility
2	Walking	44	5.1 (1.6)	4.9 (1.8)	Mobility
3	Vacuuming	27	5.6 (1.7)	5.5 (2.1)	Productivity
4	Cycling	24	5.4 (2.0)	4.2 (1.6)	Mobility
5	Showering	20	5.4 (1.3)	5.5 (1.4)	Self-care
6	Bed making	15	4.7 (1.4)	4.2 (1.5)	Productivity
6	Gardening	15	4.7 (2.1)	4.3 (2.6)	Productivity
6	Lifting	15	4.8 (1.0)	4.2 (1.6)	Productivity
9	Grocery shopping	12	4.6 (2.3)	5.0 (2.3)	Productivity
10	Window washing	10	5.3 (0.5)	6.3 (1.3)	Productivity

Abbreviations: P = mean performance score (points); S = mean satisfaction score (points); SD = Standard Deviation

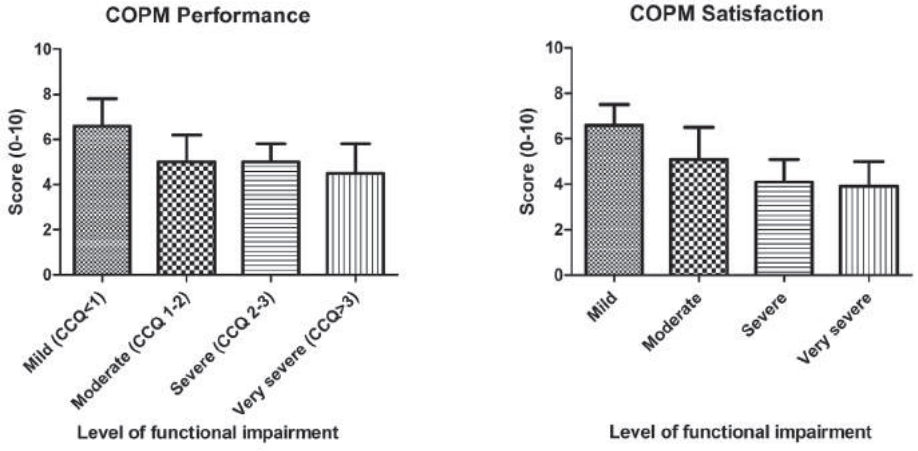


Figure 2. COPM scores for performance and satisfaction in function stratified for level of functional impairment as determined with the CCQ total score.
Abbreviations: COPM = Canadian Occupational Performance Measure; CCQ=Clinical COPD Questionnaire; mild (CCQ<1.0); moderate (CCQ 1-2); severe (CCQ 2-3), and very severe (CCQ>3) impairment

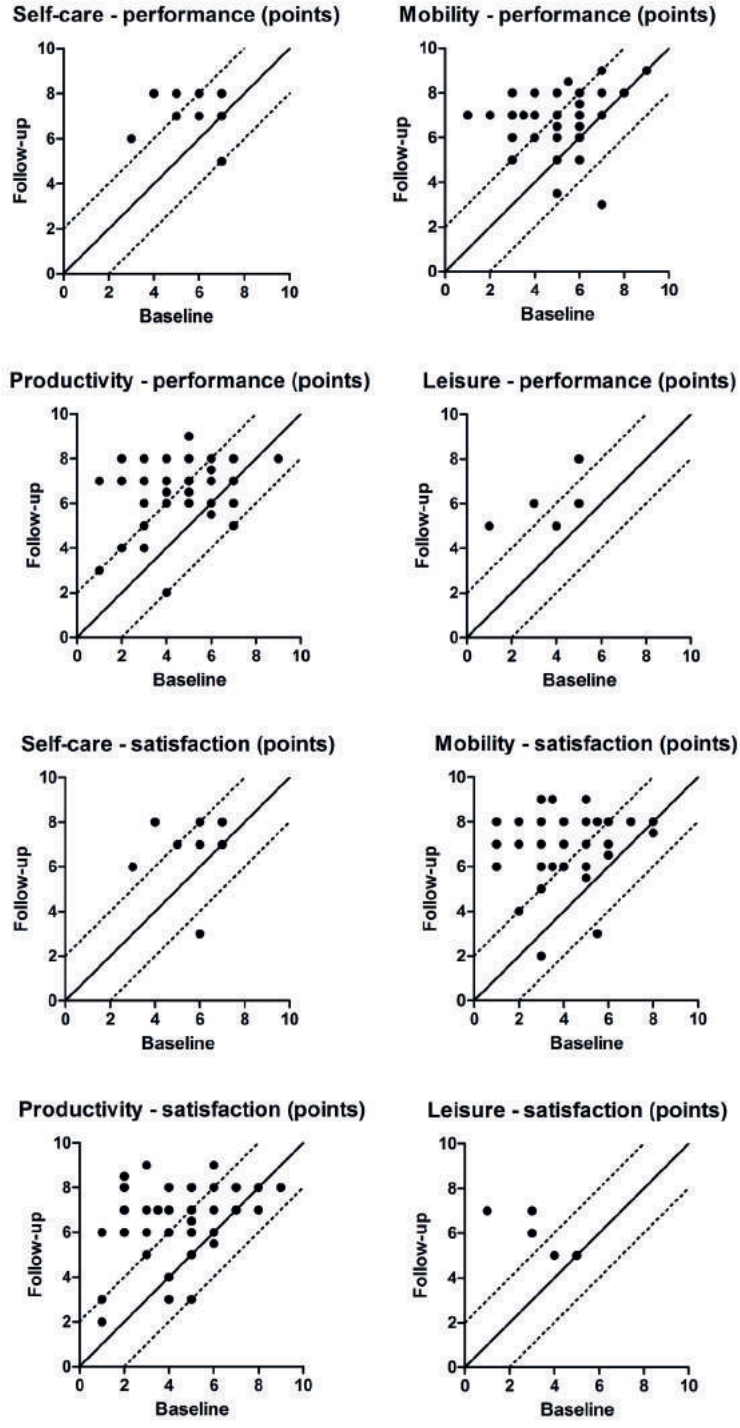


Figure 3. Scatterplots primary outcome per domain

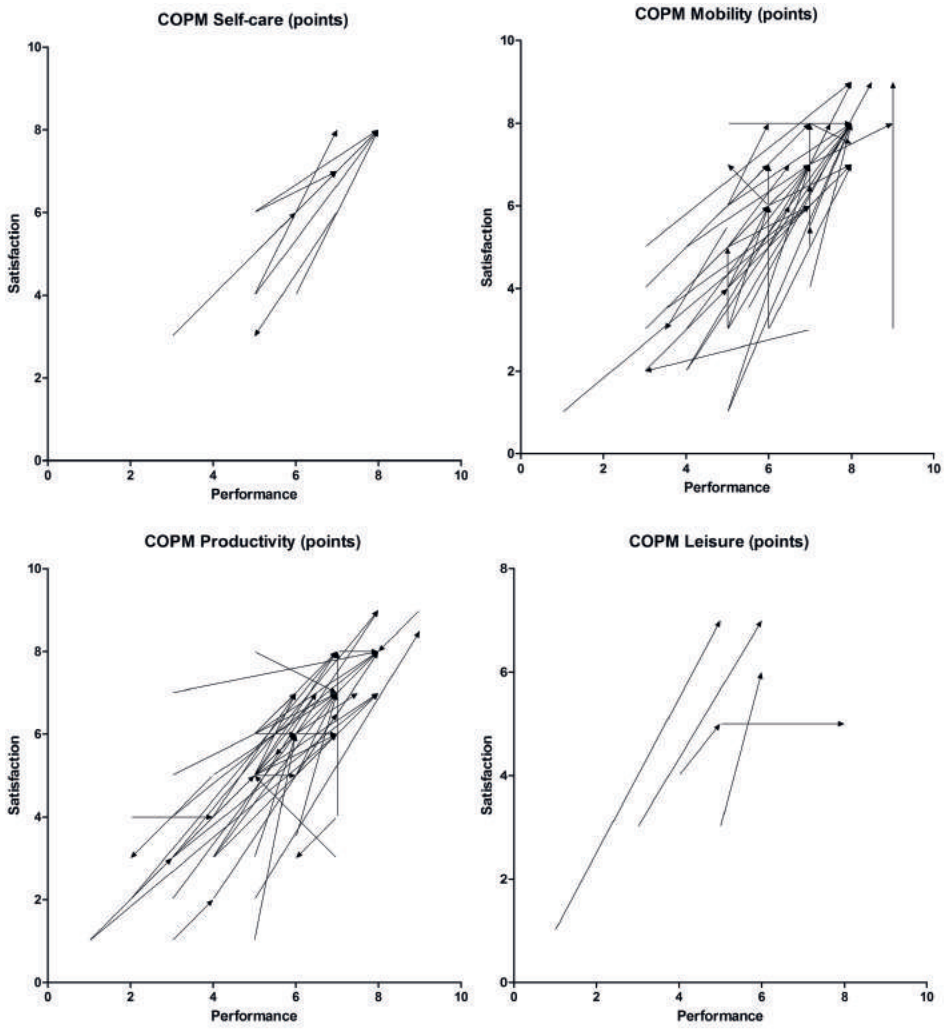


Figure 4. Vector diagrams of the COPM performance and satisfaction scores per domain

DISCUSSION

In this study, evidence in support of the effectiveness of home-based monodisciplinary OT in patients with moderate to severe COPD was found. Statistically significantly higher scores for self-perceived performance of, and satisfaction with, meaningful occupations were observed after the OT intervention. The improvements in satisfaction exceeded the minimal clinically important difference using a robust cut-off value of two points on the COPM, while the performance score approached this value very closely. Shortness of breath during meaningful occupations measured with the CRQ dyspnoea dimension decreased statistically significantly and even exceeded the threshold of clinical relevance three times. Most patients reported that the goals, set at the start of the OT intervention, were largely or completely achieved despite the large amount of, and heterogeneity in, problematic occupations found in the participating patients.

Clinical effectiveness of OT in COPD

There is little research, so far, on the effects of monodisciplinary home-based OT in patients with COPD. In the majority of studies in patients with COPD, OT was provided as part of a multidisciplinary pulmonary rehabilitation programme, which precludes any definitive conclusion as to the effect of the OT component itself.[13-16] Knowledge about the effects of monodisciplinary OT in patients with COPD only comes, to the best of the authors' knowledge, from the study by Unni Martinsen and colleagues.[17] This apparent paucity on evidence of the added value of monodisciplinary OT in patients with COPD was an important incentive for us to initiate this study. Martinsen and colleagues performed a randomised controlled trial into the effects of OT in patients with COPD but failed to show any improvement in occupational performance or satisfaction compared to usual care.[17] Although the active ingredient of the OT closely mirrors both our study and Martinsen's, that is, training ECTs, a remarkable difference is found in the total number of treatment sessions. Where Martinsen applied a median of only two treatment sessions, in the present study this was typically six to eight sessions of one hour each. We believe that it is likely that this three to four-fold larger number of therapeutic sessions can be held, at least partially, responsible for the difference in outcome. Effects of OT rely on behavioural adaptation and perpetuating new behaviour does take time. In addition, a study on the effects of OT among older adults (60+) with chronic health issues showed a clear dose-response relationship.[41] Another striking difference is the environment where the OT was provided. Where Martinsen's study was carried out in the hospital's outpatient department, in our study the occupational therapists visited the patients in their homes. Home-based OT may yield an inherent advantage because of the opportunity to practice ECTs during occupations in the context in which they are normally applied, that is, in the natural

environment of daily living.[42] For instance, dyspnoea relieving postures and breathing techniques to reduce breathlessness during bathing or showering may be difficult to practise in an exercise room, which does not completely mimic the home situation where they are most needed. In other words, the therapy works better at home, making it more easily applicable and yielding greater measurable results. The apparent discrepancy in improvement between performance and satisfaction scores of the COPM found in the present study is in agreement with results from other studies and may reflect an adaptation to the new situation.[43]

Working mechanism of OT to improve daily routines in COPD

Three recently published studies on potential working mechanisms of ECTs to relieve dyspnoea and to facilitate the performance of ADLs in patients with COPD, are in support of the clinical benefits observed in the present study. Silva and co-workers studied 18 patients with moderate to severe COPD and showed that ECTs applied during ADLs reduced dynamic hyperinflation in three out of four ADLs.[44] Dynamic hyperinflation is the lung mechanical phenomenon in which, during increased levels of ventilation engendered by, for instance, exertion, air cannot fully be exhaled and breathing becomes less efficient. Dynamic hyperinflation has been recognised as an important determinant of dyspnoea in patients with COPD.[45] Prieur and colleagues investigated the effect of fractionating the effort during a frequently occurring occupational performance problem, that is stair climbing, in a randomised crossover trial in 22 patients with severe to very severe COPD. They found that this single form of ECTs resulted in significantly lower minute ventilation, which was accompanied by a reduction of dynamic hyperinflation and significantly lower dyspnea. Interestingly, this fractionating of stair climbing did not result in a prolonged total task time.[46] Finally, Windgårdh and co-researchers evaluated the effects of a two-week ECTs training program in 32 patients with moderate to very severe COPD.[47] A significantly lower metabolic equivalent of task, and less desaturation, were found, while the time spent on the task remained unchanged. Taken these three studies together, they provide a clear rationale for the application of ECTs in patients with COPD.

Occupational performance problems in patients with COPD

Although not an explicit goal of this study, the results confirmed the wide range of possible occupational performance problems in patients with COPD as reported in the studies by Annegarn et al., and by Nakken et al..[1,2] Furthermore, these studies showed that self-reported occupational performance problems, in symptomatic COPD patients referred to pulmonary rehabilitation and in clinically stable outpatients with moderate to very severe COPD, are most often reported in the mobility domain. This is also consistent with the results of our study, in which most of the problematic ADLs reported by our patients with COPD referred to secondary care, were in the domains of

productivity or mobility and fewer in self-care or leisure. Of note, climbing the stairs and walking (first uphill and then also on the flat) have been found to be the first activities affected by COPD, followed by almost every other physical ADLs with disease progression.[48]

Concurrent validity of the COPM to capture problematic activities in COPD

Reliability of the COPM in patients with COPD has been documented[33], but to the best of the authors' knowledge, concurrent validity has not as yet been investigated in patients with COPD. Although this study was not particularly designed for this purpose, we found a significant correlation between the baseline COPM scores and the CCQ total score. The CCQ is an internationally accepted instrument to reflect general health status. Furthermore, it is recommended as a tool in the GOLD document to classify patients in the ABCD groups.[49] Moreover, with each increase in CCQ health status impairment level, statistically lower COPM satisfaction scores were found. These results suggest that the COPM may be a valid measurement instrument in patients with COPD.

Strengths and limitations of the study

In this study, home-based OT was offered as part of an integrated care model, which may have been the key to its success. Because patients referred to OT were preselected and primed during the diagnostic and self-management part of the care model, only those with a set indication for OT plus the presence of sufficient motivation for OT were referred. It follows, that without this context, it might not have been possible to obtain the same results. And perhaps this also added to the discrepancy in outcome between the study by Unni Martinsen and colleagues[17], and our study. In their study, OT was apparently provided as a stand-alone intervention and missed the context of a comprehensive type of care model. Obviously, the observational study design we applied in the current study precludes definite conclusions as to the effectiveness of OT in patients with COPD. Since there were no studies to date, to the best of the authors' knowledge, that showed an effect of monodisciplinary home-based OT in patients with COPD, we initially conducted this study as an effectiveness study.

Future research

Follow-up research, with a controlled study design, is needed to draw definite conclusions regarding the effectiveness of monodisciplinary OT in patients with COPD. Such research should also look at the long-term effects and the necessity of embedding OT in an integrated care model for obtaining the desired results.

CONCLUSIONS

Home-based monodisciplinary OT, provided with an individualized, patient-centered approach and embedded in an integrated care model, appear to be effective in improving both performance and satisfaction with important daily activities in patients with moderate to severe COPD. This effect was accompanied by a significant decrease in dyspnea during important ADLs. In a majority of patients, individual treatment goals set out at the start of the OT were attained largely or completely.

REFERENCES

1. Annegarn J, Meijer K, Passos VL, et al. Problematic activities of daily life are weakly associated with clinical characteristics in COPD. *Journal of the American Medical Directors Association.* 2012;13(3):284-290.

2. Nakken N, Janssen DJ, van den Bogaart EH, et al. Patient versus proxy-reported problematic activities of daily life in patients with COPD. *Respirology.* 2017;22(2):307-314.

3. Vaes AW, Wouters EFM, Franssen FME, et al. Task-related oxygen uptake during domestic activities of daily life in patients with COPD and healthy elderly subjects. *Chest.* 2011;140(4):970-979.

4. Sewell L, Singh SJ, Williams JE, Collier R, Morgan MD. Can individualized rehabilitation improve functional independence in elderly patients with COPD? *Chest.* 2005;128(3):1194-1200.

5. Kruapanich C, Tantisuwat A, Thaveeratitham P, Lertmaharit S, Ubolnuar N, Mathiyakom W. Effects of Different Modes of Upper Limb Training in Individuals With Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis. *Annals of Rehabilitation Medicine.* 2019;43(5):592-614.

6. Vaes AW, Delbressine JML, Mesquita R, et al. Impact of pulmonary rehabilitation on activities of daily living in patients with chronic obstructive pulmonary disease. *Journal of Applied Physiology (1985).* 2019;126(3):607-615.

7. Law MC, Dunn, W., Baum, C.M. *Measuring occupational performance: supporting best practice in occupational therapy.* 2nd ed. Thorofare (N.J.): Slack; 2005.

8. Chan SC. Chronic obstructive pulmonary disease and engagement in occupation. *American Journal of Occupational Therarpy.* 2004;58(4):408-415.

9. Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *American Journal of Respiratory and Critical Care Medicine.* 2013;188(8):e13-64.

10. Spruit MA, Pitta F, Garvey C, et al. Differences in content and organisational aspects of pulmonary rehabilitation programmes. *European Respiratory Journal.* 2014;43(5):1326-1337.

11. Velloso M, Jardim JR. Study of energy expenditure during activities of daily living using and not using body position recommended by energy conservation techniques in patients with COPD. *Chest.* 2006;130(1):126-132.

12. Velloso M, Stella SG, Cendon S, Silva AC, Jardim JR. Metabolic and ventilatory parameters of four activities of daily living accomplished with arms in COPD patients. *Chest.* 2003;123(4):1047-1053.

13. Theander K, Jakobsson P, Jorgensen N, Unosson M. Effects of pulmonary rehabilitation on fatigue, functional status and health perceptions in patients with chronic obstructive pulmonary disease: a randomized controlled trial. *Clinical Rehabilitation.* 2009;23(2):125-136.

14. van Ranst D, Otten H, Meijer JW, van 't Hul AJ. Outcome of pulmonary rehabilitation in COPD patients with severely impaired health status. *International Journal of Chronic Obstructive Pulmonary Disease.* 2011;6:647-657.

15. Norweg AM, Whiteson J, Malgady R, Mola A, Rey M. The effectiveness of different combinations of pulmonary rehabilitation program components: a randomized controlled trial. *Chest.* 2005;128(2):663-672.

16. Lorenzi CM, Cilione C, Rizzardi R, et al. Occupational therapy and pulmonary rehabilitation of disabled COPD patients. *Respiration.* 2004;71(3):246-251.

17. Martinsen U, Bentzen H, Holter MK, et al. The effect of occupational therapy in patients with chronic obstructive pulmonary disease: A randomized controlled trial. *Scandinavian Journal of Occupational Therapy.* 2017;24(2):89-97.

18. Koolen EH, van der Wees PJ, Westert GP, Dekhuijzen R, Heijdra YF, van 't Hul AJ. The COPDnet integrated care model. *International Journal of Chronic Obstructive Pulmonary Disease.* 2018;13:2225-2235.

19. Law M, Baptiste, S., Carswell, A., McColl, M., Polatajko, H., Pollock, N. *Canadian Occupational Performance Measure.* Vol 5e. Toronto: CAOT Publications; 2005.

20. Agusti A, Bel E, Thomas M, et al. Treatable traits: toward precision medicine of chronic airway diseases. *The European Respiratory Journal.* 2016;47(2):410-419.

21. Vermunt N, Elwyn G, Westert G, Harmsen M, Olde Rikkert M, Meinders M. Goal setting is insufficiently recognised as an essential part of shared decision-making in the complex care of older patients: a framework analysis. *BMC Family Practice.* 2019;20(1):76.

22. Koolen EH, van der Wees, P.J., Westert, G.P., Heijdra, Y.F., Dekhuijzen, P.N.R., van 't Hul, A.J. Evaluation of the COPDnet integrated care model in patients with COPD: the study protocol. *International Journal of Chronic Obstructive Pulmonary Disease.* 2018;13:2237-2244.

23. Craik J, Davis, J., Polatajko, H.J. Introducing the Canadian Practice Process Framework (CPPF), amplifying the context. In: E.A. Townsend HJP, ed. *Enabling occupation II: Advancing an occpational therapy vision for health, well-being and justice through occupation.* Ottawa: CAOT Publications ACE; 2007:229-246.

24. Mayer AF, Karloh M, Dos Santos K, de Araujo CLP, Gulart AA. Effects of acute use of pursed-lips breathing during exercise in patients with COPD: a systematic review and meta-analysis. *Physiotherapy.* 2018;104(1):9-17.

25. Norweg A, Bose P, Snow G, Berkowitz ME. A pilot study of a pulmonary rehabilitation programme evaluated by four adults with chronic obstructive pulmonary disease. *Occupational Therapy International.* 2008;15(2):114-132.

26. King J, Tessier S, Charette MJ, Gaudet D. Patient Education Provided by Physiotherapists for Patients with Chronic Obstructive Pulmonary Disease: Results of a Scoping Review. *Canadian Physiotherapy Association.* 2018;70(2):141-151.

27. The Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD); 2017. Available from: http://goldcopd.org/gold-reports-2017/. Accessed: September 21, 2020.

28. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *The European Respiratory Journal.* 2012;40(6):1324-1343.

29. van der Molen T, Willemse BW, Schokker S, ten Hacken NH, Postma DS, Juniper EF. Development, validity and responsiveness of the Clinical COPD Questionnaire. *Health and Quality of Life Outcomes.* 2003;1:13.

30. Smid DE, Franssen FME, Gonik M, et al. Redefining Cut-Points for High Symptom Burden of the Global Initiative for Chronic Obstructive Lung Disease Classification in 18,577 Patients With Chronic Obstructive Pulmonary Disease. *Journal of the American Medical Directors Association.* 2017;18(12):1097 e1011-1097 e1024.

31. Marshall AL, Smith BJ, Bauman AE, Kaur S. Reliability and validity of a brief physical activity assessment for use by family doctors. *British Journal of Sports Medicine.* 2005;39(5):294-297; discussion 294-297.

32. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. *Chest.* 1988;93(3):580-586.

33. Sewell L, Singh S. The Canadian Occupational Performance Measure: is it a reliable measure in clients with COPD? *British Journal of Occupational Therapy.* 2001;64:6.

34. Law M, Baptiste S, McColl M, Opzoomer A, Polatajko H, Pollock N. The Canadian occupational performance measure: an outcome measure for occupational therapy. *Canadian Journal of Occupational Therapy (Revue canadienne d'ergotherapie).* 1990;57(2):82-87.

35. Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of quality of life for clinical trials in chronic lung disease. *Thorax.* 1987;42(10):773-778.

36. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clinical Trials.* 1989;10(4):407-415.

37. Reuben DB, Tinetti ME. Goal-oriented patient care--an alternative health outcomes paradigm. *The New England Journal of Medicine.* 2012;366(9):777-779.

38. van Stel HF, Colland VT, Heins NL, Rijssenbeek-Nouwens LH, Everaerd W. Assessing inpatient pulmonary rehabilitation using the patient's view of outcome. *Journal of Cardiopulmonary Rehabilitation.* 2002;22(3):201-210.

39. Hurn J, Kneebone I, Cropley M. Goal setting as an outcome measure: A systematic review. *Clinical Rehabilitation.* 2006;20(9):756-772.

40. Sullivan GM, Feinn R. Using Effect Size-or Why the P Value Is Not Enough. *Journal of Graduate Medical Education.* 2012;4(3):279-282.

41. Nielsen SS, Christensen JR. Occupational Therapy for Adults with Overweight and Obesity: Mapping Interventions Involving Occupational Therapists. *Occupational Therarpy International.* 2018;2018:7412686.

42. Gupta J, Taff SD. The illusion of client-centred practice *Scandinavian Journal of Occupational Therapy.* 2015;22(4):244-251.

43. Wressle E, Lindstrand J, Neher M, Marcusson J, Henriksson C. The Canadian Occupational Performance Measure as an outcome measure and team tool in a day treatment programme. *Disability and Rehabilitation.* 2003;25(10):497-506.

44. Silva CS, Nogueira FR, Porto EF, et al. Dynamic hyperinflation during activities of daily living in COPD patients. *Chronic Respiratory Disease.* 2015;12(3):189-196.

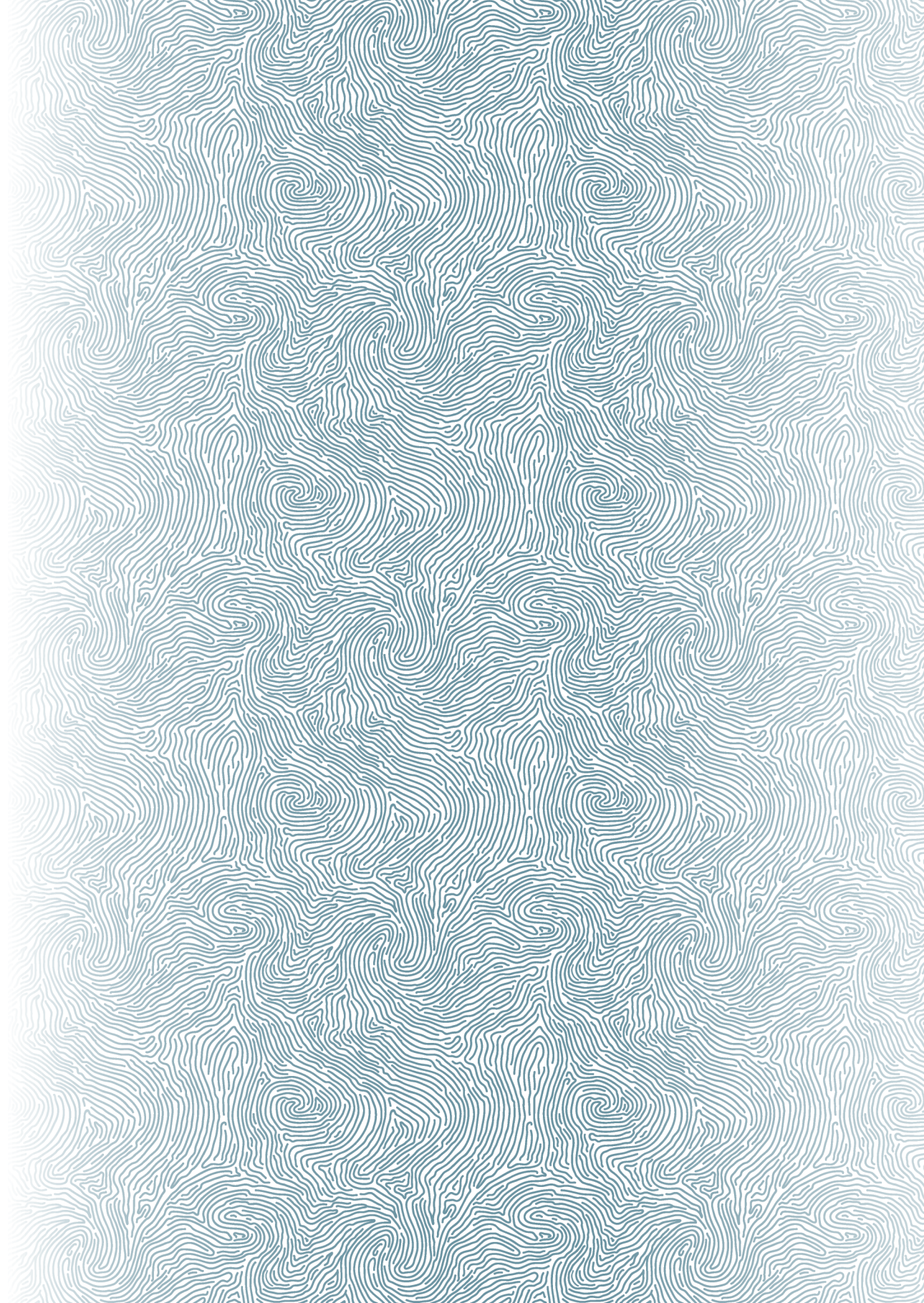
45. O'Donnell DE, Milne KM, James MD, de Torres JP, Neder JA. Dyspnea in COPD: New Mechanistic Insights and Management Implications. *Advances in Therapy.* 2020;37(1):41-60.

46. Prieur G, Combret Y, Medrinal C, et al. Energy conservation technique improves dyspnoea when patients with severe COPD climb stairs: a randomised crossover study. *Thorax.* 2020.

47. Wingardh ASL, Goransson C, Larsson S, Slinde F, Vanfleteren L. Effectiveness of Energy Conservation Techniques in Patients with COPD. *Respiration; International Review of Thoracic Diseases.* 2020:1-8.

48. Dobbels F, de Jong C, Drost E, et al. The PROactive innovative conceptual framework on physical activity. *The European Respiratory Journal.* 2014;44(5):1223-1233.

49. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmomary disease (COPD) - 2020 Report; 2020. Available from: https://goldcopd.org/wp-content/uploads/2019/12/GOLD-2020-FINAL-ver1.2-03Dec19_WMV.pdf. Accessed; September 21, 2020.



The clinical effectiveness of the COPDnet integrated care model

E.H. Koolen
B. van den Borst
M. de Man
J.C. Antons
B. Robberts
P.N.R. Dekhuijzen
J.H. Vercoulen
M.M. van den Heuvel
M.A. Spruit
P.J. van der Wees
A.J. van 't Hul

Respiratory Medicine. 2020 Oct;172:106152

ABSTRACT

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.

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 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.

MATERIAL AND METHODS

Study design

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

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).

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 ≥3)[18], 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)[1], poor nutritional status (BMI<21 or BMI>30)[19], severe fatigue (Checklist Individual Strength-Fatigue>36)[20], depressed mood (Beck Depression Inventory≥4)[21], poor exercise capacity (6-minute 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 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.

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

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.

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 7-9 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 to -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]

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.

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 $p < 0.05$.

RESULTS

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:

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

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	54±19	55±17
p5, p50, p95	25, 52, 86	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	17/35/22/15/7/3/2/0	21/27/22/16/10/2/1/1
(0/1/2/3/4/5/6/7), % p5, p50, p95	0, 1, 5	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	1.94±1.04	1.96±1.06
p5, p50, p95	0.5, 1.8, 4.2	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,	46/19/35	56/17/27
0/1/≥2 or ≥1 hospitalization, %		
Nutritional status, BMI<21/ BMI 21-25/ BMI	17/30/35/16/2	21/33/23/15/8
25-30/ BMI 30-35/ BMI >35, %		
Fatigue, CIS-F score, points	38±12	39±12
p5, p50, p95	14, 38, 56	15, 41, 56
Depressed mood, BDI score, points	2.2±2.5	2.1±2.7
p5, p50, p95	0, 1.0, 9.0	0, 1.0, 7.4
Physical capacity, 6MWD (mtr.); 6MWD	461±115; 71±17	461±127; 71±18
%predicted	270, 477, 638; 41, 72,	240, 475, 629; 39, 72,
p5, p50, p95	98	97
Habitual physical activity, steps/day	5233±2653	5615±3248
p5, p50, p95	1438, 4848, 9554	997, 5327, 11964
Activation for self-management, PAM score,	53±12; 34/26/30/10	52±10; 34/ 29/ 32/ 5
points; PAM level I/II/III/IV, %		

Note: Data are presented as n, %, n (%), mean±SD, 5th, 50th and 95th percentiles.
Abbreviations: 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-minute walking distance; PAM = Patient Activation Measure.

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%)

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 ($p < 0.01$). Figure 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.

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

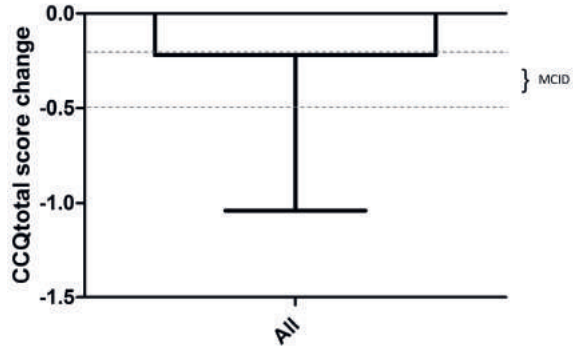


Figure 1. Average decrease (=improvement) in CCQ total score of the 154 patients with a follow-up measurement.
Abbreviations: CCQ = Clinical COPD Questionnaire; MCID = Minimal Clinically Important Difference.

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. Figure 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.

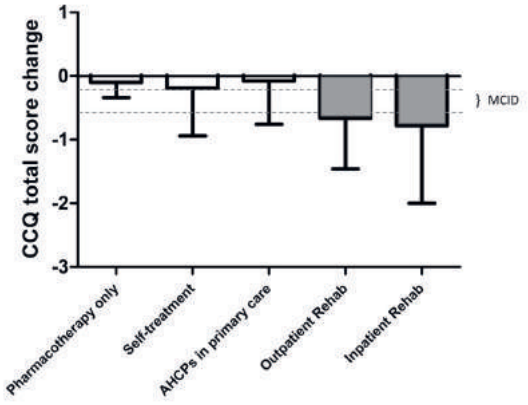


Figure 2. Mean improvement (decrease) in CCQ total score per subgroup based on the actual intervention allocation.
Abbreviations: CCQ = Clinical COPD Questionnaire; AHCP = Allied Healthcare Professional; MCID = Minimal Clinically Important Difference.

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

Attribute	Pharmacotherapy only (n=39; 11%)	Self-treatment (n=61; 17%)	AHCPs in primary care (n=218; 61%)	Outpatient pulmonary rehab (n=20; 6%)	Inpatient pulmonary rehab (n=19; 5%)	P-value
Sociodemogra-phic features:						
Age, years p5, p50, p95	62±11 45, 62, 81	63±7 51, 63, 76	65±9 50, 65, 80	60±8 42, 60, 70	60±9 39, 60, 71	*P*<0.05
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), % p5, p50, p95	36/18/23/13/0/0/0/ 3 0, 1, 4	15/38/13/23/7/2/1/ 1 0, 1, 5	17/31/26/12/9/3/ 2 0, 2, 4	15/40/10/20/5/5/ 5 0, 1, 6	16/21/26/21/16/0/ 0 0, 2, 6	*P*=0.77
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 p5, p50, p95	1.39±1.07[c,e] 0.1, 1.1, 4.0	1.65±1.07[e] 0.4/1.3/4.3	2.06±0.98[a,e] 0.7/1.9/3.9	1.96±0.83[e] 0.4/1.9/4.1	3.13±1.25[a,b,c,d] 1.5/2.7/4.2	*P*<0.001
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 p5, p50, p95	29±14[b,c,d,e] 9, 27, 54	38±12[a,e] 14, 39, 56	40±11[a] 19, 41, 56	38±11[a] 14, 40, 55	47±9[a,b] 31, 50, 55	*P*<0.001
Depressed mood, BDI score, points p5, p50, p95	2.1±3.5[e] 0, 1.0, 11.7	1.3±1.9[e] 0, 1.0, 5.75	2.1±2.5[e] 0, 1, 7.5	2.6±2.7[e] 0, 2, 8.0	5.3±3.5[a,b,c,d] 0, 5, 11.0	*P*<0.001
Physical capacity, 6MWD (mtr.); 6MWD %predicted p5, p50, p95	507±130[c,e]; 77±16[e] 269, 525, 702; 39, 77, 100	492±130[c,e]; 77±21[c,e] 355, 483, 629; 57, 75, 103	438±121[a,b]; 69±17[b] 209, 450, 621; 34, 70, 96	495±68; 74±10[e] 367, 505, 613; 56, 77, 94	401±108[a,b]; 59±15[a,b,d] 175, 420, 538; 27, 60, 83	*P*<0.001; *P*<0.001
Habitual physical activity, steps/day p5, p50, p95	6548±4306 575, 6250, 14073	5910±2340 2062, 6035, 9728	5072±2816 927, 4663, 10239	5406±2235 2045, 5114, 10791	5198±2063 1771, 5381, 7566	*P*=0.08
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

Abbreviations: 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 = 6-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]

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.

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 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 specialised 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.

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.

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 randomised 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]

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.

REFERENCES

1. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (COPD) - 2020 Report; 2020. Available from: https://goldcopd.org/wp-content/uploads/2019/12/GOLD-2020-FINAL-ver1.2-03Dec19_WMV.pdf. Accessed; Augustus 14, 2020.

2. Contoli M, Rogliani P, Di Marco F, et al. Satisfaction with chronic obstructive pulmonary disease treatment: results from a multicenter, observational study. *Therapeutic Advances in Respiratory Disease.* 2019;13:1753466619888128.

3. Disler RT, Green A, Luckett T, et al. Experience of advanced chronic obstructive pulmonary disease: metasynthesis of qualitative research. *Journal of Pain Symptom Management.* 2014;48(6):1182-1199.

4. Watson JS, Adab P, Jordan RE, Enocson A, Greenfield S. Referral of patients with chronic obstructive pulmonary disease to pulmonary rehabilitation: a qualitative study of barriers and enablers for primary healthcare practitioners. *British Journal of General Practice.* 2020.

5. Ding B, DiBonaventura M, Karlsson N, Bergstrom G, Holmgren U. A cross-sectional assessment of the burden of COPD symptoms in the US and Europe using the National Health and Wellness Survey. *International Journal of Chronic Obstructive Pulmonary Disease.* 2017;12:529-539.

6. Vanfleteren L, Hul AJV, Kulbacka-Ortiz K, Andersson A, Ullman A, Ingvar M. Challenges to the Application of Integrated, Personalized Care for Patients with COPD-A Vision for the Role of Clinical Information. *Journal of Clinical Medicine.* 2020;9(5).

7. Nici L, ZuWallack R, American Thoracic Society Subcommittee on Integrated Care of the CP. An official American Thoracic Society workshop report: the Integrated Care of The COPD Patient. *Proceedings of the American Thoracic Society.* 2012;9(1):9-18.

8. Engel GL. The need for a new medical model: a challenge for biomedicine. *Science.* 1977;196(4286):129-136.

9. Kruis AL, Smidt N, Assendelft WJ, et al. Integrated disease management interventions for patients with chronic obstructive pulmonary disease. *The Cochrane database of systematic reviews.* 2013;10:CD009437.

10. Early F, Wilson P, Deaton C, et al. Developing an intervention to increase REferral and uptake TO pulmonary REhabilitation in primary care in patients with chronic obstructive pulmonary disease (the REsTORE study): mixed methods study protocol. *BMJ Open.* 2019;9(1):e024806.

11. Kayyali R, Odeh B, Frerichs I, et al. COPD care delivery pathways in five European Union countries: mapping and health care professionals' perceptions. *International Journal of Chronic Obstructive Pulmonary Disease.* 2016;11:2831-2838.

12. Koolen EH, van der Wees PJ, Westert GP, Dekhuijzen R, Heijdra YF, van 't Hul AJ. The COPDnet integrated care model. *International Journal of Chronic Obstructive Pulmonary Disease.* 2018;13:2225-2235.

13. Koolen EH, van der Wees PJ, Westert GP, Dekhuijzen R, Heijdra YF, van 't Hul AJ. Evaluation of the COPDnet integrated care model in patients with COPD: the study protocol. *International Journal of Chronic Obstructive Pulmonary Disease.* 2018;13:2237-2244.

14. Koolen EH vdWP, Westert G, Antons JA, Dekhuijzen R, van den Heuvel M, van 't Hul AJ. Evaluation of the effects of the COPDnet comprehensive care model; an interim analysis. *European respiratory Journal.* 2019;54:Suppl. 63, PA3952.

15. van den Akker EF, van 't Hul AJ, Chavannes NH, et al. Development of an integral assessment approach of health status in patients with obstructive airway diseases: the CORONA study. *International Journal of Chronic Obstructive Pulmonary Disease.* 2015;10:2413-2422.

16. Vercoulen JH, Daudey L, Molema J, et al. An Integral assessment framework of health status in chronic obstructive pulmonary disease (COPD). *International Journal of Behavioral Medicine.* 2008;15(4):263-279.

17. Vercoulen JH. A simple method to enable patient-tailored treatment and to motivate the patient to change behaviour. *Chronic Respiratory Disease.* 2012;9(4):259-268.

18. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. *Chest.* 1988;93(3):580-586.

19. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organization Technical Report Series.* 2000;894:i-xii, 1-253.

20. Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. *Journal of Psychosomatic Research.* 1994;38(5):383-392.

21. Beck AT, Guth D, Steer RA, Ball R. Screening for major depression disorders in medical inpatients with the Beck Depression Inventory for Primary Care. *Behaviour Research and Therapy.* 1997;35(8):785-791.

22. Koolen EH, van Hees HW, van Lummel RC, et al. "Can do" versus "do do": A Novel Concept to Better Understand Physical Functioning in Patients with Chronic Obstructive Pulmonary Disease. *Journal of Clinical Medicine.* 2019;8(3).

23. Rademakers J, Nijman J, van der Hoek L, Heijmans M, Rijken M. Measuring patient activation in The Netherlands: translation and validation of the American short form Patient Activation Measure (PAM13). *BMC public health.* 2012;12:577.

24. Elwyn G, Frosch D, Thomson R, et al. Shared decision making: a model for clinical practice. *Journal of General Internal Medicine.* 2012;27(10):1361-1367.

25. Spruit MA, van 't Hul, A.J., Vreeken, H.L., Beekman, E., Post, M.H.T., Meerhoff, G.A., van der Valk, A., Zagers, C., Sillen, M.J.H., Vooijs, M., Custers, J., Muris, J., Langer, D., Donkers, J., Bregman, M., Tissink, L., Bergkamp, E., Wempe, J., Houben-Wilke, S., Augustin, I.M.L., bij de Vaate, E., Franssen, F.F.M., van Ranst, D., van der Vaart, E., Antons, J., van Doormaal, M., Koolen, E.H., van der Wees, Ph., van Snippenburg R., Janssen, D.J.A., Simons, S. Profiling of patients with COPD for adequate referral to exercise-based care: the Dutch model. *Sports Medicine.* 2020;In press.

26. Rochester CL, Vogiatzis I, Holland AE, et al. An Official American Thoracic Society/European Respiratory Society Policy Statement: Enhancing Implementation, Use, and Delivery of Pulmonary Rehabilitation. *American Journal of Respiratory Critical Care Medicine.* 2015;192(11):1373-1386.

27. Tsiligianni IG, van der Molen T, Moraitaki D, et al. Assessing health status in COPD. A head-to-head comparison between the COPD assessment test (CAT) and the clinical COPD questionnaire (CCQ). *BMC Pulmonary Medicine.* 2012;12:20.

28. van der Molen T, Willemse BW, Schokker S, ten Hacken NH, Postma DS, Juniper EF. Development, validity and responsiveness of the Clinical COPD Questionnaire. *Health and Quality of Life Outcomes.* 2003;1:13.

29. Alma H, de Jong C, Tsiligianni I, Sanderman R, Kocks J, van der Molen T. Clinically relevant differences in COPD health status: systematic review and triangulation. *European Respiratory Journal.* 2018;52(3).

30. Peters JB, Daudey L, Heijdra YF, Molema J, Dekhuijzen PN, Vercoulen JH. Development of a battery of instruments for detailed measurement of health status in patients with COPD in routine care: the Nijmegen Clinical Screening Instrument. *Quality of Life Research.* 2009;18(7):901-912.

31. Marshall AL, Smith BJ, Bauman AE, Kaur S. Reliability and validity of a brief physical activity assessment for use by family doctors. *British Journal of Sports Medicine.* 2005;39(5):294-297; discussion 294-297.

32. Smid DE, Franssen FME, Gonik M, et al. Redefining Cut-Points for High Symptom Burden of the Global Initiative for Chronic Obstructive Lung Disease Classification in 18,577 Patients With Chronic Obstructive Pulmonary Disease. *Journal of the American Medical Directors Association.* 2017;18(12):1097 e1011-1097 e1024.

33. Long Alliantie Nederland (LAN) [Lung Alliance Netherlands]. Zorgstandaard COPD [Care Standard COPD]; 2016. Available from: http://www.longalliantie.nl/zorgstandaard-copd. Accessed; Augustus 14, 2020. Dutch.

34. Kruis AL, Boland MR, Schoonvelde CH, et al. RECODE: design and baseline results of a cluster randomized trial on cost-effectiveness of integrated COPD management in primary care. *BMC Pulmonary Medicine.* 2013;13:17.

35. Kruis AL, Boland MR, Assendelft WJ, et al. Effectiveness of integrated disease management for primary care chronic obstructive pulmonary disease patients: results of cluster randomised trial. *BMJ.* 2014;349:g5392.

36. Benfante A, Messina R, Milazzo V, Scichilone N. How to unveil chronic respiratory diseases in clinical practice? A model of alliance between general practitioners and pulmonologists. *Pulmonary Pharmacology & Therapy.* 2017;44:106-110.

37. Alma HJ, de Jong C, Jelusic D, et al. Thresholds for clinically important deterioration versus improvement in COPD health status: results from a randomised controlled trial in pulmonary rehabilitation and an observational study during routine clinical practice. *BMJ Open.* 2019;9(6):e025776.

38. Rodrigues FM, Demeyer H, Loeckx M, et al. Health status deterioration in subjects with mild to moderate airflow obstruction, a six years observational study. *Respiratory Research.* 2019;20(1):93.

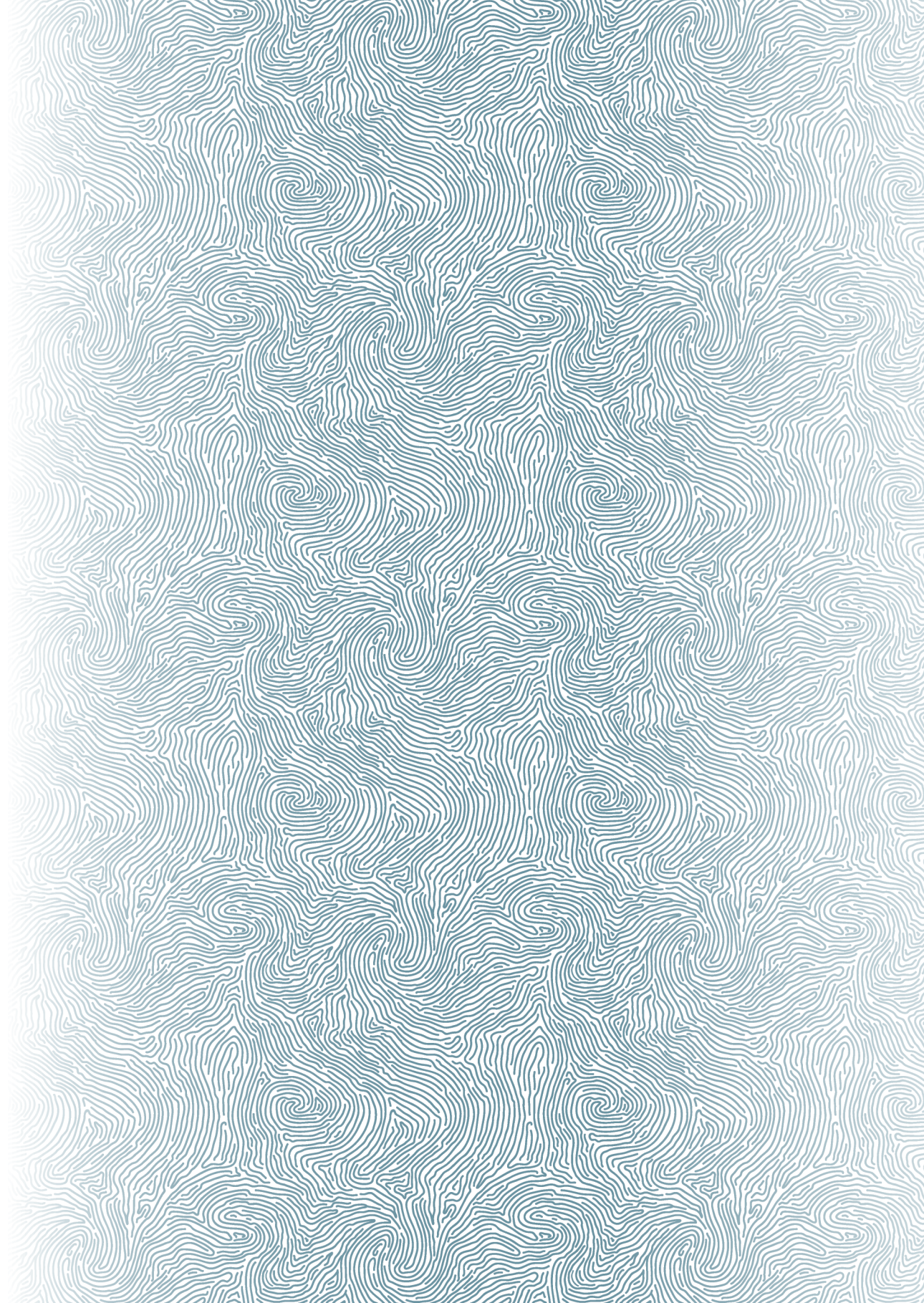
39. van Ranst D, Otten H, Meijer JW, van 't Hul AJ. Outcome of pulmonary rehabilitation in COPD patients with severely impaired health status. *International Journal of Chronic Obstructive Pulmonary Disease.* 2011;6:647-657.

40. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Systematic Review.* 2015;2:CD003793.

41. Kristman V, Manno M, Cote P. Loss to follow-up in cohort studies: how much is too much? *European Journal of Epidemiology.* 2004;19(8):751-760.

42. Kontopantelis E, Doran T, Springate DA, Buchan I, Reeves D. Regression based quasi-experimental approach when randomisation is not an option: interrupted time series analysis. *BMJ.* 2015;350:h2750.

43. Handley MA, Lyles CR, McCulloch C, Cattamanchi A. Selecting and Improving Quasi-Experimental Designs in Effectiveness and Implementation Research. *Annual Review of Public Health.* 2018;39:5-25.



GENERAL DISCUSSION

The ambition of this thesis was to improve the outcomes of care for patients with COPD. This was achieved by creating, implementing and testing a new transmural integrated care model, named the COPDnet model. The model has been designed on the basis of recent insights into effective strategies for chronic conditions in general such as the Chronic Care Model and expert opinions and evidence-based insights into integrated care. The COPDnet model stresses the more frequent use of non-pharmacological intervention options. In addition, a quality system is applied that systematically measures health care outcomes. These outcome measurements are subsequently used as input for continuous monitoring of results and may feed future improvements of the model. The heart of the COPDnet model is formed by a diagnostic trajectory in secondary care and aims to make an comprehensive analysis of the health status and to empower patients for self-management. Based on this analysis and in close collaboration with the patient, an individual care plan is drawn up. The content of the care plan depends on what is needed and the patient's preferences. The non-pharmacological intervention options comprise of monodisciplinary interventions by allied health care professionals in primary care, or in more complex situations, through multidisciplinary pulmonary rehabilitation. Pivotal is patient-centered care. In this thesis we implemented and investigated this newly developed integrated care model, named COPDnet model, in two regions in the Netherlands; Bernhoven hospital (Uden) and Radboudumc (Nijmegen). In addition, we assessed the health status of patients with COPD who had been referred for the first time to a pulmonologist in secondary care in order to gain insights in the complexity and heterogeneity of this disease and in order to have the ability to refer patients to the right intervention option. This chapter first summarizes the main findings of the studies and then puts these results in to a broader perspective.

MAIN FINDINGS

We described the development of a new integrated care model for patients with COPD, named COPDnet (**Chapter 2**). This model has been designed according to current knowledge on important disease specific aspects as well as on general insights regarding effective care in patients with a chronic condition.

In order to evaluate this newly developed COPDnet integrated care model for patients with COPD, we described a study protocol (**Chapter 3**). The study protocol sets out to evaluate three aspects of the model regarding effective COPD care. First of all, to evaluate the feasibility of employing the COPDnet model in present real life care within the context of the Dutch healthcare system. Secondly, to explore the potential health status benefits. And finally, to analyze the costs of care of this model.

Physical functioning is often impaired and tightly connected to prognosis in patients with COPD. In order to better understand physical functioning in patients with COPD, we developed a PC-PA quadrant concept, in which patients with COPD could be subdivided along axes of what they physically "can do" (physical capacity, PC), as in an exercise test, and what they actually "do do" (physical activity, PA), in their daily lives (**Chapter 4**). We found evidence that this concept may serve as a pragmatic clinical tool, that may be useful in the understanding of the impaired physical functioning in patients with COPD, and therefore may improve the selection of appropriate interventions to improve physical function.

To examine the complexity and heterogeneity of patients with COPD upon first referral to a pulmonologist in secondary care, we assessed the prevalence of nine potentially clinically relevant treatable traits (TTs) (**Chapter 5**). We found that patients with COPD showed multiple TTs, that coexist in many different combinations and are relatively independent. Furthermore, the presence of these TTs increased the likelihood of having a severely impaired health status.

The non-pharmacological primary care intervention options are part of the COPDnet integrated care model. Efficacy of occupational therapy in primary care although increasingly been applied, has hardly been investigated. Therefore, we have chosen to evaluate the clinical effectiveness of home-based monodisciplinary occupational therapy in patients with COPD (**Chapter 6**). This study showed that home-based occupational therapy can contribute significantly to the improvement of daily functioning in patients with COPD.

And finally, our latest study evaluated the clinical effectiveness of the COPDnet integrated care model on health status change in patients with COPD (**Chapter 7**). We found a statistically significant improved health status in patients with COPD who received care according to this COPDnet model.

INTERPRETATION OF THE FINDINGS

The summarized results are put into a broader perspective based on three relevant topics: 1) Integrated disease management care, 2) Complex and heterogenous disease, and 3) Multidisciplinary non-pharmacological intervention options. These topics are discussed below, based on our results and the current scientific research. The chapter ends with future perspectives regarding these topics.

INTEGRATED DISEASE MANAGEMENT CARE

The use of principles of integrated care is poor and fragmented in patients with COPD in real-life care in various health care settings, including the Netherlands.[1] This underutilization and fragmentation contrast with the scientific research showing the potential added value of an integrated approach, in terms of improving the quality and efficiency of care and even reducing health care costs.[2]

Patients with moderate or severe burden of disease, meet the criteria for shared care between a primary, secondary, and/or tertiary care setting and qualify for both pharmacological and non-pharmacological intervention options, according to the Dutch Standard of Care for COPD.[3] The assumption was made that patients with COPD with moderate or severe burden of disease could be good candidates for an integrated disease management approach because of an anticipated complexity of their impaired health status. Therefore, the aim of this thesis was, first of all, to develop an evidence-based comprehensive model of integrated care, based on principles of integrated disease management and founded on the CCM, for patients with COPD with moderate or severe burden of disease.[3] In **Chapter 2** we introduced this newly developed model, named; the COPDnet integrated care model, and in **Chapter 3** we described a study protocol to evaluate this model.

To significantly improve the outcomes of care for patients with obstructive lung disease referred to secondary care, an innovative diagnostic pathway was already successfully developed and implemented by Van den Akker et al. elsewhere in the Netherlands.[4] We have therefore used this diagnostic pathway for patients with obstructive lung disease as a base and have subsequently expanded it by adding three different elements. First of all, by deliberately adding self-management support to the diagnostic pathway provided in secondary care. Secondly, in addition to this diagnostic pathway, we developed and implemented a modular program for non-pharmacological intervention options in primary care, and, we adopted an already available center-based pulmonary rehabilitation program in secondary or tertiary care. Thirdly, we also included a Quality Management System (QMS) with the incorporation of the systematic measurement on health care outcomes using Patient Reported Outcome Measures (PROMs).

Self-management

Patients with an obstructive lung disease should be enabled to adequately adapt to their own burden of disease and assumes that they have to change their behavior.[5] However, non-adherence to treatment recommendations is common in patients with COPD, despite clear recommendations for pharmacological or non-pharmacological

treatments by a healthcare professional.[6] Self-management presupposes that patients understand that they need to actively manage their own burden of disease. To enable them to do so, patients have to gain self-efficacy to manage the individual lung disease.[7] A change in the behavior of the patient, by activating patients' self-management, will lead to a long-term improvement in health status.[7] Indeed, in patients with chronic disease a higher level of activation for self-management is associated with a positive change in burden of disease, healthcare utilization and costs of care.[8-11] Therefore, these factors stimulated us to add the activation of self-management within our COPDnet model. We have added four strategies for self-management support in our diagnostic care pathway: 1) Patient Activation Measurement (PAM) and Motivational Interviewing, 2) Capabilities Opportunities Motivation Behavior (COM-B) model, 3) shared decision making, and 4) an individual care plan.

We used the shortened 13-item version of the PAM questionnaire in our model.[12] With this questionnaire, four levels of activation for self-management can be distinguished, ranging from very low (PAM-1) to high (PAM 4). PAM levels were measured at the start of the diagnostic trajectory (pre-measurement), when the general practitioner referred the COPD patient to secondary care, and at the end of the diagnostic trajectory (post-measurement). The COPDnet diagnostic trajectory covers an average period of three months, in which the patient visits twice the pulmonologist and three times the respiratory nurse. Based on the outcomes of the pre PAM levels, the health care professionals apply motivational interviewing during the visits to actively improve the patients' self-management skills. Furthermore, the COM-B model was used in our COPDnet model, so that health care professionals could address which dimension, that is, psychological capabilities (C), social and environmental opportunities (O) and motivation (M) should be addressed to encourage patients to change their behavior (B).[13] Another important aspect of self-management support in our COPDnet model was shared decision making, based on introducing a choice during day 1, describing options during day 2 and helping to explore patients' preferences and to make informed decisions during day 3 of the diagnostic trajectory.[14] Eventually, this method of shared decision making, resulted in an individual care plan at patient's final visit in secondary care.

During a pilot study performed by our research group, we found that our diagnostic and interventional trajectory in secondary care significantly improves the activation for self-management in patients with COPD.[15] Thus, based on a simple 13-item questionnaire, in combination with motivational interviewing performed by two different health care professionals, the use of a theoretical COM-B model, including shared decision making, that resulted in an individual care plan, we could change the level of activation for self-management within only three months. Future research is

necessary to evaluate the long-term added value of what an improved PAM score could mean for a COPD patient's health status, wellbeing and health care utilization.

Non-pharmacological interventions

National and international guidelines describe that the goal of COPD management is to optimal control the lung disease through individual pharmacological and also non-pharmacological treatment options.[3,16] Within this innovative assessment schedule by van den Akker et al.[4], the pharmacological interventions have already been taken into account, but the non-pharmacological interventions were lacking.

During the diagnostic trajectory in one of our secondary care settings, the medical diagnosis is confirmed, classification of the burden of disease is made, and the number and complexity of individual treatable traits are determined. The classification of patient's burden of disease leads eventually to a possible referral to a primary, secondary or a tertiary care setting for tailor-made interventions, taking also into account patients' preferences. In principle, patients with mild or moderate burden of disease are rereferred to a primary care setting. Therefore, a modular, non-pharmacological, intervention program in primary care for patients with a mild or moderate burden of disease added to the pharmacological treatment, provided conform international clinical guidelines, has been added to our COPDnet integrated care model. All allied healthcare professionals (dieticians, physical therapists and occupational therapist), who were qualified to provide a treatment according to one of the intervention modules in primary care, were previously trained. In **Chapter 2** we described this non-pharmacological intervention program in primary care.

In order to evaluate the added value of one of the model's non-pharmacological intervention options, we chose to evaluate one of the occupational therapy modules, because effectiveness of home-based monodisciplinary occupational therapy in primary care has hardly been investigated. As a result, we described in **Chapter 6**, that home-based monodisciplinary occupational therapy can contribute significantly to the improvement of daily functioning of patients with COPD. A controlled design should be desirable for follow-up research, and shortness of breath and fatigue in relation to occupational therapy should also be subjects for follow-up research.

Outcome measures in the Quality Management System

Finally, outcome measurement is still marginally applied in general healthcare and also in healthcare for people with an obstructive lung disease.[17] Within this pathway the systematic measurement of outcomes will be standard care and the outcomes will be used to evaluate patients' health status change over time. There is evidence that the systematic provision of feedback to healthcare professionals on the outcome of care

with PROMs might stimulate innovation and result in improved effectiveness.[18-21] The systematic measurement of outcomes has been integrated within an innovative quality system and has been added to the model. By adding the QMS we supported the creation of a continuously learning organization. This will enable us to keep on introducing new improvements to our COPDnet model. A next step in the development of this QMS, should be the systematic feedback of summarized aggregated data on patients' health status to healthcare professionals or even beyond, creating a benchmark as more organizations will use the COPDnet model. However, little is known to date about the best methods for providing these summarized aggregated data to healthcare professionals, and future research is warranted.[22]

COMPLEX AND HETEROGENOUS DISEASE

After its successful development of the COPDnet integrated care model, followed by the implementation in two Dutch hospitals, we aimed to gain a better understanding of the complexity and heterogeneity of the COPD disease in patients who have been referred to secondary care for the first time. We did this from two angles, namely from the perspective of physical functioning and from the perspective of treatable traits for non-pharmacological intervention options.

Physical functioning

Physical functioning, consisting of an impaired physical capacity (PC) and/or a low-level of daily physical activity (PA), is often impaired in patients with COPD.[23-25] Van Lummel et al. published a conceptual framework in which PC and PA were represented as associated but separate domains of physical functioning in the elderly (i.e. an improvement in PC does not automatically imply an increase in PA).[26] This may explain why an intervention such as an exercise training only shows an improvement on one of the outcomes, but it does not mean that someone actually becomes more physically active in daily life. The need for further research in this field of physical functioning has been acknowledged both by the American Thoracic Society and the European Respiratory Society.[25,27] We saw this as an opportunity to investigate and gain a better understanding of physical functioning in patients with COPD. Therefore, we used this framework as a starting point for the development of a PC-PA quadrant concept, in which patients with COPD could be subdivided along axes of what they physically "can do" (PC), as in an exercise test, and what they actually "do do" (PA), in their daily lives. First of all, we wanted to determine the distribution of patients with COPD over the different PC-PA quadrants. Low PC ("can't do") defined as a six-Minute Walking Distance (6MWD) lower than 70% of the predicted value[28] and low PA ("don't do"), using a step-defined inactivity index, defined as less than 5000 steps per day.[29,30] Secondly, we

wanted to explore whether differences exist in clinical characteristics between these quadrants. As a result, described in **Chapter 4**, we found that the PC-PA quadrant concept allows us to distinguish patients with COPD along the axes of PC and PA into four exclusive subgroups with distinctive PC-PA values. Furthermore, we found that these PC-PA quadrants are considerably different in all measured multiple clinical characteristics, except for educational levels. Therefore we have stated that this PC-PA quadrant concept may serve as a pragmatic clinical tool, that may be useful in the understanding of physical functioning of patients with COPD. In that sense, determining physical functioning, is actually a simple and not an academic achievement. Future studies have to determine if the PC-PA quadrants may be useful in the selection of appropriate personalized interventions to improve physical function in patients with COPD, and their role in helping to better understand the association between low PA and/or PC and hospitalization risk. Already one other multidisciplinary research group has proposed a new Dutch model for referral of patients with COPD to the right type of exercise-based care, including a healthy lifestyle advise, physiotherapy and/or pulmonary rehabilitation, at the right time based on the instability of the disease, burden of disease, physical capacity and physical activity, but especially regardless of the degree of airflow limitation.[31]

Treatable traits

As stated above, we aimed to gain a better understanding of the complexity and heterogeneity of the COPD disease in patients who have been referred to secondary care for the first time. Despite the fact that we might have a better insight in the understanding of physical functioning in patients with COPD, we were also curious about the prevalence of relevant and modifiable pulmonary, extrapulmonary and, behavioral/lifestyle risk factors in patients with COPD upon first time referral to a pulmonologist. These so-called treatable traits (TTs), have been introduced by Agusti et al., and refers to a precision medicine approach to the diagnosis and management of chronic airway diseases in general, and asthma and COPD in particular.[32] TTs need to be identified through a comprehensive assessment and subsequently addressed in a patient-centered management plan.[33] Therefore, we found this an opportunity for our research group to assess the prevalence of nine TTs pinpointing nonpharmacological intervention options in patients who were enrolled in our COPDnet model. In **Chapter 5**, we described a study that assessed how these TTs co-occurred and whether and to what extent the TTs increased the odds of having a severely impaired health status. The results of our study showed that patients exhibited on average four out of nine TTs qualifying for nonpharmacological intervention options and that these TTs appeared to be relatively independent of each other and mostly in unique combinations. This again emphasizes the complexity and heterogeneity of the COPD disease beyond the degree of airflow limitation.[34] Furthermore, we found a positive association between

the number of TTs and the impaired health status. Thus, our study once again confirms the severe health status problems in patients who were referred for the first time from primary to secondary care.[35] We have chosen deliberately to use this set of TTs and not the biomedical traits, because for each of these TTs, evidence-based non-pharmacological interventions are available. In addition, it is striking that so few patients with COPD made use of non-pharmacological intervention options in primary care prior to the referral. Therefore, we concluded that our findings indicates the importance that the relatively simple TTs examined in our study provide an opportunity to relieve symptoms and to improve the day-to-day daily functioning of highly symptomatic patients with COPD. However, we also recognize that there is a lot of variation and fluctuation in the health status of the COPD patient, which also applies to a health condition with exacerbations, but also without exacerbations.[36-38] Therefore, the current findings emphasize even more the need to identify TTs through a comprehensive assessment in each individual patient with COPD, such as the COPDnet integrated care model, early in the disease career and followed by a patient-centered COPD management plan including pharmacological and non-pharmacological intervention options.

MULTIDISCIPLINARY NON-PHARMACOLOGICAL INTERVENTION OPTIONS

On the basis of the results of our research that we present in **Chapter 4** and **Chapter 6,** we advise pulmonologists and general practitioners to refer patients with COPD much more often to a non-pharmacological intervention option. The vast majority of the patients referred to secondary care turned out to have a severely impaired health status and show several treatable traits qualifying them for non-pharmacological intervention options. Indeed, the results of **Chapter 5** suggest that patients are better able to perform daily activities as a result of monodisciplinary occupational therapy treatment. Also the results from **Chapter 7** argue for more frequent use of non-pharmacological interventions. In this chapter we conclude that an improved health status was found in patients with COPD who received care according to the COPDnet integrated care model. However, patients who have been referred to an interdisciplinary pulmonary rehabilitation program predominantly accounted for this effect. This is understandable in retrospect. Most of the patients show multiple treatable traits. Addressing just one can have an effect on this specific trait, but may be not strong enough to translate into a measurable improvement in overall health status. Moreover, an interdisciplinary approach as in pulmonary rehabilitation in a secondary or tertiary care setting, in which multiple disciplines work together with the patient on the same goal(s), the whole may be better than the sum of its parts.[39]

The COPDnet model wishes to comply with the current Dutch care policy, in which care to patients with chronic conditions, such as COPD, is substituted in primary care as much as possible. The policy is partly prescribed because it is assumes that care in primary care can result in less expensive care. However, the data from our research shows that the effects are disappointing and the question arises whether this assumption is correct. Because care that has no effect in an improved health status for patients cannot result in cheaper care.[40] Therefore, the results of our research give reason to address this aspect in the further development of the COPDnet model.

Methodological considerations

First of all, the studies we did to evaluate the clinical effectiveness of home-based occupational therapy and the COPDnet model were performed with a before-after study design. This means that we have to be careful with the conclusions we draw from our studies and we can only apply the recommendations or a more robust conclusion to the local geographic context of our two COPDnet hospitals and primary care regions. However, randomized controlled trials may have a high internal validity, whereas real-life studies have high generalizability.[41] In addition, a longitudinal follow-up of our studies should be desirable.

Our research was performed in patients who were referred to secondary care and they all followed our COPDnet integrated care model (**Chapter 6** and **Chapter 7**). This means that selection bias may have occurred, because non-pharmacological intervention options were only offered to patients who might have been preselected and primed during the diagnostic and self-management part of the care model.

In our final study (**Chapter 7**), in which we obtained self-reported data, we concluded that we had a high percentage of lost to follow-up measurements. This may violate the internal validity of these studies. However, data appeared to have occurred completely at random.

FUTURE RESEARCH AND DEVELOPMENT

Several questions remain, or have arisen from the studies performed in this thesis, which are worth further investigation.

A further step in the evaluation of the COPDnet integrated care model would be to examine the fidelity of the model. Fidelity is defined as the degree to which an intervention was implemented as it was prescribed in the original protocol or as it was intended by the program developers.[42-44] The fidelity of this model could be evaluated from three different perspectives; the patient perspective, health care perspective and organizational perspective. Based on these perspectives, the active ingredients of the model will be identified and further adjustments can be made.

Furthermore, it would be relevant to evaluate the cost of care of the diagnostic trajectory in secondary care, as a component of the model. The content of the diagnostic trajectory contains several novel aspects and can also appear to be expensive and labor-intensive, compared to a health care trajectory in which only patients' biomedical aspects are central. Cost of care can be analyzed based on completed and registered care activities performed during the diagnostic trajectory, complying with the principles of Time-Driven Activity-Based Costing (TDABC) in value-based health care.[45] Also for this implication for future research we have already described a proposal in our study protocol (see **Chapter 3**).

Future studies have to determine if the PC-PA quadrants concept may be useful in the selection of appropriate personalized interventions to improve physical function in patients with COPD. Furthermore, in helping to better understand the association between low PA and/or PC and hospitalization risk.

In this thesis we only evaluated the monodisciplinary non-pharmacological intervention option, specifically, home-based occupational therapy in primary care. It would be interesting to investigate whether any of the other monodisciplinary options in primary care were also clinically effective.

An improved health status was found in patients with COPD who received care according to the COPDnet integrated care model. Although, subgroups participating in an interdisciplinary pulmonary rehabilitation program predominantly accounted for this effect. It could be therefore interesting to evaluate if multidisciplinary intervention options in primary care could also attribute to a better health care status in patients with COPD. In addition, it would also be interesting for the development of the COPDnet model to evaluate why one patient with the same burden of disease was referred to an interdisciplinary pulmonary rehabilitation program and the other one to a non-pharmacological intervention option in primary care (due to the wish to comply to current Dutch health care policy or due to the fact that shared-decision making is an important fact in this COPDnet model).

Implications for practice

This thesis has led to a newly developed integrated care model in secondary care in which patients with COPD with a moderate to severe burden of disease should benefit from a comprehensive multidimensional diagnostic assessment of patients' health status. Knowing the overall complexity and heterogeneity of the COPD disease.
In addition, based on this reaffirmation of the complexity and heterogeneity of this chronic disease, this should be leading in the choice of the correct referral to (a) patient-centered (multidisciplinary) (non)-pharmacological intervention option(s).

Monodisciplinary if possible, but multidisciplinary if the complexity gives rise to it. Furthermore, this thesis has led to a newly developed conceptual quadrant framework, which may serve as a pragmatic clinical tool, to better understand the impaired physical functioning in patients with COPD and to improve the selection of appropriate interventions to improve this impaired physical function.

GENERAL CONCLUSIONS

In order to gain insights in the complexity and heterogeneity of the COPD disease and in order to even have the ability to improve outcomes of care for patients with COPD, we recommend that patients with COPD with moderate to severe burden of disease should be assessed through a comprehensive assessment of the integrated health status and activation for self-management applied in an integrated transmural care model in secondary care. Furthermore, based on these diagnostic analyses and patient's preferences which resulted in a patient-centred individual care plan, we should encourage pulmonologists and general practitioners to refer these patients with COPD with moderate to severe burden of disease to multidisciplinary non-pharmacological intervention options in primary care, or to multidisciplinary pulmonary rehabilitation in secondary or tertiary care.

REFERENCES

1. Kayyali R, Odeh B, Frerichs I, et al. COPD care delivery pathways in five European Union countries: mapping and health care professionals' perceptions. *International Journal of Chronic Obstructive Pulmonary Disease.* 2016;11:2831-2838.

2. Kruis AL, Smidt N, Assendelft WJ, et al. Cochrane corner: is integrated disease management for patients with COPD effective? *Thorax.* 2014;69(11):1053-1055.

3. Long Alliantie Nederland (LAN) [Lung Alliance Netherlands]. Zorgstandaard COPD [Care Standard COPD]; 2016. Available from: http:// www.longalliantie.nl/zorgstandaard-copd. Accessed April 05, 2021. Dutch.

4. van den Akker EF, van 't Hul AJ, Chavannes NH, et al. Development of an integral assessment approach of health status in patients with obstructive airway diseases: the CORONA study. *International Journal of Chronic Obstructive Pulmonary Disease.* 2015;10:2413-2422.

5. Vercoulen JH. A simple method to enable patient-tailored treatment and to motivate the patient to change behaviour. *Chronic Respiratory Disease.* 2012;9(4):259-268.

6. Blackstock FC, ZuWallack R, Nici L, Lareau SC. Why Don't Our COPD Patients Listen to Us? The Enigma of Nonadherence. *Annals of the American Thoracic Society.* 2016.

7. Effing TW, Bourbeau J, Vercoulen J, et al. Self-management programmes for COPD: moving forward. *Chronic Respiratory Disease.* 2012;9(1):27-35.

8. Hibbard JH, Greene J, Sacks RM, Overton V, Parrotta C. Improving Population Health Management Strategies: Identifying Patients Who Are More Likely to Be Users of Avoidable Costly Care and Those More Likely to Develop a New Chronic Disease. *Health Services Research.* 2017;52(4):1297-1309.

9. Hibbard JH, Greene J, Shi Y, Mittler J, Scanlon D. Taking the long view: how well do patient activation scores predict outcomes four years later? *Medical Care Research and Review: MCRR.* 2015;72(3):324-337.

10. Shively MJ, Gardetto NJ, Kodiath MF, et al. Effect of patient activation on self-management in patients with heart failure. *Journal of Cardiovascular Nursing.* 2013;28(1):20-34.

11. McCabe PJ, Stuart-Mullen LG, McLeod CJ, et al. Patient activation for self-management is associated with health status in patients with atrial fibrillation. *Patient Preference and Adherence.* 2018;12:1907-1916.

12. Hibbard JH, Mahoney ER, Stockard J, Tusler M. Development and testing of a short form of the patient activation measure. *Health Services Research.* 2005;40(6 Pt 1):1918-1930.

13. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implementation Science: IS.* 2011;6:42.

14. Elwyn G, Frosch D, Thomson R, et al. Shared decision making: a model for clinical practice. *Journal of General Internal Medicine.* 2012;27(10):1361-1367.

15. Antons JC, Koolen EH, Van Der HN, et al. Improvements in activation for self-management in patients with chronic airway disease via the COPDnet diagnostic trajectory in secondary care; a pilot study. *European Respiratory Journal.* 2018;52.

16. Geijer RM, Tuut MK, in't Veen JC, Broekhuizen BD, Chavannes NH, Smeele IJ. [The NHG guidelines 'Adult asthma' and 'COPD']. *Nederlands Tijdschrift voor Geneeskunde.* 2015;159:A9076.

17. Porter ME, Larsson S, Lee TH. Standardizing Patient Outcomes Measurement. *The New England Journal of Medicine.* 2016;374(6):504-506.

18. Porter ME. What is value in health care? *The New England Journal of Medicine.* 2010;363(26):2477-2481.

19. Boyce MB, Browne JP. Does providing feedback on patient-reported outcomes to healthcare professionals result in better outcomes for patients? A systematic review. *Quality of Life Research: an international journal of quality of life aspects of treatment, care and rehabilitation.* 2013;22(9):2265-2278.

20. Dawson J, Doll H, Fitzpatrick R, Jenkinson C, Carr AJ. The routine use of patient reported outcome measures in healthcare settings. *BMJ.* 2010;340:c186.

21. Boyce MB, Browne JP, Greenhalgh J. The experiences of professionals with using information from patient-reported outcome measures to improve the quality of healthcare: a systematic review of qualitative research. *BMJ Quality & Safety.* 2014;23(6):508-518.

22. Hancock SL, Ryan OF, Marion V, et al. Feedback of patient-reported outcomes to healthcare professionals for comparing health service performance: a scoping review. *BMJ open.* 2020;10(11):e038190.

23. Mesquita R, Spina G, Pitta F, et al. Physical activity patterns and clusters in 1001 patients with COPD. *Chronic Respiratory Disease.* 2017;14(3):256-269.

24. Spruit MA, Watkins ML, Edwards LD, et al. Determinants of poor 6-min walking distance in patients with COPD: the ECLIPSE cohort. *Respiratory Medicine.* 2010;104(6):849-857.

25. Watz H, Pitta F, Rochester CL, et al. An official European Respiratory Society statement on physical activity in COPD. *The European Respiratory Journal.* 2014;44(6):1521-1537.

26. van Lummel RC, Walgaard S, Pijnappels M, et al. Physical Performance and Physical Activity in Older Adults: Associated but Separate Domains of Physical Function in Old Age. *PloS One.* 2015;10(12):e0144048.

27. Celli BR, Decramer M, Wedzicha JA, et al. An official American Thoracic Society/European Respiratory Society statement: research questions in COPD. *The European Respiratory Journal.* 2015;45(4):879-905.

28. Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *The European Respiratory Journal.* 2014;44(6):1428-1446.

29. Depew ZS, Novotny PJ, Benzo RP. How many steps are enough to avoid severe physical inactivity in patients with chronic obstructive pulmonary disease? *Respirology.* 2012;17(6):1026-1027.

30. Tudor-Locke C, Craig CL, Thyfault JP, Spence JC. A step-defined sedentary lifestyle index: <5000 steps/day. *Applied Physiology, Nutrition, and Metabolism.* 2013;38(2):100-114.

31. Spruit MA, Van't Hul A, Vreeken HL, et al. Profiling of Patients with COPD for Adequate Referral to Exercise-Based Care: The Dutch Model. *Sports Medicine.* 2020;50(8):1421-1429.

32. Agusti A, Bel E, Thomas M, et al. Treatable traits: toward precision medicine of chronic airway diseases. *The European Respiratory Journal.* 2016;47(2):410-419.

33. Agusti A, Bafadhel M, Beasley R, et al. Precision medicine in airway diseases: moving to clinical practice. *The European Respiratory Journal.* 2017;50(4).

34. Houben-Wilke S, Augustin IM, Vercoulen JH, et al. COPD stands for complex obstructive pulmonary disease. *European Respiratory Review : an official journal of the European Respiratory Society.* 2018;27(148).

35. de Klein MM, Peters JB, van 't Hul AJ, et al. Comparing health status between patients with COPD in primary, secondary and tertiary care. *NPJ Primary Care Respiratory Medicine.* 2020;30(1):39.

36. Jones GL. Quality of life changes over time in patients with chronic obstructive pulmonary disease. *Current Opinion in Pulmonary Medicine.* 2016;22(2):125-129.

37. Wilke S, Jones PW, Mullerova H, et al. One-year change in health status and subsequent outcomes in COPD. *Thorax.* 2015;70(5):420-425.

38. Sundh J, Montgomery S, Hasselgren M, et al. Change in health status in COPD: a seven-year follow-up cohort study. *NPJ Primary Care Respiratory Medicine.* 2016;26:16073.

39. Singh R, Kucukdeveci AA, Grabljevec K, Gray A. The role of Interdisciplinary Teams in Physical and Rehabilitation Medicine. *Journal of Rehabilitation Medicine.* 2018;50(8):673-678.

40. Kirsch F, Schramm A, Schwarzkopf L, et al. Direct and indirect costs of COPD progression and its comorbidities in a structured disease management program: results from the LQ-DMP study. *Respiratory Research.* 2019;20(1):215.

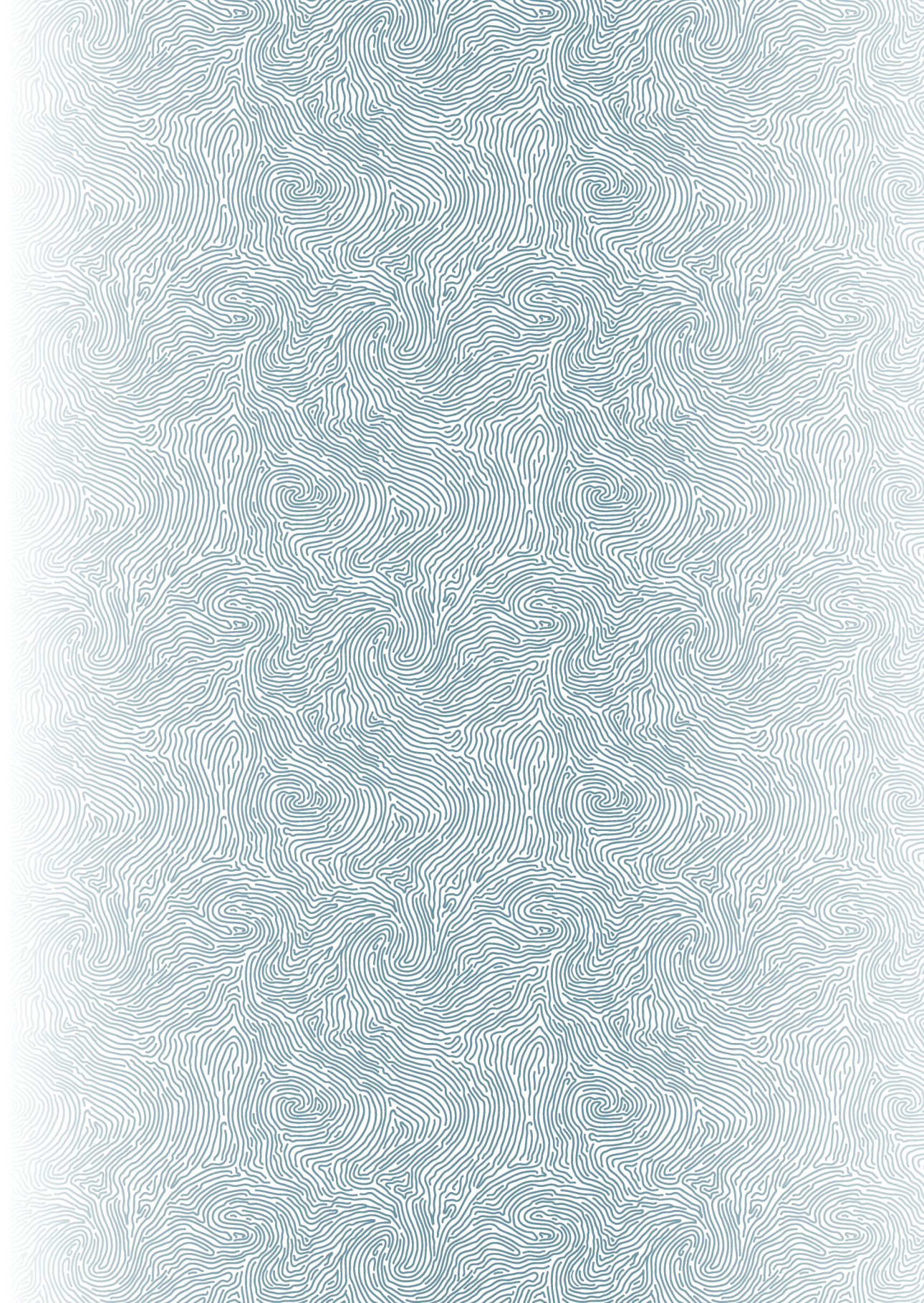
41. Saturni S, Bellini F, Braido F, et al. Randomized Controlled Trials and real life studies. Approaches and methodologies: a clinical point of view. *Pulmonary Pharmacology Therapeutics.* 2014;27(2):129-138.

42. Dusenbury L, Brannigan R, Falco M, Hansen WB. A review of research on fidelity of implementation: implications for drug abuse prevention in school settings. *Health Education Research.* 2003;18(2):237-256.

43. Rabin BA, Brownson RC, Haire-Joshu D, Kreuter MW, Weaver NL. A glossary for dissemination and implementation research in health. *Journal of Public Health Management and Practice.* 2008;14(2):117-123.

44. Proctor E, Silmere H, Raghavan R, et al. Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda. *Administration and Policy in Mental Health.* 2011;38(2):65-76.

45. Kaplan RS, Anderson SR. Time-driven activity-based costing. *Harvard Business Review.* 2004;82(11):131-138, 150.



Summary

Summary in Dutch

SUMMARY

The overall aim of the research on which this thesis is based was to improve the outcomes of care for patients with Chronic Obstructive Pulmonary Disease (COPD) with moderate or severe burden of disease who are referred to secondary care. Therefore a newly designed integrated care model, named the COPDnet integrated care model, was developed, implemented and investigated in two different regions in the Netherlands.

Chapter 2

COPD is a highly prevalent disease, with a high significant burden of disease on those affected as well as for society, and it places an inordinate burden on healthcare resources and costs. Integrated disease management interventions holds the promise to generate better outcomes, also in patients with COPD. However, integrated care models are only in limited use in our present regular COPD care pathways.

Therefore, we observed room for improvement in the current care pathways for COPD patients across all healthcare settings, in the content, as well as the organisational aspects of care. **Chapter 2** describes the results of our research project to design an integrated COPD disease management model. The COPDnet integrated care model was designed based on scientific theories and models. In addition, it was specifically created for patients with moderate or severe burden of disease, who were referred to secondary care, and qualify for both pharmacological and non-pharmacological intervention options. The COPDnet integrated care model comprises 1) a diagnostic trajectory in a secondary care setting, 2) a nonmedical intervention program in a primary care setting, and 3) a pulmonary rehabilitation service in a tertiary care setting. The model also includes a quality management system and regional agreements about exacerbation management and palliative care.

Chapter 3

Although we developed an evidence-based model of integrated care for COPD patients with moderate or severe burden of disease referred to secondary care, named the COPDnet integrated care model, in order to establish a care process that maximized outcomes in relation to the costs and efforts made, it might be a challenge to implement this model. Therefore, **Chapter 3** describes a study protocol: 1) to evaluate the feasibility of employing the COPDnet integrated care model in present day real life care within the context of the Dutch healthcare system, 2) to explore the potential health status benefits from the patients perspective, and 3) to analyse the costs of care of this model. This study protocol focuses on the implementation of this newly developed model into three hospitals and affiliated primary care regions.

Chapter 4

Patients with COPD often experience a reduced impaired physical capacity (PC) and a low-level of daily physical activity (PA). PC refers to the ability to perform physical activities and daily PA may be defined as any bodily movement produced by skeletal muscles that results in energy expenditure beyond that of the resting state. PC and PA represent associated but separate domains of physical function. This chapter had two aims: (1) to determine the distribution of patients with COPD over the PC-PA quadrants, and (2) to explore whether differences exist in clinical characteristics between these quadrants. A total of 662 patients were divided into the following quadrants: (I) low PC (6MWD <70% predicted), low PA, using a step-defined inactivity index (<5000 steps/day, "can't do, don't do" quadrant); (II) preserved PC, low PA ("can do, don't do" quadrant); (III) low PC, preserved PA ("can't do, do do" quadrant); and (IV) preserved PC, preserved PA ("can do, do do" quadrant). We found statistically significant differences between quadrants for all clinical characteristics, except for educational levels. Finally, we concluded that this study proves the applicability of the PC-PA quadrant concept in patients with COPD and this concept can serve as a pragmatic clinical tool, which may be useful in understanding the impaired physical function in patients with COPD.

Chapter 5

COPD is a complex and heterogenous disease. In order to examine this complexity and heterogeneity of the disease, patients with mild to moderate burden of disease who have been referred to a pulmonologist in secondary care, should be assessed through a comprehensive assessment. This diagnostic trajectory should focus on identifying the so-called treatable traits; relevant and modifiable pulmonary, extrapulmonary, and behavioral/lifestyle features. Such a comprehensive assessment that focuses on addressing treatable traits is common at the start of a pulmonary rehabilitation program, but is not standard in primary or secondary care. However, the diagnostic trajectory of the COPDnet integrated care model also identifies these treatable traits. In **Chapter 5** we assessed the prevalence of nine potentially clinically relevant treatable traits pinpointing non-pharmacological intervention options; 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. In addition we analyzed the combinations in which the treatable traits occur and whether the presence of multiple treatable traits increases the odds of having a severely impaired health status. Data were collected from a sample of 402 patients with COPD and a second sample of 381 patients with COPD was used for validation. We concluded patients with COPD showed multiple treatable traits indicating them to several nonpharmacological interventions, these treatable traits coexist in many different combinations and they are relatively

independent. Furthermore we found that the presence of these treatable traits increases the odds of having a severely impaired health status.

Chapter 6

One of the important parts of the COPDnet integrated care model is first of all formed by a diagnostic trajectory in secondary care with the aim to make an comprehensive analysis of the health status and to empower patients for self-management. Based on this comprehensive diagnostic analysis and patient's preferences, patients will be referred more frequent to non-pharmacological intervention options. One of the non-pharmacological primary care intervention options is home-based occupational therapy; a primary care intervention option that has hardly been investigated in patients with COPD. Therefore, in **Chapter 6**, we evaluated the clinical effectiveness of home-based monodisciplinary occupational therapy in patients with COPD. Home-based occupational therapy was offered to patients who had previously completed the comprehensive diagnostic COPDnet trajectory in the outpatient respiratory department of Bernhoven Hospital, Uden, The Netherlands, and when the diagnostic outcomes showed that breathlessness and/or fatigue had a negative effect on the performance of daily functioning. In **Chapter 6** we used the Canadian Occupational Performance Measure (COPM), which is a semi-structured interview to identify and evaluate self-perceived problems in occupational performance areas. Pre- and postintervention data, which we obtained in 41 patients with COPD, showed a statistically significant difference score in COPM performance and satisfaction scores. Therefore, we concluded that home-based monodisciplinary occupational therapy in primary care can contribute significantly to the improvement of daily functioning in patients with COPD.

Chapter 7

The overall aim of this thesis was to design a newly integrated care model in secondary care for patients with COPD with moderate or severe burden of disease. We developed this model, called the COPDnet integrated care model, and implemented it in two regions in the Netherlands; Radboudumc, Nijmegen, and Bernhoven Hospital, Uden, both in the Netherlands. In this chapter we evaluated the clinical effectiveness of the COPDnet integrated care model on health status change in 402 patients with COPD. The main outcome in this study was the Clinical COPD Questionnaire (CCQ) measurement at baseline and between 7- and 9-months later. 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. We found a statistically significant improved CCQ total score, i.e. an improved health status, in patients with COPD who received care according to this newly developed and implemented COPDnet integrated care model. Furthermore,

subgroup analyses revealed that patients with COPD, who participated in an interdisciplinary pulmonary rehabilitation program, predominantly accounted for this effect.

Chapter 8

In **Chapter 8** the findings of the various research studies on which this thesis is based were summarized and discussed in the light of current scientific research. We discussed the results based on three relevant topics.

Our first topic was described as 'Integrated disease management care'. It was discussed that patients with COPD with moderate or severe burden of disease could be good candidates for an integrated disease management approach based on their impaired health status. We developed the COPDnet integrated care model based on an innovative diagnostic pathway that was already successfully developed and implemented in the Netherlands, and expanded it by three different elements. First of all, we added self-management support to the diagnostic pathway in secondary care. Secondly, we developed and implemented a modular program for non-pharmacological intervention options in primary care, and, we adopted an already available center-based pulmonary rehabilitation program in secondary or tertiary care. Finally, we incorporated the systematic outcome measurement in a Quality Management System.

The second topic we discussed in this chapter was the complexity and heterogeneity of the COPD disease in terms of impaired physical functioning and from the perspective of treatable traits for non-pharmacological intervention options.

In the third relevant topic, we discussed that the overall health status of patients with COPD with moderate to severe burden of disease should benefit from multidisciplinary non-pharmacological intervention options in primary, in secondary or tertiary care, because most of the patients showed the presence of multiple treatable traits.

Finally, in this chapter, recommendations were made for patients with COPD with a moderate to severe burden of disease who have been referred for the first time to a pulmonologist in secondary care in order to improve health status, based on the results of our newly developed COPDnet integrated care model and the PC-PA quadrant concept, introduced in this thesis.

SUMMARY IN DUTCH

Het algemene doel van het onderzoek waarop dit proefschrift is gebaseerd, was het verbeteren van de uitkomsten van zorg voor patiënten met Chronic Obstructive Pulmonary Disease (COPD) met matige of ernstige ziektelast die worden doorverwezen naar de tweede lijn. Daarom is er een nieuw ontworpen integraal zorgmodel, genaamd het COPDnet integrale zorgmodel, ontwikkeld, geïmplementeerd en onderzocht, in twee verschillende regio's in Nederland.

Hoofdstuk 2

COPD is een veel voorkomende ziekte, met een hoge significante ziektelast voor zowel de getroffenen als voor de samenleving, en het legt een buitensporige last op de middelen voor de gezondheidszorg en kosten. 'Integrated disease management' interventies zijn veelbelovend en zouden mogelijk betere resultaten kunnen genereren, ook bij patiënten met COPD. In onze huidige reguliere COPD-zorgpaden worden modellen van geïntegreerde zorg echter slechts in beperkte mate gebruikt.

Daarom zagen we ruimte voor verbetering in de huidige zorgpaden voor patiënten met COPD in de gehele zorgsector, zowel wat betreft de inhoud, als ook de organisatorische aspecten van de zorg. **Hoofdstuk 2** beschrijft de resultaten van ons onderzoeksproject om een geïntegreerd COPD zorgmodel te ontwerpen. Het COPDnet integrale zorgmodel is ontworpen op basis van wetenschappelijke theorieën en modellen. Bovendien is het speciaal ontwikkeld voor patiënten met COPD met matige of ernstige ziektelast, die zijn verwezen naar de tweedelijnszorg, en in aanmerking komen voor zowel farmacologische als niet-farmacologische interventiemogelijkheden. Het COPDnet integrale zorgmodel omvat 1) een diagnostisch traject in de tweedelijnszorg, 2) een niet-medicamenteus interventieprogramma in de eerstelijnszorg en 3) een longrevalidatie in een derdelijnszorg. Het model omvat ook een kwaliteitsmanagementsysteem en regionale afspraken over exacerbatiemanagement en palliatieve zorg.

Hoofdstuk 3

Hoewel we een evidence-based model van geïntegreerde zorg hebben ontwikkeld, voor patiënten met COPD met een matige of ernstige ziektelast die zijn doorverwezen naar de tweedelijnszorg, genaamd het COPDnet integrale zorgmodel, met als doel een zorgproces tot stand te brengen dat maximale resultaten oplevert in relatie tot de gemaakte kosten en inspanningen, kan het een uitdaging zijn om dit model te implementeren. Daarom beschrijft **Hoofdstuk 3** een studieprotocol: 1) om de haalbaarheid te evalueren van het gebruik van het COPDnet integrale zorg model in de huidige dagelijkse zorg binnen de context van het Nederlandse zorgstelsel, 2) om

de potentiële voordelen voor de gezondheidstoestand vanuit het perspectief van de patiënt te onderzoeken, en 3) om de zorgkosten van dit model te analyseren. Dit studieprotocol richt zich op de implementatie van dit nieuw ontwikkelde zorgmodel in drie ziekenhuizen en de daarbij aangesloten eerstelijnsregio's.

Hoofdstuk 4

Patiënten met COPD ervaren vaak een verminderde fysieke capaciteit (Physical Capacity - PC) en een laag niveau van dagelijkse fysieke activiteit (Physical Activity - PA). Fysieke capaciteit verwijst naar het vermogen om fysieke activiteiten daadwerkelijk uit te kunnen voeren en dagelijkse fysieke activiteit kan worden gedefinieerd als elke lichaamsbeweging die wordt geproduceerd door skeletspieren wat resulteert in energieverbruik dat hoger is dan dat van de rusttoestand. Fysieke capaciteit en fysieke activiteit staan voor geassocieerde -, maar ook afzonderlijke domeinen van fysiek functioneren. Dit hoofdstuk had twee doelstellingen: (1) het bepalen van de verdeling van patiënten met COPD over de fysieke capaciteit en fysieke activiteit (PC-PA) kwadranten, en (2) onderzoeken of er verschillen bestaan in klinische kenmerken van de patiënten tussen deze kwadranten. In totaal werden 662 patiënten verdeeld over de volgende kwadranten: (I) lage fysieke capaciteit (6-minuten wandeltest <70% voorspeld), lage fysieke activiteit, gemeten met behulp van een stap gedefinieerde inactiviteitsindex (<5000 stappen per dag, "can't do, don't do" kwadrant); (II) behouden fysieke capaciteit, lage fysieke activiteit ("can do, don't do" kwadrant); (III) lage fysieke capaciteit, behouden fysieke activiteit ("can't do, do do" kwadrant); en (IV) behouden fysieke capaciteit, behouden fysieke activiteit ("can do, do do" kwadrant). We vonden statistisch significante verschillen tussen de kwadranten voor alle klinische kenmerken van patiënten, behalve voor opleidingsniveaus. Ten slotte concludeerden we dat deze studie de toepasbaarheid van het fysieke capaciteit-fysieke activiteit (PC-PA) kwadranten concept bij patiënten met COPD bewijst en dat dit concept kan dienen als een pragmatisch klinisch hulpmiddel, wat nuttig kan zijn bij het beter begrijpen van het verminderd fysiek functioneren bij patiënten met COPD.

Hoofdstuk 5

COPD is een complexe en heterogene ziekte. Om deze complexiteit en heterogeniteit van de ziekte te onderzoeken dienen patiënten, met milde tot matige ziektelast die zijn doorverwezen naar een longarts in de tweedelijnszorg, te worden beoordeeld aan de hand van een uitgebreid assessment. Dit diagnostische traject zou zich moeten richten op het identificeren van de zogenaamde behandelbare kenmerken ("treatable traits"); relevante en aanpasbare pulmonale, extra-pulmonale en gedrags-/levensstijlkenmerken. Zo'n uitgebreid assessment dat zich richt op het aanpakken van behandelbare kenmerken is gebruikelijk bij de start van een longrevalidatieprogramma, maar is niet standaard in de eerste of tweede lijn. Echter, het diagnostische traject van het COPDnet

integrale zorgmodel identificeert wel deze behandelbare kenmerken. In Hoofdstuk 5 hebben we de prevalentie onderzocht van negen potentieel klinisch relevante behandelbare kenmerken die duiden op niet-farmacologische interventie opties; huidige rookstatus, activiteit gerelateerde kortademigheid, frequente exacerbaties <12 maanden, ernstige vermoeidheid, depressieve stemming, slechte fysieke capaciteit, lage fysieke activiteit, slechte voedingstoestand en een lage mate van activering van zelfmanagement. Daarnaast hebben we de combinaties geanalyseerd waarin de behandelbare kenmerken voorkomen en of de aanwezigheid van meerdere behandelbare kenmerken de kans op een ernstig verminderde gezondheidstoestand vergroot. Gegevens werden verzameld van een steekproef van 402 patiënten met COPD en een tweede steekproef van 381 patiënten met COPD werd gebruikt voor validatie. We concludeerden dat patiënten met COPD meerdere behandelbare kenmerken vertoonden, die hen zouden kunnen verwijzen naar verschillende niet-farmacologische interventies, deze behandelbare kenmerken bestaan naast elkaar in veel verschillende combinaties en ze zijn relatief onafhankelijk. Verder ontdekten we dat de aanwezigheid van deze behandelbare kenmerken de kans op een ernstig verminderde gezondheidstoestand vergroot.

Hoofdstuk 6

Een van de belangrijke onderdelen van het COPDnet integrale zorgmodel wordt allereerst gevormd door een diagnostisch traject in de tweedelijnszorg met als doel een uitgebreide analyse van de gezondheidstoestand te maken en patiënten in staat te stellen zelfmanagement uit te voeren. Op basis van deze uitgebreide diagnostische analyse en de voorkeuren van de patiënt, zullen patiënten vaker worden verwezen naar niet-farmacologische interventie mogelijkheden. Een van de niet-farmacologische interventie mogelijkheden in de eerstelijnszorg is ergotherapie aan huis; een interventie mogelijkheid in de eerstelijnszorg die nauwelijks is onderzocht bij patiënten met COPD. Daarom hebben we in **Hoofdstuk 6** de klinische effectiviteit van monodisciplinaire ergotherapie aan huis bij patiënten met COPD geëvalueerd. Ergotherapie aan huis werd aangeboden aan patiënten die eerder het uitgebreide diagnostische COPDnet traject hadden doorlopen op de poliklinische longafdeling van ziekenhuis Bernhoven, Uden, Nederland, en wanneer uit de diagnostische uitkomsten bleek dat kortademigheid en / of vermoeidheid een negatief effect hadden op de prestaties van het dagelijks functioneren. In **Hoofdstuk 6** hebben we de Canadian Occupational Performance Measure (COPM) gebruikt, een semigestructureerd interview om zelf ervaren problemen op het gebied van dagelijks handelen te identificeren en te evalueren. Voor- en na-interventie gegevens, die we verkregen bij 41 patiënten met COPD, toonden een statistisch significant verschilscore in COPM prestatie- en tevredenheidsscores. Daarom concluderen we dat monodisciplinaire ergotherapie aan huis in de eerste lijn significant kan bijdragen aan de verbetering van het dagelijks functioneren bij patiënten met COPD.

Hoofdstuk 7

Het algemene doel van dit proefschrift was het ontwerpen van een nieuw geïntegreerd zorgmodel in de tweede lijn voor patiënten met COPD met een matige of ernstige ziektelast. We hebben dit model ontwikkeld, het COPDnet integrale zorgmodel genaamd, en geïmplementeerd in twee regio's in Nederland; Radboudumc, Nijmegen, en Bernhoven Ziekenhuis, Uden, beide in Nederland. In dit hoofdstuk hebben we de klinische effectiviteit van het COPDnet model geëvalueerd op basis van de verandering van de gezondheidstoestand bij 402 patiënten met COPD. Het belangrijkste resultaat van deze studie was de uitkomst van de Clinical COPD Questionnaire (CCQ) bij aanvang en tussen 7 en 9 maanden later. De primaire analyse werd uitgevoerd voor de volledige sample. Daarnaast werden subgroep analyses uitgevoerd na stratificatie voor het type niet-farmacologische interventie waarnaar patiënten waren verwezen. We vonden een statistisch significant verbeterde CCQ-totaalscore, d.w.z. een verbeterde gezondheidstoestand, bij patiënten met COPD die zorg kregen volgens dit nieuw ontwikkelde en geïmplementeerde COPDnet integrale zorgmodel. Bovendien lieten subgroep analyses zien dat patiënten met COPD, die deelnamen aan een interdisciplinair longrevalidatieprogramma, overwegend verantwoordelijk waren voor dit effect.

Hoofdstuk 8

In **Hoofdstuk 8** zijn de bevindingen van de verschillende onderzoeken waarop dit proefschrift gebaseerd is, samengevat en bediscussieerd in het licht van huidig wetenschappelijk onderzoek. We bediscussieerden de resultaten aan de hand van drie relevante onderwerpen.

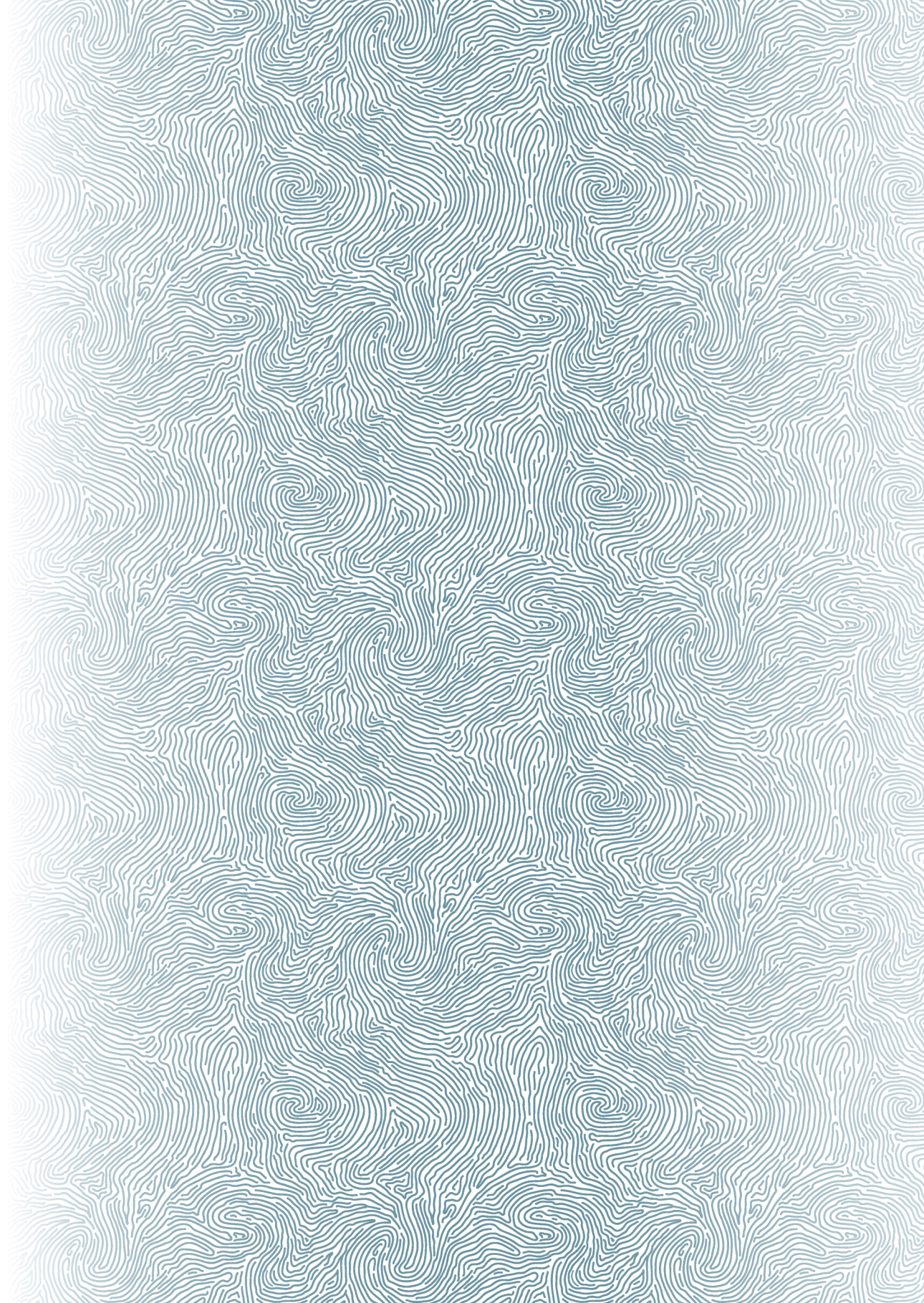
Het eerste onderwerp werd beschreven onder de subtitel 'integrated disease management care'. Er werd bediscussieerd dat patiënten met COPD met matige of ernstige ziektelast goede kandidaten zouden kunnen zijn voor een 'integrated disease management' op basis van hun verminderde gezondheidstoestand. We ontwikkelden het COPDnet integrale zorgmodel op basis van een innovatief diagnostisch traject dat al succesvol was ontwikkeld en geïmplementeerd in Nederland en breidden dit uit met drie verschillende onderdelen. Allereerst hebben we het activeren van zelfmanagement toegevoegd aan het diagnostische traject in de tweede lijn. Ten tweede hebben we een modulair programma ontwikkeld en geïmplementeerd voor niet-farmacologische interventie opties in de eerstelijnszorg, en hebben we een reeds beschikbaar centrum-gebaseerd programma voor longrevalidatie in de secundaire of tertiaire zorg meegenomen. Ten slotte hebben we het systematische meten van zorguitkomsten verwerkt in een kwaliteitsmanagementsysteem.

Het tweede onderwerp dat we in dit hoofdstuk hebben besproken, was de complexiteit en heterogeniteit van de COPD ziekte in termen van verminderd fysiek functioneren

en vanuit het perspectief van behandelbare kenmerken voor niet-farmacologische interventie opties.

In het derde relevante onderwerp bediscussieerden we dat de algehele gezondheidstoestand van patiënten met COPD met matige tot ernstige ziektelast zou moeten profiteren van multidisciplinaire niet-farmacologische interventie mogelijkheden in de eerstelijns, tweedelijns of derdelijns zorg, omdat de meeste patiënten de aanwezigheid van meerdere behandelbare kenmerken vertoonden.

Ten slotte zijn in dit hoofdstuk aanbevelingen gedaan voor patiënten met COPD met een matige tot ernstige ziektelast die voor het eerst zijn verwezen naar een longarts in de tweedelijns zorg om de gezondheidstoestand te verbeteren, gebaseerd op de resultaten van het nieuw ontwikkelde COPDnet geïntegreerd zorgmodel en het fysieke capaciteit-fysieke activiteit (PC-PA) kwadranten concept, geïntroduceerd in dit proefschrift.



Appendices

Data management

PhD Portfolio

Curriculum vitae

Curriculum vitae (NL)

Dankwoord

DATA MANAGEMENT

All studies described in this thesis have been conducted in accordance with the principles of the Declaration of Helsinki. The medical and ethical review board Committee on Research Involving Human Subjects Region Arnhem Nijmegen, Nijmegen, the Netherlands has given approval to conduct these studies.

Informed consent

The Medical Ethical Committee of the Radboudumc approved all the studies described in this thesis, and because the participants were subjected to usual care, they considered that it did not fall within the remit of the Medical Research Involving Human Subjects Act (WMO). Data from Chapter 4, 5, 6, and 7 were collected by pulmonologists or respiratory nurses.

Secured data storage

The survey and questionnaire data described in Chapter 4, 5 and 7 were collected via a secured platform version of RadQuest or CuraVista. Data from Chapter 6 were obtained from patient's Electronic Health Record (EHR). Data from the studies of Chapter 4, 5, 6 and 7 are stored on the Radboudumc, department of Pulmonary Diseases server: UCCZdata$(umcfs010) in the folder Sneldiagnostiek COPD en Astma\ COPDnet database. Data that was originally obtained on paper were scanned and then stored in an EHR.

All scanned paper data were entered into the computer by use of Microsoft Excel. Data were converged from Excel to SPSS (SPSS Inc., Chicago, Illinois, USA). All data are archived pseudonymized. Key records are locked and archived separate from the data. All data will be kept for 15 years after termination of the study.

Accessibility of data

The datasets, analyzed during these studies, are available on reasonable request with dr. Alex van 't Hul (Alex.vantHul@radboudumc.nl)

PhD PORTFOLIO

Name PhD candidate: E.H. Koolen	**PhD period: *01-12-2015 – 01-11-2019***
Department: Pulmonary Diseases and IQ Healthcare	***Promotor(s): Prof. dr. M.M. van den Heuvel, prof. dr. P.J. van der Wees***
Graduate School: Radboud Institute for Health Sciences	***Co-promotor(s): Dr A.J. van 't Hul***

	Year(s)	ECTS
TRAINING ACTIVITIES		
a) Courses & Workshops		
- Introduction day Radboudumc	2016	0.5
- Introduction course, RIHS	2016	1.0
- Course scientific writing	2016	3.0
- Opfriscursus statistiek voor promovendi	2016	2.0
- Scientific Integrity course, RIHS	2016	1.0
- Presenteren eigen Onderzoek	2018	1.5
- BROK course	2018	2.0
- Loopbaanmanagement voor promovendi	2018	2.0
b) Seminars & lectures		
- COPDnet sponsoren bijeenkomst	2015	0.1
- Spiegelbijeenkomst 'Blik in de toekomst' van OCE Nijmegen	2018	0.1
- Radboud New Frontiers Symposium	2018	0.5
- COPDnet sponsoren bijeenkomst	2019	0.1
c) Symposia & congresses		
- Symposium 'Nieuwe richtlijn economische evaluaties, verduidelijking en verdieping'	2016	0.25
- Longdagen	2016	0.5
- KNGF-Congres *	2016	0.5
- European Respiratory Society (ERS) Congress -Milan *	2017	1.5
- CAHAG – COPD & Astma Huisartsen Advies Groep *	2017	0.5
- Conference "Netwerkzorg - een wereld te winnen"	2017	0.25
- RIHS PhD retreat – CaRe Days	2018	0.5
- European Respiratory Society (ERS) Congress – Paris *	2018	1.5
- CAHAG – COPD & Astma Huisartsen Advies Groep – conferentie *	2018	0.5
TOTAL		**19.8**

*Indicate oral or poster presentation

CURRICULUM VITAE

Noortje Koolen was born on March 25, 1989 in Geldrop. In 2007 she obtained her Gymnasium diploma at the Varendonck College, Asten. From September 2008 she studied Physiotherapy at the Hogeschool van Arnhem and Nijmegen. In July 2012 she graduated as a physiotherapist. In addition, Noortje also obtained her premaster Clinical Health Sciences at the University of Utrecht in July 2012. She started working as a general physiotherapist in a primary physiotherapy practice in Valkenswaard. Noortje combined her work as a physiotherapist with a master's degree study in Clinical Health Sciences at the University of Utrecht. In July 2014 she obtained her diploma for the Clinical Health Sciences program, with a master's program in Physiotherapy Science. From January 2015, she combined her work as a physiotherapist with a part-time position as a junior researcher at the Knowledge Center Orthopedics Geldrop (KOG) of the St. Anna Hospital. At the end of 2015, Noortje started her PhD research program at the departments of Pulmonary Diseases and IQ Healthcare at Radboudumc as a PhD student. Since December 2020 she has been working as project manager Longkankernet. Noortje lives with Ralf van Oosterhout and their two children Mees (2019) and Puck (2021) in Asten.

CURRICULUM VITAE (NL)

Noortje Koolen werd op 25 maart 1989 geboren in Geldrop. In 2007 haalde zij haar Gymnasium diploma aan het Varendonck College te Asten. Daarna volgde ze vanaf september 2008 de HBO-opleiding Fysiotherapie aan de Hogeschool van Arnhem en Nijmegen. In juli 2012 studeerde zij af als fysiotherapeute. Naast het afronden van de opleiding Fysiotherapie, behaalde Noortje ook haar premaster Klinische Gezondheidswetenschappen aan de Universiteit van Utrecht in juli 2012. Vervolgens ging zij aan het werk als algemeen fysiotherapeute in een eerstelijns fysiotherapiepraktijk te Valkenswaard. Haar werk als fysiotherapeute combineerde Noortje met het volgen van de master Klinische Gezondheidswetenschappen aan de Universiteit van Utrecht. In juli 2014 behaalde zij haar diploma voor de opleiding Klinische Gezondheidswetenschappen, met als masterprogramma Fysiotherapiewetenschap. Vanaf januari 2015 combineerde ze haar werk als fysiotherapeute met een deeltijdfunctie als junior onderzoekster bij het Kenniscentrum Orthopedie Geldrop (KOG) van het St. Anna Ziekenhuis. Eind 2015 begon Noortje als PhD-student aan haar promotieonderzoek bij de afdelingen Longziekten en IQ Healthcare van het Radboudumc. Sinds december 2020 is zij werkzaam als projectmanager Longkankernet. Noortje woont samen met Ralf van Oosterhout en hun twee kindjes Mees (2019) en Puck (2021) te Asten.

DANKWOORD

En dan is het uiteindelijk zo ver. Na een periode van meer dan vijf jaar, is het mij toch gelukt om mijn proefschrift daadwerkelijk vorm en inhoud te geven. Een afronding van een intensieve fase in mijn leven en tegelijkertijd ook een fase waarin ik mij heb kunnen en mogen ontwikkelen op het wetenschappelijk terrein, maar ook zeker als individu. Gestart met veel ambitie en het volledige vertrouwen om het in de gestelde termijn van drie tot vier jaar te kunnen volbrengen, ondanks een parttime aanstelling. Echter door vertragingen die ontstonden in mijn onderzoek (o.a. vertraging in dataverzameling, verandering van onderzoeksonderwerpen, verandering van mijn promotieteam), maar ook zeker door de keuze van mijzelf om te kiezen voor mijn gezin, heeft het mij uiteindelijk wat extra jaren opgeleverd. Maar tóch is het mij uiteindelijk dan wel gelukt en daar ben ik enorm trots op. Echter, ik besef mij maar al te goed, dit proefschrift was er echt nooit gekomen zonder de hulp van velen. Hulp in verschillende vormen: een goed gesprek, een aanmoediging, kritische feedback, reflectie, steun, maar ook zeker iedere welkome afleiding buiten dit promotietraject om. Ik wil iedereen bedanken die mij hierin heeft geholpen, op welke manier dan ook. Een aantal personen in het bijzonder:

Allereerst wil ik mijn promotieteam bedanken.

Promotor **prof. dr. Michel van den Heuvel**, beste Michel, allereerst wil ik je danken voor het feit dat je zitting hebt genomen in mijn promotieteam. Pas na een aantal jaren heb je deze rol door omstandigheden opgepakt. Ik kan mij ons eerste gesprek dan ook nog goed herinneren. Jij was namelijk degene die aan mij vroeg hoe we dit traject tot een goed einde konden brengen, want succesvol afronden dat moest en zou gebeuren. Dank voor jouw hulp hierin, want het is uiteindelijk toch gelukt. En voor nu kijk ik vooral uit naar onze samenwerking binnen Longkankernet, dank voor deze kans.

Promotor **prof. dr. Philip van der Wees**, beste Philip, dank voor de goede inhoudelijke overleggen die we met elkaar hebben gevoerd. Je gaf daarin je kritische mening, je bood jouw hulp aan en dat bracht mij vervolgens altijd verder. Je wist mij vaak terug te brengen naar de essentie van het onderzoek. Dank daarvoor.

In het bijzonder, mijn co-promotor, **dr. Alex van ‘t Hul**, beste Alex, ik kan en mag iedereen bedanken in dit deel van mijn manuscript. Maar eigenlijk is dit ook een beetje jouw proefschrift en precies dát zegt voor mijn gevoel al meer dan genoeg. In mijn ogen ben jij degene geweest die mij heeft voorzien van de meeste kennis en ervaring die ik nu heb opgedaan. Jij bent en blijft de drijvende kracht achter het COPDnet model. Veel van onze overleggen vonden plaats te Dekkerswald in jouw kamertje of gewoon

bij jou thuis. De overleggen begonnen we altijd heel gestructureerd en vervolgens verloren we ons vaak in diverse gedachtes over de algehele zorg. Maar toch is het gelukt, ons gelukt! Dank voor je hulp, het delen van jouw kennis, je oprechte interesse, je humor, je gastvrijheid (ook Sjoukje natuurlijk) en je inspirerende woorden om mij in te zetten om de zorg voor de COPD patiënt te optimaliseren. Deze doelgroep mag blij zijn met jou!

Daarnaast een speciale dank aan drie personen die eerder bereid waren in mijn promotieteam zitting te nemen of ook echt namen: **prof. dr. Gert Westert**, **prof. dr. Richard Dekhuijzen** en ook **prof. dr. Yvonne Heijdra**

Mijn manuscriptcommissie, bestaande uit **prof. dr. B.R. Bloem, prof. dr. J.W.M. Muris** en **prof. dr. H.A.M. Kerstjens**, wil ik graag hartelijk danken voor het feit dat u allen bereid waren en de tijd hebben genomen om mijn manuscript te beoordelen.

Ook wil ik graag mijn mentor, **prof. dr. Pim Assendelft,** danken voor uw neutrale blik in relatie tot mijn promotietraject. Zo hielp u in het vinden van de juiste ingangen, op het moment er opnieuw een wisseling plaatsvond in mijn promotieteam. Dank voor uw tijd, goede gesprekken en inhoudelijke adviezen.

Ik wil ook graag de overige **coauteurs** van mijn publicaties bedanken voor de samenwerking bij het schrijven van de papers en het beschikbaar stellen van data: **Jeroen van Hees, Rob van Lummel, Remco Djamin, Hans in 't Veen, Sami Simons, Bram van den Borst, Elieke Nijhuis, Nienke Nakken, Daisy Janssen en Jan Vercoulen**. In het bijzonder **prof. dr. Martijn Spruit**, beste Martijn, dank voor jouw kritische reacties, je eerlijke mening en het delen van jouw expertise. Ik blijf het ongelofelijk vinden hoe snel je iedere keer reageert, ondanks alles wat je doet.

Het COPDnet model wordt op dit moment toegepast in twee ziekenhuizen, Bernhoven te Uden en Radboudumc te Nijmegen. Graag wil ik iedereen danken voor de geboden hulp en inzet, als (zorg)professional vanuit een van de deelnemende ziekenhuizen. En speciaal wil ik danken: **Jeanine Antons, Bas Robberts, Heleen van der Niet, Netty Plat, Kees Groot, Marianne de Man, Freek Cox, Lotte Hartjes, Dorien Kooiman-Van der Scheer, Pleuntje van Wetten, Ingrid de Jonge en Mieke van der Linden-Adriaans.** En ook **Petra Zwaans-Ruijs**: dankjewel.

Jeannette Jacobs-Peters, **Laura Elbers-van de Ven** en **Tiny Fasotti-Dumont**, jullie wil ik graag danken voor de hulp die jullie aan mij hebben geboden bij de dataverwerking vanuit RadQuest.

COPDnet sponsoren en in het bijzonder **PICASSO Zorgoptimalisatie** dank ik voor het vertrouwen en het mogelijk maken van dit proefschrift.

De initiatiefnemers van **ParkinsonNet** wil ik bedanken voor de inspiratie die ze ons gaven.

Renata Straver (in memoriam), wat had ik jou graag in het echt willen bedanken voor al jouw talige correcties. Je zorgde er echt voor dat mijn artikelen 'next level' werden.

Uiteraard ook een woord van dank aan alle **patiënten** die hebben geparticipeerd in een van de studies. Zonder jullie was dit manuscript er niet geweest. Jullie zijn bereid geweest om informatie met mij te delen, om vragenlijsten in te vullen en deel te nemen aan interviews. Ik hoop dat dit in de toekomst voor jullie allen een verbetering van zorg als resultaat mag gaan hebben, door het inkijkje wat jullie mij hebben gegeven in de afgelopen jaren.

Als promovendus was ik verbonden aan de afdeling Longziekten en de afdeling IQ Healthcare van het Radboudumc. Echter was ik vooral te vinden op de afdeling Longziekten. Toch had ik wel één echte persoonlijke verbinding met IQ Healthcare en dat was jij **Esther Kuipers**. Ik weet nog goed dat we allebei naar de (verplichte) introductiedagen gingen. We kwamen naast elkaar te zitten, spraken elkaar aan en sindsdien hebben we altijd contact gehouden. In die zin kon ik stiekem van jou leren, want jij was een jaar eerder gestart en had al het een en ander meegemaakt. Alle opvolgende verplichte cursussen schreven we dan ook gelijk samen in. Een van de medecursisten vroeg ons een keer hoelang wij elkaar al wel niet kenden?! We hebben daar flink om moeten lachen. Voor de buitenwereld leek het dus ook alsof we elkaar door en door kenden en we hechte collega's waren. Sterker nog, ik denk dat als we echt samen op de afdeling hadden gewerkt, dit ook zeker zo ontstaan zou zijn. Ieder gesprek wat ik met je voerde, of we elkaar nu al maanden wel of niet hadden gesproken, was alsof ik met een meer dan gewaardeerde collega sprak. Esther, dankjewel!

Natuurlijk wil ik ook heel graag **mijn familie en vrienden** bedanken. En dan vooral een dank voor een fijne afleiding naast dit werk! In het bijzonder:

Lieke, Lianne, Moniek, Senna, Ivon en Chantal, ook Leanne, Rianne en Ellen, dankjewel voor jullie oprechte vragen en interesses in mijn voortgang. Ik weet dat het voor jullie allemaal een enorm onbekende wereld is. Ik kan me ook voorstellen dat jullie vaak hebben gedacht, waar is ze toch mee bezig?! Maar desondanks, steunden jullie mij allemaal. En die steun vond ik terug in kleine dingen, een berichtje om mij te motiveren, een goed gesprek, of gewoon de vraag hoe het gaat. Maar vooral in enorm

welkome afleiding buiten dit werk om! Dank voor jullie vriendschap en op naar nog meer mooie momenten samen. **Chantal**, ik noemde je al, toch wil ik jou nog in het bijzonder extra bedanken, omdat ik vind dat onze vriendschap en jouw meer dan oprechte interesse dat verdient. Dankjewel!

Lieve **Tim en Kim**, altijd vroegen jullie met oprechte interesse hoe het met mijn promotie ging. Ondanks dat jullie vaak hebben gezegd dat jullie dit traject nooit zelf zouden starten, heb ik juist veel respect voor wat jullie allemaal doen. Zowel in jullie carrières, als ook zeker in het gezin met die drie kleine meiden. Dankjewel voor alles! En Tim, heel fijn dat je mijn paranimf wilt zijn.

Lieve **Bas en Noortje**, jullie weten als geen ander wat ik meemaak, omdat jullie allebei ook gepromoveerd zijn. Bas, dankjewel dat ik je om hulp mocht vragen wanneer ik het nodig had. Je zorgde er voor dat ik uiteindelijk toch doorging, ondanks dat ik op het punt stond om te stoppen. Ik hoop voor jullie beiden dat jullie eindelijk die fijne, mooie, uitdagende vaste plek mogen vinden als KNO-arts (Noor) en als chirurg (Bas). Het is jullie meer dan gegund. En blijf genieten van jullie twee kleine mannen en dat toekomstige kleine meisje. Dankjewel voor alles! En Bas, heel fijn dat je mijn paranimf wilt zijn.

Lieve **pap en mam**, dankjewel voor alles. Jullie hebben vaak gezegd dat jullie trots op mij zijn, maar dat jullie dat ook waren geweest als ik iets totaal anders had gedaan. Ik heb dat ook echt zo ervaren. Welke keuze ik ook maakte, jullie luisterden naar mij, adviseerden mij en vervolgens steunden jullie mij onvoorwaardelijk. Dit deden jullie in de keuzes die ik heb gemaakt in relatie tot mijn carrière, maar ook daar buiten. Ik ben enorm trots op jullie!

Liefste **Ralf**, hoe kan ik je ooit bedanken? Zonder jouw onvoorwaardelijke steun, je liefde, je humor en (ja toch ook echt) je nuchtere blik was me dit nooit gelukt. Jij zorgt ervoor dat ik met beide benen op de grond blijf staan. Ik ben trots op jou, trots op ons samen en nog trotser op ons gezin. Ik kijk enorm uit naar onze toekomst samen met Mees en Puck.