Self-management exacerbation action plans in patients with Chronic Obstructive Pulmonary Disease and common comorbidities:

the COPE-III study

by

Anke Lenferink

Thesis
Submitted to Flinders University
for the degree of

Doctor

Flinders University, School of Medicine, Adelaide, Australia
This doctoral degree program was undertaken jointly with the University of Twente, Enschede, the Netherlands

15th of September 2017

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THE COPE-III STUDY

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Department of Pulmonary Medicine, Medisch Spectrum Twente, Enschede, the Netherlands;
Department of Research Methodology, Measurement, and Data-Analysis, Faculty of Behavioural Sciences, University of Twente, Enschede, the Netherlands;
School of Medicine, Flinders University, Adelaide, Australia.
Thesis, University of Twente, 2017.

Cotutelle agreement with the Flinders University, Adelaide, Australia. This Cotutelle is a doctoral degree program that was undertaken jointly at Flinders and the University of Twente.

ISBN: 978-90-365-4373-6
DOI: 10.3990/1.9789036543736
Layout: Anke Lenferink
Cover design: Nick Aalders, Conceptra (conceptra.nl)
Printed by: Ipskamp Printing, Enschede

The publication of this thesis was financially supported by Lung Foundation Netherlands (Longfonds) and Medical School Twente, Medisch Spectrum Twente, Enschede.

SELF-MANAGEMENT EXACERBATION ACTION PLANS IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND COMMON COMORBIDITIES: THE COPE-III STUDY

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Twente,

op gezag van de rector magnificus,

Prof. dr. T.T.M. Palstra

volgens besluit van het College voor Promoties

in het openbaar te verdedigen

op vrijdag 15 september 2017 om 14:45 uur

door

Anke Lenferink

geboren op 17 november 1985

te Tubbergen

Dit proefschrift is goedgekeurd door:

Prof. dr. J.A.M. van der Palen (promotor)
Dr. T.W. Effing (co-promotor)
Dr. P.D.L.P.M. van der valk (co-promotor)

This doctoral degree program was undertaken jointly with the Flinders University, Adelaide, Australia.

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General Introduction

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a common progressive lung condition with distressing exacerbations - acute deteriorations in respiratory health - that contribute to impaired quality of life and increased hospitalisations, mortality and healthcare costs.[1] In 2012, COPD caused more than 3 million deaths.[1] By 2020, COPD is expected to be the third leading cause of death worldwide.[1,2] This increased mortality is mainly driven by the expanding global epidemic of smoking, reduced mortality from other common causes of death, and ageing of the world population.[1]

COPD and comorbidities

COPD is considered to be a complex, heterogeneous, and multi-component condition;[3] more than half of the COPD patients have at least one comorbidity.[4,5] COPD comorbidities include clinical conditions that share common risk factors and pathophysiology with COPD.[6] Comorbid conditions in COPD, such as cardiac diseases, mental health issues, and diabetes, have an important impact on disease severity, hospital admission rate, and survival.[7-9] Comorbidities in COPD are often undiagnosed,[5] leading towards a large variation and an underestimation of the true prevalence of these comorbidities.

Ischaemic heart disease and heart failure are two of the most frequent and important cardiac comorbidities in patients with COPD.[10] These cardiac diseases share common risk factors with COPD (e.g., smoking), and have overlap in symptoms (e.g., breathlessness, fatigue). Acute cardiac events frequently occur during COPD exacerbations; around 20% of the COPD exacerbations could be directly related to acute decompensated heart failure and cardiac arrhythmias.[11] Although cardiac comorbidities have serious consequences in COPD patients as they contribute to disease severity, hospitalisations and mortality, they are frequently missed.[3,11] Patients with severe COPD have a more than twofold risk of cardiovascular disease compared to patients with a normal lung function.[8] The prevalence of heart failure in patients with COPD (10-30%) is therefore significantly higher than in the general population (1-2%).[10]

Two of the most common and least-treated comorbidities of COPD are anxiety and depression.[12] At least half of the patients with depression also have anxiety,[15] and anxiety and depression often co-occur in COPD patients.[13] Anxiety and depression in COPD are associated with e.g., physical disability, low body mass index, severe dyspnoea, poor quality of life, living alone, smoking, female gender, low social class status and the presence of comorbidities.[13] Prevalence estimates vary widely due to the use of varied measurement tools for anxiety and depression symptoms and to the different degrees of disease severity across studies.[12] Anxiety has been recognised as a significant problem in COPD, with an estimated prevalence of up to 40%.[13,14] Patients with anxiety tend to have more intense

shortness of breath, higher rates of readmission after an exacerbation, and higher mortality rates.[6]

Results from a review demonstrated that 25% of the COPD patients experience clinically significant depressive symptoms.[16] Depression reduces physical activity, quality of life, and adherence to medical treatment.[17] It is associated with higher rates of COPD exacerbations, hospitalisations and mortality.[6,18,19] Approximately 25% of the COPD patients have undiagnosed depression, and two thirds of COPD patients with depression do not receive any antidepressant treatment.[6] In stable COPD, the prevalence of clinical depression ranges between 10-42%.[12] In patients who have recently recovered from a COPD exacerbation, the prevalence of depression ranges between 19-50%.[12]

There is also an increased risk of diabetes mellitus in COPD patients as treatment of COPD exacerbations with corticosteroids increases blood glucose levels, specifically in patients with pre-existing diabetes mellitus. The prevalence of diabetes mellitus in COPD patients varies between 10-20%,[8,20,21,22] with an increased risk in active smokers,[21] and in more severe COPD.[8] Diabetes mellitus affects the prognosis of COPD, e.g., the time to first hospitalisation and the 5-year mortality rate.[8] In addition to mortality, hyperglycaemia is associated with increased morbidity and length of hospital stay during a COPD exacerbation.[23,24]

All these frequently existing comorbidities in COPD patients share common risk factors (e.g., ageing, smoking, inactivity) and should be treated appropriately when present as they can influence mortality and hospitalisations independently.[1] Since the symptoms of COPD and serious comorbid conditions overlap, a "one size fits all" approach that focuses solely on traditional COPD symptoms is inadequate. For example, increased dyspnoea could relate to either an impending COPD exacerbation or a deterioration of cardiac disease (e.g., heart failure). Reliance on COPD-specific actions and treatment could therefore lead to the initiation of incorrect or delayed treatment. Despite the huge impact that comorbidities have on quality of life and mortality in COPD patients,[7,9] self-management interventions and self-treatment action plans are frequently not adjusted for these comorbidities and it is unknown whether in case of comorbidities this is effective or even safe in these patients.

Self-management interventions including action plans

Wagner's Chronic Care model[25] suggests to improve chronic disease management through health systems that: 1) have well-developed processes and incentives for making change in the care delivery system; 2) assure behaviourally sophisticated self-management support that gives priority to increasing patients' confidence and skills for ultimate management of their disease; 3) reorganise team function and practice systems to meet the patient's needs; 4) develop and implement evidence-based guidelines and support those

guidelines (e.g., provider education, reminders, interaction); and 5) enhance information systems to facilitate the development of disease registries, tracking systems, and reminders and to give feedback on performance. This model indicates patient education, written management plans, 24/7 access to healthcare, and case-management are required to reduce the healthcare utilisation in chronic diseases.[25]

A COPD self-management intervention is structured, but personalised, and often multi-component, with goals of motivating, engaging and supporting the patients to positively adapt their health behaviour(s) and develop skills to better manage their disease.[26] In addition, case-manager support is recognised as a key component to achieve effective and safe self-management, targeted at behavioural change, and it represents a feasible and possible effective form of healthcare delivery to reduce COPD readmissions.[27,28] It is therefore not surprising that multi-component COPD self-management interventions including an iterative process between patient and healthcare provider(s) are associated with improved health-related quality of life, reduced hospitalisations, and improved dyspnoea.[29]

Action plans are an intrinsic part of COPD self-management interventions. Improvement of self-management skills facilitates proper use of action plans. A self-management intervention should therefore ideally include training with feedback to improve self-management skills: problem solving, decision making, resource utilisation, formatting of patient-provider partnerships, action planning and self-tailoring.[30] The use of symptom-based COPD action plans in self-management interventions, however, is potentially limited, might lower effectiveness, and is potentially unsafe when serious comorbidities are present; comorbid symptoms may overlap with COPD symptoms, lead to incorrect actions and to delay of proper treatment. Moreover, the effectiveness of action plans may be limited if it is just supplied to patients and if it is not incorporated in more extensive, individualised, multi-faceted self-management interventions[31] that also take into account the added complexity of major comorbidities.

Rationale COPE-III study

Whereas comorbidities have a large impact on morbidity and mortality in COPD patients, self-management interventions and self-treatment action plans are frequently not adjusted for comorbid conditions, and may therefore not be as effective or even unsafe for use in these patients. In the COPE-III study, we included COPD patients with the added complexity of major comorbidities and took into account these comorbidities in patient-tailored action plans. We developed patient-tailored action plans, applicable for COPD patients who have serious comorbidities (ischemic heart disease, chronic heart failure, (glucocorticoid-induced) diabetes mellitus, anxiety, depression).[32]

The aim of this study was to evaluate whether COPD patients with frequently existing comorbidities, who are trained in using an individualised multi-morbidity action plan for the self-management of deteriorating symptoms, have fewer COPD exacerbation days over 12 months compared to a usual care control group.[33] We hypothesised that this approach with patient-tailored action plans directed towards COPD and comorbidities would accelerate appropriate treatment and lead to better and more rapid control of deteriorating symptoms, and therefore would lead to reduced COPD exacerbation duration and thus less exacerbation days.

Outline of this thesis

This thesis is directed towards the effectiveness of self-management interventions including action plans for patients with COPD and comorbidities. In **Chapter 2** we start with a Cochrane review 'Self-management interventions including action plans for exacerbations versus usual care in patients with chronic obstructive pulmonary disease'. It provides an overview of the effectiveness of self-management interventions including action plans in patients with (relatively uncomplicated) COPD. In **Chapter 3** we present the COPE-III study design while **Chapter 4** provides information regarding the integration of information from two previous COPD self-management interventions (COPE-I and COPE-II) in the development of our COPE-III self-treatment approach. **Chapter 5** presents a validation of the Partners in Health scale to measure self-management behaviour and knowledge in Dutch COPD patients with comorbidities. In **Chapter 6** we demonstrate the effectiveness of exacerbation action plans integrated in a self-management intervention in COPD patients with comorbidities. In **Chapter 7** we put our findings into a wider context of self-management interventions, assess methodological issues, and provide implications for future research and clinical practice. A summary of the main findings concludes this thesis in **Chapter 8**.

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Self-management interventions including action plans for exacerbations versus usual care in patients with Chronic Obstructive Pulmonary Disease

A. Lenferink
M. Brusse-Keizer
P.D.L.P.M. van der Valk
P.A. Frith
M. Zwerink
E.M. Monninkhof
J. van der Palen
T.W. Effing

Cochrane Database Syst Rev 2017;8:Art. No.: CD011682

ABSTRACT

Background

Chronic Obstructive Pulmonary Disease (COPD) self-management interventions should be structured but personalised and often multi-component, with goals of motivating, engaging and supporting the patients to positively adapt their behaviour(s) and develop skills to better manage their disease. Exacerbation action plans are considered to be a key component of COPD self-management interventions. Studies assessing these interventions show contradictory results. In this Cochrane Review, we compared the effectiveness of COPD self-management interventions that include action plans for acute exacerbations of COPD (AECOPD) with usual care.

Objectives

To evaluate the efficacy of COPD-specific self-management interventions that include an action plan for AECOPD with usual care in terms of health-related quality of life (HRQoL), respiratory-related hospital admissions and other health outcomes.

Search methods

We searched the Cochrane Airways Group Specialised Register of trials, trials registries, and the reference lists of included studies to May 2016.

Selection criteria

We included randomised controlled trials evaluating a self-management intervention for COPD patients published since 1995. To be eligible for inclusion, the self-management intervention included a written action plan for AECOPD and an iterative process between patient and healthcare provider(s) in which feedback was provided. We excluded disease management programmes classified as pulmonary rehabilitation or exercise classes offered in a hospital, at a rehabilitation centre, or in a community-based setting to avoid overlap with pulmonary rehabilitation as much as possible.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data. We resolved disagreements by reaching consensus or by involving a third review author. Study authors were contacted to obtain additional information and missing outcome data where possible. When appropriate, study results were pooled using a random-effects modelling meta-analysis. The primary outcomes of the review were HRQoL and number of respiratory-related hospital admissions.

Main results

We included 22 studies that involved 3,854 patients with COPD. The studies compared the effectiveness of COPD self-management interventions that included an action plan for AECOPD with usual care. The follow-up time ranged from two to 24 months and the content of the interventions was diverse.

Over 12 months, there was a statistically significant beneficial effect of self-management interventions with action plans on HRQoL, as measured by the St. George's Respiratory Questionnaire total score, where a lower score represents better HRQoL. We found a mean difference from usual care of -2.69 points (95% confidence interval (CI) -4.49 to -0.90; 1,582 patients; 10 studies; high-quality evidence). Intervention patients were at a statistically significant lower risk for at least one respiratory-related hospital admission compared with patients who received usual care (Odds Ratio (OR) 0.69, 95% CI 0.51 to 0.94; 3,157 patients; 14 studies; moderate-quality evidence). The number needed to treat to prevent one respiratory-related hospital admission over one year was 12 (95% CI 7 to 69) for patients with a high baseline risk and 17 (95% CI 11 to 93) for patients with a low baseline risk (based on the seven studies with respectively the highest and lowest baseline risk).

There was no statistically significant difference in the probability of at least one all-cause hospital admission in the self-management intervention group compared to the usual care group (OR 0.74, 95% CI 0.54 to 1.03; 2,467 patients; 14 studies; moderate-quality evidence). Furthermore, we observed no statistically significant difference in the number of all-cause hospitalisation days, emergency department visits, general practitioner visits, and dyspnoea scores as measured by the (modified) Medical Research Council questionnaire for patients who participated in self-management interventions compared to usual care. There was no statistically significant effect observed from self-management on the number of COPD exacerbations and no difference in all-cause mortality was observed (risk difference 0.0019, 95% CI -0.0225 to 0.0263; 3,296 patients; 16 studies; moderate-quality evidence). Exploratory analysis showed a very small, but significant higher respiratory-related mortality rate in the self-management intervention group compared to the usual care group (risk difference 0.028, 95% CI 0.0049 to 0.0511; 1,219 patients; 7 studies; very low-quality evidence).

Subgroup analyses showed significant improvements in HRQoL in the self-management interventions with a smoking cessation programme (MD -4.98, 95% CI -7.17 to -2.78) compared to studies without a smoking cessation programme (MD -1.33, 95% CI - 2.94 to 0.27, test for subgroup differences: $Chi^2 = 6.89$, $df = 1$ ($P = 0.009$), $I^2 = 85.5\%$). The number of behavioural change techniques clusters integrated in the self-management intervention, the duration of the intervention and adaptation of maintenance medication as part of the action plan did not affect HRQoL. Subgroup analyses did not detect any potential explanatory variables for differences in respiratory-related hospital admissions between studies.

Authors' conclusions

Self-management interventions that include a COPD exacerbation action plan are associated with improvements in HRQoL, as measured with the SGRQ, and lower probability of respiratory-related hospital admissions. No excess all-cause mortality risk was observed, but exploratory analysis showed a small, but significant higher respiratory-related mortality rate for self-management compared to usual care.

For future studies, we would like to urge only using action plans together with self-management interventions that meet the requirements of the most recent COPD self-management intervention definition. To increase transparency, future study authors should provide more detailed information regarding interventions provided. This would help inform further subgroup analyses and increase the ability to provide stronger recommendations regarding effective self-management interventions that include action plans for AECOPD. For safety reasons, COPD self-management action plans should take into account comorbidities when used in the wider population of patients with COPD who have comorbidities. Although we were unable to evaluate this strategy in this review, it can be expected to further increase the safety of self-management interventions. We also advise to involve Data and Safety Monitoring Boards for future COPD self-management studies.

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) is characterised by respiratory symptoms that are caused predominantly by persistent airflow limitation, which is usually progressive. It is associated with an enhanced chronic inflammatory response in the lung to noxious particles or gases.[1] Many patients with COPD experience increasing functional impairment and progressive loss of quality of life over many years.[2-4] Acute exacerbations of COPD (AECOPD), defined as acute deteriorations in respiratory health, contribute to functional impairment and risk of mortality in individual patients.[3,5] COPD leads to more than six million deaths annually and will be the third leading cause of death worldwide.[1,6] This increased mortality is driven mainly by the expanding global epidemic of smoking, reduced mortality from other common causes of death (e.g. ischaemic heart disease, infectious disease) and increasing age of the world population.[1] Besides mortality, COPD is a leading cause of morbidity. In 2010, COPD was the fifth largest cause of years of life lived with disability.[7] Apart from personal distress, COPD confers a substantial and increasing economic and social burden on society,[1] with its exacerbations accounting for most direct costs.[8]

Description of the intervention

Wagner's Chronic Care model[9] suggested to improve chronic illness care through health systems that: 1) have well-developed processes and incentives for making change in the

care delivery system; 2) assure behaviourally sophisticated self-management support that gives priority to increasing patients' confidence and skills so that they can be the ultimate manager of their illness; 3) reorganise team function and practice systems (e.g., appointments and follow-up) to meet the needs of chronically ill patients; 4) develop and implement evidence-based guidelines and support those guidelines through provider education, reminders, and increased interacting between generalists and specialists; 5) enhance information systems to facilitate the development of disease registries, tracking systems, and reminders and to give feedback on performance. Patient education, written management plans, access to healthcare 24/7, and a case manager are required to reduce the healthcare utilisation.[9]

Self-management interventions are defined as structured interventions for individuals aimed at improvement in self-health behaviours and self-management skills.[10] Lorig et al.[10] indicated that a self-management programme should ideally include training with feedback to improve the following patient skills: problem solving, decision making, resource utilisation, formation of patient-provider partnerships, action planning and self-tailoring. Mastery, modelling, interpretation of symptoms and social persuasion skills are believed to contribute to enhanced self-efficacy.[10] Patients will progressively achieve greater confidence in (self-) managing their health, and this will be a powerful factor in inducing new and sustaining behaviours that provide perceived benefit.[10,11]

Self-management has been proposed as an essential part of disease management targeted towards helping patients develop skills to manage a disease more effectively. This is especially important in patients with chronic disease (e.g. COPD, for which the patient is responsible for day-to-day care over the duration of the illness).[10] COPD self-management interventions are associated with reduced duration of exacerbations and hospitalisations and decreased healthcare costs, as well as improved health-related quality of life (HRQoL), for patients with COPD.[12-14] COPD self-management training aims to help patients acquire and improve through practice the skills they need to carry out disease-specific medical regimens.[15,16] It also guides changes in health behaviour and provides emotional support for optimal function of patients with COPD and control of their disease.[15,16] Self-management training is considered an increasingly important component of treatment and management of COPD. This training should occur as an interactive and iterative process aimed at sustained behavioural change and instillation of confidence to recognise when an exacerbation is starting and to self-manage it effectively and safely.[15] Self-management will not be successful without effective co-operation between patient and healthcare provider.[17] Ongoing case manager support is recognised as an additional component required to achieve effective and safe self-management.[16]

Recently, an international expert group reached consensus regarding a conceptual definition for a COPD self-management intervention.[18] Self-management interventions should be structured but personalised and often multi-component, with goals of motivating, engaging and supporting the patients to positively adapt their behaviour(s) and develop skills to better manage their disease. Our review inclusion criteria were developed in line with this recently published definition.

Action planning is a frequently applied planning technique in generic self-management programmes and adopted to change behaviour.[19,20] COPD exacerbation action plans are disease-specific and considered to be an intrinsic part of COPD self-management interventions.[14,16] Patients are trained to use COPD exacerbation action plans if they experience a worsening of their respiratory symptoms. Appropriate actions can include contacting a healthcare provider for support or initiating self-treatment.[21] Furthermore, written action plans can include instructions regarding, for example, maintenance treatment.

How the intervention might work

Using action plans for exacerbations of COPD within a self-management intervention provides training for COPD patients to recognise symptoms earlier, accelerate the initiation of appropriate treatment and lead to better control of deteriorating symptoms. This may lead to improved HRQoL, reduced exacerbation duration and hospitalisations, and decreased healthcare costs in patients with COPD.

Why it is important to do this review

A Cochrane Review on COPD self-management concluded that self-management is associated with improved HRQoL, reduced respiratory-related and all-cause hospitalisations and improved dyspnoea.[14] Subgroup analyses indicate that a standardised exercise component in self-management interventions did not change the effects of self-management interventions on HRQoL and respiratory-related hospital admissions. However, the review could not reveal the effective components within self-management interventions, not least because of heterogeneity among interventions, study populations, follow-up time and outcome measures.[14] In recently published individual patient data (IPD) meta-analyses on the effectiveness of COPD self-management the included self-management interventions also differed from each other in terms of dose, mode and content.[22] Because of the very frequent use of action plans for exacerbations in the included studies, sub-analyses on the use of action plans could not be performed by Zwerink et al.[14] As COPD action plans are currently considered as an intrinsic part of COPD self-management interventions, in the current review written action plans for AECOPD were included as part of the self-management intervention.

Since the publication of Zwerink et al.[14], several studies have been published and new opinions have been raised regarding the limitations and contents of COPD self-management interventions with exacerbation action plans for patients with COPD. So far, the evidence regarding COPD action plans is somewhat contradictory. After two years of follow-up, a self-management programme including action plans for the self-treatment of exacerbations in COPD patients without significant comorbidities resulted in reduced exacerbation duration, exacerbation severity and healthcare utilisation.[23] Furthermore, a review showed that the use of action plans with a single short educational component along with ongoing support, but without a comprehensive self-management programme, reduces in-hospital healthcare utilisation and increases treatment of COPD exacerbations.[24] This review showed a small improvement in HRQoL with action plans compared to usual care and it was unlikely to increase or decrease mortality.[24] As a result of using individualised action plans and ongoing support, the impact of exacerbations on health status decreased and the recovery of an exacerbation might be accelerated.[25] A study evaluating the efficacy of a comprehensive care management programme in reducing the risk for COPD hospitalisations with COPD-specific action plans was prematurely terminated because of significantly higher mortality rates in the intervention group.[26] No definitive explanation for these study outcomes has emerged, and they conflict with the positive study outcomes of another highly comparable self-management study from Rice et al.[13] The significantly higher mortality rates in the intervention group reported by Fan et al.[26] may be partly explained by the use of COPD-specific action plans for patients with COPD and comorbidities. A single-centre RCT that included nurse support identified only 42% of the intervention group as successful self-managers. This group of successful self-managers had a significantly reduced risk of hospital readmissions.[27] This study implies that not all COPD patients derive benefit from a COPD self-management intervention. All COPD self-management interventions discussed above have included a COPD exacerbation action plan as a key intervention component, underlining that these action plans are currently seen as an intrinsic part of COPD self-management interventions. Nevertheless, these studies show contradictory results. We assessed the effectiveness of COPD self-management interventions that include action plans for AECOPD compared with usual care for this review.

OBJECTIVES

To evaluate the efficacy of COPD-specific self-management interventions that include an action plan for exacerbations of COPD compared with usual care in terms of health-related quality of life, respiratory-related hospital admissions and other health outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

We considered RCTs reported in full text, those published as abstracts only and unpublished data from RCTs.

2

Types of participants

We included studies that included patients with a diagnosis of COPD according to the GOLD (Global Initiative for Chronic Obstructive Lung Disease) classification criteria[1]; patients with a post-bronchodilator forced expiratory volume in one second (FEV_1)-to-forced vital capacity (FVC) ratio < 0.70. Patients with primary diagnoses of asthma as were excluded.

Types of interventions

We included trials comparing COPD self-management interventions that included a written action plan for AECOPD versus usual care. For this review, an action plan refers to specific behaviour to be initiated when respiratory symptoms deteriorate; the plan needed to describe when, where and how one should act. An action plan is an agreed upon strategy by which patients will act appropriately when symptoms deteriorate (indicating the start of a COPD exacerbation), e.g., by contacting a healthcare provider for support, by initiating self-treatment. It may also include maintenance treatment and advice to avoid situations in which viral infection might be prevalent.

The self-management intervention needed to include formal training on how and when to use an action plan for AECOPD. To be eligible for inclusion, the formal training programme had to be an iterative process between patient and healthcare provider(s) in which feedback was provided to patients' self-management skills (e.g., how and when to use an action plan for AECOPD). Training should ideally include techniques directed to achieving behavioural change.[28] The intervention could also include other components that were directed to achieving behaviour change (e.g., smoking behaviour, exercise or physical activity, diet, use of maintenance medication and correct device use, coping with breathlessness). The intervention content could be delivered to patients verbally, in writing (hardcopy or digital) or via audio-visual media.

Disease management programmes classified as pulmonary rehabilitation or exercise classes offered in a hospital, at a rehabilitation centre or in a community-based setting were excluded to avoid possible overlap with pulmonary rehabilitation as much as possible. The study was considered if the patients were randomised and allocated to self-management or usual care after pulmonary rehabilitation. The study was excluded if this randomisation was performed before pulmonary rehabilitation. Home-based (unsupervised) exercise programmes that included action plans for AECOPD were included, as these studies asked

a more active role of patients and were more clearly aimed at patient self-management skills compared to supervised exercise programmes.

As the definition, content and focus of COPD self-management training in particular, and of COPD treatment in general, have dramatically changed over the past 20 years, we excluded studies published before 1995. We included studies that were published in full-text and excluded abstracts if there was no additional information available from the study authors.

Usual care differs significantly between countries and healthcare systems, and sometimes some elements of self-management interventions will already be included as part of usual care. We defined usual care as de facto routine clinical care.

Types of outcome measures

Primary outcomes

- Health-related quality of life (HRQoL)
- Respiratory-related hospital admissions

Secondary outcomes

- Number of all-cause hospital admissions
- Use of (other) healthcare facilities (e.g. number of emergency department (ED) visits, number of all-cause and respiratory-related hospitalisation days in total and per patient, general practitioner (GP), number of nurse and specialist visits)
- Rescue medication use
- Health status
- Number of COPD exacerbations
- All-cause mortality
- Self-efficacy
- Days lost from work

Reporting one or more of the listed outcomes was not an inclusion criterion for our review. We intended to divide COPD exacerbations into those based on COPD symptom scores (e.g., symptom diary), courses of oral corticosteroids and courses of antibiotics.

Search methods for identification of studies

Electronic searches

We identified studies from the Cochrane Airways Trials Register, which is maintained by the Information Specialist for the Group. The Cochrane Airways Trials Register contains studies identified from several sources:

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies Online (crso.cochrane.org);

2. Weekly searches of MEDLINE Ovid SP 1946 to date;
3. Weekly searches of Embase Ovid SP 1974 to date;
4. Monthly searches of PsycINFO Ovid SP;
5. Monthly searches of CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature);
6. Monthly searches of AMED EBSCO (Allied and Complementary Medicine);
7. Handsearches of the proceedings of major respiratory conferences.

Studies contained in the Trials Register are identified through search strategies based on the scope of Cochrane Airways. We searched the Cochrane Airways Trials Register from 1995 to May 2016, with no restriction on language of publication. We contacted the authors of included studies to ask for further information, if needed.

Searching other resources

We checked reference lists of all primary studies and reviewed articles for additional references. We searched for additional trials using ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (WHO ICTRP, www.who.int/ictrp/en/databases).

Data collection and analysis

Selection of studies

Two review authors (AL and TE) independently assessed titles and abstracts of all references retrieved. Subsequently, two review authors (AL and TE or MB) independently reviewed full-text versions of potentially relevant reports, assessed eligibility for inclusion and resolved disagreements by discussion with the third review author (TE or MB).

Data extraction and management

Two review authors (AL and TE or MB) independently assessed trial quality and extracted the following data from included studies: relevant outcome measures; sample size; demographics of included patients; disease severity; setting, duration and contents of the intervention and potential effect modifiers. We used standard data extraction forms and spreadsheets. We completed a data extraction form for study characteristics and outcome data that was piloted on two studies in the review.

We noted in 'Characteristics of included studies' tables whether outcome data were reported in a useable way. We resolved disagreements by reaching consensus or by involving a third (TE or MB) or fourt review author (JP or PV). Data were transferred into the Review Manager (RevMan) 5.3[29] file (AL) and double-checked for accuracy by comparing data presented in the systematic review versus data in the study reports (TE).

Assessment of risk of bias in included studies

Two review authors (AL and TE or MB) independently assessed the risk of bias according to recommendations outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*[30] for the following items.

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective reporting
- Other potential sources of bias

For each included study we graded all listed domains to whether high, low or unclear risk of bias was present (AL and TE or MB). An unclear risk indicated that there was insufficient detail of what happened in the study; that what happened in the study was known but the risk of bias was unknown; or that an entry was not relevant to the study at hand. Each judgement of risk of bias is supported by a short description of what was reported to have happened in the specific study. The grade of each potential bias from the included study together with a quote from the study report and justification for our judgement is reported in 'Risk of bias' tables. In the case of cluster-RCTs, we assessed the risk of recruitment bias, risk of bias for baseline imbalance, risk of bias due to loss of clusters, risk of bias due to incorrect analysis and publication bias. We resolved disagreements by discussion or with involvement of another review author (JP or PV).

Assessment of bias in conducting the systematic review

We conducted the review according to the published protocol and reported deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We analysed the results of studies using random-effects modelling (REM) in RevMan.[29] We used forest plots to compare results across trials. We expressed the results of each RCT as odds ratios (ORs) with corresponding 95% confidence intervals (95% CIs) for dichotomous outcomes, and as mean differences (MDs) or standardised mean differences (SMDs) for continuous outcomes. For primary analyses, we used the calculator tool in RevMan along with information from adjusted scores (analysis of co-variance (ANCOVA)), change from baseline scores or final scores to create a single forest plot. We used the calculator tool with the generic inverse variance method for dichotomous or continuous data to allow transformation from data on effect sizes, confidence intervals and standard errors to data required by RevMan to create forest plots with, for example, RRs or MDs. We determined the

clinical relevance of treatment effects by using the minimal clinically important difference (MCID), when available. If possible, numbers needed to treat for an additional beneficial outcome (NNTB) were calculated for both respiratory-related and all-cause hospital admissions using pooled ORs and control group data from individual studies within the meta-analysis to obtain study-specific NNTB, with Visual Rx 3.[31]

Unit of analysis issues

The patient was the unit of analysis for included RCTs. We intended to include cluster-RCTs with the cluster as the unit of analysis. We had envisaged that for more recent studies, clusters would have been taken into account in the analyses. However, if this was not the case, we intended to adjust for the clusters.

Dealing with missing data

We contacted the study authors to obtain missing or incomplete outcome data where possible. If study authors did not respond, we made two further attempts to request missing data. If study authors did not respond after a third attempt, we analysed and described the available data and indicated that data were missing.

Assessment of heterogeneity

Variability among studies was explored by performing visual inspection and using the I^2 statistic.[30] If we identified substantial heterogeneity ($I^2 > 50\%$), we discussed possible explanations and critically reconsidered the appropriateness of a meta-analysis. We used a REM, rather than a fixed-effects model (FEM) in meta-analyses to account for heterogeneity.

Assessment of reporting biases

We explored possible reporting bias by assessing asymmetry in funnel plots to determine whether studies were selectively reported as indicated in the paragraph 'Assessment of risk of bias in included studies'. We considered a funnel plot when at least ten studies could be included.

Data synthesis

When appropriate, we performed meta-analysis using RevMan. We considered a meta-analysis when at least three studies reported sufficient data for the outcome. Because of the nature of the intervention, we expected to see clinical heterogeneity among studies. If pooling was possible, we performed meta-analyses using the REM.

Summary of findings Table

Using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*,[30] we created a 'Summary of findings' (SOF) Table that includes key information concerning

the quality of evidence, the magnitude of effect of the self-management intervention and the sum of available data on the main out-comes. We used the five GRADE (Grades of Recommendation, Assessment, Development and Evaluation) considerations regarding: 1) study limitations; 2) consistency of effect; 3) imprecision; 4) indirectness; and 5) publication bias, to assess the quality of a body of evidence as it relates to studies that contribute data to the meta-analyses for pre-specified outcomes. We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions*[30] by using GRADEpro[32] software. We justified all decisions to downgrade or upgrade the quality of studies by using footnotes, and we provided comments to aid the reader's understanding of the review when necessary.

Subgroup analysis and investigation of heterogeneity

We considered subgroup analyses when at least three studies could be included in each subgroup. We intended to perform the following subgroup analyses to detect potential explanatory variables and determine whether outcomes differed in terms of the following:

- Duration of follow-up: fewer than 12 months of follow-up after the start of the study versus 12 or more months of follow-up after the start of the study. Shorter-term and longer-term effects of self-management interventions including action plans might be different. In addition, we will perform explorative analyses by using different cut-off points for follow-up times (e.g., six months, 18 months).
- Inclusion of patients in the acute phase: inclusion of patients with COPD in the acute unstable phase (with an acute exacerbation of COPD) versus inclusion of patients in the non-acute stable phase (at least four weeks post exacerbation and six weeks post hospitalisation). Acute exacerbations may threaten self-management improvements. Awareness of the clinical sequelae of acute exacerbations of COPD enables approaches such as early post-exacerbation rehabilitation to mitigate its negative effects.[33]
- Use of a standardised exercise programme as part of the intervention: use of an exercise component in self-management versus no exercise component. Increased exercise capacity may result in better HRQoL and potentially fewer hospital admissions.[34]
- Use of a smoking cessation programme in the intervention: smoking cessation component in self-management versus no smoking cessation component. Smoking cessation may result in improved HRQoL.[35,36]
- Self-management as part of usual care: low-level usual care versus high-level usual care. Usual care differs significantly between countries and healthcare systems, and sometimes self-management will already be included as part of usual care. We classified according to whether self-management was likely to be part of usual care.

We used the formal test for subgroup interactions in RevMan.[29]

In addition, we have assessed the integration of 16 clusters of behavioural change techniques (BCTs) in an explorative subgroup analysis to promote uptake and optimal use of COPD-specific self-management behaviour patterns in the intervention:

- Goals and planning
- Feedback and monitoring
- Social support
- Shaping of knowledge
- Natural consequences
- Comparison of behaviours
- Associations
- Repetition and substitution
- Comparison of outcomes
- Reward and threat
- Regulation
- Antecedents
- Identity
- Scheduled consequences
- Self-belief
- Covert learning

The BCT taxonomy is a methodological tool for specifying intervention content.[28] The BCT taxonomy (version 1) published by Michie et al.[28] describes 93 hierarchically clustered techniques in 16 clusters. The BCT must be an observable, replicable and irreducible component of an intervention designed to alter or redirect causal processes that regulate behaviour; that is, a technique that is proposed to be an "active ingredient".[37] In this subgroup analysis, we classified interventions by their number of BCT taxonomy clusters ('lower or equal' vs 'higher' than the median of BCT clusters found in all included interventions).[28]

In exploratory analyses, we assessed potential effect modifiers by participant and self-management intervention levels (e.g., casemanager support). We also aimed to collect information about the intention of the self-management intervention and how it was delivered to patients.

Sensitivity analysis

We carried out sensitivity analyses under different assumptions to investigate the robustness of effect sizes found in this review. Sensitivity analyses were performed to identify whether review findings were dependent on study characteristics, using random-effects versus fixed-effects modelling.

RESULTS

Description of studies

See 'Characteristics of included studies' section.

Results of the search

Searches identified 1,811 titles and abstracts (Figure 2.1). In total, 255 potentially eligible articles about self-management interventions including an action plan for AECOPD were identified, of which 22 studies (described in 30 articles) were included. One study[38] could not be included in the quantitative synthesis (meta-analysis) because insufficient data were provided.

This review fully incorporates the results of searches conducted up to May 2016. A further nine reports were identified by a search update conducted in May 2017. However, these have not yet been incorporated into the results and will be addressed in the next update (see 'Characteristics of studies awaiting classification' section).

Included studies

All 22 included studies compared a self-management intervention using an action plan for AECOPD with a usual care control group.[13,26,27,38-56] Twenty-one included studies were parallel RCTs and one study was a cluster-RCT.[50] Details of patient and intervention characteristics (Table 2.1 and Table 2.2, respectively) were tabulated. We structured both tables according to potential effect modifiers on patient and self-management intervention levels (e.g., lost to follow-up, duration and delivery of intervention).

Patients and recruitment

A total of 3,854 patients (self-management intervention n = 1,931, usual care control n = 1,923) were assessed in the 22 included studies (Table 2.1). Drop-out rates in the studies ranged from 0% to 59%, and in total 3,293 (85%) patients completed the study follow-up. Seventeen studies recruited patients from a hospital; 12 studies[13,26,27,39,40,42,43,45,46,48,49,52] from the outpatient clinic and five[41,44,51,53,55] from the inpatient population. Tabak et al.[52] reported recruitment from both outpatient clinic and primary care physiotherapy practices. Five studies[38,47,50,54,56] recruited patients from general practices or from primary healthcare clinics.

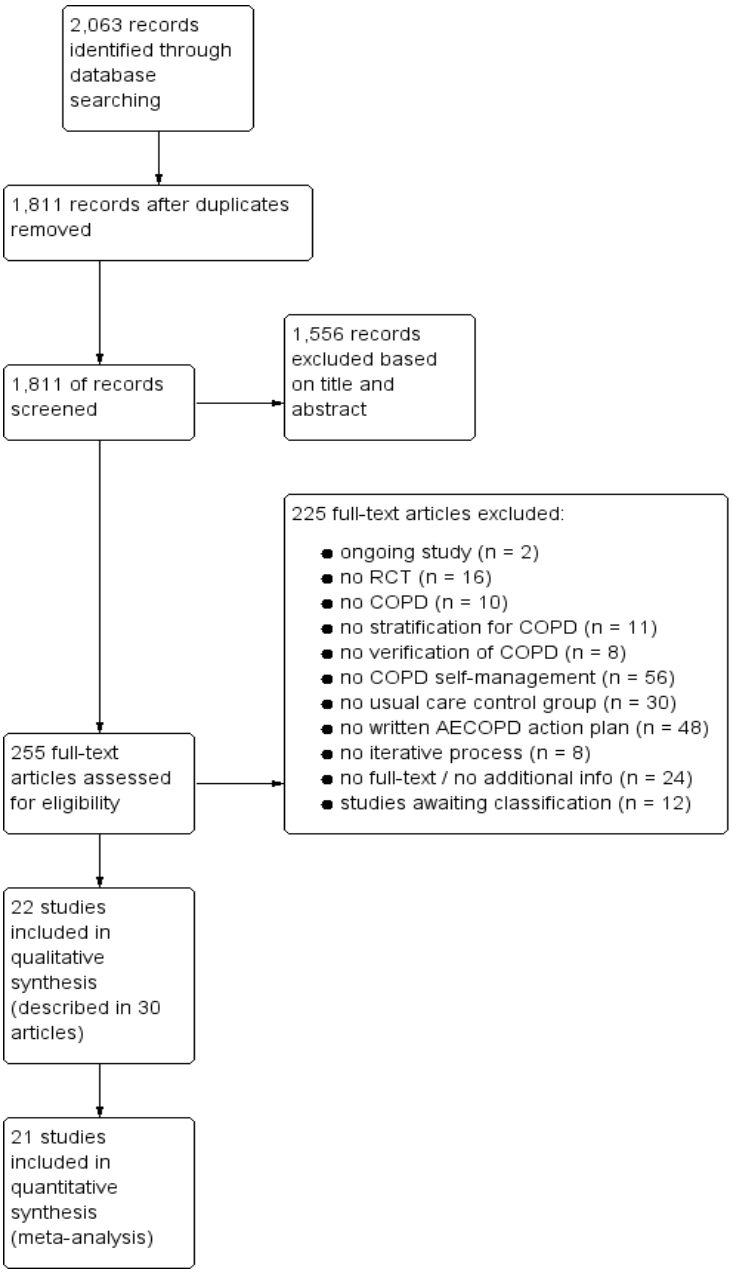

Figure 2.1. Study flow diagram

Interventions

Contents of the interventions assessed by the 22 included studies were diverse (Table 2.2). The median follow-up duration was 12 months (interquartile range (IQR) 5.3 to 12.0). The duration of follow-up was three months or less in three (14%) studies[44,46,51], three to five months in one (4%) study[38], six months in one (4%) study[56], nine months in one (4%) study[52], 12 months in 13 (59%) studies[13,26,27,39,41-43,45,47-50,55] and 24 months in three (14%) studies[40,53,54]. Self-management interventions were delivered individually in ten (45%) studies[27,38,44,45,47,50,51,53,54,56] and in small groups in three (14%) studies[39,40,48], and included both individual and group sessions in nine (41%) studies.[13,26,41-43,46,49,52,55] The median duration of the intervention including self-management reinforcement was nine months (IQR 1.0 to 12.0). The intervention duration was less than one month in two (9%) studies[42,44] and one month in four (18%) studies.[41,49,51,56] In four (18%) studies[38,39,46,48], the intervention duration was over one month up to six months. The intervention duration was nine months in two (9%) studies[52,55], 12 months in eight (36%) studies[13,26,27,40,43,45,47,50] and 24 months in two (9%) studies[53,54].

In nine (41%) studies[38,40,43,46,48,49,51,52,56] a standardised exercise programme was part of the intervention. A smoking cessation programme was part of the intervention in six (27%) studies[13,38,39,43-45]. Self-management topics about (maintenance) medication were discussed in all but one study[44], while coping with breathlessness or breathing techniques was discussed in all but two studies[47,50]. Other major topics addressed were diet and/or nutrition (n = 17; 77%)[27,38-46,48,49,52-56], and correct device use (n = 13; 59%)[13,27,38,41,43-45,48-50,53,55,56].

The AECOPD action plan components discussed in the interventions were self-recognition of COPD exacerbations (n = 20)[13,26,27,38-43,45,47-56], self-treatment of COPD exacerbations (n = 20)[13,26,27,38-43,45,47-56], contact healthcare providers for support (n = 18)[13,26,27,38-45,48,50,52-56], use of maintenance treatment (n = 10)[27,39-43,47,49,54,55], avoid situations in which viral infection might be prevalent (n = 6)[39,43,46,49,53,56], and self-treatment of comorbidities (n = 2)[43,47].

A total of 204 BCT clusters[28] were integrated in the interventions with a median of 9.5 (IQR 8.0 to 10.0) clusters per study (minimum 6 BCT clusters[46], maximum 12 BCT clusters[27]). The behaviour change clusters that were integrated to promote the uptake and optimal use of COPD specific self-management behaviour patterns in the intervention were: goals and planning (n = 22); feedback and monitoring (n = 22); shaping knowledge (n = 22); associations (n = 22); regulation (n = 21; all but one study[44]); antecedents (n = 20; all but two studies[46,51]); social support (n = 19; all but three studies[42,46,50]); comparison of behaviour (n = 18; all but four studies[26,46,51,53]); repetition and substitution (n = 16; all but six studies[38,39,43,46,47,50]); natural consequences (n = 15; all but seven studies[39,43,44,47,49,51,53]); identity (n = 3)[38,51,56] self-belief (n = 3)[27,51,52] and comparison of outcomes (n = 1)[27]. There

were no rewards and threats, scheduled consequences or covert learning integrated in any of the self-management intervention.

Adherence

Half of the studies reported details regarding patient adherence to the intervention. Of these, six studies reported adherence as the number or percentage of sessions attended by patients. In the study of Bischoff 2012 et al.[54] the number of sessions that were offered depended on the patient's needs, but was at least two sessions. Patients in this study received a mean of 3.4 (SD 1.5) sessions; 13% of the patients did not attend any of the sessions or received telephone contact. The self-management education course in the study of Monninkhof 2003 et al.[48,57] consisted of five group sessions; of these, four were scheduled at one-week intervals and the final session three months later. Mean attendance frequency was 0.77 (SD 0.22) sessions per week, and five (4%) patients randomised to the intervention group refused to attend the self-management education course.[48] Fan 2012 et al.[26] reported that during the entire follow-up period, a total of eight of 209 patients in the intervention group and ten of 217 patients in the usual care group either did not attend scheduled visits or formally withdrew from the study. The study authors also reported that in the intervention group 87% completed all four individual educational visits and 57% completed the scheduled group visit.[26] Early termination after the intervention was enforced by the Data and Safety Monitoring Committee and the apparently low attendance rate of the group visit may well be a consequence.[26]

Tabak 2014 et al.[52] reported that the self-management module on the web portal, including the self-treatment of COPD exacerbations, was used on 86% of the treatment days per patient. Ninot 2011 et al.[49] found that one of 23 patients from the intervention group did not fulfil their adherence criteria to the four-week self-management programme, defined as completing at least seven of the eight sessions. In the study of Gallefoss 1999 et al.[42], the intervention group patients who did not attend the individual or group sessions were withdrawn (n = 5, 16%). Three studies reported adherence according to different definitions. Self-reported scales in the studies of Casas 2006 et al.[41] and Garcia-Aymerich 2007 et al.[55] showed better adherence to recommended oral treatment in the intervention group than in the control group (90% vs 85%, respectively) and inhaled treatment regimens (71% vs 37%). Khdour 2009 et al.[45] reported that 78% of the patients in the intervention group versus 60% of the patients in the control group reported high adherence to maintenance medication after the 12-month follow-up, reflecting a lower number of medication omissions in the intervention group compared to the control group.

Comparisons

As per inclusion criteria, in this review self-management interventions that included an

action plan for AECOPD were compared with usual care in 22 studies. Bischoff 2012 et al.[54], reported two intervention groups (one with and one without an action plan for AECOPD) and one usual care group. We used only data from the intervention group that included an action plan for AECOPD and the usual care group for this review.

Outcomes

See Additional Table 2.3 for details on the number of included studies reporting outcomes of interest.

Missing data

We have listed the authors from whom we received responses to requests for additional data in the 'Acknowledgements' section. However, not all study authors were able to provide the requested additional information. If the requested data were not provided for meta-analyses, we described the data that were available.

Excluded studies

We excluded 225 studies following the assessment of the full-text (Figure 2.1). The most frequent reasons for exclusion were: no COPD self-management intervention (n = 56); no written action plan for AECOPD (n = 48); no usual care control group (n = 30).

Studies awaiting classification

A total of 12 studies await classification. Koff 2009 et al.[58], Leiva-Fernández 2014 et al.[59], and Lou 2015 et al.[60] await classification because we could not reach the study authors to verify whether the studies met our eligibility criteria. From a search in May 2017, we identified nine studies[61-69] that could be included in a future update of the review. These have been added to the 'Characteristics of studies awaiting classification' section and have not been fully incorporated into the review.

Ongoing studies

We identified two ongoing studies.[75,84]

Risk of bias in included studies

A summary of our risk of bias assessment is presented in Figure 2.2. Assessments were performed based on the content of the study articles and no extra information was requested from the authors. Further details and the rationale for judgments can be found in the 'Characteristics of included studies' section.

Figure 2.2. Risk of bias summary for each study according to authors' judgements

Allocation

Computer-generated random number lists or other computerised methods were most

frequently used to generate allocation sequences in studies (n = 13).[26,27,40,41,43-45,49,50,52,54-56] Two[27,45] of these studies used stratification or minimisation to balance for potential confounders. All these 13 studies had a well-defined rule for allocating the intervention to patients and were therefore judged as having a low risk of selection bias. Two studies used random number tables or lists in sealed envelopes[42,48] or an independent person drew lots for allocation[38] and were assessed at low risk of bias. Six studies[13,39,46,47,51,53] did not report how the allocation sequence was generated and were judged as having an unclear risk of bias.

In most studies (n = 12)[26,27,38,40-43,45,48,49,52,55] the investigators or staff were not able to influence the allocation concealment, or the randomisation was performed by an independent person who was not involved in the study; the risk of bias was considered to be low. The risk of bias was judged to be unclear in nine studies[13,39,44,46,47,51,53-56] which did not report who performed the allocation or which method was used for the allocation concealment. One study was cluster-randomised and no allocation concealment was provided; therefore, the risk of bias was considered to be high.[50]

Blinding

Because of the nature of the self-management intervention, blinding of patients and personnel to group assignment is complicated. None of the included studies reported blinding of patients and personnel; performance bias risk was considered to be high in all included studies.

The detection bias was considered to be low in ten studies[13,26,40,43,44,48,49,54-56], because these studies were investigator blinded, the outcome assessment was performed by an independent assessor, the evaluator was unaware of patient assignment or only objective outcome measures were used. In 11 studies[27,39,41,42,45-47,50-53] the detection bias was judged to be unclear, since the outcome assessment was not reported or the outcome assessment was only partly blinded. In one study[38] the outcome assessments were performed or supervised by the same person who provided the intervention and was considered to have a high risk of detection bias.

Incomplete outcome data

In 12 studies[38,40-42,45,46,48-51,54,56], outcome data were complete and there were no systematic differences detected between the intervention and usual care groups in withdrawals. In these 12 studies the risk of attrition bias was considered to be low. There were incomplete data in two studies due to early termination; one as a result of significantly higher mortality rates in the intervention group,[26] and one because interim analysis at three years did not demonstrate the desired 10% between-group differences in ED visits or rehospitalisations.[44]

The risk of attrition bias in these two studies was therefore judged to be unclear.[26,44] The risk of attrition bias was also considered to be unclear in three other studies, because there was insufficient information to permit judgment,[43] there was no information provided regarding the differences in dropout rates,[47] or only a part of the outcome data was missing.[13] In five studies[27,39,52,53,55] the quantities of missing outcome data were high and the risk of attrition bias was considered to be high.

Selective reporting

Five studies[13,26,42,54,56] were judged to have low risk for reporting bias; there were no signs for selective outcome reporting when comparing the reported outcomes and study findings with the information provided in the study protocols. In 13 studies[38-41,43,45-51,55] there were no signs of selective reporting. However, for these studies there were no study protocols available and the reporting bias was considered to be unclear. One study reported a slightly different primary outcome in the paper compared to primary outcome as defined in the study protocol; this study was therefore judged as unclear risk of reporting bias.[44] Three studies[27,52,53] were considered to have a high risk of reporting bias, because not all relevant outcome measures were completely reported.

Other potential sources of bias

We additionally assessed Rea 2004 et al.[50] for biases which are important in cluster-RCTs. This study reported that general practices were randomly assigned before the patients were included. For reasons unknown, the number of patients screened and included was higher in the intervention group than in the usual care. Rea 2004 et al.[50] reported there were no significantly between-group differences for baseline characteristics. We considered the risk of recruitment bias to be unclear and the risk of bias for baseline imbalance to be low. The risk of bias due to loss of clusters was judged as low, because no clusters were lost after patient enrolment. Rea 2004 et al.[50] did not correct for clustering in their analyses. The risk of bias due to incorrect analysis was considered to be high. No other potential sources of bias were observed in this study.

We judged three studies[39,49,52] in which per protocol analyses were performed as having an unclear risk of other bias. In these studies the baseline characteristics were not reported for all randomised patients. However, in Bösch 2007 et al.[39] and Ninot 2011 et al.[49] no differences were reported for baseline characteristics among withdrawals after randomisation and the patients who completed the study. In Tabak 2014 et al.[52] no differences were reported for baseline characteristics between withdrawals after randomisation and patients who completed the questionnaires at inclusion.

In addition, we explored possible reporting bias by assessing asymmetry in funnel plots

for HRQoL (Figure 2.3) and respiratory-related hospital admissions (Figure 2.4). A negative mean difference (MD) of the St. George's Respiratory Questionnaire (SGRQ) total score indicates better HRQoL in the self-management group compared to usual care. The funnel plot of the SGRQ, with MD in SGRQ total score plotted against the standard error (SE) of the MD, seems to show a gap on the lower right side of the graph (Figure 2.3). This could indicate that smaller studies with effects in favour of the usual care group (positive MD in SGRQ scores) are published less frequently. On the contrary, the funnel plot of the Odds Ratio (OR) per study plotted against the SE (log OR) in respiratory-related hospital admissions seems to show a gap on the left side of the graph (Figure 2.4), indicating that smaller studies and studies of moderate size with effects in favour of the self-management group are published less frequently. We could not rule out the contribution of other study factors to funnel plot asymmetry.

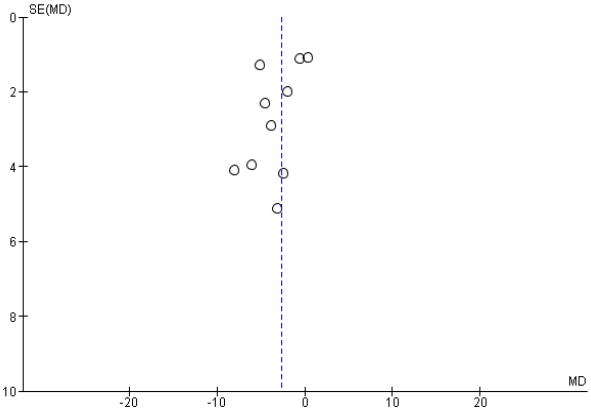

Figure 2.3. Funnel plot of comparison: Self-management versus usual care, outcome: 1.1 HRQoL: adjusted SGRQ total score

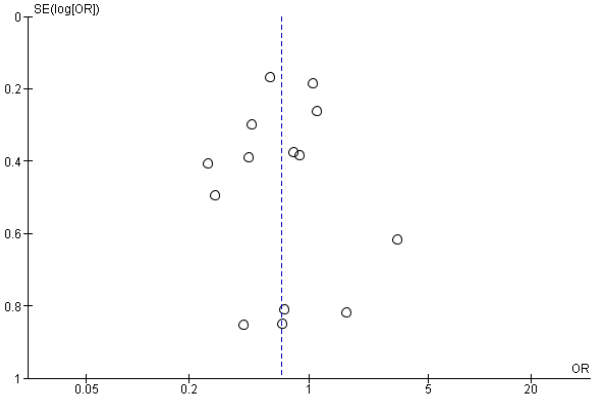

Figure 2.4. Funnel plot of comparison: Self-management versus usual care, outcome: 1.2 Healthcare utilisation: respiratory-related hospital admissions (number of patients with at least one admission)

Summary of Findings Table						
Patient or population: patients with chronic obstructive pulmonary disease (COPD) **Setting:** hospital, outpatient clinic, primary care, home-based **Intervention:** self-management interventions including action plans for COPD exacerbations **Comparison:** usual care						
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Risk with usual care	**Risk with self-management interventions including action plans for exacerbations**				
Health-related quality of life (HRQoL) assessed with: St. George's Respiratory Questionnaire adjusted total score Scale from: 0 to 100 follow up: 12 months	The mean HRQoL ranged from 37.7 to 70.4 points	MD 2.69 points lower (4.49 lower to 0.9 lower)	-	1,582 (10 RCTs)	⊕⊕⊕⊕ HIGH	Lower score indicates better health-related quality of life.
Respiratory-related hospital admissions assessed with: number of patients with at least one respiratory-related hospital admission follow up: range 6 months to 24 months	312 per 1,000	238 per 1,000 (188 to 298)	OR 0.69 (0.51 to 0.94)	3,157 (14 RCTs)	⊕⊕⊕⊖ MODERATE [1]	
All-cause hospital admissions assessed with: number of patients with at least one all-cause hospital admission follow up: range 6 months to 12 months	427 per 1,000	356 per 1,000 (287 to 434)	OR 0.74 (0.54 to 1.03)	2,467 (10 RCTs)	⊕⊕⊕⊖ MODERATE [2]	

All-cause mortality assessed with: number of all-cause deaths follow up: range 3 months to 24 months	102 per 1,000	107 per 1,000 (74 to 153)	OR 1.06 (0.71 to 1.59)	3,296 (16 RCTs)	⊕⊕⊕⊖ MODERATE[3]	Pooled risk difference of 0.0019 (95% CI -0.0225 to 0.0263).
Respiratory-related mortality assessed with: number of respiratory-related deaths follow up: range 3 months to 24 months	48 per 1,000	89 per 1,000 (57 to 136)	OR 1.94 (1.20 to 3.13)	1,219 (7 RCTs)	⊕⊖⊖⊖ VERY LOW [4]	Pooled risk difference of 0.028 (95% CI 0.0049 to 0.0511).
Dyspnoea assessed with: (modified) Medical Research Council Dyspnoea Scale Scale from: 0 to 4 follow up: 12 months	The mean dyspnoea ranged from 2.4 to 2.6	MD 0.63 lower (1.44 lower to 0.18 higher)	-	217 (3 RCTs)	⊕⊕⊖⊖ LOW [5]	Lower score indicates improvement in dyspnoea.
COPD exacerbations assessed with: number of COPD exacerbations per patient follow up: range 3 months to 24 months [7]	The mean COPD exacerbations ranged from 1.13 to 4.3	MD 0.01 higher (0.28 lower to 0.29 higher)	-	740 (4 RCTs)	⊕⊕⊕⊖ MODERATE [6]	
Courses of oral steroids assessed with: number of patients who used at least one course of oral steroids follow up: 12 months	497 per 1,000	812 per 1,000 (352 to 972)	OR 4.38 (0.55 to 34.91)	963 (4 RCTs)	⊕⊕⊖⊖ LOW [8]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: Confidence interval; **MD**: mean difference; **OR:** Odds ratio; **RCT**: randomised controlled trial

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Effects of interventions

We included a 'Summary of Findings' (SOF) Table of the 22 included studies that compared self-management with usual care. This SOF Table reflects the endpoints related to HRQoL, hospital admissions, mortality, dyspnoea, number of COPD exacerbations, and courses of oral steroids.

Health-related quality of life

COPD-specific HRQoL was measured by the SGRQ in ten studies[13,26,27,40,42,43,45,48,49,55] with a total of 1,582 patients. We used adjusted mean difference scores when available. If not available, we included the change from baseline scores and otherwise the mean total scores of these studies on a single forest plot to perform a meta-analysis on SGRQ total score. Over 12 months of follow-up, the included studies showed lower mean SGRQ total scores (meaning better HRQoL) in the self-management intervention compared with the usual care group. The MD of -2.69 (95% CI -4.49 to -0.90), indicating better HRQoL in the intervention group compared to the control group, was statistically significant at the 5% level (Analysis 1.1) with a heterogeneity I^2 of 46%. The pooled MD of -2.69 did not reach the MCID of four points.[70] However, four individual studies[13,27,43,49] reached the MCID of four points for the SGRQ total score. Only Fan 2012 et al.[26] reported a statistically non-significant positive MD of 0.31 for the change from baseline SGRQ total score among patients who completed 12 months follow-up, indicating that the self-management intervention group decreased by 0.31 points less from baseline compared with the usual care group. Three studies[38,47,51] provided insufficient data for inclusion in the meta-analysis. Österlund Efraimsson 2008 et al.[38] reported significant and clinically relevant lower total SGRQ total scores in the self-management intervention group (HRQoL was improved by 8.2 points) compared with the usual care group (no change noted). Martin 2004 et al.[47] found no significant difference in SGRQ total score after 12 months of follow-up. The SGRQ total score in Song 2014 et al.[51] was significantly lower in the experimental group after two months, which meant better HRQoL. Sensitivity analysis using FEM resulted in a lower effect size of the SGRQ total score (MD -2.08, 95% CI -3.21 to -0.95) compared to REM.

Three studies[50,54,56] measured COPD-specific HRQoL with the Chronic Respiratory Questionnaire (CRQ) with a total of 394 patients. The CRQ consists of four domain scores: dyspnoea, fatigue, emotional function, and mastery (sense of control over the disease).[71] A higher CRQ domain score indicates better HRQoL and the MCID is reflected by a change in a CRQ domain score of at least 0.5 on a 7-point scale.[72,73] Rea 2004 et al.[50] reported the CRQ domains on a different scale and did not provide SDs. This study could therefore not be included in a meta-analysis, leaving an insufficient number of two studies to perform a meta-analysis. In Rea 2004 et al.,[50] two of the four CRQ domains, fatigue and mastery, showed

statistically significant higher scores, indicating better HRQoL, for the self-management intervention group (17.7 and 21.4, respectively) compared to usual care (15.7 and 20.7, respectively) after 12-months follow-up. Mitchell 2014 et al.[56] reported that both groups improved CRQ dyspnoea over time and only the self-management group maintained within-group changes that exceeded the MCID of 0.5. The between-group differences were non-significant at six months of follow-up.[56] A non-comprehensive approach with a lack of group support, supervised exercise training and healthcare professional-led education might have limited the effectiveness of the intervention.[56] Bischoff 2012 et al.[54] reported no statistically significant mean treatment difference between the self-management intervention and usual care group for the CRQ total score at 24 months of follow-up. Although more patients in the intervention group showed a clinically important improvement compared to the usual care group, this difference was not statistically significant.

Only Rea 2004 et al.[50] used the Short Form-36 (SF-36) to measure the generic HRQoL. There were no differences noted between the intervention and usual care group after 12 months of follow-up for any dimension of the SF-36.

Bucknall 2012 et al.[27] and Tabak 2014 et al.[52] reported the generic HRQoL by means of the EuroQol-5Dimensions (EQ-5D). Bucknall 2012 et al.[27] reported no significant differences in the EQ-5D areas under the curve between the two groups after 12 months of follow-up. The study findings reported by Tabak 2014 et al.[52] showed a trend towards a higher EQ-5D index, indicating better HRQoL, in the intervention group compared to the control group after three months of follow-up (mean 0.78 ± SE 0.08 vs. mean 0.61 ± SE 0.09). However, these data were reported only descriptively.

In Tabak 2014 et al.[52] the individual's HRQoL state was also reported by a vertical Visual Analogue Scale (VAS). There was a trend towards a higher VAS score, indicating better HRQoL, reported for self-management (72.3 ± SE 3.1) compared to usual care (62.4 ± SE 3.5). Again, these data were only reported descriptively. Garcia-Aymerich 2007 et al.[55] reported slight, non-significant improvements in quality of life scores in both groups according to the VAS in the follow-up year (intervention 1.56 ± SD 1.77, control 0.93 ± SD 2.11).

In Ninot 2011 et al.[49] generic HRQoL and health status were further measured using the short version of the questionnaire validated by the Nottingham Health Profile. Statistically significant beneficial effects of the self-management intervention on the energy (between-group difference -19.8, 95% CI -38 to -1) and emotional reaction (between-group difference -10.4, 95% CI -20 to 0) dimensions of the NHP, after adjustment for baseline values were reported.[49]

Respiratory-related hospital admissions

Respiratory-related hospital admissions were reported in 14 studies[13,26,27,40,42-45,48-50,52,53,56] with 3,157 patients. A statistically significant lower probability of at least one respiratory-related hospital admission was noted among patients receiving the self-management intervention that included an action plan compared with those who received usual care (OR 0.69, 95% CI 0.51 to 0.94, Analysis 1.2). Heterogeneity was high (I^2 = 57%). Sensitivity analysis using FEM resulted in a similar effect size (OR 0.71, 95% CI 0.60 to 0.85) compared to REM.

Two studies[39,47] could not be included in the meta-analysis due to a lack of the required data. In Martin 2004 et al.[47] more respiratory-related hospitalisations were found in the intervention group (1.1 per patient per year) compared to usual care (0.7 per patient per year). Due to a lack of SDs, this study could not be included in the meta-analysis. There were six studies[38,41,46,51,54,55] that did not report any data on the respiratory-related hospital admissions and could therefore not be included in the meta-analysis.

The study-specific NNTBs for respiratory-related hospital admissions ranged from 11 (95% CI 7 to 65) to 71 (95% CI 44 to 367). To calculate NNTB, the pooled effect on respiratory-related hospital admissions (OR 0.69, 95% CI 0.51 to 0.94) was used and this was applied to the mean control event risks of the studies with the highest and lowest baseline risks. The seven studies[13,27,40,44,45,50,52] with the highest baseline risks for respiratory-related hospital admissions had a mean control event risk (mean observed risk of the respiratory-related hospital admissions in the usual care group) of 38.99 (Figure 2.5). Over 12 months of follow-up, 12 patients (95% CI 7 to 69) with high baseline risk of respiratory-related hospital admissions needed to be treated to prevent one patient with at least one respiratory-related hospital admission. The seven studies[26,42,43,48,49,53,56] with the lowest baseline risks for respiratory-related hospital admissions had a mean control event risk of 23.10 (Figure 2.6). Over 12 months of follow-up, 17 patients (95% CI 11 to 93) with low baseline risk of respiratory-related hospital ad-missions needed to be treated to prevent one patient with at least one respiratory-related hospital admission.

Five studies[27,39,44,52,53] wereincluded in a meta-analysis on the mean number of respiratory-related hospital admissions. No difference was found (MD -0.15, 95% CI -0.36 to 0.05, Analysis 1.3). Using fixed-effect modelling in the sensitivity analysis produced similar effects.

All-cause hospital admissions

All-cause hospital admissions were reported in 10 studies[13,26,27,41,43,45,49,50,52,56] with 2,467

Figure 2.5. Cates plot of COPD patients with high baseline risk of respiratory-related hospital admissions in self-management interventions including action plans for AECOPD compared to usual care. In the usual care group, 39 of 100 patients had at least one respiratory-related hospital admission over 52 weeks, compared with 31 (95% CI 25 to 38) of 100 patients in the self-management intervention group with the highest baseline risks for respiratory-related hospital admissions

Figure 2.6. Cates plot of COPD patients with low baseline risk of respiratory-related hospital admissions in self-management interventions including action plans for AECOPD compared to usual care. In the usual care group, 23 of 100 patients had at least one respiratory-related hospital admission over 52 weeks, compared with 17 (95% CI 13 to 22) of 100 patients in the self-management intervention group with the lowest baseline risks for respiratory-related hospital admissions

patients. There was no statistically significant difference in all-cause hospital admissions (OR 0.74, 95% CI 0.54 to 1.03, Analysis 1.4). Heterogeneity was high (I^2 = 62%). Sensitivity analysis using fixed-effect modelling resulted in statistically significant fewer all-cause hospital admissions in the self-management group compared to usual care (OR 0.74, 95% CI 0.63 to 0.88). Since the beneficial effect of the self-management intervention on all-cause hospital admissions observed when analysing using a random effects model was the same when analysing using random-effect and fixed-effect models, the presence of small study effects was considered unlikely.

Twelve studies[38-40,42,44,46-48,51,53-55] could not be included in the meta-analysis due to a lack of the required information. It was not possible to calculate the NNTB for all-cause hospital admissions, because the 95% CI of the pooled OR for at least one all-cause hospital admission included the possibilities of both benefit and harm.

Four[27,41,47,52] of the six studies that reported on the mean number of all-cause hospital admissions were included in a meta-analysis. No difference in this number was found (MD -0.04, 95% CI -0.38 to 0.29, Analysis 1.5). Heterogeneity was non-significant (I^2 = 35%. Two studies[40,49] could not be included in the meta-analysis because SDs were not reported. A sensitivity analysis using fixed-effect modelling resulted in an effect size (MD -0.07, 95% CI -0.33 to 0.19) similar to the random-effect model.

Healthcare utilisation

All-cause hospitalisation days

The total number of all-cause hospitalisation days was reported in three studies[40,45,50] with 469 patients. The data reported in these studies were heavily skewed and unsuitable for meta-analysis. All three studies[40,45,50] reported a lower number of all-cause hospitalisation days in the intervention group (n = 688, n = 164, and n = 263, respectively) compared to the usual care group (n = 1,190, n = 466, n = 352, respectively). This difference was reported to be statistically significant in one study[45], but the other studies did not report significance of the differences.

The number of all-cause hospitalisation days per patient was assessed in eight studies. Seven studies[13,27,40,43,45,48,49] with 1,982 patients could be included in the meta-analysis and no statistically significant between-group differences were found (MD -0.65, 95% CI -2.01 to 0.71, Analysis 1.6). Heterogeneity was high (I^2 = 60%). Sensitivity analysis using a fixed-effect model resulted in statistically significantly lower all-cause hospitalisation days per patient (MD -0.69, 95% CI -1.36 to -0.02). Rea 2004 et al.[50] could not be included in the meta-analysis because no SD was reported. The mean number of all-cause bed days in this study was lower in the intervention group than the usual care group (3.2 vs 6.8); however,

this difference did not reach statistical significance.

Respiratory-related hospitalisation days

The total number of respiratory-related hospitalisation days was reported in three studies[50,52,53] with 333 patients. The data reported in these studies were unsuitable for a meta-analysis. All three studies[50,52,53] reported a lower number of respiratory-related hospitalisation days in the intervention group (n = 90, n = 22, and n = 486, respectively) compared to the usual care group (n = 210, n = 36, n = 954, respectively). The studies did not report on significance of these differences. However, Titova 2015 et al.[53] reported that in the intervention group the number of respiratory-related hospitalisation days was statistically significantly reduced during the first year of follow-up and remained low during the second year of follow-up.

The number of respiratory-related hospitalisation days per patient was reported in three studies[42,49,50] with 226 patients. However, Rea 2004 et al.[50] did not provide the SD so the study could not be included in the meta-analysis. There were an insufficient number of studies remained to perform a meta-analysis, and the data provided were heavily skewed. Although Gallefoss 1999 et al.[42] reported a non-significant lower mean number of respiratory-related hospitalisation days in the intervention group (0.7 ± SD 2) compared to the usual care group (2.5 ± SD 11), Ninot 2011 et al.[49] reported a non-significant higher mean number of respiratory-related hospitalisation days in the intervention group (1.9 ± SD 3.7) compared to usual care (0.3 ± SD 0.7). Rea 2004 et al.[50] reported significantly fewer respiratory-related hospitalisation days per patient per year in the intervention group (from 2.8 to 1.1) compared to a significant increase for the usual care group (from 3.5 to 4.0 days). Tabak 2014 et al.[52] could not be included in this meta-analysis because the median length of stay was reported (intervention 5.5 (IQR 4.8 to 6.3), usual care 7.0 (IQR 6.0 to 7.0)).

Emergency department (ED) visits

Nine studies[13,26,27,40,43-45,50,52] reported ED visits. Three studies[27,40,44] were included in a meta-analysis; ED visit data were reported for 827 patients. There was no statistically significant difference between intervention and usual care (MD -0.31, 95% CI -0.74 to 0.12, Analysis 1.7). Sensitivity analysis using a fixed-effect model resulted in a statistically significant lower number of ED visits in the intervention group compared to the control group (MD -0.35, 95% CI -0.43 to -0.27). The observed effect sizes in the fixed-effect (MD -0.35) and random-effect (-0.31) models were comparable. The presence of small study effects was therefore considered to be unlikely.

Six studies[13,26,43,45,50,52] could not be meta-analysed because different methods were used to report the outcome. Fan 2012 et al.[26] reported fewer patients who had at least one ED

visit in the intervention group (n = 99, 47%) compared to the usual care group (n = 119, 55%) and a lower total number of ED visits in the intervention group (intervention n = 173 vs usual care n = 203) at 12 months of follow-up. It was not reported whether these differences were statistically significant or if numbers were adjusted for incomplete follow-up. Hernández 2015 et al.[43] reported a lower mean number of respiratory-related ED visits in the intervention group (10 ± SD 12.11) compared to the usual care group (23 ± SD 27.4). After adjusting for baseline differences, the intervention significantly reduced the risk of ED visits (OR 0.33, 95% CI 0.13 to 0.84). However, these data could not be meta-analysed because there was a different process reported for co-ordination of hospital admissions in both groups; 80% of the admissions in the intervention group were co-ordinated between primary care and the hospital team, thus by-passing the ED.[43] By contrast, all admissions in the usual care group were processed as unplanned through the ED.[43] The number of ED visits was dependent on group allocation. Khdour 2009 et al.[45] reported a statistically significant lower number of COPD-related ED visits in the intervention group compared to the usual care group (40 vs 80) after 12 months of follow-up. Rea 2004 et al.[50] observed five (6%) all-cause ED visits in the intervention group and seven (13.5%) visits in the usual care group after 12 months of follow-up. Rice 2010 et al.[13] found significantly fewer all-cause ED visits in the intervention group than in the usual care group (67.0 vs 91.2 per 100 person-years) after 12 months of follow-up. Tabak 2014 et al.[52] reported five (42%) patients with at least one COPD-related ED visit in both groups.

General practitioner (GP) visits

GP visits were reported in seven studies[27,40-42,45,47,48]. Three studies[27,42,47] were included in a meta-analysis with 605 patients. There was no statistically significant difference noted between the intervention and usual care (MD -0.36, 95% CI -2.64 to 1.93, Analysis 1.8). Sensitivity analysis using a fixed-effect model resulted in a non-significant lower effect on GP visits (MD -0.09, 95% CI -0.24 to 0.06). Four studies[40,41,45,48] could not be included in the meta-analysis because different methods were used to report the outcome[41,45] and because of missing SDs[40,48]. Bourbeau 2003 et al.[40] reported significantly fewer unscheduled GP visits in the intervention group (n = 46) compared to usual care (n = 112) after 12 months of follow-up. However, the scheduled GP visits were comparable between groups. Monninkhof 2003 et al.[48] showed a reduction in unscheduled doctor and nurse visits per person per year between the intervention and control group (difference -0.4). Casas 2006 et al.[41] reported no statistically significant differences in the number of GP h me visits between the intervention (median 10, IQR 7 to 18) and control group (median 13, IQR 9 to 27). Khdour 2009 et al.[45] reported a similar number of GP visits in both groups; a lower total number of scheduled GP visits in the intervention group (145 vs 183), although the total number of unscheduled visits in this study was somewhat higher in the intervention group (119 vs 75).

Specialist visits

Four studies[40,41,44,47] reported data on specialist visits. These studies could not be included in a meta-analysis, since different methods and definitions were used to report visits. Bourbeau 2003 et al.[40] reported comparable unscheduled (intervention n = 24, control n = 26) and scheduled specialist visits (intervention n = 347, control n = 316) in both groups. Casas 2006 et al.[41] reported a non-significantly higher number of doctor and nurse visits (defined as unplanned visits to the GP, specialist outside the hospital, chest physician from the hospital, private doctors, domiciliary visits from the primary care team and visits to the day hospital) in the intervention group compared to the usual care group (14 ± SD 24 vs 10 ± SD 23). However, these data were heavily skewed. Martin 2004 et al.[47] reported a non-significantly higher number of all-cause doctor and nurse visits in the intervention group compared to the control group (15.6 ± SD 12.68 vs 11.6 ± SD 8.02). Jennings 2015 et al.[44] reported a non-significantly lower number of primary care provider visits in the intervention group (0.46 ± SD 0.5) compared to the control group (0.53 ± SD 0.5) after three months of follow-up.

Rescue medication use

Two studies[13,42] included rescue medication use as an outcome, but used different definitions. Gallefoss 1999 et al.[42] reported the use of dispensed short-acting beta$_2$-agonists as rescue medication. This was coded as defined daily dosages (DDDs) for comparison of medications within the same chemical therapeutic group. In this study, patients receiving self-management used statistically significantly less rescue medication (median DDD 125, IQR 100 to 344) than the control group (median DDD 290, IQR 150 to 550) after 12 months of follow-up. Rice 2010 et al.[13] reported the use of short-acting beta$_2$-agonists as the mean number of metered-dose inhalers and found no statistically significant differences between intervention and control groups (6.4 ± 8.3 vs 5.6 ± 8.0).

Health status

In only two studies[46,52] the change in severity of COPD was measured by means of the Clinical COPD Questionnaire (CCQ), so meta-analysis could not be performed. A lower CCQ score indicates better HRQoL and the MCID of the CCQ total score is reflected by a change in score of 0.4 or more on a 6-point scale. Kheirabadi 2008 et al.[46] reported that the intervention did not have a significant effect on the severity of COPD in the CCQ total score (mean 1.99 for both groups), but it did significantly decrease (meaning better HRQoL) three domain scores of the CCQ (symptoms, functional and mental). This improvement in HRQoL was clinically relevant for the self-management group as the three domain scores reached the MCID of 0.4 points.[46] Tabak 2014 et al.[52] reported the CCQ total score for both groups after one and three months of follow-up. These data were descriptive only, but showed trends toward a lower CCQ total score for the intervention group after three months of

follow-up (mean 1.8 ± SE 0.24) compared to usual care (mean 2.3 ± SE 0.26).

Dyspnoea symptoms

The effect of a self-management intervention on dyspnoea as measured by the (modified) Medical Research Council questionnaire ((m)MRC) was assessed in three studies[39,43,55]. Garcia-Aymerich 2007 et al.[55] assessed dyspnoea using the MRC and the other two studies used the mMRC. The outcomes of the three studies were combined in a meta-analysis representing 217 patients. A non-significant difference in dyspnoea scores was noted (MD -0.63, 95% CI -1.44 to 0.18, Analysis 1.9). Sensitivity analysis using a fixed-effect model resulted in statistically significant lower dyspnoea scores in the intervention group compared with the control group (MD -0.59, 95% CI -0.89 to -0.29). The observed effect sizes in the fixed- (MD -0.59) and random- (MD -0.63) effects models were comparable. The presence of small study effects was considered to be unlikely.

Bourbeau 2003 et al.[40] reported a non-significant difference of patient-recorded dyspnoea deterioration in 90% of acute exacerbations in the intervention group versus 88% in the control group. Monninkhof 2003 et al.[48] used breathlessness extracted from two-week diary data and reported non-significant between-group differences. Song 2014 et al.[51] reported a non-significant difference in the degree of dyspnoea by using the BORG scale (range 0 to 10) after walking between the intervention (7.4 ± 2.0) and control group (4.8 ± 2.1) after two months of follow-up.

Other COPD symptoms

Bourbeau 2003 et al.[40] reported non-significant increases in sputum volume (intervention 54%; control 57%) and purulent sputum was present in 48% in the intervention group and 53% in the control group. Monninkhof 2003 et al.[48] reported non-significant differences in sputum production over a two-week period. Whereas borderline beneficial significant differences in mean cough and sputum colour scores were reported for the self-management intervention group, the study authors stated that these differences probably were not clinically relevant.

Number of COPD exacerbations

Data representing with 740 patients from four studies[26,39,44,54] on the mean number of exacerbations per patient were not statistically significant (MD 0.01, 95% CI -0.28 to 0.29, Analysis 1.10). The same effect was found when a fixed-effect rather than a random-effect model was used in a sensitivity analysis. Monninkhof 2003 et al.[48] reported an average of 2.8 exacerbations in the intervention group and 1.5 in the control group. This study could not be included in the meta-analysis because SDs were not reported.

Similar definitions were used for COPD exacerbations among studies. Bischoff 2012 et al.[54] defined exacerbations as a change for at least two consecutive days in either two or more major symptoms (dyspnoea, sputum purulence, sputum amount) or any one major symptom plus at least one minor symptom (colds, wheeze, sore throat, cough); Fan 2012 et al.[26] defined AECOPD as an increase in or new onset of one or more respiratory symptoms (cough, sputum, wheezing, dyspnoea, or chest tightness) persisting for at least two days. Jennings 2015 et al.[44] defined an exacerbation as an acute event characterised by a worsening of the patient's respiratory symptoms beyond normal day-to-day variations, leading to a change in medication. Bösch 2007 et al.[39] did not provide a definition of exacerbations, but indicated that the exacerbations were treated with antibiotics. Monninkhof 2003 et al.[48] defined exacerbations as worsening of respiratory symptoms that required treatment with a short course of oral corticosteroids or antibiotics.

The total number of exacerbations were reported in five studies[26,40,48,52,54]. Bischoff 2012 et al.[54] reported 280 exacerbations in the intervention group (N = 55) and 235 in the control group (N = 55) after 24 months of follow-up. Bourbeau 2003 et al.[40] reported 299 exacerbations in the intervention group (N = 96) and 362 exacerbations in the control group (N = 95) after 12 months of follow-up. Fan 2012 et al.[26] reported 600 self-reported exacerbations in the intervention group (N = 209) and 610 in the control group (N = 217) during the first 12 months of follow-up. Monninkhof 2003 et al.[48] reported 360 exacerbations in the intervention group (N = 127) and 177 exacerbations in the control group (N = 121) after 12 months of follow-up.

Use of oral steroids and antibiotics

Thirteen studies[27,38,40,41,43-46,48,49,51-53] did not report any data on the use of oral steroids or antibiotics or both and could not be included in meta-analyses. Two studies[45,54] reported data on combined use of oral steroids and antibiotics. Bischoff 2012 et al.[54] reported a similar number of patients who started prednisolone, antibiotics or both to manage exacerbations in the self-management group (n = 16, 11%) compared to the usual care group (n = 13, 10%) in the first year of follow-up. In the second year of follow-up, a higher number of exacerbations in the self-management group were managed by starting prednisolone, antibiotics or both (OR 3.98, 95% CI 1.10 to 15.58). Khdour 2009 et al.[45] observed a significant difference with less oral steroids and antibiotic courses in the intervention group compared with the control group (3.08, 95% CI 2.57 to 3.59 vs 4.03, 95% CI 3.37 to 4.69).

Courses of oral steroids

The use of oral steroids for respiratory problems was reported by six studies[13,26,42,47,50,55]. However, the number of patients who used at least one course of steroids was available for four studies[13,42,50,55]; data from these studies were included in a meta-analysis. A non-

significant higher probability of using at least one course of oral steroids in the self-management group compared with the control group was observed (OR 4.38, 95% CI 0.55 to 34.91, Analysis 1.11), with high heterogeneity (I^2 = 94%). In this meta-analysis the probability of using at least one course of oral steroids was reported to be in favour of the usual care group. However, it could also be argued that the higher probability of using at least one course of oral steroids is in favour of the self-management group; it might lead to earlier appropriate treatment of AECOPD and may prevent hospital admissions. Rice 2010 et al.[13] was an outlier in our meta-analysis (Analysis 1.11); it included many more patients than were included in the other three studies. In addition, the proportion of patients who received at least one course of oral steroids in the self-management group of Rice 2010 et al.[13] was relatively high (97.6%) compared with the other studies (Garcia-Aymerich 2007 et al.[55]= 9.5%, Gallefoss 1999 et al.[42] = 69.2%, Rea 2004 et al.[50] = 47.6%). Rice 2010 et al.[13] reported that the much higher rates of oral steroids use in the intervention group suggested that patients were recognising and self-(over)treating respiratory events that otherwise might have resulted in ED visits or hospital admissions. The OR in Rice 2010 et al.[13] was 32.7 which is probably an overestimation of the risk ratio due to the fact that the event is common. This meta-analysis should therefore be interpreted with caution.

Fan 2012 et al.[26] reported a significantly higher mean of 2.5 exacerbations per patient-year treated with prednisolone in the self-management group compared with 2.1 in the control group (rate ratio 1.25, 95% CI 1.05 to 1.48). In Martin 2004 et al.[47], the frequency of oral prednisolone courses per 12 months was not statistically significant higher in the intervention group (2.3, 95% CI 1.4 to 3.2) compared to the control group (1.3, 95% CI 0.8 to 1.8).

Courses of antibiotics

The use of antibiotics for respiratory problems was reported by six studies[13,26,39,47,50,56]. However, the number of patients that used at least one course of antibiotics was available for only two studies[13,50]. A meta-analysis was not justified. Rea 2004 et al.[50] reported fewer patients receiving at least one course of antibiotics in the intervention group than in the control group (59% vs 69%), whereas Rice 2010 et al.[13] reported the opposite (92% vs 56%). Again, Rice 2010 et al.[13] reported that the much higher rates of antibiotic use in the intervention group suggested that patients were recognising and self-(over)treating respiratory events that otherwise might have resulted in ED visits or hospital admissions. Bösch 2007 et al.[39] reported a statistically significant reduction in the mean number of exacerbations (2.0 ± SD 1.4 to 1.4 ± SD 1.6) that were treated with antibiotics in the intervention group, with no changes observed in the control group. Fan 2012 et al.[26] reported a non-significantly higher mean of 2.7 exacerbations per patient-year treated with an antibiotic in the self-management group compared with 2.5 in the control group

(rate ratio 1.11, 95% CI 0.97 to 1.27). In Martin 2004 et al.[47], there was no significant difference in the use of antibiotics between the groups (intervention 3.6, 95% CI 2.5 to 4.7 vs control 2.5, 95% CI 1.7 to 3.3) after 12 months of follow-up. Mitchell 2014 et al.[56] also reported no statistically significant difference between groups in the number of antibiotic courses (intervention n = 82 vs control n = 70, OR 1.20, 95% CI 0.77 to 1.86) six months post-randomisation.

Mortality

Mortality as reported as an outcome measure in five studies [13,26,27,41,53]. We extracted mortality data from sections describing the participant flow and reasons for losses to follow-up from 11 studies[40,42,43,45-50,52,56]. Mortality data reported by Garcia-Aymerich 2007 et al.[55] could not be included in the meta-analysis, since the same data were already incorporated in the study of Casas 2006 et al.[41] Five studies provided no information on mortality (Bischoff 2012 et al.[54], N = 110 participants; Bösch 2007 et al.[39] N = 50 participants; Jennings et al.[44] N = 172 participants; Österlund Efraimsson et al.[38] N = 52 participants; Song 2014 et al.[51] N = 40 participants) and could not be included in the meta-analysis.

All-cause mortality

We included data from 16 studies[13,26,27,40-43,45-50,52,53,56] with 3,296 patients in a meta-analysis. of all-cause mortality. No statistically significant differences in mortality were found between intervention and control group patients (risk difference (RD) 0.00, 95% CI -0.02 to 0.03, I^2= 48%, Analysis 1.12). Four studies[42,46,49,52] reported no deaths in the self-management and control groups. Sensitivity analysis using a fixed effect model resulted in a similar non-significant effect on all-cause mortality (RD 0.01, 95% CI -0.01 to 0.03).

Twelve studies were included in a subgroup meta-analysis on one-year all-cause mortality[13,27,40-43,45,47-50,53] with 2,620 patients. No statistically significant differences in mortality were found between intervention and control (RD -0.0070, 95% CI -0.0326 to 0.0186, I^2 = 33%, Analysis 1.12). Sensitivity analysis using a fixed-effect model resulted in a similar non-significant effect on the one-year all-cause mortality (RD 0.0078, 95% CI -0.0128 to 0.0283).

Only two studies[40,53] provided data on two-year all-cause mortality, so meta-analysis could not be performed. Bourbeau 2003 et al.[40] reported a non-significant lower two-year all-cause mortality rate in the intervention group compared to the usual care group (MD -0.05, 95% CI -0.16 to 0.05). Titova 2015 et al.[53] reported a non-significant higher two-year all-cause mortality rate in the intervention group compared to the usual care group (MD 0.13, 95% CI -0.01 to 0.26).

Respiratory-related mortality

We included data from seven studies[26,27,42,46,49,52,53] in a meta-analysis of respiratory-related mortality. A small, but statistically significant higher, respiratory-related mortality rate was found for the intervention group compared to the control group (RD 0.028, 95% CI 0.0049 to 0.0511, 1,219 participants, $I^2 = 0\%$, Analysis 1.13). Four studies[42,46,49,52] reported no deaths in the self-management and control groups after 12, 3, 12 and 9 months of follow-up, respectively. Two studies[26,27] dominated the overall effect after 12 months of follow-up. A similar small, but significant higher one-year respiratory-related mortality rate was found for self-management compared to usual care (RD 0.03, 95% CI 0.00 to 0.05, four studies, 981 participants, $I^2 = 0\%$, Analysis 1.13). Sensitivity analysis using a fixed-effect model resulted in a similar statistically significantly higher respiratory-related mortality in the intervention group compared to the control group (RD 0.04, 95% CI 0.01 to 0.07).

Self-efficacy

Only two studies[27,54] reported on self-efficacy, so it was not possible to perform a meta-analysis. Both studies measured self-efficacy using the COPD Self-Efficacy Scale (CSES). Bischoff 2012 et al.[54] reported no statistically significant changes or difference in patient's self-efficacy between the intervention and control group according to the CSES total (MD -0.17, 95% CI -0.64 to 0.30) and domain scores after 24 months of follow-up. Bucknall 2012 et al.[27] also reported a non-significant difference in CSES total scores between the intervention and control group (MD 2.65, 95% CI -5.85 to 11.14).

Days lost from work

Two studies[42,48] reported days lost from work, so it was not possible to perform a meta-analysis. Gallefoss 1999 et al.[42] reported no significant differences between groups. Almost 50% of the patients with COPD in this study were employed. Three of 14 (21%) participants in the intervention group and two of 13 (15%) in the control group reported absence from work. Monninkhof 2003 et al.[48] used the term 'restrictive activity days', defined as days on which work was missed or days when activities were significantly reduced because of health problems. A reduction in the average number of restricted activity days during exacerbation recovery was seen in the intervention compared with the control group (4.1 ± 4.2 vs 5.3 ± 5.3), but no significant between-group differences were detected.

Subgroup analyses

We performed subgroup analysis on two outcomes; HRQoL and respiratory-related hospital admissions.

Duration of follow-up

We performed a subgroup analysis on the duration of follow-up to assess the short- and

long term effects of self-management compared to usual care. Six studies[38,44,46,51,52,56] reported a follow-up period shorter than 12 months after the start of the study and sixteen studies[13,26,27,39-43,45,47-50,53-55] reported a long-term follow-up (12 or more months of follow-up after the start of the study).

It was not possible to perform a follow-up subgroup analysis for the effects on HRQoL, because follow-up of the 10 included studies were all long-term (≥ 12 months). In addition, a subgroup analysis based on a follow-up duration with a cut-off point of 18 months was not possible to perform, since the criterion of at least three studies per subgroup was not met.

There was no statistically significant difference in respiratory-related hospital admissions between studies with a long-term (n = 11) or short-term follow-up (n = 3) (test for subgroup differences: $Chi^2 = 0.02$, df = 1 (P = 0.90), $I^2 = 0$ %, Analysis 2.1). It was not possible to perform a subgroup analysis with six months as cut-off point for the effects on respiratory-related hospitalisations, since this resulted in an insufficient number of studies for the subgroup analysis. A cut-off point of 18 months for the duration of follow-up resulted in a subgroup with only two studies[40,53] and therefore we could not perform a subgroup analysis.

COPD stability at time of inclusion

Five studies[41,44,51,53,55] reported inclusion of patients with COPD who were in the unstable phase, eight studies[26,40,43,47-49,52,56] reported inclusion of patients in the stable phase; and nine studies[13,27,38,39,42,45,46,50,54] did not report if the patients were in stable or unstable phases. It was not possible to perform a subgroup analysis on the inclusion of patients in the unstable phase versus the stable phase for the effects on HRQoL or on the number of patients with at least one respiratory-related hospital admission, because of the relatively small number of studies that reported inclusion of patients in the unstable phase.

Use of a standardised exercise programme

We performed subgroup analyses on the use of a standardised exercise programme as part of the self-management intervention. No statistically significant difference was observed for the effects on HRQoL observed among studies (n = 4) with an exercise programme and studies (n = 6) without an exercise programme (test for subgroup differences: $Chi^2 = 0.10$, df = 1 (P = 0.76), $I^2 = 0$%, Analysis 2.2). The difference in effects on respiratory-related hospital admissions among studies with (n = 6) and without (n = 8) an exercise programme was not statistically significantly different between subgroups (test for subgroup differences: $Chi^2 = 0.79$, df = 1 (P = 0.37), $I^2 = 0$% Analysis 2.3).

Use of a smoking cessation programme

Studies included for subgroup analyses on use of a smoking cessation programme reported no statistically significant between-group baseline differences in smoking status. There were two studies[43,45] with a smoking cessation programme and one study[53] without, in which changes in smoking rates over time were observed. Khdour 2009 et al.[45] observed 22.2% self-reported abstinence in the self-management group at the six- and 12-month follow-up compared with 5.3% and 10.5% in the usual care group smokers, respectively. However, the differences in stage of change status in relation to smoking did not reach statistical significance.[45] After 12 months of follow-up, Hernández 2015 et al.[43] reported a statistically significantly lower percentage of current smokers (self-management 3% vs usual care 16%). Titova 2015 et al.[53] reported a non-significant trend toward a reduction in the percentage of current smokers in the self-management group from 35.3% at baseline to 31.4% after 12 months and to 27.5% after 24 months. In the usual care group these percentages were 30.6% at baseline and after 12 months, and 26.5% after 24 months.

Subgroup analyses on the use of a smoking cessation programme as part of the self-management intervention showed a statistically significantly larger improvement in HRQoL in the three studies[13,43,45] with a smoking cessation programme (MD -4.98, 95% CI -7.17 to -2.78, Analysis 2.4) compared to the seven studies[26,27,40,42,48,49,55] without a smoking cessation programme (MD -1.33, 95% CI -2.94 to 0.27, test for subgroup differences: Chi^2 = 6.89, df = 1 (P = 0.009), I^2 = 85.5%).

No statistically significant effect was observed in a subgroup analysis of four studies with and ten studies without a smoking cessation programme on the probability of respiratory-related hospital admissions in the self-management group compared to usual care (test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.98), I^2 = 0%, Analysis 2.5).

Self-management as part of usual care

In Song 2014 et al.[51] self-management was likely to be part of usual care, so it was not possible to perform a subgroup analysis on the level of self-management as part of usual care. Song 2014 et al.[51] reported that the control group received usual care consisting of education on COPD management, proven benefits of exercise, and maintaining daily activities.

Integration of behavioural change techniques (BCT) clusters

No statistically significant difference was observed for the effects on HRQoL among studies (n = 6) with a high number of BCT clusters (higher than the median number of 9.5) and studies (n = 4) with few BCT clusters (test for subgroup differences: Chi^2 = 0.01, df = 1 (P = 0.94), I^2 = 0%, Analysis 2.6).

There were no statistically significant differences observed in respiratory-related hospital admissions among studies (n = 7) with a high number of BCT clusters versus studies (n = 7) with few BCT clusters (test for subgroup differences: $Chi^2 = 0.82$, df = 1 (P = 0.37), $I^2 = 0\%$, Analysis 2.7). An additional subgroup analysis using a lower cut-off point of BCT clusters (> 8 BCT clusters (n = 10) versus ≤ 8 BCT clusters (n = 4) integrated) showed no statistically significant differences in respiratory-related hospital admissions (test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 0.97), $I^2 = 0\%$, Analysis 2.8).

Case-manager support

In this review, case manager support was defined as unscheduled ongoing support from a case manager based on the individual needs and capabilities in which reinforcement is directed to the patient's self-management skills, and delivered face-to-face, by telephone or by telemedicine. We included ten studies[13,26,27,40,41,48,52-55] that reported case manager support. No statistically significant difference was observed of effects on HRQoL among studies (n = 6) with case manager support and those without case manager support (n = 4) (test for subgroup differences: $Chi^2 = 1.86$, df = 1 (P = 0.17), $I^2 = 46.1\%$, Analysis 2.9).

No statistically significant differences were observed for the effects on respiratory-related hospital admissions among the eight studies with case manager support and the six studies without case manager support (test for subgroup differences: $Chi^2 = 0.13$, df = 1 (P = 0.72), $I^2 = 0\%$, Analysis 2.10).

Duration of intervention

Subgroup analyses on the duration of the self-management intervention showed no statistically significant differences in HRQoL in studies with at least six months of intervention duration (MD -2.96, 95% CI -5.20 to -0.72) compared to studies with less than six months of intervention duration (MD -2.57, 95% CI -6.96 to 1.82, test for subgroup differences: $Chi^2 = 0.02$, df = 1 (P = 0.88), $I^2 = 0\%$, Analysis 2.11).

There was no statistically significant difference in respiratory-related hospital admissions among studies with longer intervention duration (OR 0.65, 95% CI 0.43 to 0.96) compared to studies of less than six months intervention duration (OR 0.84, 95% CI 0.53 to 1.32, test for subgroup differences: $Chi^2 = 0.68$, df = 1 (P = 0.41), $I^2 = 0\%$, Analysis 2.12).

Action plan components

We performed subgroup analyses on the different components of the action plans for COPD exacerbations. There was no statistically significant difference in HRQoL effect among studies that defined an action for adaptation of maintenance medication (MD -3.75, 95%

CI -6.16 to -1.33) and studies that had not defined this action in their action plans for COPD exacerbations (MD -2.02, 95% CI -4.77 to 0.72, test for subgroup differences: $Chi^2 = 0.85$, df = 1 (P = 0.36), $I^2 = 0\%$, Analysis 2.13). Nor was there a statistically significant difference in effect on respiratory-related hospital admissions in studies that included an action for adaptation of maintenance medication (OR 1.01, 95% CI 0.54 to 1.88) compared to studies that not included this action (OR 0.59, 95% CI 0.42 to 0.83, test for subgroup differences: $Chi^2 = 2.16$, df = 1 (P = 0.14), $I^2 = 53.7\%$, Analysis 2.14). Two studies[43,49] defined an action 'when to avoid situations in which viral infections might be prevalent' and reported data on the HRQoL. It was not possible to perform a subgroup analysis on the action plan component of 'avoiding situations in which viral infections might be prevalent'. There was no statistically significant difference observed in respiratory-related hospital admissions in studies that defined an action 'when to avoid situations in which viral infections might be prevalent' (OR 0.88, 95% CI 0.25 to 3.13) compared to studies that did not include this action (OR 0.68, 95% CI 0.50 to 0.91, test for subgroup differences: $Chi^2 = 0.16$, df = 1 (P = 0.69), $I^2 = 0\%$, Analysis 2.15). Four studies[46,47,49,51] did not define an action 'when to contact healthcare providers for support'. Only one study[49] did not define an action 'when to contact healthcare providers for support' and reported data on HRQoL or respiratory-related hospital admissions, so we could not perform subgroup analyses. Two studies[44,46] did not include self-recognition of COPD exacerbations in their action plans and these studies had not defined an action of 'when to self-initiate treatment of a COPD exacerbation'. We were unable to perform subgroup analyses on these action plan components. Two studies[43,47] reported an action 'when to initiate self-treatment of comorbidities'. There were too few studies for subgroup analysis on the self-initiation of comorbidities as a COPD exacerbation action plan component.

DISCUSSION

Summary of main results

We systematically evaluated 22 RCTs (described in 30 articles) on the effectiveness of COPD self-management interventions that included an action plan for AECOPD in comparison with usual care. An action plan was defined as an agreed upon strategy including actions to be initiated by patients when symptoms deteriorate.

We observed a statistically significant beneficial effect of self-management on HRQoL over 12 months, measured by the SGRQ adjusted total score (MD -2.69, 95% CI -4.49 to -0.90; 10 studies; N = 1,582). The pooled MD of the SGRQ total score did not reach the MCID of four points and therefore could not be considered as clinically relevant.[70]

A beneficial self-management effect was also observed for respiratory-related hospital

admissions as reported in 14 studies with 3,157 patients. Patients in a self-management intervention study arms that included an action plan for AECOPD were at statistically significantly lower risk for at least one respiratory-related hospital admission compared with patients who received usual care (OR 0.69, 95% CI 0.51 to 0.94). The number needed to treat to prevent one respiratory-related hospital admission over one year was 12 (95% CI 7 to 69) for patients with a high baseline risk and 17 (95% CI 11 to 93) for patients with a low baseline risk.

We observed no statistically significant difference in the probability of at least one all-cause hospital admission in the self-management intervention group compared to the usual care group (OR 0.74, 95% CI 0.54 to 1.03; 14 studies; N = 2,467). Furthermore, we observed no statistically significant difference in the number of all-cause hospitalisation days (MD -0.65, 95% CI -2.01 to 0.71), ED visits (MD -0.31, 95% CI -0.74 to 0.12), GP visits (MD -0.36, 95% CI -2.64 to 1.93) and (m)MRC dyspnoea scores (MD -0.63, 95% CI -1.44 to 0.18). There was no statistically significant effect observed for self-management on the number of COPD exacerbations (MD 0.01, 95% CI -0.28 to 0.29) and no excess all-cause mortality risk was observed (RD 0.0019, 95% CI -0.0225 to 0.0263) in 16 studies (n = 3,296). However, a small, but statistically significant higher respiratory-related mortality rate was observed in the self-management intervention group compared to the usual care group (RD 0.028, 95% CI 0.0049 to 0.0511) in seven studies (N = 1,219).

Subgroup analyses

Subgroup analyses showed significantly more improvement in HRQoL in studies that included a smoking cessation programme as part of the self-management intervention (MD -4.98, 95% CI -7.17 to -2.78) compared to studies with no smoking cessation programme (MD -1.33, 95% CI -2.94 to 0.27). The number of BCT clusters integrated in the self-management intervention, intervention duration, and adaptation of maintenance medication as part of an action plan did not affect HRQoL. Subgroup analyses did not detect potential explanatory variables for differences in respiratory-related hospital admissions among studies.

Overall completeness and applicability of evidence

Our review showed a beneficial effect on HRQoL and respiratory-related hospital admissions in a group of studies that differed considerably with regard to follow-up duration, intervention duration, and self-management and action plan components. The results were based on a total of 3,854 participants with COPD, verified with a post-bronchodilator FEV_1 to FVC ratio < 0.70. We included studies performed in 14 countries on four continents (14 in Europe, 4 in North America, 2 in Asia, and 2 in Oceania).

In our review, self-management interventions including AECOPD action plans were associated with improvement in HRQoL (measured by the SGRQ) and lower probability of respiratory-related hospital admissions. Although the improvement in HRQoL did not reach the MCID, self-management interventions are part of COPD management and should be based on individualised assessment of COPD to reduce: 1) current symptoms to decrease personal burden and improve HRQoL; and 2) future risks of exacerbations, hospitalisations, mortality and costs.[1] We observed no statistically significant difference in the probability of all-cause hospital admissions, the number of all-cause hospitalisation days, ED visits, GP visits, and dyspnoea scores as measured by the (m)MRC questionnaire for participants in self-management interventions compared to usual care. No excess all-cause mortality risk was observed, but exploratory analysis indicated a small significant higher respiratory-related mortality rate for self-management compared to usual care. Subgroup analyses indicated significant improvements in HRQoL from self-management interventions with a smoking cessation programme. The number of BCT clusters integrated in the self-management intervention, intervention duration, inclusion of a standardised exercise programme, and adaptation of maintenance medication as part of an action plan did not affect HRQoL.

There are some limitations for the generalisability of our results. We had difficulties with information collection from three studies.[58-60] We made five attempts to request information from the authors of these studies on whether an action plan for AECOPD was used. No responses were received so we could not verify if these studies met our eligibility criteria. No definite decision regarding eligibility could therefore be made. In addition, one included study[38] could not be included in the meta-analyses because insufficient data were provided.

Three studies (14%) had follow-up durations of three months or less.[44,46,51] Depending on the time of patient enrolment (e.g., during summer) in these three studies, the seasonal variation may have influenced the outcomes (e.g., the number of exacerbations) and may have resulted in an underestimation or overestimation of the actual effect. It was also difficult to interpret behavioural change effects for studies with short follow-up durations. Since the study by Fan et al.[26] was prematurely stopped with a mean follow-up of 250 days, it is uncertain if a true effect was observed. The results of this study need to be interpreted with caution.

In addition, some hospitalisations may have been triggered by the COPD self-management intervention because AECOPD action plans encouraged people to seek help when they may not have otherwise and therefore increased healthcare utilisation. However, the reduction in hospitalisations found in this review strengthens our hypothesis that self-

recognition and self-treatment of symptoms prevent some of the severe exacerbations that otherwise would have needed hospitalisation. The definition of an exacerbation is also a factor that can influence the number of exacerbations found.[74] For example, in the study of Monninkhof 2003 et al.[48] an exacerbation was not based on an increase of symptoms, but on the number of courses of prednisolone and an additional course of antibiotics in the case of increased purulent sputum. This number of courses was driven by the self-management intervention, which was based on symptoms, and the corresponding action plan stated to initiate self-treatment with prednisolone and antibiotics if needed. For each individual it is important to recognise what constitutes an exacerbation and to identify what the usual symptoms are in a person's stable health state for COPD and comorbidities.[23,75,76] Because of heterogeneity in exacerbations and other patient characteristics, tailoring of consisting (standardised) action plans should always be considered.

Furthermore, usual care is diverse among countries, healthcare systems and populations. Although we excluded studies that did not include a usual care group, it was likely that in one study[51] self-management was integrated in usual care. The study authors indicated that usual care management was directed towards COPD management education, exercise, and maintaining daily activities.[51] Moreover, effects may be a result of optimised COPD management (e.g., medication treatment) during the self-management intervention or the results may reflect better compliance and concordance with medication treatment in the intervention group.[45]

Data were skewed for continuous outcomes (the number and duration of hospital admissions, the number of exacerbations). In the analyses of mean differences these skews may have led to reduced power to detect a treatment difference for these continuous outcomes. The analyses of Incident Rate Ratios using regression models would have been more appropriate to use to reduce the impact of the skew. However, we could not perform these analyses, because individual study data were not available.

Differences in study design and characteristics of included participants were not taken into account in the analyses of this review. An analysis of individual participant data, such as Jonkman 2016 et al.[22,82], could contribute to the knowledge of factors influencing proper self-management. The additional results of the recently published studies and the review with individual participant data do not automatically fit with the results reported in the current review. Future review updates should demonstrate how gained knowledge from recent studies influences and fits the results of the current meta-analyses.

Quality of the evidence

We graded the quality of evidence for HRQoL as high. However, the significant improvement

in HRQoL did however not reach the MCID, and may therefore only have been clinically relevant for part of the population. We graded the quality of evidence for all-cause mortality as high; and moderate for respiratory-related hospital admissions because substantial heterogeneity resulted in inconsistency. We graded the quality of evidence for all other secondary outcomes as moderate to very low; assessments were based on fewer studies or smaller sample sizes, or both. The quality of evidence for respiratory-related mortality was downgraded to very low because, as well as few studies and small sample sizes, the overall effect was driven by two of the seven studies[26,27]; four studies[42,46,49,52] had no events, and there was a high risk of bias for incomplete outcome data and selective reporting for three studies[27,52,53].

Potential biases in the review process

Debate about the definition and the most effective content of COPD self-management interventions is ongoing.[16] Althoug we included only studies that aligned with the most recent published conceptual definition of COPD self-management interventions,[18] the self-management interventions were diverse in duration (2 to 24 months of follow-up), self-management intervention components (one to six self-management components), and action plan components (one to six actions defined). Furthermore, a large variety of topics were included in the educational sessions. Operationalisation of the conceptual definition of a COPD self-management intervention would be helpful to refine future eligibility criteria and thus reduce heterogeneity in interventions.

The inclusion of studies in this review was not based on reported outcome measures. Hence, the included studies used a broad spectrum of outcome measures with different methods for assessment (e.g., different questionnaires) and different calculations (e.g., mean number versus the percentage of participants). This added to heterogeneity among studies. Furthermore, there were insufficient data available for some outcome measures, even after contact with study authors. Moreover, some meta-analyses could not be performed due to insufficient (< 3 studies) reported outcome data.

Because of the nature of the self-management intervention, we expected a priori to see clinical heterogeneity among studies so we decided to use random-effects modelling for the meta-analyses. The random-effects model weighs by study rather than number of participants when heterogeneity is present. When only a few large studies and many small studies are included, this may result in bias introduced by small-study effects. We therefore checked the fixed weights in sensitivity analyses. The beneficial effects of the self-management intervention on all-cause hospital admissions and all-cause hospitalisation days became statistically significant when the fixed-effect model was used instead of random-effects modelling. Since the observed effect sizes in fixed-effect and random-

effects modelling were comparable, the bias introduced by small-study effects was considered to be unlikely.

Agreements and disagreements with other studies or reviews

Action plans for AECOPD

A written action plan for AECOPD was a requisite for inclusion of studies reporting self-management interventions in this review. Multi-component self-management action plans with iterative processes aimed at sustained behavioural change, providing support and instilling confidence for self-recognition of AECOPD are recognised as important factors to self-manage symptoms effectively and safely.[15,16] The actions defined for AECOPD differed among studies (e.g., take direct action when symptoms get worse versus start action 48 hours after onset of symptoms if AECOPD symptoms persist or do not improve), and were not always very detailed (e.g., participants could call a team if they think they have an infection and the team would "maybe" advise to take antibiotics[43]). Because AECOPD self-recognition, self-treatment, and contacting healthcare providers for support were included in the AECOPD action plans in almost all included studies, we could not perform subgroup analyses. As a result, we were unable to determine the effectiveness of these action plan components and the most effective component of action plans.

Many patients with COPD have comorbidities,[77,78] which has an impact on disease severity, hospital admissions and survival.[79,80] Tailored approaches with individualised care plans are needed to reduce the treatment burden and optimise care for patients with COPD and comorbid conditions.[81] Using COPD-specific action plans for patients with COPD and comorbidities may lead to delayed or incorrect treatment due to symptom overlap (e.g., breathlessness may be caused by COPD, but also by heart failure or anxiety). Future COPD self-management action plans should account for comorbidities. This would not only increase the safety of COPD self-management interventions by appropriate and timely treatment actions, but would likely also increase benefits for all-cause hospital admissions. Unfortunately, only two[43,47] of the 11 studies that included patients with the added complexity of major comorbidities defined an action for the self-treatment of comorbidities. Therefore, we were unable to evaluate the effects of tailoring action plans for patients with comorbidities in this review.

Health-related quality of life

Previously reported COPD self-management review data on HRQoL showed similar mean differences in SGRQ total scores. In the most recent Cochrane Review evaluating the effects of self-management interventions in patients with COPD, not focusing on action plan use, a MD of -3.51 (95% CI -5.37 to -1.65) was observed for the SGRQ total score and a MD of -2.68 (95% CI -4.16 to -1.20) for the change from baseline SGRQ total score.[14] These

results are very comparable to our findings (MD -2.69, 95% CI -4.49 to -0.90). In the review of Zwerink et al.[14], action plans were part of most study interventions. The review authors could therefore not perform subgroup analyses and were unable to confirm whether action plans were an essential component of self-management.[14] The main HRQoL effects reported by the current review are also in line with recently published IPD meta-analyses on the effectiveness of self-management.[22,82] Although were were unable to perform a subgroup analysis on follow-up duration, Jonkman et al.[22] showed improved HRQoL at 12 months with a standardised mean difference of 0.08, but not at six months (SMD 0.05). Subgroup analyses did not show a consistent pattern across health outcomes of patients benefiting most from the self-management interventions.[22]

Self-management interventions aim to change health behaviours,[10,11] one of which in many patients is smoking. Smoking cessation programmes are currently considered by all evidence-based and society guidelines as an essential component of patient care to help patients to quit smoking and stay abstinent[1] and should be offered at the earliest possible stage. This implies ensuring that smoking cessation could be routinely offered in primary care. We observed a clinically relevant and significantly better HRQoL resulting from COPD self-management interventions including smoking cessation programmes (MD -4.98) compared to interventions without smoking cessation programmes (MD -1.33). Although we could not compare our findings with other reviews, our results indicate that a smoking cessation programme seems to be an essential part of self-management interventions to achieve a clinically relevantly improved HRQoL. Smoking cessation could also be offered and delivered to patients as part of self-management interventions to achieve optimal improvement in HRQoL.

Hospital admissions

Patients in self-management interventions that included AECOPD action plans were at a significantly lower risk for at least one respiratory-related hospital admission compared with those who received usual care (OR 0.69). Earlier reviews show similar beneficial effects of self-management on respiratory-related hospital admissions. A lower risk for at least one respiratory-related hospital admission was observed in the review on self-management interventions (OR 0.57).[14] Recent IPD meta-analysis showed a significant risk reduction at 12 months of follow-up (RR 0.77) and interventions improved the time to the first respiratory-related hospital admission (hazard ratio 0.79).[22] Whether these lower risks are clinically relevant is unclear, because there is no MCID for hospital admissions. However, a lower number of hospital admissions would potentially result in better HRQoL, reduced mortality, and a reduction of healthcare costs.[11,12] Our subgroup analyses did not identify any specific components of self-management interventions that were linked to the risk reduction of respiratory-related hospital admissions.

We observed no significant difference in all-cause hospital admissions. Based on the observed effect size (OR 0.74, 95% CI 0.54 to 1.03), its 95% CI and low power, we could not rule out there is no actual difference. Significant effects on all-cause hospital admissions were found in previously published COPD self-management reviews in which self-management interventions led to a somewhat lower OR for at least one all-cause hospital admission (OR 0.60),[14] reduced relative risk of all-cause hospital admission within 12 months (RR 0.84) and a longer time to the first all-cause hospital admission (hazard ratio 0.80).[22] Because all AECOPD action plans were COPD-specific in our review, it was perhaps unlikely that the interventions would lead to a reduced risk of all-cause hospital admissions. This could probably only be expected for two studies[43,47] that had also defined an action for the self-treatment of comorbidities. This was not reflected by their study results; Hernández 2015 et al.[43] showed an unexplained opposite beneficial effect for usual care, and Martin 2004 et al.[47] provided insufficient data to enable meta-analysis. A trend toward a lower probability of respiratory-related hospital admissions was present when case manager support was included in COPD self-management interventions.

Mortality

Like this review, the authors of a previous Cochrane Review on COPD self-management interventions did not observe an effect from self-management on all-cause mortality. Zwerink 2014 et al.[14] observed a trend towards lower all-cause mortality for self-management compared to usual care (OR 0.79, 95% CI 0.58 to 1.07). However, this current review includes some more recently conducted large studies, including Fan 2012 et al.[26] which was prematurely terminated because of significantly higher mortality rates in the intervention group. No effects were observed on all-cause mortality (RD 0.00, 95% CI -0.02 to 0.03). Nevertheless, we observed a small, but statistically significantly higher respiratory-related mortality rate in the self-management intervention group compared to the usual care group (RD 0.04, 95% CI 0.01 to 0.07). However, these respiratory mortality data should be interpreted with caution because: 1) differentiating between 'mortality with respiratory problems as a contributing factor' and 'respiratory-specific mortality' is challenging and misclassification is common,[83] future studies should ensure that this classification of death is performed in a similar way in all study groups to avoid any bias; 2) the overall effect on respiratory-related mortality was dominated by two studies[26,27]; and, most importantly, 3) the robust analyses for all-cause mortality did not show any effect (nor trend) toward higher mortality due to self-management. Since none of the seven included studies where respiratory-related mortality was an a priori defined outcome, there may be a risk that the cause of mortality was defined differently in the study groups (misclassification). Preliminary findings from a recent large home-based multi-component COPD self-management intervention with 319 patients showed unambiguously higher mortality rates in the usual care group (N = 23 (14.2%)) compared to self-management (N = 3 (1.9%)) that were mainly

respiratory-related.[84]

Other secondary outcomes

All-cause hospitalisation days, ED visits, GP visits and (m)MRC dyspnoea scores showed no difference in healthcare utilisation where self-management with action plans for AECOPD were used. Trappenburg 2011 et al.[25] observed that beneficial effects for self-management resulted from improved skills for self-recognition of AECOPD, quicker start of appropriate self-initiated treatment, and decreased impact of exacerbations on health status and accelerated recovery. A reduction in dyspnoea score was observed in a Cochrane Review on self-management interventions for COPD.[14] The review authors reasoned that the reduction may be related to components of self-management interventions directed to learning strategies to cope with breathlessness.[14,85] In this review, coping with breathlessness or breathing techniques was discussed in all but two included studies.

Although we used an established taxonomy[28] to assess the integration of BCTs into self-management interventions, we observed no differences in HRQoL and respiratory-related hospital admissions among studies with high and low integration levels of BCT clusters. The additional value of integrating BCT clusters was difficult to determine. Our inclusion criteria required that studies contained at least four BCTs (goals and (action) planning, feedback and monitoring, shaping knowledge, and associations). The lowest number of BCTs that we extracted from the included studies in our review was six. We expect the actual number of applied BCTs to be higher since we only extracted data that what was explicitly reported. To increase the meaningfulness of the BCT subgroup analysis, future studies should provide more detailed information regarding the behavioural techniques that were integrated.

Recently published studies

We searched up to May 2016 and fully incorporated the results of these trials into this review. An update search conducted in 2017 identified several new studies published on the effectiveness of self-management interventions.[61-69] These will be fully incorporated in a future update of this review.

AUTHORS' CONCLUSIONS

Implications for practice

COPD management should be based on individualised assessment of COPD to reduce both current symptoms (which reduce personal burden and improve HRQoL) and future risks (e.g., risk reduction of exacerbations, which reduces mortality and costs).[1] In this review, self-management interventions including AECOPD action plans are associated with improvement in HRQoL (measured by the SGRQ) and lower probability of respiratory-

related hospital admissions. Improvement in HRQoL did not reach the MCID. We observed a non-significant lower probability of all-cause hospital admissions associated with self-management interventions. We observed no statistically significant difference in the number of all-cause hospitalisation days, emergency department visits, general practitioner visits, and dyspnoea scores as measured by the (modified) MRC questionnaire for patients who participated in self-management interventions compared to usual care. No excess all-cause mortality risk was observed, but exploratory analysis indicated a small significant higher respiratory-related mortality rate for self-management compared to usual care (very low-quality level of evidence). Subgroup analyses indicated significant improvements in HRQoL from self-management interventions with a smoking cessation programme. The number of BCT clusters integrated in the self-management intervention, the intervention duration, including a standardised exercise programme, and adaptation of maintenance medication as part of an action plan did not affect HRQoL.

Future clinical practice may focus on the following strategies:

- Ensuring that offered interventions meet the criteria of the most recent definition of COPD self-management interventions (e.g., include patient-centred iterative interactions with a healthcare provider).[18]
- Smoking cessation strategies could also be included in self-management interventions for smokers to achieve clinically relevant HRQoL improvements.
- For safety reasons, COPD self-management interventions may consider taking comorbidities into account in action plans, avoid offering action plans as a sole component, take literacy into account, and evaluate patients' adherence to action plans over time.

Implications for research

Future (review) studies may focus on the following to ensure clear information for optimal content of self-management interventions including AECOPD action plans:

- Future studies should consider focusing on different populations (e.g., COPD severity, comorbid conditions, continent) to facilitate population subgroup analyses in future reviews and provide useful information for data that can be generalised for different healthcare systems. This would lead to higher likelihood of detecting potential explanatory variables for hospital admissions and dentify components that might influence HRQoL.
- Study authors should aim to provide more detailed, uniformly reported data on the self-management intervention and AECOPD action plan components, and behavioural change techniques that were used. This will permit stronger recommendations regarding effective self-management interventions including AECOPD action plans in a future review.

- Investigators should aim to ensure blinding for classification of deaths to prevent misclassification for respiratory-related mortality and ensure that classification is applied consistently for all study groups to avoid bias. For safety reasons, we also involve Data and Safety Monitoring Boards.
- Future studies should endeavour to report assessment of economic evaluation (benefits and costs) of the implementation of self-management interventions.

Since COPD is defined to be a systemic disease with comorbidities,[81] we strongly feel that COPD self-management action plans should take comorbidities into account. We were unable to evaluate this strategy, because patients with comorbidities were excluded from half of the included studies and only two studies tailored action plans for comorbidities. Benefits from the using tailored action plans are expected to further increase the effectiveness and safety of self-management interventions by accounting for overlap in COPD and comorbid symptoms, and initiating appropriate actions for exacerbations of COPD and comorbidities that are very common in this population. An international multicentre RCT[75,76] showed that exacerbation action plans for COPD patients with frequently existing comorbidities embedded in an individualised are effective in reducing COPD exacerbation duration and respiratory-related hospitalisations without excess all-cause mortality. These action plans were embedded in an individualised, multi-faceted self-management intervention.[75,76]

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We only included studies that were published in full-text, and excluded abstracts if there was no additional information available from the authors.

For the included cluster-RCT of Rea 2004 et al.[50] we planned to use the cluster as the unit of analysis. However, Rea 2004 et al.[50] provided insufficient data on cluster level and did not correct for clustering in their analyses. We could therefore only use the patient as the unit of analysis.

We planned to divide the COPD exacerbations into exacerbations based on COPD symptom scores (e.g., symptom diary), based on courses of oral corticosteroids or based on courses of antibiotics. There were, however, insufficient data available to divide the COPD exacerbations and to perform a meta-analysis with the data provided.

We have performed exploratory analysis on the respiratory-related mortality rate as during the extracting process it became clear that these data were available and we felt that this would be an important additional outcome for evaluation of safety of self-management interventions.

ACKNOWLEDGEMENTS

The Background and Method sections of the review were based on a standard template used by Cochrane Airways.

We would like to thank the following authors for their assistance: E. Bischoff (Bischoff 2012), J. Bourbeau (Bourbeau 2003), D. Bösch (Bösch 2007), C. Bucknall (Bucknall 2012), J. Roca and J. Garcia-Aymerich (Casas 2006), J. Garcia-Aymerich (Garcia-Aymerich 2007), V. Fan (Fan 2012), F. Gallefoss (Gallefoss 1999), C. Hernández (Hernández 2015), J. Jennings (Jennings 2015), J. McElnay and M. Khdour (Khdour 2009), G. Kheirabadi (Kheirabadi 2008), R. Taylor and I. Martin (Martin 2004), K. Mitchell (Mitchell 2014), E. Monninkhof (Monninkhof 2003), G. Ninot (Ninot 2011), A. Ehrenberg and E. Österlund Efraimsson (Österlund Efraimsson 2008), H. Rea (Rea 2004), K. Rice (Rice 2010), H. Song (Song 2014), M. Tabak (Tabak 2014), E. Titova (Titova 2015).

Furthermore, we would like to thank Paul Cafarella for independently assessing the integration of BCTs in the included studies. We would also like to thank Chris Cates for his critical comments and helpful discussions regarding statistical issues. Ian Yang served as the Editor for the protocol and review, and commented critically on it.

This project was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to Cochrane Airways. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS, or the Department of Health.

Contributions of authors

Anke Lenferink coordinated the review, independently assessed the eligibility of titles, abstracts and full-text versions of potentially relevant reports, independently extracted data from the included studies, independently assessed the integration of BCTs in the included studies, generated the 'Summary of findings' table and wrote the review. Tanja Effing independently assessed the eligibility of titles and abstracts, assessed the eligibility of half of the full-text versions of potentially relevant reports, independently extracted data from half of the included studies, double-checked data entry and helped to write the review. Marjolein Brusse-Keizer assessed the eligibility of half of the full-text versions of potentially relevant reports, independently extracted data from half of the included studies, and helped to write the review. All other review authors provided critical comments on the review.

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Characteristics of included studies

Bischoff 2012

Methods	**Design:** RCT **Follow-up:** 24 months **Control group:** usual care	
Participants	**Recruitment:** general practice **Assessed for eligibility:** 748 **Randomly assigned:** Intervention (I): 55; Control (C): 55 **Completed:** I: 49; C: 44 **Mean age:** I: 65.5 ± 11.5 years; C: 63.5 ± 10.3 years **Gender (% male):** I: 67; C: 51 **COPD diagnosis:** GOLD, mild, moderate, severe airflow obstruction **Inclusion of participants in the acute phase:** not reported **Major inclusion criteria:** aged at least 35 years, post-bronchodilator ratio of FEV_1/FVC < 0.70 **Major exclusion criteria:** post-bronchodilator FEV_1 < 30% predicted, treatment by a respiratory physician, severe comorbid conditions with a reduced life expectancy, inability to communicate in the Dutch language, and objections to one or more of the modes of disease management used in the study	
Interventions	**Mode:** individual sessions at the general practice, paper modules "Living well with COPD", telephone calls **Duration:** two-four face-to-face individual sessions of one hour each scheduled in four to six consecutive weeks, six telephone calls to reinforce self-management skills **Professional:** practice nurse of each participating practice **Training of case managers:** before the study, all nurses were trained in how to apply the self-management programme **Self-management components:** action plan COPD exacerbations, iterative process with feedback on actions, self-recognition of COPD exacerbations, education regarding COPD **Self-management topics:** (home) exercise, (maintenance) medication, coping with breathlessness/breathing techniques, maintaining a healthy lifestyle, managing stress and anxiety. **Exercise programme:** no **Smoking cessation programme:** no **Behavioural change techniques:** 10 clusters: goals and planning, feedback and monitoring, social support, shaping knowledge, natural consequences, comparison of behaviour, associations, repetition and substitution, regulation, antecedents. **Action plan components:** self-recognition of exacerbations, self-treatment of exacerbations, use of maintenance treatment, contact healthcare providers for support	
Outcomes	1. change from baseline in health-related quality of life (CRQ) 2. change in CRQ domain scores 3. exacerbation frequency and management 4. total and five domain scores for self-efficacy (CSES)	
Notes	A third group of patients (n = 55) were assigned to routine monitoring through scheduled periodic monitoring visits as an adjunct to usual care. However, this group does not include an action plan.	
Bias	**Authors's judgement**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	"We randomised participants by using a computer generated two block randomisation procedure with stratification on severity of COPD (mild or moderate v severe airflow obstruction), smoking status (current v former smoker), and frequency of exacerbations in the previous 24 months (<2 v ≥ 2 exacerbations)." p. 2 Comment: Random sequence generation was adequately performed.

Allocation concealment (selection bias)	Unclear risk	"We randomly allocated patients to usual care, self management or routine monitoring." p. 2. "To ensure that the investigators were blinded to individual treatment allocation, practice nurses informed the patients of their allocation." p. 2 Comment: No information on who performed the allocation.
Blinding of participants and personnel (performance bias)	High risk	"This was a 24 month, multicentre, investigator blinded, three arm, parallel group, randomised controlled trial." p. 2 Comment: No blinding of participants and personnel.
Blinding of outcome assessment (detection bias)	Low risk	"Investigator blinded study." p. 2 "Outcome assessment with standardised questionnaires and a telephonic exacerbation assessment system (TEXAS)." Comment: Outcome assessment was blinded.
Incomplete outcome data (attrition bias)	Low risk	Baseline characteristics did not differ between dropouts and participants who completed follow-up (p. 3). The dropout rate was lowest in the self management group, which may suggest that patients in this group were more motivated to adhere to COPD treatment because they were more "involved" in the long term management of their disease. p. 4 Our primary analysis was based on intention to treat principle and included all available data for all participants. We did not impute any missing data. p. 3 Comment: Almost 16% of the participants dropped out during follow-up (intervention 11%; usual care 20%). However, baseline characteristics did not differ between dropouts and participants who finished follow-up. Exclusion is well described in flow chart. Intention-to-treat analyses were used.
Selective reporting (reporting bias)	Low risk	"Data sharing: Technical appendix, statistical code, and dataset are available from the corresponding author." p. 5 Comment: Not all secondary outcome measures were assessed. However, no signs for selective outcome reporting.
Other bias	Low risk	-

Bourbeau 2003

Methods	**Design:** RCT **Follow-up:** 12 and 24 months **Control group:** usual care
Participants	**Recruitment:** hospital (outpatient) **Assessed for eligibility:** not reported **Randomly assigned:** I: 96; C: 95 **Completed:** I: 86; C: 79 **Mean age:** I: 69.4 ± 6.5 years; C: 69.6 ± 7.4 years **Gender (% male):** I: 52; C: 59 **COPD diagnosis:** FEV_1 after the use of a bronchodilator between 25% and 70% of the predicted normal value and FEV_1–FVC ratio less than 70% **Inclusion of participants in the acute phase:** no **Major inclusion criteria:** hospitalised at least once in the preceding year for an exacerbation, stable COPD (respiratory symptoms and medication unchanged for at least 4 weeks before enrolment), at least 50 years of age, current or previous smoker (at least 10 pack-years), FEV_1 after the use of a bronchodilator between 25% and 70% of the predicted normal value 14 and FEV_1–FVC ratio less than 70%, no previous diagnosis of asthma, left congestive heart failure, terminal disease, dementia, or uncontrolled psychiatric illness, no participation in a respiratory rehabilitation programme in the past year, and no longterm-care facility stays. **Major exclusion criteria:** patients with asthma as a primary diagnosis and those with major comorbidities (documented left ventricular failure and any terminal disease), dementia or uncontrolled psychiatric illness
Interventions	**Mode:** individual sessions at the participant's home, "Living well with COPD" programme with patient workbook, telephone calls **Duration:** seven face-to-face individual sessions of one hour each scheduled in seven to eight consecutive weeks, 18 telephone calls (weekly calls for eight weeks educational period, after eight weeks monthly phone calls for 12 months) **Professional:** experienced health professionals (nurses, respiratory therapists, a physiotherapist) who acted as case managers with the supervision and collaboration of the treating physician **Training of case managers:** "The programme was supervised by experienced and trained health professionals..." p. 586 "Half-day training sessions were dedicated to interactive lecturing sessions on each aspect of COPD given by different members of the multidisciplinary team. The rest of the training days included workshops oriented toward how to assess patient needs and the acquisition of motivational and teaching skills using group discussion, demonstration and practice of techniques, case scenarios, and role modeling." Bourbeau 2006, p. 1705 **Self-management components:** action plan COPD exacerbations, iterative process with feedback on actions, self-recognition of COPD exacerbations, education regarding COPD, exercise or physical activity component **Self-management topics:** smoking cessation, exercise, diet, (maintenance) medication, coping with breathlessness/breathing techniques, other: energy conservation during day-by-day activities, relaxation exercises, adopting a healthy lifestyle, leisure activities and travelling, long-term oxygen when appropriate **Exercise programme:** yes, home-based exercise program. The exercise teaching began at about the 7th week, and the training program was initiated with a supervised session at home. The exercise program included warm-up and stretching exercises, muscle exercises, and cardiovascular exercises (stationary bicycle, walking, or climbing stairs). Patients were encouraged to follow the exercise program at least 3 times per week for 30 to 45 minutes per session. **Smoking cessation programme:** no **Behavioural change techniques:** 10 clusters: goals and planning, feedback and monitoring, social support, shaping knowledge, natural consequences, comparison of behaviour, associations, repetition and substitution, regulation, antecedents **Action plan components:** self-recognition of exacerbations, self-treatment of exacerbations, use of maintenance treatment, contact healthcare providers for support, other: symptom monitoring list for different situations (stress, environmental change, and respiratory tract infection) linked to appropriate therapeutic actions

Outcomes	1. hospital admissions 2. scheduled and unscheduled physician visits 3. emergency department visits 4. health-related quality of life (SGRQ) 5. pulmonary function 6. functional exercise capacity 7. exacerbations	
Notes	Completed first year of follow-up: n = 165 (based on hospital registry database) Completed second year of follow-up: n = 175 (based on provincial health insurance and hospitalisation database records)	
Bias	**Authors's judgement**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	"… central computer generated list of random numbers. Randomisation was stratified per center and in blocks of 6, and patients were assigned to the self-management programme (intervention group) or to usual care." p. 586 Comment: Random sequence generation was adequately performed.
Allocation concealment (selection bias)	Low risk	"The blocking factor was not known by the investigators or their staff in each participating center." p. 586 Comment: Allocation was adequately concealed.
Blinding of participants and personnel (performance bias)	High risk	"Since a double-blind design was impossible..." p. 586 Comment: Participants and personnel were not blinded.
Blinding of outcome assessment (detection bias)	Low risk	"... an independent evaluator unaware of the patient assignment was responsible for the evaluation process in each center. The evaluator was cautioned not to ask about the workbook modules and types of contact." p. 586 Comment: Outcome assessment was blinded.
Incomplete outcome data (attrition bias)	Low risk	"At the end of the 2nd year of follow-up, data were available for 75 patients in the standard-care group (two subjects were lost to follow-up, nine patients died in the 1st year and nine in the 2nd year) and 83 patients following the self-management programme (five patients died in the 1st year and eight in the 2nd year)." Gadoury 2005, p. 855 Comment: Drop out in the usual care group was somewhat higher than in the self-management group; however, an intention-to-treat analysis was used.
Selective reporting (reporting bias)	Unclear risk	Comment: No signs of selective reporting, however no protocol available.
Other bias	Low risk	-

Bucknall 2012

Methods	**Design:** RCT **Follow-up:** 12 months **Control group:** usual care
Participants	**Recruitment:** hospital (inpatient) **Assessed for eligibility:** 1,405 **Randomly assigned:** I: 232; C: 232 **Completed:** I: 211; C: 200 **Mean age:** I: 70.0 ± 9.3 years; C: 68.3 ± 9.2 years **Gender (% male):** I: 38; C: 35 **COPD diagnosis:** chronic irreversible airflow limitation with FEV_1 less than 70% predicted and a FEV_1 /FVC ratio of less than 70%. FVC is defined as the total amount of air that can be expelled from the chest by a forced expiratory manoeuvre **Inclusion of participants in the acute phase:** not reported **Major inclusion criteria:** admitted to hospital with an acute exacerbation of COPD **Major exclusion criteria:** a history of asthma or left ventricular failure, evidence of active malignant disease or any evidence of confusion/poor memory, assessed with the abbreviated mental test (scores of 9/10 or 10/10 required).
Interventions	**Mode:** individual sessions at the participant's home, adapted "Living well with COPD" booklets, telephone calls **Duration:** four face-to-face individual sessions of 40 minutes each scheduled fortnightly over a two month period. There were also 828 phone calls to the intervention group patients (mean 4.6 phone calls per intervention patient). There were at least six subsequent home visits (but more frequently on request) thereafter for a total of 12 months **Professional:** study nurse **Training of case managers:** "Study nurses' training was based on self regulation theory ." (p. 2). "Nurses were trained to deliver a structured self management programme in four fortnightly home visits (…). Nurses without previous respiratory training completed three half day training sessions." (p. 3) **Self-management components:** action plan COPD exacerbations, iterative process with feedback on actions, self-recognition of COPD exacerbations, education regarding COPD **Self-management topics:** smoking cessation, exercise, diet, (maintenance) medication, correct device use, coping with breathlessness/breathing techniques **Exercise programme:** no **Smoking cessation programme:** no **Behavioural change techniques:** 12 clusters: goals and planning, feedback and monitoring, social support, shaping knowledge, natural consequences, comparison of behaviour, associations, repetition and substitution, comparison of outcomes, regulation, antecedents, self-belief **Action plan components:** self-recognition of exacerbations, self-treatment of exacerbations, use of maintenance treatment, contact healthcare providers for support
Outcomes	1. time to first acute hospital admission with a COPD exacerbation 2. death due to COPD within 12 months of randomisation 3. morbidity (change from baseline at six and 12 months in SGRQ) 4. likelihood of anxiety or depression (HADS) 5. sense of self efficacy (CSES) 6. quality of life (EuroQol 5D)
Notes	Self management materials based on the Living Well with COPD programme and previously adapted for the UK population and healthcare setting by an iterative process, were used (p. 2). Extra information author: "We used adapted "Living with COPD" booklets and daily diary cards (Stockley et al. – originally developed for use in Bronchiecistasis, piloted these and adapted them for this study, to include a line for recording steroid and antibiotic usage."

Bias	Authors's judgement	Support for judgment
Random sequence generation (selection bias)	Low risk	"We used a minimisation technique to stratify randomisation of participants by demographic factors (deprivation category of area of residence,11 age and sex, FEV1 per cent predicted at the time of randomisation, smoking status, participation in pulmonary rehabilitation within two years, and number of previous admissions) to control for key aspects of disease severity and predictors of readmission. We constructed a computer generated sequence by using the method of randomised permuted blocks of length four, with allocations being made at random and two by minimisation." p. 2 Comment: Random sequence generation was adequately performed.
Allocation concealment (selection bias)	Low risk	"Treatment group allocations were obtained by telephone, after baseline assessment had been made. This registered the participant on the system, and a researcher entered the characteristics necessary for the minimisation algorithm by using an interactive voice response system. The researcher did not know whether a participant was being allocated at random or by minimisation and could therefore not determine the next treatment allocation before enrolling each participant" p. 2 Comment: Allocation was adequately concealed.
Blinding of participants and personnel (performance bias)	High risk	Comment: No blinding of participants and personnel.
Blinding of outcome assessment (detection bias)	Unclear risk	"Participants received monthly telephone calls from an independent researcher, blinded to the patients' randomisation status, to collect information on health service usage and exacerbations."p. 2 Comment: Outcome assessor partly blinded (researcher was blinded, patients were not blinded).
Incomplete outcome data (attrition bias)	High risk	"The number of questionnaires available for analysis varied between outcomes and time points owing to the number of questionnaires returned and the completeness of the returned questionnaires." p. 4 "Completion rates for study questionnaires were also disappointing and were lower in the control arm of the study. Consequently, the apparent improvements in the intervention arm (impacts subscale of St George's Respiratory Questionnaire, hospital anxiety and depression scale anxiety) could be biased, and these results cannot be taken as convincing evidence in favour of the intervention." p. 5 Comment: A lot of missing data for study questionnaires.

Selective reporting (reporting bias)	High risk	"Participants received monthly telephone calls from an independent researcher, blinded to the patients' randomisation status, to collect information on health service usage and exacerbations." Comment: Healthcare usage and number of exacerbations during follow-up were not reported. Difference in length of hospital stay (all causes and sub classified by principle diagnosis) not reported.
Other bias	Low risk	-

Bösch 2007

Methods	**Design:** RCT **Follow-up:** 12 months **Control group:** usual care
Participants	**Recruitment:** outpatient clinic **Assessed for eligibility:** not reported **Randomly assigned:** I: 38; C: 12 **Completed:** I: 30; C: 11 **Mean age:** I: 63.8 ± 8.4 years; C: 64.6 ± 6.8 years **Gender (% male):** 63% of 41 participants who completed the study; the distribution of males per group is not reported **COPD diagnosis:** GOLD, COPD with obstruction confirmed by spirometry and FEV_1 / FVC < 70% **Inclusion of participants in the acute phase:** not reported **Major inclusion criteria:** diagnosis of COPD with obstruction proven by spirometry and a FEV1/FVC < 70% **Major exclusion criteria:** comorbidities which significantly influences symptoms, capacity or spirometry (symptomatic cardiopulmonary disease)
Interventions	**Mode:** group sessions (six to eight participants) at the participant's home **Duration:** four face-to-face group sessions of two hours each with the final session scheduled six weeks later **Professional:** respiratory nurse under supervision of a respiratory specialist **Training of case managers:** nurses were trained for 10 hours **Self-management components:** action plan COPD exacerbations, self-recognition of COPD exacerbations, education regarding COPD, smoking cessation, other: travelling, daily live (life style modification) **Self-management topics:** smoking cessation, exercise, diet, (maintenance) medication, coping with breathlessness/breathing techniques **Exercise programme:** no **Smoking cessation programme:** yes, motivation and guidance by the smoking cessation program **Behavioural change techniques:** eight clusters: goals and planning, feedback and monitoring, social support, shaping knowledge, comparison of behaviour, associations, comparison of outcomes, regulation, antecedents **Action plan components:** self-recognition of exacerbations, self-treatment of exacerbations, use of maintenance treatment, avoid situations in which viral infection might be prevalent, contact healthcare providers for support
Outcomes	1. mMRC 2. courses of antibiotics 3. FEV_1 (L) 4. hospital admissions 5. 6MWT
Notes	-

Bias	Authors's judgement	Support for judgment
Random sequence generation (selection bias)	Unclear risk	Comment: The method used to generate the random sequence generation was not clearly reported.
Allocation concealment (selection bias)	Unclear risk	Information from the author: 'Pick of envelope. Enrolment and selection were right before the start of the study – a selection bias cannot be fully excluded.' Comment: This information is too concise to assess the risk of bias for allocation concealment.
Blinding of participants and personnel (performance bias)	High risk	Comment: Blinding of participants and personnel was not reported.
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: Blinding of outcome assessment was not reported.
Incomplete outcome data (attrition bias)	High risk	Comment: Eight participants in the intervention group and one participant in the control group dropped out. Reasons for dropout were not clearly reported, and only participants who completed follow-up were included in the baseline characteristics and analysis.
Selective reporting (reporting bias)	Unclear risk	Comment: No signs for selective outcome reporting, results were reported extensively; however, no protocol available.
Other bias	Unclear risk	Comment: Per protocol analysis, baseline characteristics only assessed for the patients who completed the study. No differences reported for baseline characteristics between the withdrawals after randomisation (n = 9) and the patients who completed the study.

Casas 2006

Methods	**Design:** RCT **Follow-up:** 12 months **Control group:** usual care
Participants	**Recruitment:** hospital (inpatient) **Assessed for eligibility:** 850 **Randomly assigned:** I: 65; C: 90 **Completed:** I: 48; C: 72 **Mean age:** I: 70 ± 9 years; C: 72 ± 9 years **Gender (% male):** I: 77; C: 88 **COPD diagnosis:** 21 (14%) of patients had an FEV_1/FVC > 70%. However, these patients cannot be identified from the article. **Inclusion of participants in the acute phase:** yes, during hospitalisation **Major inclusion criteria:** admitted because of a previous episode of exacerbation requiring hospitalisation for > 48 hours **Major exclusion criteria:** not living in the healthcare area, severe comorbid conditions, logistical limitations due to extremely poor social conditions and being admitted to a nursing home

Interventions	**Mode:** individual and group sessions at the hospital and the participant's home, telephone calls, ICT platform **Duration:** 3-13 face-to-face individual sessions, one group session of 40 minutes and six phone calls; three individual sessions at the hospital of 40 minutes each and one to 10 (depending on the patient's needs) of 20 minutes each at the participant's home. Barcelona: one joint visit at home. Leuven: GP regularly visited patients at home. Weekly phone calls during the first month and phone calls after three and nine months **Professional:** respiratory nurse, GP, primary care team (physician, nurse, social worker) **Training of case managers:** GP's in Leuven were trained, also by the specialized respiratory nurse specifically trained for the study intervention **Self-management components:** action plan COPD exacerbations, iterative process with feedback on actions, self-recognition of COPD exacerbations, education regarding COPD, other: reinforcement of the logistics for treatment of comorbidities and social support was carried out accordingly **Self-management topics:** smoking cessation, exercise, diet, (maintenance) medication, correct device use, coping with breathlessness/breathing techniques, other: travelling, end-of-life decision making, interpretation of medical testing, irritant avoidance, anxiety and panic control **Exercise programme:** no **Smoking cessation programme:** no **Behavioural change techniques:** 10 clusters: goals and planning, feedback and monitoring, social support, shaping knowledge, natural consequences, comparison of behaviour, associations, repetition and substitution, regulation, antecedents **Action plan components:** self-recognition of exacerbations, self-treatment of exacerbations, use of maintenance treatment, contact healthcare providers for support, other: reinforcement of the logistics for treatment of comorbidities and social support was carried out accordingly	
Outcomes	1. all-cause (re-)hospitalisations 2. all-cause mortality 3. use of healthcare resources	
Notes	The current study was conducted in two cities, Barcelona (Spain) and Leuven (Belgium), with marked differences in the primary care settings. Consequently, the intervention required customisation to country specificities, particularly regarding the interactions between hospital and primary care teams. The subgroup of Barcelona (Spain) was also reported in the study of Garcia-Aymerich 2007. However, in the current study other outcome measures and different number of participants were reported.	
Bias	**Authors's judgement**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	"All 155 patients included in the study were blindly assigned (1:1 ratio) using computer generated random numbers to either IC or usual care (UC)." p. 124 Comment: Random sequence generation was adequately performed.
Allocation concealment (selection bias)	Low risk	"Adequacy of the assignment process to either IC or UC was ensured by both the generation of the allocation sequence by a random process and preventing foreknowledge of the treatment assignments in the specialised team that implemented the allocation sequence." p. 128 Comment: Allocation was adequately concealed.
Blinding of participants and personnel (performance bias)	High risk	Comment: Blinding of participants and personnel was not reported.

Blinding of outcome assessment (detection bias)	Unclear risk	"Early assessment of patients at study admission was identical for both groups. Assessment included a blind administration of a questionnaire, described in detail elsewhere. (…) Assessment of the use of healthcare resources by phone or personal interview was carried out at 1, 3, 6, 9 and 12 months in both arms of the study. Data regarding admissions during follow-up were obtained from hospital records. Data regarding mortality were obtained from hospital records and direct family interviews." p. 125 Comment: Only part of the baseline assessment was blinded; the other assessments were not blinded, and it is unclear who performed the phone, personal or family interviews.
Incomplete outcome data (attrition bias)	Low risk	"A strength of the present analysis was that there were no subjects lost to follow-up, since all drop-outs were due to appearance of exclusion criteria or death (fig. 1) and, in any case, valid information about re-hospitalisations was available from the national health services." p. 128 Comment: Data on healthcare utilization were presented for all included participants, leading to a low risk of bias.
Selective reporting (reporting bias)	Unclear risk	Comment: No signs of selective reporting; however, no protocol available.
Other bias	Low risk	-

Fan 2012

Methods	**Design:** RCT **Follow-up:** 12 months **Control group:** guideline-based usual care
Participants	**Recruitment:** outpatient clinic **Assessed for eligibility:** 467 **Randomly assigned:** I: 209; C: 217 **Completed:** I: 201 continued, 101 completed baseline and 1-year study visits; C: 207 continued, 108 completed baseline and 1-year study visits **Mean age:** I: 66.2 ± 8.4 years; C: 65.8 ± 8.2 years **Gender (% male):** I: 97.6; C: 96.3 **COPD diagnosis:** GOLD, a post-bronchodilator ratio of FEV_1/FVC < 0.70 with an FEV_1 < 80% predicted. At baseline and 1-year study visits, we performed post-bronchodilator spirometry according to ATS criteria **Inclusion of participants in the acute phase:** no **Major inclusion criteria:** hospitalised for COPD in the 12 months before enrolment, post-bronchodilator ratio of FEV_1 to FVC < 0.70 with an FEV_1 < 80% predicted, age older than 40 years, current or past history of cigarette smoking (>10 pack-years), at least 1 visit in the past year to either a primary care or pulmonary clinic at a Veterans Affairs medical center, no COPD exacerbation in the past 4 weeks, ability to speak English, and access to a telephone. **Major exclusion criteria:** primary diagnosis of asthma or any medical conditions that would impair ability to participate in the study or to provide informed consent.

Interventions	**Mode:** individual and group sessions at hospital outpatient clinics, telephone calls, educational booklet **Duration:** four face-to-face individual sessions of 90 minutes each scheduled weekly. The individual lessons were reinforced during a group session and by six phone calls, one per month for three months and every three months thereafter. **Professional:** case manager (various health-related professionals) **Training of case managers:** before starting the study, all case managers received a three-day training course with workshops covering detailed aspects of the self-management programme, and all were supervised by the site investigator **Self-management components:** action plan COPD exacerbations, iterative process with feedback on actions, self-recognition of COPD exacerbations, education regarding COPD **Self-management topics:** smoking cessation, exercise, (maintenance) medication, coping with breathlessness/breathing techniques **Exercise programme:** no **Smoking cessation programme:** no **Behavioural change techniques:** nine clusters: goals and planning, feedback and monitoring, social support, shaping knowledge, natural consequences, associations, repetition and substitution, regulation, antecedents **Action plan components:** self-recognition of exacerbations, self-treatment of exacerbations, contact healthcare providers for support	
Outcomes	1. time from randomisation to first COPD hospitalisation 2. all-cause mortality 3. number of exacerbations 4. health-related quality of life 5. patient satisfaction 6. medication adherence 7. COPD-related knowledge, skill acquisition and self-efficacy	
Notes	This multisite RCT of an educational and acute care management programme was stopped early when a safety monitoring board noted excess mortality in the intervention group. The mean follow-up time was 250 days.	
Bias	**Authors's judgement**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	"Randomisation lists were generated on the basis of random, permuted blocks of variable size to ensure approximate balance over time." p. 674 Comment: Random sequence generation was adequately performed.
Allocation concealment (selection bias)	Low risk	"The CSP Coordinating Center in Boston, Massachusetts, randomly assigned eligible patients in equal numbers to 2 groups, stratifying patients per site to allow for possible regional differences in patient characteristics and clinical practice patterns." p. 674 Comment: The allocation was adequately concealed.
Blinding of participants and personnel (performance bias)	High risk	"The 2 groups differed on the basis of a complex behavioral intervention that made blinding impossible." p. 674 Comment: No blinding of participants and personnel.

Blinding of outcome assessment (detection bias)	Low risk	"Telephone-based ascertainment of study outcomes (COPD hospitalizations and exacerbations) was performed by centralized research staff blinded to assignment. All outcomes were collected by centralized staff blinded to study group, and all hospitalizations were adjudicated by a committee that was also blinded to study group." p. 674 Comment: Outcome assessment was blinded.
Incomplete outcome data (attrition bias)	Unclear risk	"This multi-site, randomised, controlled trial of an educational and acute care management programme was stopped early when a safety monitoring board noted more deaths in the intervention group." p. 674 Comment: There is incomplete outcome data due to early termination of the study.
Selective reporting (reporting bias)	Low risk	Comment: The primary and secondary outcomes were reported, only healthcare costs as (secondary objective) were not reported.
Other bias	Low risk	-

Gallefoss 1999

Methods	**Design:** RCT **Follow-up:** 12 months **Control group:** usual care
Participants	**Recruitment:** hospital (outpatient) **Assessed for eligibility:** not reported **Randomly assigned:** I: 31; C: 31 **Completed:** I: 26; C: 27 **Mean age:** I: 57 ± 9 years; C: 58 ± 10 years **Gender (% male):** I: 48; C: 52 **COPD diagnosis:** FEV_1 equal to or higher than 40% and lower than 80% of predicted **Inclusion of participants in the acute phase:** not reported **Major inclusion criteria:** patients with COPD, <70 years of age, a FEV_1 equal to or higher than 40% and lower than 80% of predicted **Major exclusion criteria:** not suffering from any serious disease such as unstable coronary heart disease, heart failure, serious hypertension, diabetes mellitus, kidney or liver failure
Interventions	**Mode:** individual and group sessions at an outpatient clinic **Duration:** one to two face-to-face individual sessions by a nurse and one to two face-to-face individual sessions by a physiotherapist of 40 minutes each. Two two-hour group education sessions (five to eight persons) were scheduled on two separate days. **Professional:** nurse, physiotherapist, pharmacist, medical doctor **Training of case managers:** specially trained nurse **Self-management components:** action plan COPD exacerbations, iterative process with feedback on actions, self-recognition of COPD exacerbations, education regarding COPD, other: compliance, self-care **Self-management topics:** smoking cessation, exercise, diet, (maintenance) medication, coping with breathlessness/breathing techniques **Exercise programme:** no **Smoking cessation programme:** no **Behavioural change techniques:** nine clusters: goals and planning, social support, feedback and monitoring, shaping knowledge, natural consequences, comparison of behaviour, associations, repetition and substitution, regulation, antecedents **Action plan components:** self-recognition of exacerbations, self-treatment of exacerbations, use of maintenance treatment, contact healthcare providers for support

Outcomes	1. health-related quality of life (SGRQ and four simple questions) 2. hospital admissions 3. days lost from work 4. GP consultation 5. FEV_1 % predicted	
Notes	-	
Bias	**Authors's judgement**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	"The patients signed a written consent and were then randomly assigned using random number tables supplied by an external statistician in sealed envelopes" Gallefoss 2002, p. 425 Comment: Random sequence generation was adequately performed
Allocation concealment (selection bias)	Low risk	"The patients signed a written consent and were then randomly assigned using random number tables supplied by an external statistician in sealed envelopes" Gallefoss 2002, p. 425 Comment: Allocation was adequately concealed
Blinding of participants and personnel (performance bias)	High risk	Comment: Blinding of participants and personnel was not reported.
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: Blinding of outcome assessment was not reported; not clear who performed the measurements.
Incomplete outcome data (attrition bias)	Low risk	"In the intervention group, four patients failed to complete the educational programme (social problems (n = 1), unannounced emigration (n = 1), failure to meet at educational group sessions for unknown reasons (n = 1) and serious myocardial infarction (n = 1)). Another patient was withdrawn from the study during the follow-up due to lymphoma (n = 1). This left us with 26 patients (81%) for a 1-year follow-up. The patients who were withdrawn from the intervention group did not, to our knowledge, have any serious deterioration in their obstructive lung disease, and none were hospitalised. In the control group four patients were withdrawn (lack of co-operation (n = 2), diagnosis of rectal cancer (n = 1) and emigration (n = 1)). Two of the withdrawn control group patients were hospitalised for exacerbations of their COPD. This left us with 27 patients (84%) for the 1-year follow-up" Gallefoss 2002, p. 427 Comment: The number of drop-outs was relatively low, and reasons for drop-out were comparable over groups.
Selective reporting (reporting bias)	Low risk	Comment: No signs of selective outcome reporting; study extensively described in various articles.
Other bias	Low risk	-

Garcia-Aymerich 2007

Methods	**Design:** RCT **Follow-up:** 12 months **Control group:** usual care
Participants	**Recruitment:** hospital (inpatient) **Eligible:** not reported **Randomly assigned:** I: 44; C: 69 **Completed:** I: 21; C: 41 **Mean age:** I (follow-up): 72 ± 10 years, I (no follow-up): 73 ± 6 years; C (follow-up): 73 ± 9 years, C (no follow-up): 74 ± 8 years **Gender (% male):** I: 75; C: 93 **COPD diagnosis:** some of the patients had an FEV_1/FVC > 70%. However, these patients cannot be identified from the article. **Inclusion of participants in the acute phase:** yes, during hospitalisation **Major inclusion criteria:** admitted because of a previous episode of exacerbation requiring hospitalisation for > 48 hours **Major exclusion criteria:** not living in the healthcare area or living in a nursing home, lung cancer or other advanced malignancies, logistical limitations due to extremely poor social conditions and extremely severe neurological or cardiovascular comorbidities
Interventions	**Mode:** individual sessions at the hospital and the participant's home, telephone calls, ICT platform **Duration:** 3-13 face-to-face individual sessions at the hospital of 40 minutes each and one to 10 (depending on the patient's needs) of 20 minutes each at the participant's home. six phone calls, weekly during the first month and phone calls after three and nine months. **Professional:** specialised respiratory nurse and primary care team (physician, nurse, social worker) **Training of case managers:** an educational session of approximately two hours duration on self-management of the disease was administered at discharge, also by the specialized respiratory nurse specifically trained for the study **Self-management components:** action plan COPD exacerbations, iterative process with feedback on actions, self-recognition of COPD exacerbations, education regarding COPD, other: reinforcement of the logistics for treatment of comorbidities and social support was carried out accordingly **Self-management topics:** smoking cessation, exercise, diet, (maintenance) medication, correct device use, coping with breathlessness/breathing techniques, other: travelling, end-of-life decision making, interpretation of medical testing, irritant avoidance, anxiety and panic control **Exercise programme:** no **Smoking cessation programme:** no **Behavioural change techniques:** 10 clusters: goals and planning, feedback and monitoring, social support, shaping knowledge, natural consequences, comparison of behaviour, associations, repetition and substitution, regulation, antecedents **Action plan components:** self-recognition of exacerbations, self-treatment of exacerbations, use of maintenance treatment, contact healthcare providers for support, other: reinforcement of the logistics for treatment of comorbidities and social support was carried out accordingly
Outcomes	1. health-related quality of life (SGRQ and EQ-5D) 2. FEV_1 (L) 3. FEV_1/FVC 4. clinical factors (comorbidities, MRC dyspnoea, BMI) 5. lifestyle (smoking, alcohol, physical activity) 6. self-management (knowledge, identification and early treatment, adherence 7. satisfaction with health services
Notes	The current study was conducted in Barcelona (Spain) only. This subgroup was also reported in the study of Casas 2006. However, in the current study other outcome measures and different number of participants were reported.

Bias	Authors's judgement	Support for judgment
Random sequence generation (selection bias)	Low risk	"and were blindly assigned (1:2 ratio) using computer generated random numbers either to integrated care (IC) or to usual care (UC)." p. 1463 Comment: Random sequence generation was adequately performed.
Allocation concealment (selection bias)	Low risk	"and were blindly assigned (1:2 ratio) using computer generated random numbers either to integrated care (IC) or to usual care (UC)." p. 1463 Comment: No information on allocation concealment. The allocation was adequately concealed.
Blinding of participants and personnel (performance bias)	High risk	Comment: Blinding of participants and personnel was not reported.
Blinding of outcome assessment (detection bias)	Low risk	"Early assessment of patients at their admission to the study was identical for both groups. It included a blind administration of a questionnaire, described in detail elsewhere." p. 1464 Comment: The administration of a questionnaire was blinded.
Incomplete outcome data (attrition bias)	High risk	"During follow-up, a priori defined exclusion criteria, such as lung cancer, appeared in 9 subjects. Twente-one subjects died, and 16 were lost to follow-up. Only 57% of subjects finished the study at 12 months. (…) Since date about outcome variables was not available in the lost subjects (whether due to exclusion, loss to follow-up or death), an intention-to-treat principle was not possible." p. 1464 Comment: More than 40% of the data on functional status and HRQoL reported was missing, leading to a high risk of bias.
Selective reporting (reporting bias)	Unclear risk	Comment: VAS was reported, but the Euroqol (EQ-5D) was not reported. No signs of selective reporting; however, no protocol available.
Other bias	Low risk	-

Hernández 2015

Methods	**Design:** RCT **Follow-up:** 12 months (and 72 months passive follow-up thereafter) **Control group:** usual care
Participants	**Recruitment:** hospital (outpatient) **Assessed for eligibility:** 860 **Randomly assigned:** I: 71; C: 84 **Completed:** I: 54; C: 55 **Mean age:** I: 73 ± 8 years; C: 75 ± 9 years **Gender (% male):** I: 83; C: 86 **COPD diagnosis:** a person not involved in the study identified the cases with COPD (ICD9-CM 491, 492, 493 or 496) as the primary diagnosis for admission. However, lung function testing was also assessed before randomisation **Inclusion of participants in the acute phase:** no **Major inclusion criteria:** clinically stable COPD patients with a history of at least two hospital admissions owing to severe respiratory exacerbations during two consecutive years, we considered a broad spectrum of COPD diagnostic terms that include chronic obstructive inflammatory diseases namely, emphysema, asthma, tuberculosis, chronic bronchitis and COPD, aged above 45 years and living at home within the healthcare area of the hospital (Barcelona-Esquerra) **Major exclusion criteria:** nursing home or not living in the area, participants in another randomised controlled trial, exitus prior to contact
Interventions	**Mode:** individual and group sessions at an outpatient clinic and at the participant's home **Duration:** at least one face-to-face individual session of 40 minutes at the patient's home within 72 hours after entry into the study by the primary care team (patients without mobility problems), four face-to-face individual sessions of 15 minutes education each at the patient's home by the primary care team (patients with mobility problems), one two-hour individual or group educational programme of 40 minutes. Three group sessions for patients without mobility problems (two comprehensive assessments of 90 minutes each at the outpatient clinic and one two-hour educational programme) and for patients with mobility problems, the programme was done at home. In all visits, the nurses dedicated 15 minutes for education. **Professional:** specialised respiratory nurse, primary care team (physician, nurse and social worker) **Training of case managers:** the community care teams received training: a two-hour face-to-face educational training and one-day stay at the hospital ward, aiming at enhancing home-based management of frail COPD patients. **Self-management components:** action plan COPD exacerbations, self-recognition of COPD exacerbations, education regarding COPD, smoking cessation, exercise or physical activity component, other: instructions on non-pharmacological treatment **Self-management topics:** smoking cessation, exercise, diet, (maintenance) medication, correct device use, coping with breathlessness/breathing techniques, other: vaccination **Exercise programme:** yes, no extra information available **Smoking cessation programme:** yes, no extra information available **Behavioural change techniques:** eight clusters: goals and planning, feedback and monitoring, social support, shaping knowledge, comparison of behaviour, associations, regulation, antecedents **Action plan components:** self-recognition of exacerbations, self-treatment of exacerbations, use of maintenance treatment, avoid situations in which viral infection might be prevalent, contact healthcare providers for support, self-treatment of comorbidities

Outcomes	1. mental status 2. activities of daily living (Lawton index) 3. anxiety and depression (HADS) 4. health-related quality of life (SGRQ) 5. sleepiness (Epworth sleepiness scale) 6. 6MWT 7. noctural pulse oximetry and body mass distribution 8. exacerbations	
Notes	-	
Bias	**Authors's judgement**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	"A computer-generated list of random numbers with no restrictions and administered by personnel who were not involved in the study ensured blinded randomisation (1:1 ratio)." p. 2 Comment: Random sequence generation was adequately performed.
Allocation concealment (selection bias)	Low risk	"(…) and administered by personnel who were not involved in the study" p. 2 Comment: The allocation was adequately concealed.
Blinding of participants and personnel (performance bias)	High risk	Comment: No blinding of participants or personnel
Blinding of outcome assessment (detection bias)	Low risk	"A blind evaluation of the study group carried out before randomisation and after the 12-month follow-up consisted of a patient interview and analysis of medical records, self-administered questionnaires and lung function testing." p. 2 Comment: Outcome assessment was blinded.
Incomplete outcome data (attrition bias)	Unclear risk	Comment: Insufficient information to permit judgement.
Selective reporting (reporting bias)	Unclear risk	"The RCT was not included in the clinicaltrials.gov registry because at that time it was not compulsory." p. 5 Comment: Not all outcome measures are reported (e.g. Epworth sleepiness scale, lung function, 6-MWT). However, no protocol available.
Other bias	Low risk	-

Jennings 2015

Methods	**Design:** RCT **Follow-up:** 3 months **Control group:** usual care
Participants	**Recruitment:** hospital (inpatient) **Assessed for eligibility:** 1225 **Randomly assigned:** I: 93; C: 79 **Completed:** I: 93; C: 79 **Mean age:** I: 64.88 ± 10.86 years; C: 64.43 ± 10.47 years **Gender (% male):** I: 43.4; C: 46.8 **COPD diagnosis:** based on spirometric testing in the prior year that demonstrated airflow obstruction (FEV_1/FVC , 70% and FEV_1 < 80%) based on GOLD criteria. If spirometric data were not available, a previously validated questionnaire was used in the diagnosis of COPD for purposes of study inclusion. The presence of airflow obstruction was then confirmed by spirometry prior to discharge. **Inclusion of participants in the acute phase:** yes, during hospitalisation **Major inclusion criteria:** diagnosis of COPD with the presence of an acute exacerbation, age > 40 years, and current or ex-smoker with a history equivalent to at least 20 pack-years. The diagnosis of AECOPD was made by the primary team but was confirmed by the research team prior to assessing eligibility for inclusion. AECOPD was defined as an acute event characterized by a worsening of the patient's respiratory symptoms beyond normal day-to-day variations, leading to a change in medication. If there was a question about a true diagnosis of AECOPD, a pulmonologist on the research team evaluated the patient. **Major exclusion criteria:** a medical history of asthma, interstitial lung disease, bronchiectasis, presence of airway hardware (e.g., tracheal stents), lung cancer, any other cancer with an associated life expectancy of < 1 year, any cancer where the patient was receiving active chemotherapy or radiation treatment, active substance abuse, or neuromuscular disorders affecting the respiratory system, language barriers, residence in a nursing home, ICU stay during the current admission, and significant delirium or dementia.
Interventions	**Mode:** individual sessions at a hospital and at the participant's home, telephone calls **Duration:** one face-to-face individual session of one hour at the hospital by a member of the research team 24 hours prior to the anticipated discharge day. 48 hours after discharge, patients were contacted by telephone to reinforce the items in the bundle. **Professional:** research team and research nurse **Training of case managers:** not reported **Self-management components:** action plan COPD exacerbations, iterative process with feedback on actions, education regarding COPD, smoking cessation, other: the primary team was notified if a patient was identified as having anxiety or depressive symptoms, and referral to outpatient behavioral health services or pharmacologic treatment was deferred to the primary team **Self-management topics:** smoking cessation, diet, correct device use, coping with breathlessness/breathing techniques, other: assess current behaviours to manage COPD **Exercise programme:** no **Smoking cessation programme:** yes, active smokers received smoking cessation counseling and, with patient agreement, were enrolled in the Henry Ford Health System Smoking Cessation Program **Behavioural change techniques:** eight clusters: goals and planning, feedback and monitoring, social support, shaping knowledge, comparison of behaviour, associations, repetition and substitution, antecedents **Action plan components:** contact healthcare providers for support
Outcomes	1. 30-day risk of readmission or ED visits for AECOPDs 2. 90-day rate of COPD readmission
Notes	The trial was stopped early after an interim analysis at 3 years did not demonstrate that further accrual could achieve the desired 10% difference in the primary composite end point of ED visit or rehospitalisation between the two groups.

Bias	Authors's judgement	Support for judgment
Random sequence generation (selection bias)	Low risk	"A computer-generated list was used to randomise patients in a 1:1 ratio, stratified by age and sex, to either the bundle or the control group." Comment: Random sequence generation was adequately performed.
Allocation concealment (selection bias)	Unclear risk	Comment: No information provided regarding allocation concealment.
Blinding of participants and personnel (performance bias)	High risk	Comment: No information provided regarding blinding of participants and personnel. However, the participants and personnel could not be blinded as all patients assigned to the bundle group received a 60-min visit by a member of the research team.
Blinding of outcome assessment (detection bias)	Low risk	Comment: No information provided regarding blinding of outcome assessment; however, objective outcome measures are used.
Incomplete outcome data (attrition bias)	Unclear risk	"The trial was stopped early after an interim analysis at 3 years did not demonstrate that further accrual could achieve the desired 10% difference in the primary composite end point of ED visit or rehospitalization between the two groups." p. 1229 Comment: it seems that there were no drop-outs after randomisation.
Selective reporting (reporting bias)	Unclear risk	"The primary end point was the difference in the composite risk of hospitalizations or ED visits for AECOPDs between the two groups in the 30 days following discharge." p. 1229 Comment: According to the protocol available in the Clinical Trials register the primary outcomes were the 30 day readmission rate and the time until readmission or ER visit, 30 days.
Other bias	Low risk	-

Khdour 2009

Methods	**Design:** RCT **Follow-up:** 12 months **Control group:** usual hospital outpatient care
Participants	**Recruitment:** hospital (outpatient clinic) **Assessed for eligibility:** not reported **Randomly assigned:** I: 86; C: 87 **Completed:** I: 71; C: 72 **Mean age:** I: 65.63 ± 10.1 years; C: 67.3 ± 9.2 years **Gender (% male):** I: 44.2; C: 43.7 **COPD diagnosis:** confirmed diagnosis of COPD (by the hospital consultant) for at least 1 year, having a FEV_1 of 30–80% of the predicted normal value **Inclusion of participants in the acute phase:** not reported **Major inclusion criteria:** confirmed diagnosis of COPD for at least 1 year, having a FEV_1 of 30–80% of the predicted normal value and >45 years old **Major exclusion criteria:** having congestive heart failure, moderate to severe learning difficulties (as judged by hospital consultant), attended a pulmonary rehabilitation programme in the last 6 months, and severe mobility problems or terminal illness
Interventions	**Mode:** individual sessions at an outpatient clinic, telephone calls, booklet on techniques for expectoration **Duration:** one face-to-face individual session of 45 minutes (one hour for smokers) and two telephone calls at three and nine months **Professional:** clinical pharmacist, respiratory specialist, respiratory nurse **Training of case managers:** not reported **Self-management components:** action plan COPD exacerbations, iterative process with feedback on actions, self-recognition of COPD exacerbations, education regarding COPD, smoking cessation **Self-management topics:** smoking cessation, exercise, diet, (maintenance) medication, correct device use, coping with breathlessness/breathing techniques **Exercise programme:** no **Smoking cessation programme:** yes, advice, using the motivational interviewing technique, was provided to the patients who still smoked and referral to a special smoking cessation programme run within the hospital was made **Behavioural change techniques:** ten clusters: goals and planning, feedback and monitoring, social support, shaping knowledge, natural consequences, comparison of behaviour, associations, repetition and substitution, regulation, antecedents **Action plan components:** self-recognition of exacerbations, self-treatment of exacerbations, contact healthcare providers for support
Outcomes	1. health-related quality of life (SGRQ) 2. FEV_1 3. hospital admissions for acute exacerbations 4. ED visits for acute exacerbations 5. GP visits, scheduled and unscheduled 6. knowledge of medication and disease management (COPD knowledge questionnaire) 7. adherence to prescribed medication
Notes	-

Bias	Authors's judgement	Support for judgment
Random sequence generation (selection bias)	Low risk	"Recruited patients were randomly assigned to one of two groups: the intervention group and the usual care (control group). Both groups were matched as closely as possible for the following parameters: severity of COPD (measured by FEV1), age, gender and other concomitant illness. The randomisation was carried out using the minimization method described by Gore." p. 589 Comment: Random sequence generation was performed adequately.
Allocation concealment (selection bias)	Low risk	"Recruited patients were randomly assigned to one of two groups: the intervention group and the usual care (control group). Both groups were matched as closely as possible for the following parameters: severity of COPD (measured by FEV1), age, gender and other concomitant illness. The randomisation was carried out using the minimization method described by Gore." p. 589 Comment: Allocation was adequately concealed.
Blinding of participants and personnel (performance bias)	High risk	Comment: Blinding of participants and personnel was not reported.
Blinding of outcome assessment (detection bias)	Unclear risk	"Baseline measurements were performed by the research pharmacist (…) for operational reasons, the researcher could not be blinded to the group to which the patient belonged." p. 590 Comment: Outcome assessment was not blinded; it was not clearly reported how the research pharmacist was related to the study.
Incomplete outcome data (attrition bias)	Low risk	"A per-protocol analysis was used. (…) During the study period, three patients from the intervention group and five from the control group died and a total of 22 patients withdrew from the study; 12 patients from the intervention group and 10 from the control group." p. 590 Comment: In both groups, 15 participants (17%) dropped out during the 12-month follow-up. Reasons for drop-out were comparable across groups.
Selective reporting (reporting bias)	Unclear risk	Comment: No signs of selective reporting; however, no protocol available.
Other bias	Low risk	-

Kheirabadi 2008

Methods	**Design:** RCT **Follow-up:** 3 months **Control group:** usual care	
Participants	**Recruitment:** hospital (outpatient clinic) **Assessed for eligibility:** not reported **Randomly assigned:** I: 21; C: 21 **Completed:** I: 21; C: 21 **Mean age:** I: 56.6 ± 5.7 years; C: 56.2 ± 4.1 years **Gender (% male):** I: 61.9; C: 76.2 **COPD diagnosis:** diagnosed by a pulmonologist according to ATS criteria **Inclusion of participants in the acute phase:** not reported **Major inclusion criteria:** diagnosed by a pulmonologist according to ATS criteria, consent for participation in the study, being literate and having sufficient knowledge (at least to understand and fill out the questionnaires), having physical and mental ability to tolerate the interventions, absence of disease that limit the function and other medical conditions affecting the mortality **Major exclusion criteria:** primary diagnosis of asthma, hospitalisation during the intervention, main treatment with oxygen and occurrence of serious unexpected stresses during the study.	
Interventions	**Mode:** group sessions at a hospital (outpatient clinic), telephone calls **Duration:** eight face-to-face educational group sessions of 60-90 minutes each (3-4 member groups) with one week interval and during this 8-week programme, patients of the intervention group were followed up by phone **Professional:** psychologist, trained psychiatric residents **Training of case managers:** the psychiatric residents are trained, but no further information is provided **Self-management components:** action plan COPD exacerbations, self-recognition of COPD exacerbations, education regarding COPD, exercise or physical activity component **Self-management topics:** smoking cessation, exercise, diet, (maintenance) medication, coping with breathlessness/breathing techniques, other: healthy lifestyle, avoid places with air pollution, healthy sleep, sexual habits, stress management, free time activities, travelling, and behavioral interventions focusing on common issues like independence, decreased self-esteem, feeling insecure, limited relation with family and friends **Exercise programme:** yes, simple regular exercise programme at home **Smoking cessation programme:** no **Behavioural change techniques:** six clusters: goals and planning, feedback and monitoring, shaping knowledge, natural consequences, associations, regulation **Action plan components:** avoid situations in which viral infection might be prevalent	
Outcomes	1. severity of disease (CCQ questionnaire)	
Notes	-	
Bias	**Authors's judgement**	**Support for judgment**
Random sequence generation (selection bias)	Unclear risk	Comment: The method of random sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	Comment: The method of allocation concealment was not reported.

Blinding of participants and personnel (performance bias)	High risk	Comment: Blinding of participants and personnel was not reported.
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: Blinding of outcome assessment was not reported. Not clear who performed the measurements.
Incomplete outcome data (attrition bias)	Low risk	"We also encouraged and followed up the patients by phone and even when someone was absent, we teached him/her over the phone. In this way, all patients accompanied us till the end of the course and no patient was excluded from the study." p. 28 Comment: All patients completed follow-up.
Selective reporting (reporting bias)	Unclear risk	Comment: No signs of selective reporting, although only one outcome measure was reported. No protocol available.
Other bias	Low risk	-

Martin 2004

Methods	**Design:** RCT **Follow-up:** 12 months **Control group:** usual care
Participants	**Recruitment:** general practice **Assessed for eligibility:** not reported **Randomly assigned:** I: 44; C: 49 **Completed:** I: 35; C: 45 **Mean age:** I: 71.1 (95% CI 68.7-73.5) years; C: 69.1 (95% CI 63.5-74.7) years **Gender (% male):** I: 34.1; C: 65.3 **COPD diagnosis:** GOLD, a diagnosis of moderate or severe COPD **Inclusion of participants in the acute phase:** no (use of the plan was commenced at a time when each patient was in a stable condition) **Major inclusion criteria:** diagnosis of COPD, aged 55 years or over, at least one hospital admission or two acute exacerbations of COPD requiring GP care during the previous 12 months, a Mini Mental State Examination score > 22 **Major exclusion criteria:** terminally ill, coexisting lung cancer, admission to hospital with cardiac disease within previous 12 months, receiving home oxygen therapy.

Interventions	**Mode:** individual sessions at a GP, hospital, ambulance service, emergency department or home-based **Duration:** four face-to-face individual sessions, during the 12-months period all patients were visited by a respiratory nurse at three, six and 12 months to provide routine support and further education regarding use of the plan **Professional:** respiratory physician, respiratory nurse, GP, ED consultant, medical staff hospital **Training of case managers:** not reported **Self-management components:** action plan COPD exacerbations, iterative process with feedback on actions, self-recognition of COPD exacerbations **Self-management topics:** (maintenance) medication **Exercise programme:** no **Smoking cessation programme:** no **Behavioural change techniques:** eight clusters: goals and planning, feedback and monitoring, social support, shaping knowledge, comparison of behaviour, associations, regulation, antecedents **Action plan components:** self-recognition of exacerbations, self-treatment of exacerbations, use of maintenance treatment, self-treatment of comorbidities, other: when/how to use oxygen therapy and when to use diuretics	
Outcomes	1. health care utilisation (GP visits, hospital admissions, ambulance calls) 2. quality of life (SGRQ) 3. medication use (courses of oral steroids and antibiotics)	
Notes	Three patients subsequently withdrew for personal reasons. However, it was not reported in what group. A further 13 died during the follow-up period (nine in the intervention group and four in the control group).	
Bias	**Authors's judgement**	**Support for judgment**
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly assigned to the intervention (care plan) or control (usual care) groups." p. 192 Comment: The method of random sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	"Patients were randomly assigned to the intervention (care plan) or control (usual care) groups." p. 192 Comment: The method of allocation concealment was not reported.
Blinding of participants and personnel (performance bias)	High risk	Comment: Blinding of participants and personnel was not reported.
Blinding of outcome assessment (detection bias)	Unclear risk	"Quality of life was measured by the St George's Respiratory Questionnaire (SGRQ). The questionnaire was administered by the research nurse (DMcN) at each visit." Comment: The blinding of outcome assessment was not reported.

Incomplete outcome data (attrition bias)	Unclear risk	"Three subsequently withdrew for personal reasons. A further 13 died during the follow-up period (…) [nine in the intervention group and four in the control group (NS)]" p. 192 Comment: The number of withdrawals was higher in the intervention group compared to the control group. However, no information provided regarding the differences in dropout rates.
Selective reporting (reporting bias)	Unclear risk	Comment: No signs of selective reporting, however no protocol available.
Other bias	Low risk	-

Mitchell 2014

Methods	**Design:** RCT **Follow-up:** 6 months **Control group:** usual care
Participants	**Recruitment:** general practice **Assessed for eligibility:** 326 **Randomly assigned:** I: 89; C: 95 **Completed:** I: 65; C: 79 **Mean age:** I: 69 ± 8 years; C: 69 ± 10.1 years **Gender (% male):** I: 60.7; C: 49.5 **COPD diagnosis:** a diagnosis of COPD confirmed by spirometry, with a FEV_1/FVC ratio < 0.7 **Inclusion of participants in the acute phase:** no **Major inclusion criteria:** have a diagnosis of COPD confirmed by spirometry, with a FEV_1/FVC ratio < 0.7, grade 2-5 MRC dyspnoea scale, clinically stable for 4 weeks **Major exclusion criteria:** unable to undertake an exercise regime due to neurological, musculoskeletal or cognitive comorbidities, unable to read English to the reading age of an 8-year-old, completed pulmonary rehabilitation within the previous 12 months
Interventions	**Mode:** individual sessions at a GP or home-based, telephone calls, workbook **Duration:** one face-to-face individual session for 30-45 minutes by a physiotherapist and two telephone calls at two and four weeks into the programme to reinforce skills and providing encouragement to progress **Professional:** physiotherapist, trainee health psychologist **Training of case managers:** not reported **Self-management components:** action plan COPD exacerbations, iterative process with feedback on actions, self-recognition of COPD exacerbations, education regarding COPD, exercise or physical activity component **Self-management topics:** smoking cessation, exercise, diet, (maintenance) medication, correct device use, coping with breathlessness/breathing techniques **Exercise programme:** yes, home exercise programme consisting of a daily walking programme, and resistance training of the upper and lower limbs using free weights three times per week. **Smoking cessation programme:** no **Behavioural change techniques:** 11 clusters: goals and planning, feedback and monitoring, social support, shaping knowledge, natural consequences, comparison of behaviour, associations, repetition and substitution, regulation, antecedents, identity **Action plan components:** self-recognition of exacerbations, self-treatment of exacerbations, avoid situations in which viral infection might be prevalent, contact healthcare providers for support, other: discussion with participants about self-administration and requesting rescue medication from their primary care physician

Outcomes	1. health status (CRQ dyspnoea domain) 2. fatigue, emotion and mastery domains of the CRQ 3. disease knowledge (Bristol COPD Knowledge Questiionnaire) 4. anxiety and depression (HADS) 5. exercise capacity (ISWT, ESWT) 6. self-efficacy (Pulmonary Rehabilitation Adapted Index of Self-Efficacy) 7. healthcare utilisation (admissions, GP visits, ED visits, nurse home visits) 8. medication use (courses of antibiotics) 8. self-reported smoking status	
Notes	-	
Bias	**Authors's judgement**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	"Patients were assigned to either usual care or SPACE FOR COPD via a web-based, concealed allocation programme, using simple randomisation codes prepared by the trial statistician (J. Bankart)." p. 1539 Comment: Random sequence generation was adequately performed.
Allocation concealment (selection bias)	Unclear risk	"Randomisation was conducted by the trial investigator responsible for administering the intervention (K.E. Mitchell)." p. 1539 Comment: The method of allocation concealment was not reported.
Blinding of participants and personnel (performance bias)	High risk	"Lack of participant blinding may have increased motivation when receiving the treatment and attempts to satisfy the researchers might have increased the observed treatment effects in the intervention arm. We cannot, therefore, rule out the possible impact of attention." p. 1546 Comment: No blinding of participants.
Blinding of outcome assessment (detection bias)	Low risk	"The assessments at week 6 and 6 months were conducted by a member of the research team who was blind to randomisation allocation (V. Johnson-Warrington)." p. 1540 Comment: The outcome assessment was blinded.
Incomplete outcome data (attrition bias)	Low risk	"There were no significant differences in demographics or baseline variables between those who completed and those who did not complete the study. Analysis was carried out on an intention-to-treat basis. Missing data were imputed in Stata using multiple imputed chained equations. Analysis on imputed data sets were carried out using the micombine command in Stata, which analyses each dataset separately and combines the results." p. 1540 Comment: No signs of incomplete outcome data. A bit more missing data in control group, maximum around 20%.
Selective reporting (reporting bias)	Low risk	Comment: No signs for selective outcome reporting. The primary outcome measure and most of the secondary outcome measures were reported.
Other bias	Low risk	-

Monninkhof 2003

Methods	**Design:** RCT **Follow-up:** 12 months **Control group:** usual care
Participants	**Recruitment:** hospital (outpatient clinic) **Assessed for eligibility:** 615 **Randomly assigned:** I: 127; C: 121 **Completed:** I: 122; C: 114 **Mean age:** I: 65 ± 7 years; C: 65 ± 7 years **Gender (% male):** I: 85; C: 84 **COPD diagnosis:** clinical diagnosis of stable COPD, as defined by ATS criteria; FEV_1% predicted (pre): 25% to 80%; FEV_1/VC (pre): < 60% **Inclusion of participants in the acute phase:** no **Major inclusion criteria:** clinical diagnosis of stable COPD, no history of asthma, no exacerbation in the month prior to enrolment, current or former smoker, aged 40–75 yrs, baseline prebronchodilator (FEV1) 25–80% predicted, pre-bronchodilator ratio FEV1/VC < 60% **Major exclusion criteria:** maintenance treatment of oral steroids or antibiotics, medical condition with low survival or serious psychiatric morbidity, any other active lung disease
Interventions	**Mode:** group sessions (approximately eight patients) at the outpatient clinic and community-based, educational booklet **Duration:** five face-to-face group sessions for two hours each by a respiratory nurse (four sessions with a one-week interval and the last (feedback) session was given three months after the fourth session) and one or two small group training sessions per week for 30-45 minutes by a physiotherapist trained in COPD care **Professional:** respiratory nurse, respiratory physiotherapist **Training of case managers:** physiotherapists trained in COPD care **Self-management components:** action plan COPD exacerbations, iterative process with feedback on actions, self-recognition of COPD exacerbations, education regarding COPD, exercise or physical activity component **Self-management topics:** smoking cessation, exercise, diet, (maintenance) medication, correct device use, coping with breathlessness/breathing techniques, other: ergonomic posture and energy conservation during daily activities or work, communication and social relationships, coping with disease, recognising participants' individual capacity, social interactions and behavioural changes **Exercise programme:** yes, one or two 1-h small group training sessions per week under guidance of a physiotherapist trained in COPD care. In the first few months, inactive patients were offered two sessions per week to get started. Incorporation of exercise in daily life above the fitness training was the patients' own responsibility. The programme included strength training, breathing and cardiovascular exercises (stationary bicycling, walking etc.). **Smoking cessation programme:** no **Behavioural change techniques:** ten clusters: goals and planning, feedback and monitoring, social support, shaping knowledge, natural consequences, comparison of behaviour, associations, repetition and substitution, regulation, antecedents **Action plan components:** self-recognition of exacerbations, self-treatment of exacerbations, contact healthcare providers for support
Outcomes	1. health-related quality of life (SGRQ) 2. self-confidence 3. walking distance (6MWT) 4. exacerbations 5. COPD symptoms 6. healthcare utilisation (doctor consultations, hospital admissions) 7. healthcare costs (days lost from work) 8. preference-based utilities (EuroQol, QALYs)
Notes	-

Bias	Authors's judgement	Support for judgment
Random sequence generation (selection bias)	Low risk	"Randomisation was performed in blocks of four, stratified by sex and smoking status, using sealed envelopes. " p. 816 Comment: Random sequence generation was adequately performed.
Allocation concealment (selection bias)	Low risk	"Randomisation was performed in blocks of four, stratified by sex and smoking status, using sealed envelopes. " p. 816 Comment: The allocation was adequately concealed.
Blinding of participants and personnel (performance bias)	High risk	Comment: Participants and personnel were not blinded.
Blinding of outcome assessment (detection bias)	Low risk	Comment: Outcome assessment was not blinded. However, measurements were performed by an assessor who was independent of the study.
Incomplete outcome data (attrition bias)	Low risk	"In the intervention group five patients (three deaths, two other) dropped out, as did seven patients (three deaths, two carcinoma, two other) in the control group." page 818 Comment: The number of withdrawals and reasons for withdrawal in both groups were comparable. Moreover, an intention-to-treat analysis was used and drop out was low.
Selective reporting (reporting bias)	Unclear risk	Comment: No signs of selective reporting; however, no protocol available
Other bias	Low risk	-

Ninot 2011

Methods	**Design:** RCT **Follow-up:** 12 months **Control group:** usual care
Participants	**Recruitment:** hospital (outpatient, university-based center) **Assessed for eligibility:** 101 **Randomly assigned:** I: 23; C: 22 **Completed:** I: 20; C: 18 **Mean age:** I: 65 (range 59-74) years; C: 61 (range 56-65) years **Gender (% male):** I: 90; C: 77.8 **COPD diagnosis:** a FEV_1/FVC ratio of less than 0.70 **Inclusion of participants in the acute phase:** no **Major inclusion criteria:** stable COPD, 40 years of age or older, FEV_1/FVC ratio of less than 0.70, not previously been involved in pulmonary rehabilitation or had lived in a long-term care facility, understood, read, and wrote French. **Major exclusion criteria:** previous diagnosis of asthma, oxygen dependence, unstable and/or uncontrolled cardiac disease, musculoskeletal problems precluding exercise training, a terminal disease, dementia or an uncontrolled psychiatric illness

Interventions	**Mode:** individual and group sessions (four-eight participants) at the hospital, telephone calls **Duration:** eight face-to-face group sessions (two per week) for two hours each by a health professional for four weeks, eight exercise sessions for 30-45 min each under the supervision of a qualified exercise trainer, three telephone calls to encourage personalised endurance training and on reporting symptoms **Professional:** health professional and qualified exercise trainer **Training of case managers:** not reported **Self-management components:** action plan COPD exacerbations, self-recognition of COPD exacerbations, education regarding COPD, exercise or physical activity component **Self-management topics:** smoking cessation, exercise, diet, (maintenance) medication, correct device use, coping with breathlessness/breathing techniques **Exercise programme:** yes, after each educational session (8 in total) within the same group, participants performed the usual exercise program used in our laboratory (i.e. cycling at the level of the ventilatory threshold for 30-45 min under the supervision of a qualified exercise trainer). **Smoking cessation programme:** no **Behavioural change techniques:** nine clusters: goals and planning, feedback and monitoring, social support, shaping knowledge, comparison of behaviour, associations, repetition and substitution, regulation, antecedents **Action plan components:** self-recognition of exacerbations, self-treatment of exacerbations, use of maintenance treatment, avoid situations in which viral infection might be prevalent	
Outcomes	1. exercise training (change in 6MWD) 2. 6MWT 3. COPD-specific health status (SGRQ) 4. perceived health status (Nottingham Health Profile) 5. maximal exercise capacity (peak work rate) 6. daily physical activity (Voorrips questionnaire) 7. healthcare utilisation (hospital admissions) 8. healthcare costs (cost of medication, hospitalisations)	
Notes	-	
Bias	**Authors's judgement**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	"Participants were randomly assigned either to the self-management programme or usual care group. The trial statistician, MCP, generated the random allocation sequence using the random procedure in SAS (SAS v.9.1 e SAS Institute, Cary NC), with a 1:1 allocation using block size of 5 (…)" p. 379 Comment: Random sequence generation was adequately performed.
Allocation concealment (selection bias)	Low risk	"(…) After the physician had obtained the patient's consent, he sent by fax the randomisation form to the Clinical Research Unit (AJ) for allocation consignment re-addressed by fax" p. 379 Comment: Alllocation was adequately concealed.
Blinding of participants and personnel (performance bias)	High risk	"Due to the nature of the intervention conditions, it is not possible to blind research participants or assessors. Several stratagems were adopted in an effort to ensure that objectivity was maintained as rigorously as possible. Participants were unaware of their group allocation until they had completed all of their pre-intervention assessment" p. 379 Comment: Patients and personnel were not blinded.

Blinding of outcome assessment (detection bias)	Low risk	"(…) The individuals carrying out the assessment were not part of the intervention team. Research participants were asked not to divulge information regarding their group allocation in conversation during assessment at 12 month." p. 379 Comment: Outcome assessment was not blinded; however, assessors were not part of the intervention team.
Incomplete outcome data (attrition bias)	Low risk	"One patient from the intervention group did not fulfil our adherence criteria to the 4-week programme, and also did not complete the 1-year evaluation. Six more patients were not available for follow-up evaluation; four in the usual care group, and two in the intervention group. The withdrawals were due to miscellaneous medical conditions (n = 3), and COPD exacerbation (n = 3). Due to the missing data, we did not retain these patients in our 1-year analyses" p. 380 "Baseline characteristics of the patients who withdrew from the study were similar to those of patients who completed the trial" p. 380 Comment: The number of withdrawal was relatively low and equally distributed over groups. Also, reasons for withdrawal in the two groups were comparable.
Selective reporting (reporting bias)	Unclear risk	Comment: No signs of selectively reporting; however, no protocol available.
Other bias	Unclear risk	Comment: Per protocol analysis, baseline characteristics were not reported for all randomised patients.

Österlund-Efraimsson 2008

Methods	**Design:** RCT **Follow-up:** 3 to 5 months **Control group:** usual care
Participants	**Recruitment:** nurse-led primary healthcare clinic **Assessed for eligibility:** 110 **Randomly assigned:** I: 26, C: 26 **Completed:** I: 26, C: 26 **Mean age:** I: 66 ± 9.4 years; C: 67 ± 10.4 years **Gender (% male):** I: 50.0, C: 50.0 **COPD diagnosis:** mild, moderate, severe or very severe COPD based on spirometry, lung capacity after bronchodilator use, based on GOLD criteria **Inclusion of participants in the acute phase:** not reported **Major inclusion criteria:** diagnosed with mild, moderate, severe or very severe COPD based on spirometry, lung capacity after bronchodilator use, based on GOLD criteria **Major exclusion criteria:** diagnosed severe mental disorders such as schizophrenia, dementia or alcohol or drug abuse

Interventions	**Mode:** individual sessions at the outpatient and nurse-led primary healthcare clinic **Duration:** two face-to-face individual sessions for self-care education during 3-5 months for one hour each by the nurse **Professional:** COPD nurse, physician, if needed: dietician, medical social worker, physical therapist, occupational therapist **Training of case managers:** not reported **Self-management components:** action plan COPD exacerbations, iterative process with feedback on actions, self-recognition of COPD exacerbations, education regarding COPD, smoking cessation, exercise or physical activity component **Self-management topics:** smoking cessation, exercise, diet, (maintenance) medication, correct device use, coping with breathlessness/breathing techniques, other: instructions on the coughing technique to prevent infections and exacerbations, measurement on oxygen saturation before and after exertion, psycho-social counselling and support, counselling on infection prevention **Exercise programme:** yes (optional), dialogue on physical activity and exercise. When needed, a dietician, a medical social worker, a physical therapist and an occupational therapist were consulted. **Smoking cessation programme:** yes (optional), motivational dialogue on smoking cessation based on Prochaska and DiClementes' transtheoretical model of the stages of change. The model is based on open questions to help patients reflect on their smoking habits and empower patients to quit smoking. **Behavioural change techniques:** ten clusters: goals and planning, feedback and monitoring, social support, shaping knowledge, natural consequences, comparison of behaviour, associations, repetition and substitution, comparison of outcomes, reward and threat, regulation, antecedents, identity, scheduled consequences, self-belief, covert learning. **Action plan components:** self-recognition of exacerbations, self-treatment of exacerbations, contact healthcare providers for support	
Outcomes	1. health-related quality of life (SGRQ) 2. smoking 3. COPD knowledge	
Notes	-	
Bias	**Authors's judgement**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	"The randomisation was performed when two patients with the same variables agreed to participate in the study by assigning each individual an identity number. An independent person drew lots for allocation to either intervention or control group." p. 2-3 Comment: The random sequence generation was performed adequately.
Allocation concealment (selection bias)	Low risk	"The randomisation was performed when two patients with the same variables agreed to participate in the study by assigning each individual an identity number. An independent person drew lots for allocation to either intervention or control group." p. 2-3 Comment: Allocation was adequately concealed.
Blinding of participants and personnel (performance bias)	High risk	Comment: Blinding of participants and personnel was not reported.

Blinding of outcome assessment (detection bias)	High risk	"Each visit lasted for about 1 hour and the same nurse (Eva Österlund Efraimsson) was responsible for all consultations. At the first and last visits, all patients responded to the two questionnaires, which were completed by each participant in an undisturbed area. The nurse in charge was available to answer questions and to check that the patients responded to all the items." p. 180 Comment: Outcome assessment was not blinded, and measurements were performed/supervised by the same person who provided the intervention (who was also the principal investigator).
Incomplete outcome data (attrition bias)	Low risk	"The drop-out rate was 10 patients (five women and five men) (…) The severity of the illness was evenly distributed between men and women: three women and three men had moderate COPD, one woman and one man had severe COPD and one woman and one man had very severe COPD. The drop-out group did not differ from the sample in any of these aspects." p. 180 Comment: The drop-out group did not differ from the sample. However, it was unclear when the patients did drop-out and in which group.
Selective reporting (reporting bias)	Unclear risk	Comment: All subscales of the two questionnaires used were reported; no signs of selective reporting were noted. However, no protocol available.
Other bias	Low risk	-

Rea 2004

Methods	**Design:** cluster-RCT **Follow-up:** 12 months **Control group:** conventional care
Participants	**Recruitment:** general practice **Assessed for eligibility:** 700 **Randomly assigned:** I: 83; C: 52 **Completed:** I: 71; C: 46 **Mean age:** 68 (range 44-84) years for total group **Gender (% male):** 41.5% for total group **COPD diagnosis:** diagnosis of COPD by ICD-9-CM codes and GP records for a clinical diagnosis of moderate to severe COPD **Inclusion of participants in the acute phase:** not reported **Major inclusion criteria:** clinical diagnosis of moderate to severe COPD **Major exclusion criteria:** chronic asthma, bronchiectasis, comorbidity more significant than COPD, unable to give informed consent; prognosis < 12 months, LTOT or too unwell, deceased, no longer enrolled with participating GP or moved out of area, unable to contact patient; insufficient practice nurse resource

Interventions	**Mode:** individual sessions at the outpatient clinic, GP and at the participant's home **Duration:** at least 17 individual face-to-face sessions (monthly visits to practice nurse to review their progress (n = 12), at least three monthly visits to GP (n = 4), at least one home visit by the respiratory nurse specialist and one following hospital admissions) **Professional:** respiratory physician, respiratory nurse specialist, GP **Training of case managers:** not reported **Self-management components:** action plan COPD exacerbations, iterative process with feedback on actions, self-recognition of COPD exacerbations, other: annual influenza vaccination and attendance at a PR programme were recommended **Self-management topics:** smoking cessation, exercise, (maintenance) medication, correct device use **Exercise programme:** no **Smoking cessation programme:** no **Behavioural change techniques:** eight clusters: goals and planning, feedback and monitoring, shaping knowledge, natural consequences, comparison of behaviour, associations, regulation, antecedents **Action plan components:** self-recognition of exacerbations, self-treatment of exacerbations, contact healthcare providers for support	
Outcomes	1. quality of life (SF-36) 2. CRQ 3. distance walked (Shuttle Walk Test) 4. hospital admissions 5. spirometry (FEV_1 (L), FEV_1 % predicted) 6. medication use (courses of oral steroids and antibiotics)	
Notes	Randomisation is done at the level of GP practice; 26 practices were randomised to intervention and 25 were randomised to usual care. Analysis is performed at the level of participants	
Bias	**Authors's judgement**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	"Fifty-one eligible practices with 116 GPs were randomised, using a set of computer-generated random numbers (…)" p. 609 Comment: Random sequence generation was adequately performed.
Allocation concealment (selection bias)	High risk	Comment: The study was cluster-randomised. Therefore, there was no allocation concealment provided.
Blinding of participants and personnel (performance bias)	High risk	Comment: Blinding of participants and personnel was not reported.
Blinding of outcome assessment (detection bias)	Unclear risk	"For all patients, an initial assessment with the GP and practice nurse included clinical history and the Short Form (SF)-36. Spirometry, the Shuttle Walk Test and the Chronic Respiratory Questionnaire (CRQ) were administered at the hospital outpatient clinic by a respiratory physician, respiratory nurses and experienced interviewers, respectively. At the completion of a 12-month trial period, an identical reassessment was undertaken." p. 609 Comment: Blinding of outcome assessment was not reported, measurements were predominantly performed by study personnel at the outpatient clinic.

Incomplete outcome data (attrition bias)	Low risk	"During the trial period, six patients died, six patients withdrew from the study, four patients developed cancer and two patients moved from the area. The 12 month follow-up assessment was completed by 117 patients (71 INT, 46 CON), although hospital admission data were available for all 135 patients." p. 609 Comment: 12 participants dropped out in the intervention group (14%), six in the control group (12%). Reasons were comparable. Intention-to-treat analysis was performed on the primary outcome.
Selective reporting (reporting bias)	Unclear risk	Comment: No signs of selective reporting; however, no protocol available.
Other bias	Low risk	"GP practices were randomised rather than patients to try to avoid contamination of treatment groups within practices." p. 609 "The characteristics of non-participating and participating practices were similar, so a selection bias between INT and CON practices seems unlikely." p. 613 Comment: We additionally assessed this study on bias specifically important in cluster-randomised trials. In Rea's study, the general practises were randomly assigned before the participants were included. For reasons unknown, the number of participants screened and included was lower in the control group than in the intervention group. The study authors state that baseline characteristics were not significantly different between groups. Therefore, the risk of recruitment bias is unclear, and risk of bias for baseline imbalance is low. The risk of bias due to loss of clusters is low because no clusters were lost after participant enrolment. Rea et al. did not correct for clustering in their analyses, so risk of bias due to incorrect analysis is high.

Rice 2010

Methods	**Design:** RCT **Follow-up:** 12 months **Control group:** usual care
Participants	**Recruitment:** hospital (Veterans Affairs medical centers) **Assessed for eligibility:** 1739 **Randomly assigned:** I: 372; C: 371 **Completed:** I: 336; C: 323 **Mean age:** I: 69.1 ± 9.4 years; C: 70.7 ± 9.7 years **Gender (% male):** I: 97.6%; C: 98.4% **COPD diagnosis:** clinical diagnosis of COPD with post-bronchodilator spirometry showing an FEV_1 < 70% predicted and a FEV_1/FVC < 0.70 **Inclusion of participants in the acute phase:** not reported **Major inclusion criteria:** a diagnosis of COPD at high risk of hospitalisation as predicted by one or more of the following during the previous year: hospital admission or ED visit for COPD, chronic home oxygen use or course of systemic corticosteroids for COPD **Major exclusion criteria:** inability to have access to a home telephone line or sign a consent form, any condition that would preclude effective participation in the study or likely to reduce life expectancy to less than a year

Interventions	**Mode:** group sessions at an outpatient clinic, one-page handout summary and number for helpline, telephone calls **Duration:** one group session of 1-1.5 hours by a respiratory therapist case manager, 12 monthly phone calls of 10-15 minutes each **Professional:** respiratory therapist case manager **Training of case managers:** "case managers were respiratory therapists who had completed a one-day training session." Appendix 1, p. 2 **Self-management components:** action plan COPD exacerbations, iterative process with feedback on actions, self-recognition of COPD exacerbations; education regarding COPD, smoking cessation **Self-management topics:** smoking cessation, exercise, (maintenance) medication, correct device use, coping with breathlessness/breathing techniques, other: oximetry, recommendation concerning influenza and pneumococcal vaccinations, instruction in hand hygiene **Exercise programme:** no **Smoking cessation programme:** yes (optional), smoking cessation counseling **Behavioural change techniques:** 10 clusters: goals and planning, feedback and monitoring, social support, shaping knowledge, natural consequences; comparison of behaviour, associations, repetition and substitution, regulation, antecedents **Action plan components:** self-recognition of exacerbations, self-treatment of exacerbations, contact healthcare providers for support	
Outcomes	1. hospital admissions and ED visits for COPD 2. all-cause hospitalisations and all-cause ED visits 3. hospital and intensive care unit lengths of stay 4. respiratory medication use 5. change in respiratory quality of life (SGRQ) 6. all-cause mortality	
Notes	-	
Bias	**Authors's judgement**	**Support for judgment**
Random sequence generation (selection bias)	Unclear risk	"We assigned subjects in equal proportions to each of the two treatment arms by permuted-block randomisation." Appendix 1, p. 3 Comment: Information on the method of random sequence allocation was not reported.
Allocation concealment (selection bias)	Unclear risk	Comment: Information on the method of allocation concealment was not reported.
Blinding of participants and personnel (performance bias)	High risk	"We performed a randomised, adjudicator-blinded, controlled, 1-year trial (…)." p. 890 Comment: Blinding of participants and personnel was not reported.
Blinding of outcome assessment (detection bias)	Low risk	"Blinded pulmonologists independently reviewed all discharge summaries and ED reports and assigned a primary cause for each." p. 891 Comment: Outcome assessment was blinded.

Incomplete outcome data (attrition bias)	Unclear risk	"All patients were followed for 12 months or until the time of death if it occurred before 12 months." p. 981 "Fifty-five percent of patients in the usual care group and 60% of patients in the disease management group returned a completed the Saint George's Respiratory Questionnaire in response to a single mailing at the end of the study." p. 982 Comment: Low response rates on SGRQ leading to a high risk of bias. However, data on healthcare utilisation seem complete with no risk of bias.
Selective reporting (reporting bias)	Low risk	Comment: All primary and secondary outcome measures were reported; no signs of selective reporting.
Other bias	Low risk	-

Song 2014

Methods	**Design:** RCT **Follow-up:** 2 months **Control group:** usual care
Participants	**Recruitment:** hospital (inpatient) **Assessed for eligibility:** 62 **Randomly assigned:** I: 20; C: 20 **Completed:** I: 17, C: 17 **Mean age:** I: 66.6 ± 7.12 years; C: 68.1 ± 6.46 years **Gender (% male):** I: 55.0, C: 75.0 **COPD diagnosis:** a diagnosis of moderate COPD, based on the GOLD staging system **Inclusion of patients in the acute phase:** yes, during hospitalisation **Major inclusion criteria:** diagnosis of moderate COPD, based on the GOLD staging system, confirmed discharge date at the discretion of the responsible medical doctors, age 65-75 years, independent mobility **Major exclusion criteria:** history of other lung diseases, any concomitant diseases that could interfere with the general condition, neuromuscular impairment that would interfere with the patient's mobility

Interventions	**Mode:** individual sessions at the hospital and at the outpatient clinic, telephone calls, written instruction **Duration:** three face-to-face individual sessions (two inpatient sessions for 90+45 minutes each on the day before discharge and on the day of discharge, one outpatient session for 90 minutes on the first follow-up day which is usually planned one week after discharge) by two nurse interventionists, booster sessions were delivered through two phone calls with a two-week interval **Professional:** nurse interventionists **Training of case managers:** "**i**ntervention sessions were delivered by two nurse interventionists selected on the basis of their previous experience in COPD care. They also received 6 hours of training sessions to ensure their consistency." p. 152 **Self-management components:** action plan COPD exacerbations, iterative process with feedback on actions, self-recognition of COPD exacerbations, education regarding COPD, exercise or physical activity component **Self-management topics:** exercise, (maintenance) medication, coping with breathlessness/breathing techniques, other: identifying barriers to self-care adherence **Exercise programme:** yes, each face-to-face session consisted of the education accompanied by practicing exercise. Participants learned 10 sets of upper and lower extremities stretching with pursed lip breathing. They also performed a 10-minute-per-toleration walk on a course 30-m corridor in the unit. The written instruction, plus illustrations, was given to the participants as a reminder for instructional support and practice at home. At the end of the outpatient session, participants were reminded and advised to continue and expand the exercises according to their own goals at home over a period of 2 months. **Smoking cessation programme:** no **Behavioural change techniques:** nine clusters: goals and planning, feedback and monitoring, social support, shaping knowledge, associations, repetition and substitution, regulation, identity, self-belief **Action plan components:** self-recognition of exacerbations, self-treatment of exacerbations	
Outcomes	1. exercise capacity (PEFR and 6MWD) 2. health-related quality of life (SGRQ) 3. self-care adherence (medication and exercise compliance)	
Notes	Randomisation after matching for lung function, age and gender. Not all participants fulfilled the inclusion criterion 'a diagnosis of moderate COPD, based on the GOLD staging systems', because the mean FEV1/FVC % predicted was > 0.70	
Bias	**Authors's judgement**	**Support for judgment**
Random sequence generation (selection bias)	Unclear risk	"After being matched for lung function, age, and gender, participants were randomly allocated to either an experimental or a control group." p. 149 Comment: There is no method described that was used to generate the allocation sequence.
Allocation concealment (selection bias)	Unclear risk	"After being matched for lung function, age, and gender, participants were randomly allocated to either an experimental or a control group." p. 149 Comment: There is no method described that was used to conceal the allocation.
Blinding of participants and personnel (performance bias)	High risk	"This single-blinded, randomised control group, pre-/posttest study (…)" p. 148 Comment: No blinding of participants and personnel.

Blinding of outcome assessment (detection bias)	Unclear risk	Comment: Most of the outcome measures were self-reported. There is insufficient information to permit judgement.
Incomplete outcome data (attrition bias)	Low risk	"There were no significant differences in the aforementioned baseline characteristics between the final sample and those who withdrew." p. 149 Comment: Whereas Table 3 states that data of 20 patients have been analysed, this cannot be the case, because t-tests have been used and not all patients had complete data (15% non-complete data in each group).
Selective reporting (reporting bias)	Unclear risk	Comment: No signs for selective outcome reporting, results were reported extensively; however, no protocol available.
Other bias	Low risk	-

Tabak 2014

Methods	**Design:** RCT **Follow-up:** 9 months **Control group:** usual care
Participants	**Recruitment:** hospital, primary care physiotherapy practices **Assessed for eligibility:** not reported (101 patients eligible) **Randomly assigned:** I: 15; C: 14 **Completed:** I: 10; C: 2 **Mean age:** I: 64.1 ± 9.0 years; C: 62.8 ± 7.4 years **Gender (% male):** I: 50.0; C: 50.0 **COPD diagnosis:** GOLD II-IV, a clinical diagnosis of COPD according to the GOLD criteria **Inclusion of participants in the acute phase:** no **Major inclusion criteria:** fulfil COPE-II study (effects of self-treatment and an exercise programme within a self-management programme in outpatients with COPD) criteria: no exacerbation in the month prior to enrolment, three or more exacerbations or one hospitalisation for respiratory problems in the 2 years preceding study entry, a computer with Internet access at home **Major exclusion criteria:** serious other disease with a low survival rate, other diseases influencing bronchial symptoms and/or lung function, severe psychiatric illness, uncontrolled diabetes mellitus or a hospitalisation for diabetes mellitus in the 2 years preceding the study, need for regular oxygen therapy, maintenance therapy with antibiotics, known a1- antitrypsin deficiency, disorders or progressive disease seriously influencing walking ability

Interventions	**Mode:** individual and group sessions at the outpatient clinic, primary care physiotherapy practices and at the participant's home, web-based teleconsultation module **Duration:** at least one face-to-face individual session by the primary care physiotherapist (no protocol for education, offered as blended care, depending on physiotherapist and patient) and a teleconsultation module. For research purposes there was one intake by a physiotherapist for baseline measure activity coach and explanations. Furthermore, there were additional meetings after one, three, six and nine months. Before the start of the programme, participants had to attend two group sessions of 90 minutes each by a nurse practitioner **Professional:** respiratory nurse practitioner, respiratory physiotherapist **Training of case managers:** not reported **Self-management components:** action plan COPD exacerbations, iterative process with feedback on actions, self-recognition of COPD exacerbations, education regarding COPD, exercise or physical activity component **Self-management topics:** smoking cessation, exercise, diet, (maintenance) medication, coping with breathlessness/breathing techniques **Exercise programme:** yes, a web-based exercise program on the web portal. For every individual patient, exercise schemes were created by the patient's physiotherapist via the web portal. A scheme represents which exercises should be performed by the patient for which day, and which part of the day. Every exercise consists of a text description and movie. The patient is able to log in at home, follow the exercise scheme, execute the exercises, and provide feedback to the physiotherapist. There was no standardized exercise protocol: the physiotherapist could freely select the exercises for each patient for the online exercise program. This exercise program could be adapted during the intervention period following the progress of the patient at the discretion of the therapist. Both primary and secondary care professionals could supervise the patient at a distance by checking progress on the web portal. **Smoking cessation programme:** no **Behavioural change techniques:** 11 clusters: goals and planning, feedback and monitoring, social support, shaping knowledge, natural consequences, comparison of behaviour, associations, repetition and substitution, regulation, antecedents, self-belief **Action plan components:** self-recognition of exacerbations, self-treatment of exacerbations, contact healthcare providers for support	
Outcomes	1. use of application 2. adherence (online diary, exercise scheme) 3. satisfaction (Client Satisfaction Questionnaire) 4. hospitalisations (number and length of stay) 5. emergency department visits 6. exacerbations 7. level of activity (activity coach, accelerometer) 8. self-perceived activity levels (Baecke Phsycial Activity Questionnaire) 9. exercise tolerance (6MWT) 10. fatigue (Multidimensional Fatigue Inventory 20) 11. health status (CCQ) 12. dyspnoea (MRC) 13. quality of life (EuroQol-5D)	
Notes	-	
Bias	**Authors's judgement**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	"Patients were randomised using a computer-generated randomisation list (Blocked Stratified Randomisation version 5; Steven Piantadosi), where randomisation was applied in blocks of two and four." p. 936 Comment: Random sequence generation was adequately performed.

Allocation concealment (selection bias)	Low risk	"Participants were allocated by a data manager in order of inclusion following the randomisation list, placed in a sealed envelope." p. 936 Comment: The allocation was adequately concealed.
Blinding of participants and personnel (performance bias)	High risk	Comment: Participants and personnel were not blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	"The decision-support diary automatically identified exacerbations following previously described criteria for the intervention group, while the control group filled in a paper version of the diary" p. 938 Comment: Unclear whether outcome assessors were blinded. Questionnaires used are validated questionnaires.
Incomplete outcome data (attrition bias)	High risk	"A large number of patients were not able or willing to continue study participation: 33% in the intervention group and 86% in the control group." p. 939 Comment: Most outcome measures are reported for 3 months follow-up, whereas there was a total of 9 months follow-up. There was a high number of withdrawals for the 9 months follow-up (more dropouts in the control group).
Selective reporting (reporting bias)	High risk	Comment: Not all outcome measures were reported for the 9 month follow-up. Exacerbations (duration) was not reported. Also, no information or results provided for the use of diaries in the control group.
Other bias	Unclear risk	Comment: Per protocol analysis, baseline characteristics only assessed for the patients who completed the study. No differences reported for baseline characteristics between the withdrawals after randomisation (n = 6) and the patients who completed the questionnaires at T0 (inclusion).

Titova 2015

Methods	**Design:** RCT **Follow-up:** 24 months **Control group:** usual care
Participants	**Recruitment:** hospital (inpatient) **Assessed for eligibility:** 199 **Randomly assigned:** I: 91; C: 81 **Completed:** I: 51; C: 49 **Mean age:** I: 74.1 ± 9.26 years; C: 72.6 ± 9.33 years **Gender (% male):** I: 42.9; C: 43.2 **COPD diagnosis:** GOLD stage III or IV **Inclusion of participants in the acute phase:** yes, during hospitalisation **Major inclusion criteria:** admission due to AECOPD, COPD (GOLD stage III or IV, 2007), living in the Trondheim municipality, ability to communicate in Norwegian, ability to sign the informed consent form **Major exclusion criteria:** any serious diseases that might cause a very short lifespan (expected survival time less than six months)

Interventions	**Mode:** individual sessions at the participant's home, telephone calls, e-learning programme, "My COPD book" **Duration:** six face-to-face individual sessions (one at discharge, five joint visits at home at approximately three days, 14 days, six months, 12 months, and 24 months post-discharge) by the specialist nurse, one interactive 15-minute e-learning programme, at least 24 telephone calls (routinely phone calls at least once a month and during COPD exacerbations) **Professional:** specialist nurse **Training of case managers:** "an education session for home-care nurses: a three-hour theoretical session covering several aspects of COPD and two days of practice at the DTM (Department of Thoracic Medicine)" p. 3 **Self-management components:** action plan COPD exacerbations, iterative process with feedback on actions, self-recognition of COPD exacerbations, education regarding COPD **Self-management topics:** smoking cessation, exercise, diet, (maintenance) medication, correct device use, coping with breathlessness/breathing techniques **Exercise programme:** no **Smoking cessation programme:** no **Behavioural change techniques:** eight clusters: goals and planning, feedback and monitoring, social support, shaping knowledge, associations, repetition and substitution, regulation, antecedents **Action plan components:** self-recognition of exacerbations, self-treatment of exacerbations, avoid situations in which viral infection might be prevalent, contact healthcare providers for support	
Outcomes	1. hospital utilisation (admissions caused by AECOPD, in-hospital days due to AECOPD) 2. mortality 3. inhaled medication use (LAMA, LABA)	
Notes	-	
Bias	**Authors's judgement**	**Support for judgment**
Random sequence generation (selection bias)	Unclear risk	"They were randomly allocated to either integrated care (IC) or usual care (UC) based on their address of permanent residence. In order to create two pairs of districts with approximately equal numbers of citizens, a pair-wise matching of districts was carried out. It was decided by lottery that participants from District Pair 1 were assigned to the UC group, and participants from District Pair 2 were assigned to the IC group." p. 2 Comment: It was unclear whether random sequence allocation was performed on patient or health center level.
Allocation concealment (selection bias)	Unclear risk	Comment: No information provided about the allocation concealment
Blinding of participants and personnel (performance bias)	High risk	"The study was a prospective, open, single-centre intervention study." p. 2 Comment: No blinding of participants and personnel.
Blinding of outcome assessment (detection bias)	Unclear risk	"Data concerning HA (hospital admissions) and HD (hospital days) were collected from the hospital registry database's medical charts." p. 3 Comment: Unclear who was the outcome assessor.

Incomplete outcome data (attrition bias)	High risk	"Data from patients who completed a minimum of two years of follow-up were included in the analysis." p. 3 Comment: A lot of missing data; after two years of follow-up 58% of the included patients were available for evaluation.
Selective reporting (reporting bias)	High risk	"Information concerning the number and duration of the COPD exacerbations, as well as the time from onset of symptoms until the start of self-initiated treatment is insufficient due to many incomplete registrations in "My COPD book" p. 9 Comment: No mortality reported; however, Figure 1 shows higher mortality for the IC group, n = 35 (38.4%), compared to the UC group, n = 21 (25.9%)
Other bias	Low risk	-

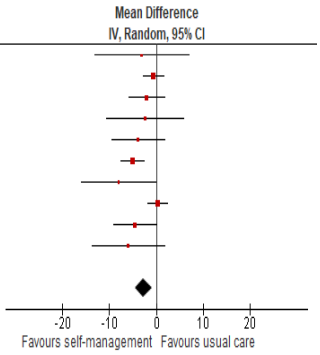
6MWD: 6 Minute Walking Distance; 6MWT: 6 Minute Walking Test; CCQ: Clinical COPD Questionnaire; COPD: Chronic Obstructive Pulmonary Disease; CRQ: Chronic Respiratory Questionnaire; CSES: COPD Self-Efficacy Scale; ED: emergency department; ESWT: endurance shuttle walk test; EQ-5D: EuroQol-5Dimensions; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; GP: general practitioner; HADS: Hospital Anxiety and Depression Scale; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; ISWT: incremental shuttle walk test; LABA: long-acting beta agonists; LAMA: long-acting muscarinic antagonists; (m)MRC: (modified) Medical Research Council dyspnoea score; PEFR: peak expiratory flow rate; RCT: Randomised Controlled Trial; SF-36: 36-item Short Form quality of life; SGRQ: St. Georg 's R spiratory Questionnaire; QALY: Quality-Adjusted Life Year.

DATA AND ANALYSES

Self-management versus usual care

Study or Subgroup	Mean Difference	SE	Self-management Total	Usual care Total	Weight	Mean Difference IV, Random, 95% CI	Year
Gallefoss 1999 (1)	-3.1	5.1166	26	27	2.9%	-3.10 [-13.13, 6.93]	1999
Monninkhof 2003 (2)	-0.6	1.1225	122	113	18.9%	-0.60 [-2.80, 1.60]	2003
Bourbeau 2003 (3)	-2	1.9898	81	76	11.8%	-2.00 [-5.90, 1.90]	2003
Garcia-Aymerich 2007 (4)	-2.39	4.1684	21	41	4.1%	-2.39 [-10.56, 5.78]	2007
Khdour 2009 (5)	-3.8	2.9082	71	72	7.2%	-3.80 [-9.50, 1.90]	2009
Rice 2010 (6)	-5.1	1.2755	237	212	17.5%	-5.10 [-7.60, -2.60]	2010
Ninot 2011 (7)	-8	4.0817	20	18	4.2%	-8.00 [-16.00, -0.00]	2011
Fan 2012 (8)	0.31	1.0998	101	108	19.1%	0.31 [-1.85, 2.47]	2012
Bucknall 2012 (9)	-4.52	2.3215	69	53	9.8%	-4.52 [-9.07, 0.03]	2012
Hernández 2015 (10)	-6	3.9471	59	55	4.5%	-6.00 [-13.74, 1.74]	2015
Total (95% CI)			807	775	100.0%	**-2.69 [-4.49, -0.90]**	

Heterogeneity: Tau² = 3.18; Chi² = 16.66, df = 9 (P = 0.05); I² = 46%
Test for overall effect: Z = 2.94 (P = 0.003)

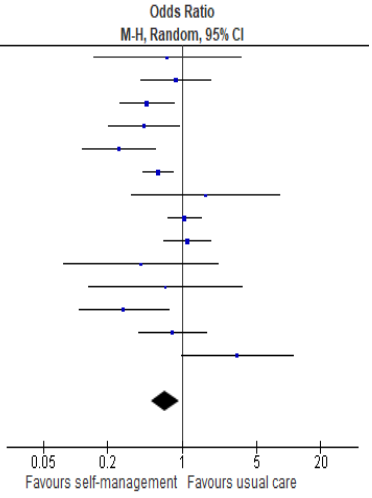


Footnotes
(1) Based on final SGRQ scores
(2) Based on change from baseline scores
(3) Based on change from baseline scores
(4) Based on change from baseline scores
(5) Based on unit differences
(6) Based on change from baseline scores
(7) Adjusted for the baseline value of the SGRQ total score
(8) Based on change from baseline scores
(9) Adjusted for the baseline scores and stratification variables
(10) Based on final SGRQ scores

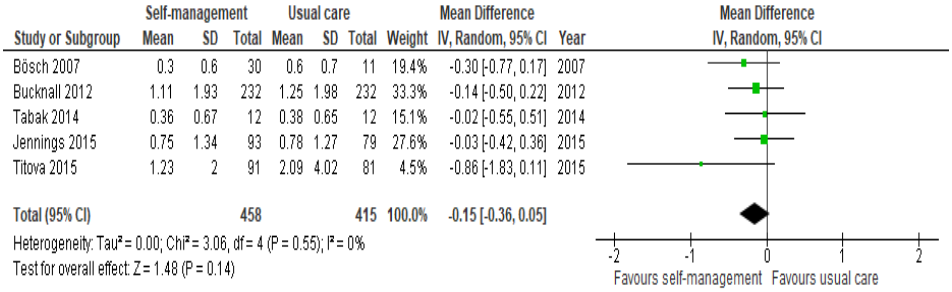
Analysis 1.1. HRQoL: adjusted SGRQ total score after 12 months of follow-up

Study or Subgroup	Self-management Events	Total	Usual care Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Gallefoss 1999	3	31	4	31	3.0%	0.72 [0.15, 3.54]	1999
Monninkhof 2003	15	127	16	121	8.0%	0.88 [0.41, 1.87]	2003
Bourbeau 2003	31	96	48	95	9.8%	0.47 [0.26, 0.84]	2003
Rea 2004	18	83	20	52	7.9%	0.44 [0.21, 0.95]	2004
Khdour 2009	11	71	30	72	7.5%	0.26 [0.12, 0.57]	2009
Rice 2010	79	372	116	371	13.1%	0.59 [0.43, 0.83]	2010
Ninot 2011	5	20	3	18	2.9%	1.67 [0.34, 8.26]	2011
Bucknall 2012	111	232	108	232	12.7%	1.05 [0.73, 1.52]	2012
Fan 2012	36	209	34	217	10.8%	1.12 [0.67, 1.87]	2012
Mitchell 2014	2	89	5	95	2.8%	0.41 [0.08, 2.19]	2014
Tabak 2014	4	12	5	12	2.8%	0.70 [0.13, 3.68]	2014
Titova 2015	71	91	75	81	6.1%	0.28 [0.11, 0.75]	2015
Jennings 2015	18	93	18	79	8.2%	0.81 [0.39, 1.70]	2015
Hernández 2015	10	71	4	84	4.5%	3.28 [0.98, 10.96]	2015
Total (95% CI)		**1597**		**1560**	**100.0%**	**0.69 [0.51, 0.94]**	
Total events	414		486				

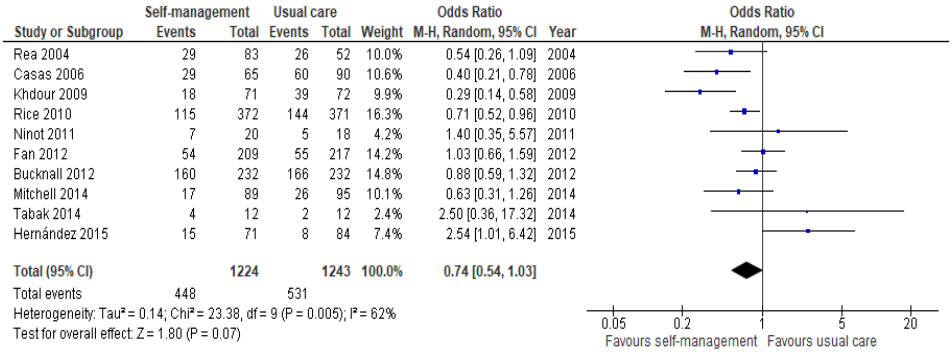
Heterogeneity: Tau² = 0.16; Chi² = 29.92, df = 13 (P = 0.005); I² = 57%
Test for overall effect: Z = 2.38 (P = 0.02)



Analysis 1.2. Healthcare utilisation: respiratory-related hospital admissions (number of patients with at least one admission)

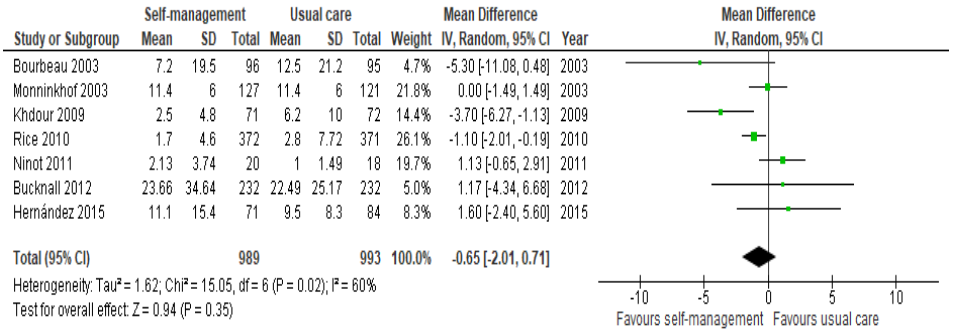


Analysis 1.3. Healthcare utilisation: respiratory-related hospital admissions (mean number per patient)

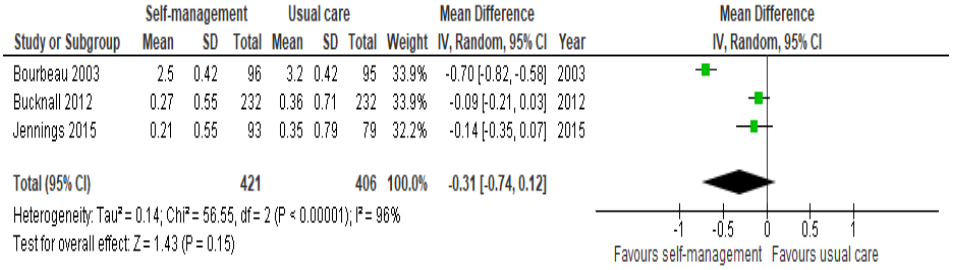


Analysis 1.4. Healthcare utilisation: all-cause hospital admissions (number of patients with at least one admission)

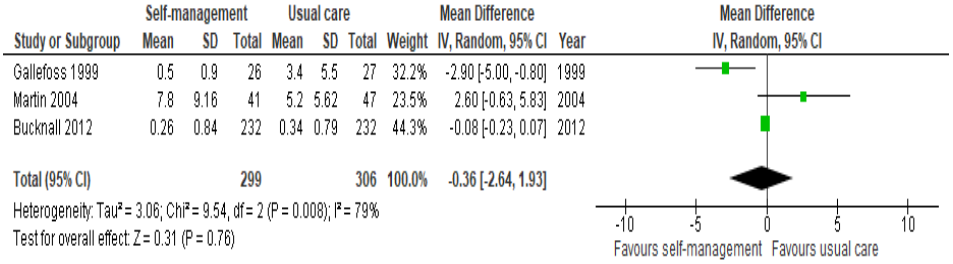
Analysis 1.5. Healthcare utilisation: all-cause hospital admissions (mean number per patient)



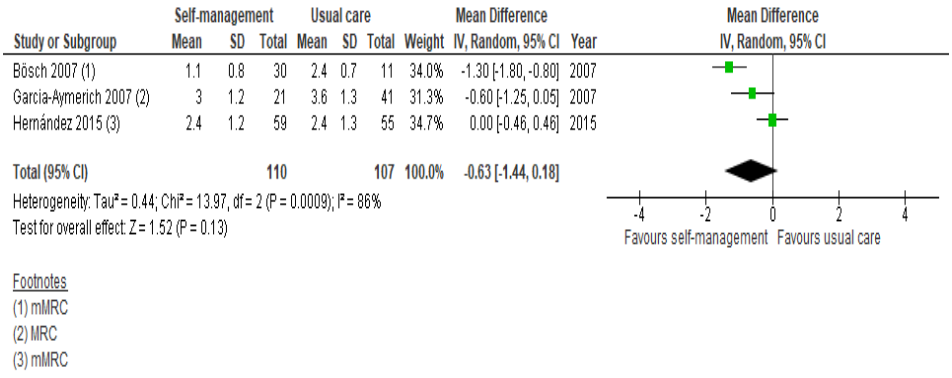
Analysis 1.6. Healthcare utilisation: all-cause hospitalisation days (per patient)



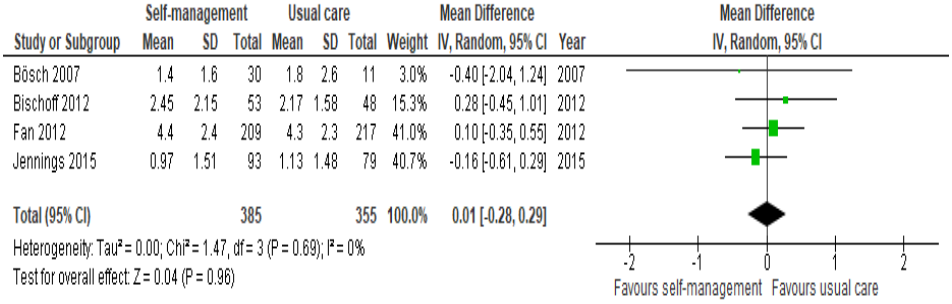
Analysis 1.7. Healthcare utilisation: emergency department visits (mean number per patient)



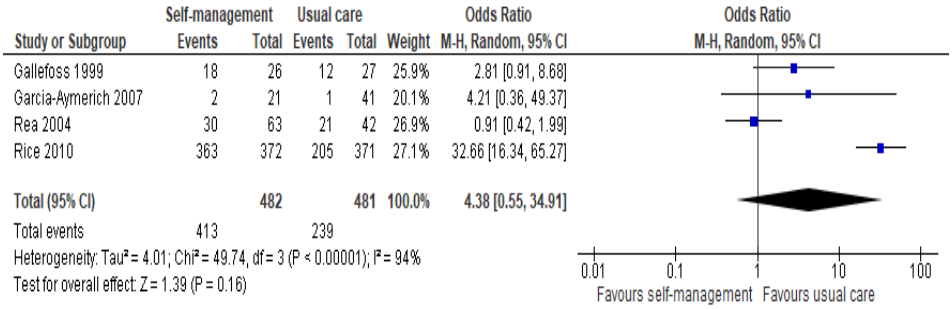
Analysis 1.8. Healthcare utilisation: GP visits (mean number per patient)



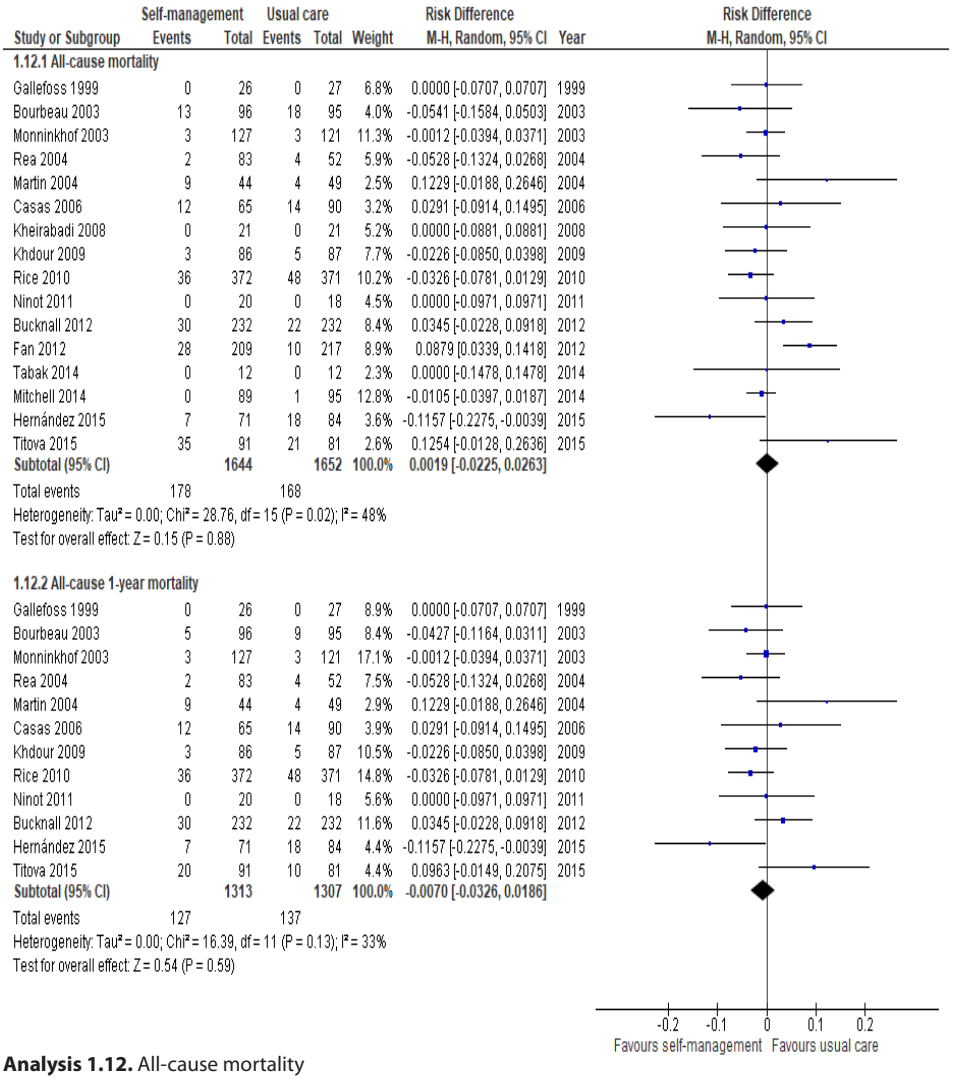
Analysis 1.9. Health status: (modified) Medical Research Council Dyspnoea Scale ((m)MRC))



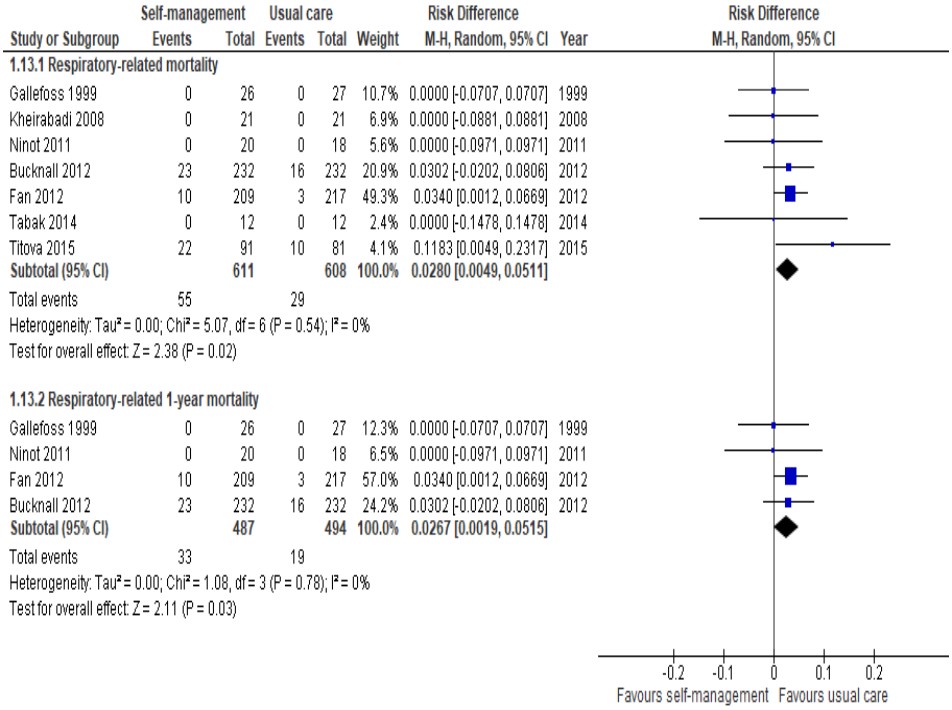
Analysis 1.10. COPD exacerbations (mean number per patient)



Analysis 1.11. Courses of oral steroids (number of patients used at least one course)

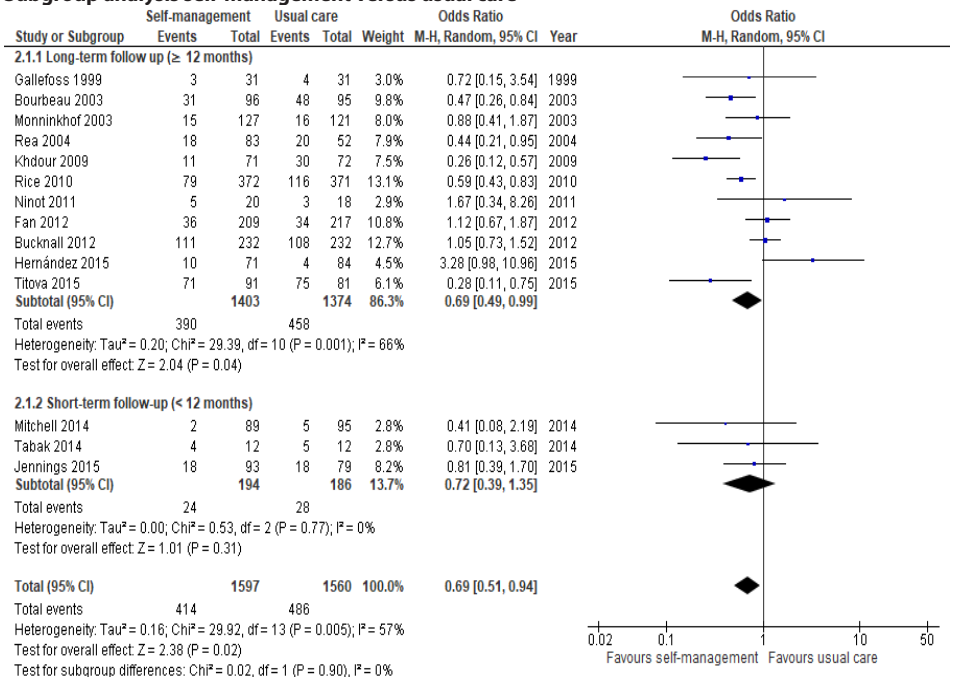


Analysis 1.12. All-cause mortality

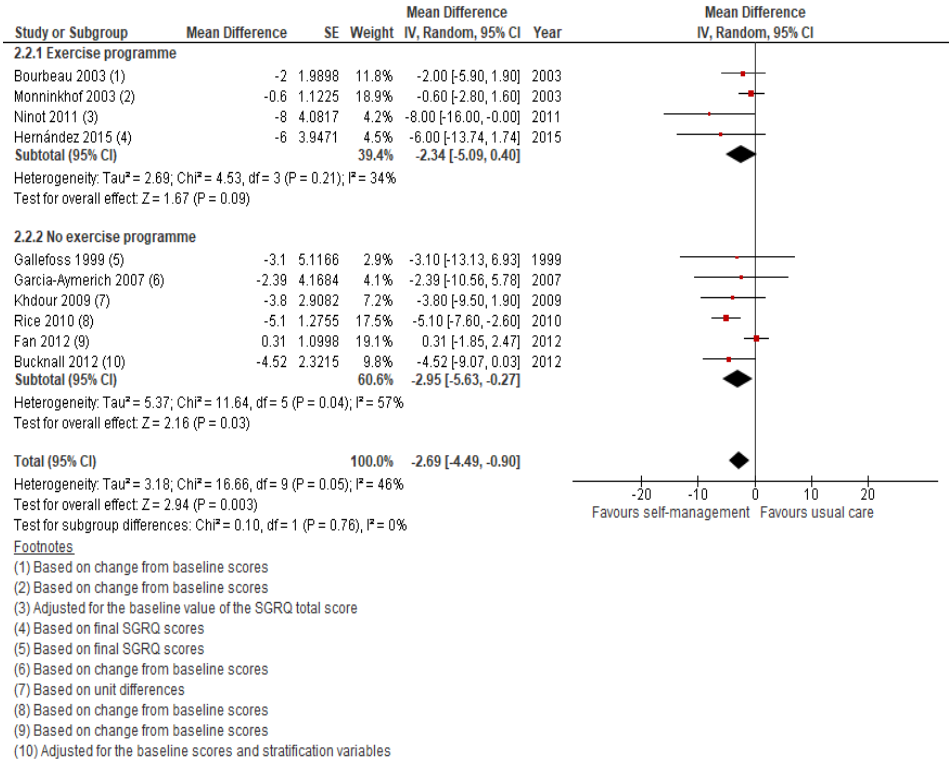


Analysis 1.13. Respiratory-related mortality

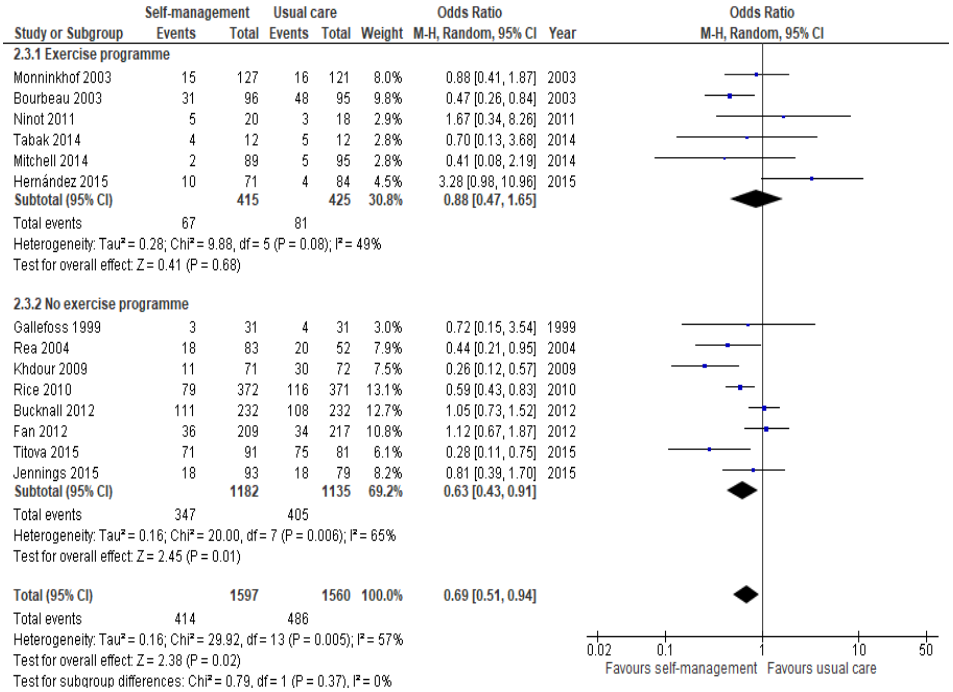
Subgroup analysis self-management versus usual care



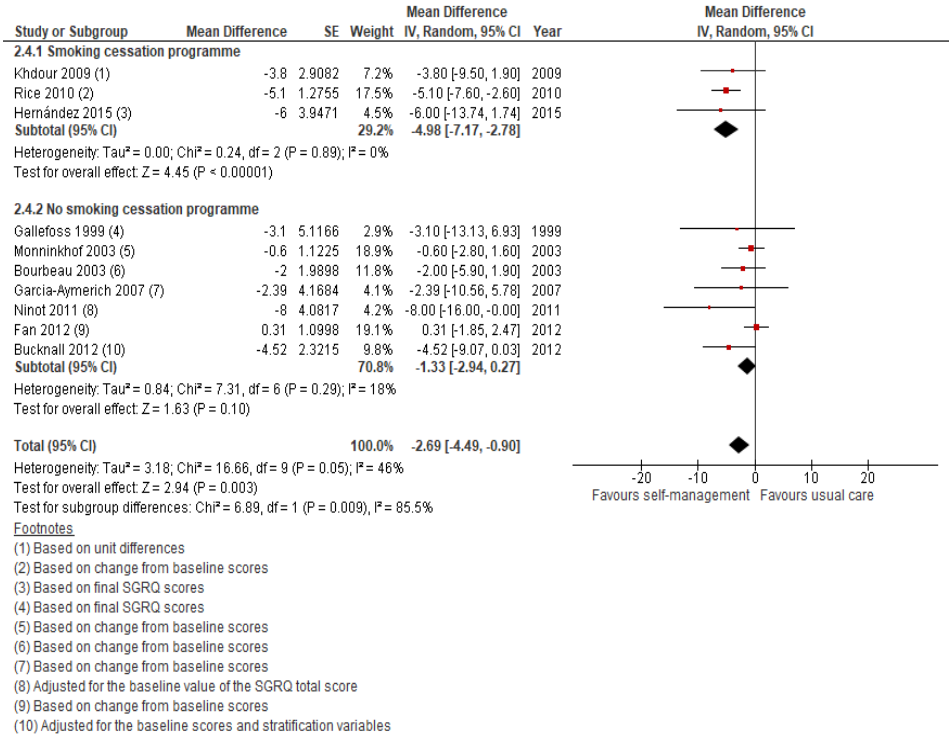
Analysis 2.1. Healthcare utilisation: respiratory-related hospital admissions (subgroup by follow-up duration



Analysis 2.2. HRQoL: adjusted SGRQ total score (subgroup by exercise programme)



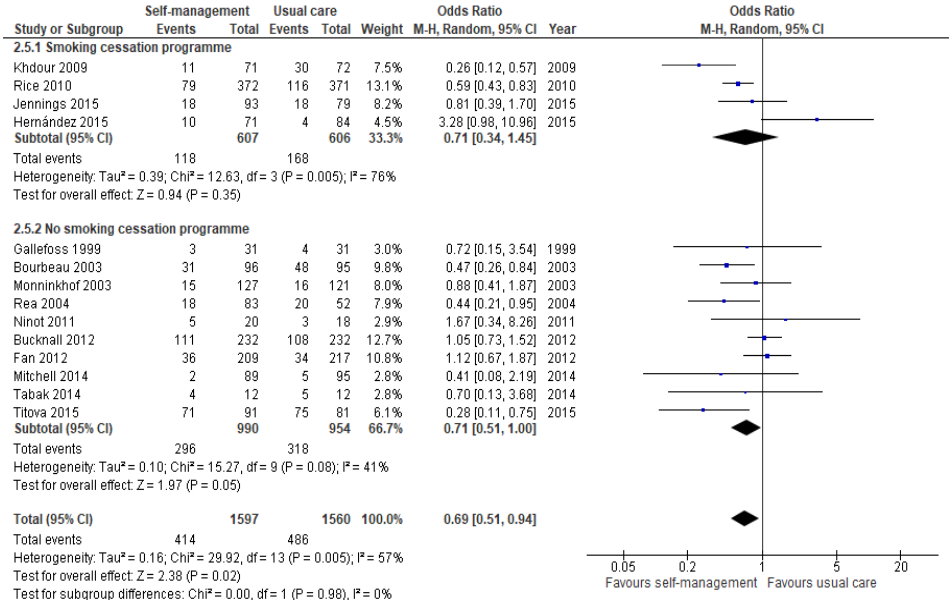
Analysis 2.3. Healthcare utilisation: respiratory-related hospital admissions (subgroup by exercise programme)



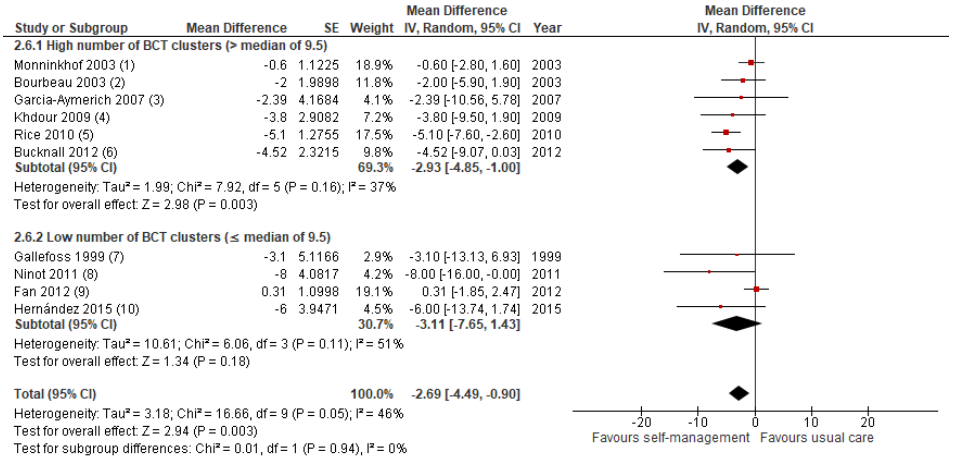
Footnotes

(1) Based on unit differences
(2) Based on change from baseline scores
(3) Based on final SGRQ scores
(4) Based on final SGRQ scores
(5) Based on change from baseline scores
(6) Based on change from baseline scores
(7) Based on change from baseline scores
(8) Adjusted for the baseline value of the SGRQ total score
(9) Based on change from baseline scores
(10) Adjusted for the baseline scores and stratification variables

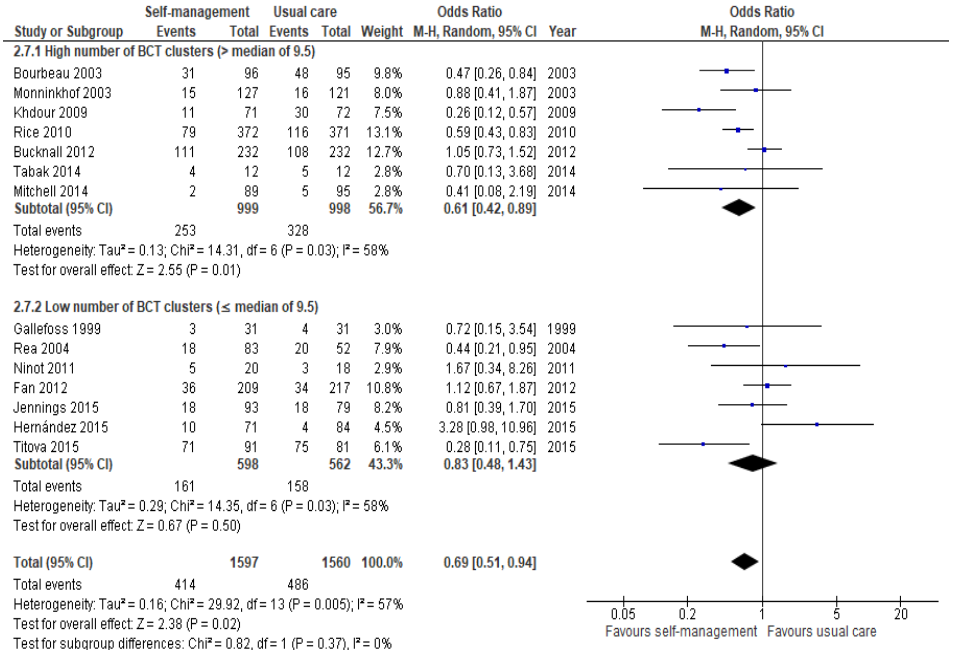
Analysis 2.4. HRQoL: adjusted SGRQ total score (subgroup by smoking cessation programme)



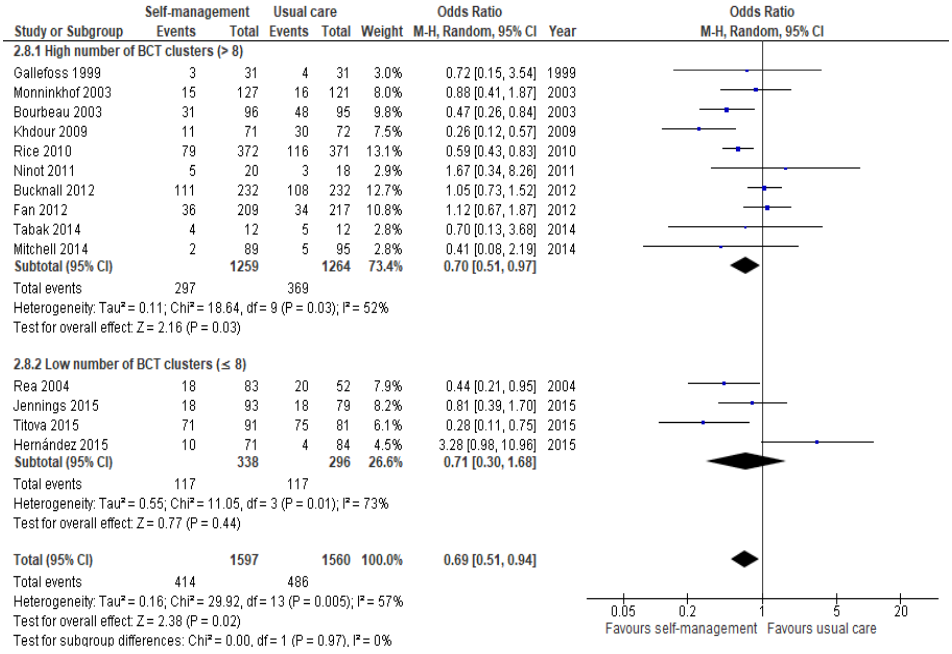
Analysis 2.5. Healthcare utilisation: respiratory-related hospital admissions (subgroup by smoking cessation programme)



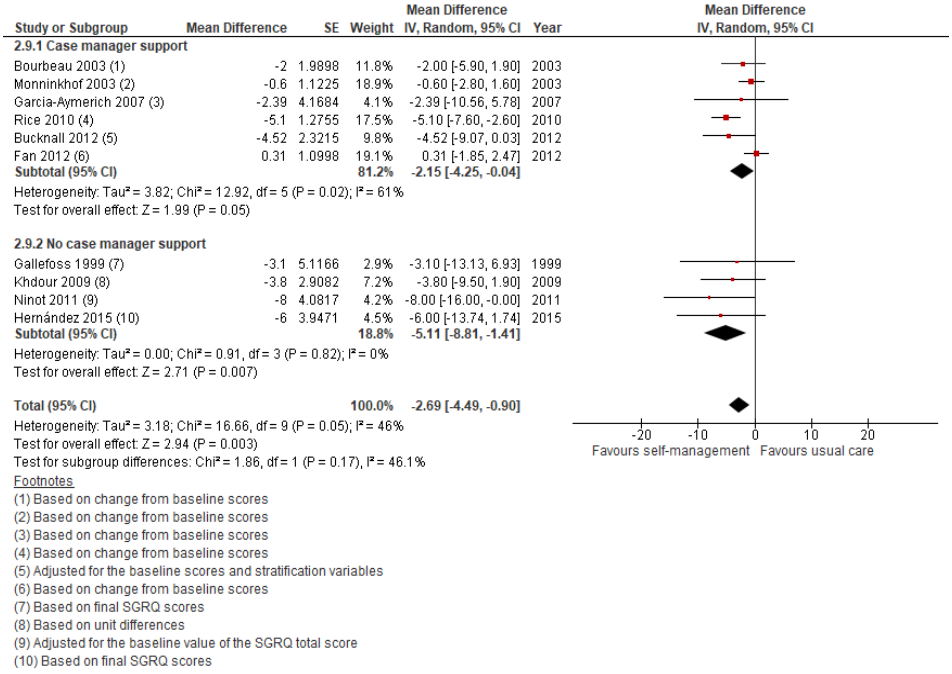
Analysis 2.6. HRQoL: adjusted SGRQ total score (subgroup by median number of BCT clusters)



Analysis 2.7. Healthcare utilisation: respiratory-related hospital admissions (subgroup by median number of BCT clusters)

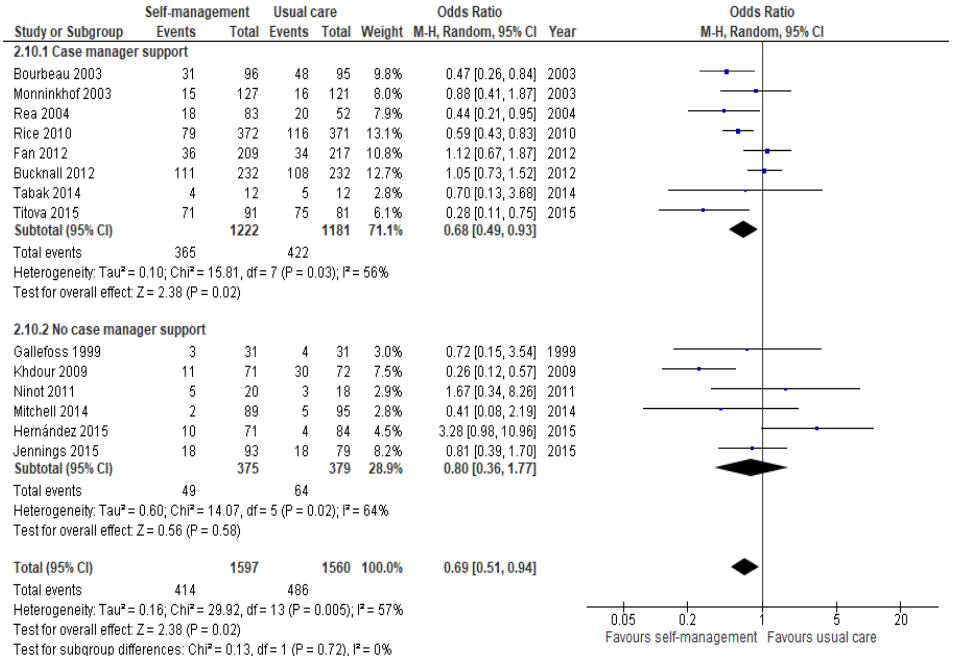


Analysis 2.8. Healthcare utilisation: respiratory-related hospital admissions (subgroup by number of BCT clusters)

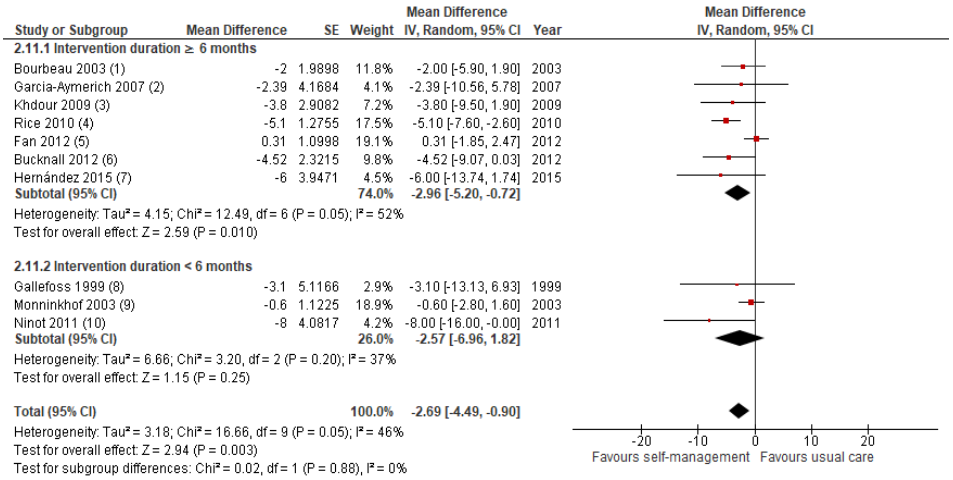


Footnotes
(1) Based on change from baseline scores
(2) Based on change from baseline scores
(3) Based on change from baseline scores
(4) Based on change from baseline scores
(5) Adjusted for the baseline scores and stratification variables
(6) Based on change from baseline scores
(7) Based on final SGRQ scores
(8) Based on unit differences
(9) Adjusted for the baseline value of the SGRQ total score
(10) Based on final SGRQ scores

Analysis 2.9. HRQoL: adjusted SGRQ total score (subgroup by case manager support)

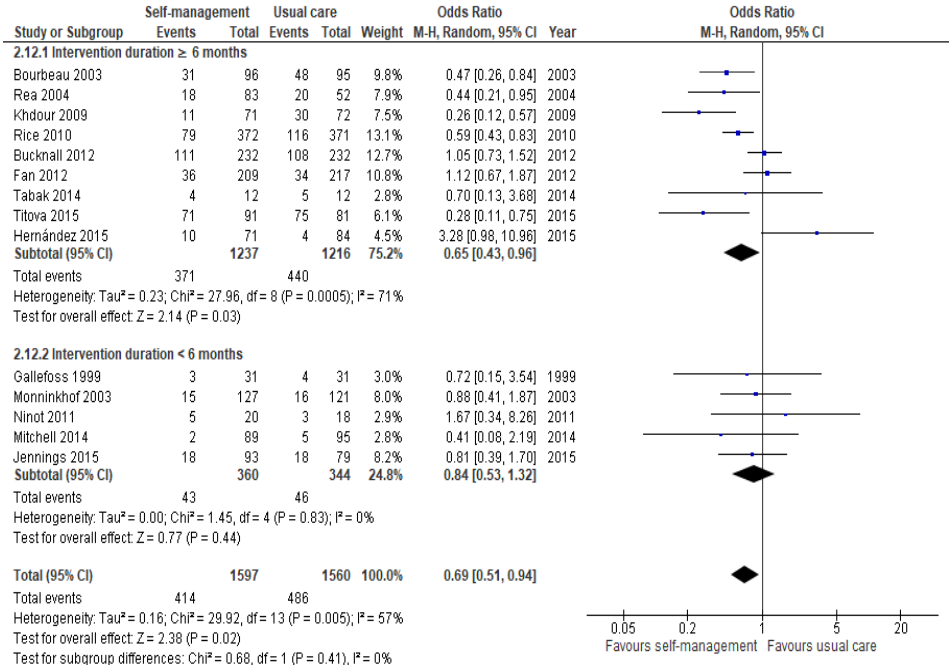


Analysis 2.10. Healthcare utilisation: respiratory-related hospital admissions (subgroup by case manager support)

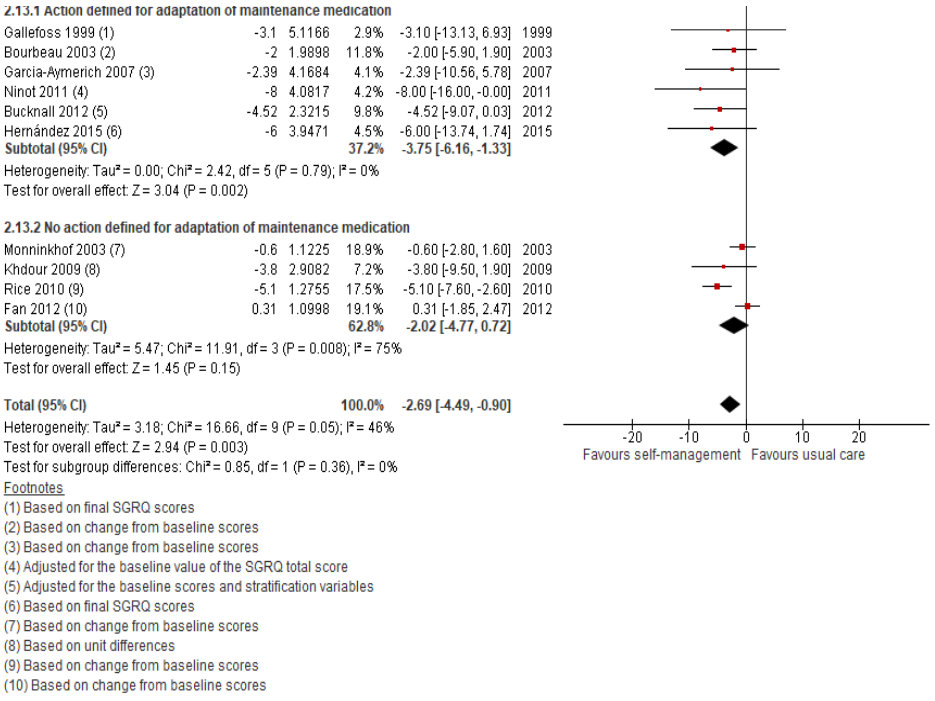


Footnotes
(1) Based on change from baseline scores
(2) Based on change from baseline scores
(3) Based on unit differences
(4) Based on change from baseline scores
(5) Based on change from baseline scores
(6) Adjusted for the baseline scores and stratification variables
(7) Based on final SGRQ scores
(8) Based on final SGRQ scores
(9) Based on change from baseline scores
(10) Adjusted for the baseline value of the SGRQ total score

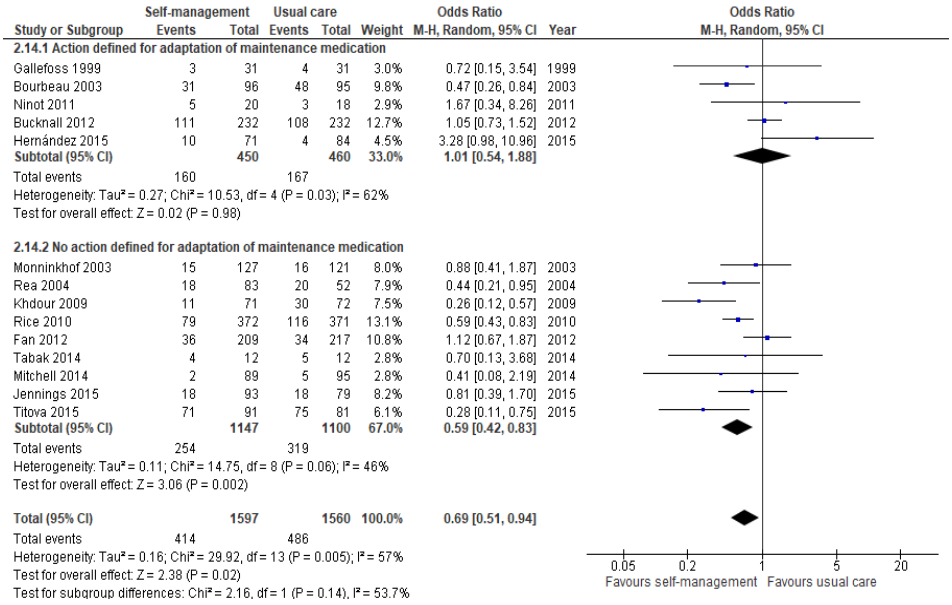
Analysis 2.11. HRQoL: adjusted SGRQ total score (subgroup by intervention duration)



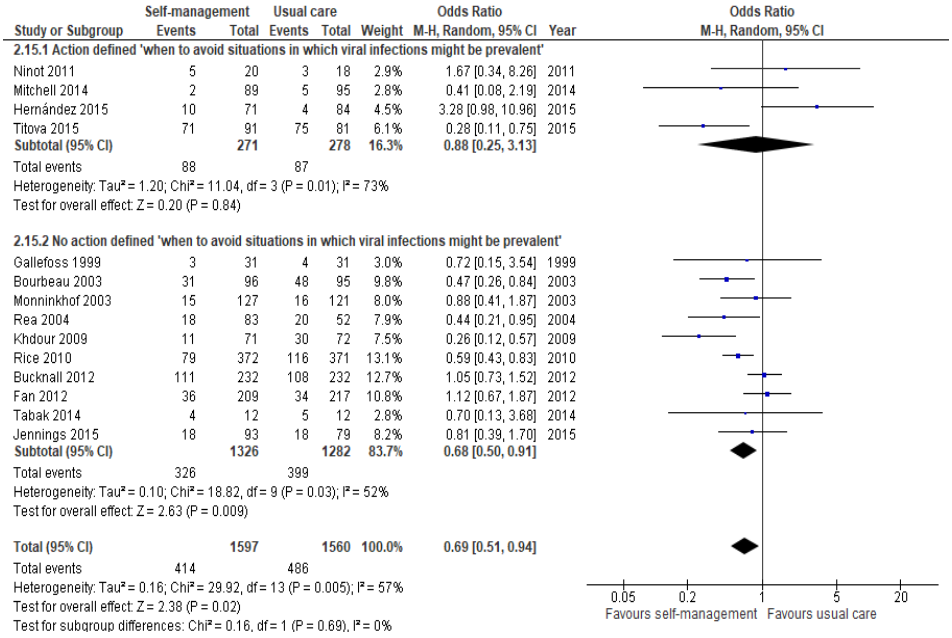
Analysis 2.12. Healthcare utilisation: respiratory-related hospital admissions (subgroup by intervention duration)



Analysis 2.13. HRQoL: adjusted SGRQ total score (subgroup by action plan component 'adaptation of maintenance medication')



Analysis 2.14. Healthcare utilisation: respiratory-related hospital admissions (subgroup by action plan component 'adaptation of maintenance medication')



Analysis 2.15. Healthcare utilisation: respiratory-related hospital admissions (subgroup by action plan component 'when to avoid situations in which viral infections might be prevalent')

ADDITIONAL TABLES

Table 2.1. Characteristics of patients in included studies

Study	Included participants (n)		Lost to follow-up (%)		Age (years; mean (SD))		Gender (% male)		FEV_1 (% predicted unless stated otherwise (SD))	
	Self-management	Usual care	Self-management	Usual care	Self-management	Usual care	Self-management	Usual care	Self-management	Usual care
Bischoff 2012	55	55	10.9	20.0	65.5 (11.5)	63.5 (10.3)	67.0	51.0	66.3 (16.5)	67.0 (18.0)
Bösch 2007	38	12	21.1	8.3	63.8 (8.4)	64.6 (6.8)	63.0% of completers		45.9 (17.5)	47.8 (16.9)
Bourbeau 2003	96	95	10.4	16.8	69.4 (6.5)	69.6 (7.4)	52.0	59.0	1.0 L (0.33)	0.98 (0.31)
Bucknall 2012	232	232	9.1	13.8	70.0 (9.3)	68.3 (9.2)	38.0	35.0	41.2 (13.4)	39.8 (13.8)
Casas 2006	65	90	26.2	20.0	70 (9.0)	72 (9.0)	77.0	88.0	43 (20)	41 (15)
Garcia-Aymerich 2007	44	69	52.3	40.6	72 (10.0)	73 (9.0)	75.0	93.0	1.2 L (IQR 0.8-1.4)	1.0 L (IQR 0.8-1.5)
Fan 2012	209	217	3.8[a]; 51.7[b]	4.6[a]; 50.2[b]	66.2 (8.4)	65.8 (8.2)	97.6	96.3	38.2 (14.3)	37.8 (14.5)
Gallefoss 1999	31	31	16.0	13.0	57 (9.0)	58 (10.0)	48.0	52.0	59 (9)	56 (11)
Hernández 2015	71	84	23.9	34.5	73 (8.0)	75 (9.0)	83.0	86.0	41 (19)	44 (20)
Jennings 2015	93	79	0	0	64.9 (10.9)	64.4 (10.5)	43.1	46.8	44.1 (23.1)	48.3 (22.2)
Khdour 2009	86	87	17.4	17.2	65.6 (10.1)	67.3 (9.2)	44.2	43.7	52.0 (15.9)	52 (17.8)

Table 2.1. Continued

Kheirabadi 2008	21	21	0	0	56.6 (5.7)	56.2 (4.1)	61.9	76.2	N/A	N/A
Martin 2004	44	49	20.5	8.2	71.1 (95% CI 68.7-73.5)	69.1 (95% CI 63.5-74.7)	34.1	65.3	35.4 (95% CI 31.6-39.2)	34.3 (95% CI 31.2-37.4)
Mitchell 2014	89	95	26.9	16.8	69 (8.0)	69 (10.1)	60.7	49.5	56.0 (16.8)	59.6 (17.4)
Monninkhof 2003	127	121	3.9	5.8	65 (7.0)	65 (7.0)	85.0	84.0	56.1 (15.4)	58.4 (14.5)
Ninot 2011	23	22	13.0	18.2	65 (range 59-74)	61 (range 56-65)	90.0	77.8	56 (range 42-67)	54 (range 42-57)
Österlund Efraimsson 2008	26	26	0	0	66 (9.4)	67 (10.4)	50.0	50.0	N/A	N/A
Rea 2004	83	52	14.5	11.5	68 (range 44-84) for the total group		41.5% for the total group		51.8 (18.1)	50.0 (20.3)
Rice 2010	372	371	9.7	12.9	69.1 (9.4)	70.7 (9.7)	97.6	94.8	36.1 (14.5)	38.2 (14.4)
Song 2014	20	20	15.0	15.0	66.6 (7.1)	68.1 (6.5)	55.0	75.0	57.0 (10.0)	60.4 (24.9)
Tabak 2014	15	14	33.3	85.7	64.1 (9.0)	62.8 (7.4)	50.0	50.0	50.0 (IQR 33.3-61.5)	36.0 (IQR 26.0-53.5)
Titova 2015	91	81	44.0	39.5	74.1 (9.3)	72.6 (9.3)	42.9	43.2	33.6 (9.9)	33.0 (9.7)

[a]discontinued; [b]incomplete baseline and 1-year study visits; CI: confidence interval; IQR: interquartile range; L: liters; N/A: not applicable.

Table 2.2. Characteristics of interventions in included studies

Study	Follow-up months)	Setting; provision intervention	Duration intervention	Content intervention	Content action plan
Bischoff 2012	24	general practice; trained practice nurse	2-4 FTF individual sessions (60 min each) scheduled in 4-6 consecutive weeks, 6 phone calls	iterative process, self-recognition of COPD exacerbations, education regarding COPD	self-recognition and self-treatment of exacerbations, use of maintenance treatment, contact healthcare providers for support
Bösch 2007	12	outpatient clinic; trained respiratory nurse under supervision of a respiratory specialist	4 FTF group sessions (120 min each) and final session scheduled 6 weeks later	self-recognition of COPD exacerbations, education regarding COPD, smoking cessation, other: travelling, daily live	self-recognition and self-treatment of exacerbations, use of maintenance treatment, avoid situations in which viral infection might be prevalent, contact healthcare providers for support
Bourbeau 2003	24	hospital (outpatient); trained professionals (nurses, respiratory therapists, a physiotherapist)	7 FTF individual sessions (60 min each) scheduled in 7-8 consecutive weeks, 18 phone calls	iterative process, self-recognition of COPD exacerbations, education regarding COPD, exercise or physical activity component	self-recognition and self-treatment of exacerbations, use of maintenance treatment, contact healthcare providers for support, other: symptom monitoring list linked to appropriate therapeutic actions
Bucknall 2012	12	hospital (inpatient); trained study nurse	4 FTF individual sessions (40 min each) in 2 months, at least 6 subsequent home visits, 828 phone calls intervention group	iterative process, self-recognition of COPD exacerbations, education regarding COPD	self-recognition and self-treatment of exacerbations, use of maintenance treatment, contact healthcare providers for support
Casas 2006	12	hospital (inpatient); trained respiratory nurse and GP, physician, nurse, social worker	3-13 FTF individual sessions, 1x group (40 min), 6 phone calls; Barcelona: 1 joint visit at home. Leuven: GP regularly visited patients at home	iterative process, self-recognition of COPD exacerbations, education regarding COPD, other: reinforcement of the logistics for treatment of comorbidities and social support	self-recognition and self-treatment of exacerbations, use of maintenance treatment, contact healthcare providers for support, other: reinforcement of the logistics for treatment of comorbidities

Table 2.2. Continued

Garcia-Aymerich 2007	12	hospital (inpatient); trained specialised respiratory nurse and physician, nurse, social worker	3-13 FTF individual sessions at the hospital (40 min each) or at home (20 min), 6 phone calls	iterative process, self-recognition of COPD exacerbations, education regarding COPD, other: reinforcement of the logistics for treatment of comorbidities and social support	self-recognition and self-treatment of exacerbations, use of maintenance treatment, contact healthcare providers for support, other: reinforcement of the logistics for treatment of comorbidities
Fan 2012	12	outpatient clinic; trained case manager (various health-related professionals)	4 FTF individual sessions (90 min each) scheduled weekly, 1x group, 6 phone calls	iterative process, self-recognition of COPD exacerbations, education regarding COPD	self-recognition and self-treatment of exacerbations, contact healthcare providers for support
Gallefoss 1999	12	hospital (outpatient); trained nurse, physiotherapist, pharmacist, medical doctor	1-2 FTF individual sessions by a nurse and 1-2 by physiotherapist (40 min each), 2x group (120 min each)	iterative process, self-recognition of COPD exacerbations, education regarding COPD, other: compliance, self-care	self-recognition and self-treatment of exacerbations, use of maintenance treatment, contact healthcare providers for support
Hernández 2015	12	hospital (outpatient); trained specialised respiratory nurse, physician, nurse, social worker	patients-no mobility problems: 1 FTF individual session (40 min) at home by primary care team, 3x group at outpatient clinic (2x 90 min, 1x 120 min) patients-mobility problems: 4 FTF individual sessions (15 min each), 1x individual (120 min) or 1x group (40 min), all at home by primary care team	self-recognition of COPD exacerbations, education regarding COPD, smoking cessation, exercise or physical activity component, other: instructions on non-pharmacological treatment	self-recognition and self-treatment of exacerbations, use of maintenance treatment, avoid situations in which viral infection might be prevalent, contact healthcare providers for support, self-treatment of comorbidities

Table 2.2 Continued

Jennings 2015	3	hospital (inpatient); research team and research nurse	1 FTF individual session (60 min) at the hospital by research team member 24 hours prior to discharge, phone call 48 hours after discharge	iterative process, education regarding COPD, smoking cessation, other: primary team was notified if patient was identified as having anxiety or depressive symptoms	contact healthcare providers for support
Khdour 2009	12	hospital (outpatient); clinical pharmacist, respiratory specialist, respiratory nurse	1 FTF individual session of 45 min (60 min for smokers) and 2 phone calls	iterative process, self-recognition of COPD exacerbations, education regarding COPD, smoking cessation	self-recognition and self-treatment of exacerbations, contact healthcare providers for support
Kheirabadi 2008	3	hospital (outpatient); psychologist, trained psychiatric residents	8 FTF group sessions (60-90 minutes each) with 1 week interval and follow-up by phone	self-recognition of COPD exacerbations, education regarding COPD, exercise or physical activity component	avoid situations in which viral infection might be prevalent
Martin 2004	12	general practice; respiratory physician and nurse, GP, ED consultant, medical staff hospital	4 FTF individual sessions and respiratory nurse visits at 3, 6 and 12 months	iterative process, self-recognition of COPD exacerbations	self-recognition and self-treatment of exacerbations, use of maintenance treatment, self-treatment of comorbidities, other: when to use oxygen therapy and diuretics
Mitchell 2014	6	general practice; physiotherapist, trainee health psychologist	1 FTF individual session (30-45 min) by a physiotherapist and 2 phone calls	iterative process, self-recognition of COPD exacerbations, education regarding COPD, exercise or physical activity component	self-recognition and self-treatment of exacerbations, avoid situations in which viral infection might be prevalent, contact healthcare providers for support, other: self-administration, requesting rescue medication
Monninkhof 2003	12	hospital (outpatient); trained respiratory nurse, respiratory physiotherapist	5 FTF group sessions (120 min each) by a respiratory nurse (4x with a 1-week interval and 3 months later) and 1-2x group (30-45 min) by a physiotherapist	iterative process, self-recognition of COPD exacerbations, education regarding COPD, exercise or physical activity component	self-recognition and self-treatment of exacerbations, contact healthcare providers for support

Table 2.2. Continued

Ninot 2011	12	hospital (outpatient); health professional and qualified exercise trainer	8 FTF group sessions (120 min each) by a health professional for 4 weeks, 8 exercise sessions (30-45 min each) by a qualified exercise trainer, 3 phone calls	self-recognition of COPD exacerbations, education regarding COPD, exercise or physical activity component	self-recognition and self-treatment of exacerbations, use of maintenance treatment, avoid situations in which viral infection might be prevalent
Österlund Efraimsson 2008	3-5	primary healthcare clinic; COPD nurse, physician, if needed: dietician, medical social worker, physical and occupational therapist	2 FTF individual sessions for self-care education during 3-5 months (60 min each) by the nurse	iterative process, self-recognition of COPD exacerbations, education regarding COPD, smoking cessation, exercise or physical activity component	self-recognition and self-treatment of exacerbations, contact healthcare providers for support
Rea 2004	12	general practice; respiratory physician, respiratory nurse specialist, GP	at least 17 individual FTF sessions (monthly visits to practice nurse (n = 12), 3-monthly to GP (n = 4), 1x home visit by the respiratory nurse specialist, 1x after admission)	iterative process, self-recognition of COPD exacerbations, other: annual influenza vaccination and PR programme attendance	self-recognition and self-treatment of exacerbations, contact healthcare providers for support
Rice 2010	12	hospital (Veterans Affairs medical centers); trained respiratory therapist case manager	1 group session (60-90 min) by a respiratory therapist case manager, 12 monthly phone calls (10-15 min each)	iterative process, self-recognition of COPD exacerbations; education regarding COPD, smoking cessation	self-recognition and self-treatment of exacerbations, contact healthcare providers for support

Table 2.2. Continued

Song 2014	2	hospital (inpatient); trained nurse interventionists	3 FTF individual sessions (2x inpatient (90+45 min each) on the day before and on the day of discharge, 1x outpatient (90 min) on the first follow-up day) by 2 nurse interventionists, 2 phone calls with a 2-week interval	iterative process, self-recognition of COPD exacerbations, education regarding COPD, exercise or physical activity component	self-recognition and self-treatment of exacerbations
Tabak 2014	9	hospital (outpatient); primary care physiotherapy practices; respiratory nurse practitioner, respiratory physiotherapist	2 group sessions (90 min each) by a nurse practitioner, 1 FTF individual session and 1x intake by the physiotherapist, additional meetings after 1, 3, 6 and 9 months	iterative process, self-recognition of COPD exacerbations, education regarding COPD, exercise or physical activity component	self-recognition and self-treatment of exacerbations, contact healthcare providers for support
Titova 2015	24	hospital (inpatient); trained specialist nurse	6 FTF individual sessions (1x at discharge, 5x home visits at 3 and 14 days, and at 6, 12, 24 months) by the specialist nurse, 1 e-learning programme (15 min), at least 24 phone calls	iterative process, self-recognition of COPD exacerbations, education regarding COPD	self-recognition and self-treatment of exacerbations, avoid situations in which viral infection might be prevalent, contact healthcare providers for support

COPD: Chronic Obstructive Pulmonary Disease; FTF: face-to-face; PR: pulmonary rehabilitation.

Table 2.3. Number of included studies reporting outcomes of interest**s**

Outcome of interest	**Number of studies**
Primary outcomes	
Health-related quality of life	16
Respiratory-related hospital admissions	16
Secondary outcomes	
All-cause hospital admissions	11
All-cause hospitalisation days	8
Respiratory-related hospitalisation days	5
Emergency department visits	9
General practitioner visits	7
Specialist visits	4
Rescue medication use	2
Health status	3
COPD exacerbations	6
Use of courses of oral corticosteroids or antibiotics	9
All-cause mortality	16
Respiratory-related mortality	7
Self-efficacy	2
Days lost from work	2

2

3

A self-management approach using self-initiated action plans for symptoms with ongoing nurse support in patients with Chronic Obstructive Pulmonary Disease (COPD) and comorbidities: the COPE-III study protocol

A. Lenferink
P. Frith
P. van der Valk
J. Buckman
R. Sladek
P. Cafarella
J. van der Palen
T. Effing

Contemp Clin Trials 2013;36(1):81-9

ABSTRACT

Background

Chronic Obstructive Pulmonary Disease (COPD) frequently coexists with other diseases. Whereas COPD action plans are currently part of usual care, they are less suitable and potentially unsafe for use in the presence of comorbidities. This study evaluates whether an innovative treatment approach directed towards COPD and frequently existing comorbidities can reduce COPD exacerbation days. We hypothesise that this approach, which combines self-initiated action plans and nurse support, will accelerate proper treatment actions and lead to better control of deteriorating symptoms.

Methods

In this multicenter randomised controlled trial we aim to include 300 patients with COPD (GOLD II-IV), and with at least one comorbidity (cardiovascular disease, diabetes, anxiety and/or depression). Patients will be recruited from hospitals in the Netherlands (n = 150) and Australia (n = 150) and will be assigned to an intervention or control group. All patients will learn to complete daily symptom diaries for 12-months. Intervention group patients will participate in self-management training sessions to learn the use of individualised action plans for COPD and comorbidities, linked to the diary. The primary outcome is the number of COPD exacerbation days. Secondary outcomes include hospitalisations, quality of life, self-efficacy, adherence, patient's satisfaction and confidence, health care use and cost data.

Analyses

Intention-to-treat analyses (random effect negative binomial regression and random effect mixed models) and cost-effectiveness analyses will be performed.

Discussion

Prudence should be employed before extrapolating the use of COPD specific action plans in patients with comorbidities. This study evaluates the efficacy of tailored action plans for both COPD and common comorbidities.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a major public health problem affecting 1:10 adults in Western Society, and increasing in prevalence globally.[1] COPD is a leading cause of burden of disease.[2] COPD is characterised by airflow obstruction and episodes of acute deterioration in respiratory health, termed 'exacerbations', which account for much of the morbidity, mortality, hospitalisations, and worsening of quality of life.[3,4] The majority of costs in patients with COPD are related to treatment of exacerbations, with hospitalisation costs as a major component.[5,6] Hospitalised patients with COPD often have comorbidities that increase the length of hospital stay and lead to higher cost and mortality rates.[7-10]
Other important diseases frequently coexist with COPD: the prevalence of heart failure varies from 7.2% to 20.9%,[11-15] depression from 10% to 42%,[15,16] and anxiety from 9.3% to 58%.[16] There is an increased risk of diabetes (OR 2.04)[17] and patients with severe COPD have a more than twofold increased risk of cardiovascular disease compared to patients with normal lung function.[10] A 2004 cross-sectional study using administrative health services databases indicated that 68.4% of COPD patients suffer from at least one chronic comorbidity and that about 16% COPD patients have two comorbid conditions.[18]

Self-treatment of exacerbations is an important component of self-management training.[19] A self-management program should ideally include training with feedback to improve the following skills: problem solving, decision making, resource utilisation, formatting of patient-provider partnerships, action planning and self-tailoring.[20] Improvement of these skills should facilitate proper use of the self-treatment action plan.

Self-treatment of exacerbations with action plans reduces exacerbation duration, hospitalisations, and health care costs in non-complex patients with COPD.[21,22] The most recent Cochrane review regarding COPD self-management emphasised that self-treatment of exacerbations is an important component of COPD self-management.[23] Effects might result from a quicker start of appropriate treatment via self-initiation of corticosteroids and/or antibiotics.[24] However, action plans are not always suitable and have a potential to be unsafe for patients with multi-morbidities. Comorbid symptoms can overlap symptoms of COPD and therefore limit the applicability, effectiveness and safety of symptom-based COPD selftreatment guidelines. The use of symptom-based COPD action plans can lead to initiation of incorrect actions and/or delay of proper treatment for the comorbidities. Moreover, data on the impact of self-management and action plans are conflicting.[25] Literature shows that the effectiveness of action plans is limited if not incorporated in more extensive, individualised, self-management training programs.[25] Self-management training intends to change behaviour and instils the confidence to recognise exacerbations and self-manage exacerbations.[26] Also, ongoing case manager support is recognised as an additional component to achieve effective and safe self-management.[27]

This manuscript describes the COPE-III study, a randomised controlled trial evaluating the effectiveness of an innovative self-management approach in patients with a combination of COPD and other morbidities. A previously used symptombased self-treatment strategy for non-complex patients with COPD[21] has been adjusted for use in patients with COPD and common comorbidities. The effectiveness of these adjusted action plans will be evaluated in patients with COPD and comorbidities.

Objectives

The main study objective is to investigate whether complex patients with COPD who are trained in the use of individualised action plans for appropriate responses regarding deterioration of their symptoms, have fewer COPD exacerbation days over 12 months compared to a control group. We will also investigate effects on general and COPD-specific health measures, and the cost-effectiveness of this intervention. Finally, adherence, satisfaction and confidence of intervention patients to self-manage and self-treat will be evaluated.

Hypotheses

We hypothesise that over 12 months, compared to usual care, the intervention will lead to fewer COPD exacerbation days. In addition, it will lead to fewer hospitalisation days for COPD and comorbidities, a reduction of chronic heart failure exacerbation severity, anxiety or depression symptoms and health care use, and a better general and COPD-specific health status. In addition, it will lead to increased self-efficacy, high adherence levels, patient's satisfaction and confidence, and a direct saving in health care costs.

METHODS

Design

The COPE-III study is an international multicenter randomised controlled trial of a training intervention in patients with COPD and comorbidities. We aim to enroll 300 consecutive patients with COPD over 24 months from outpatient visits and hospitalisations at one hospital in the Netherlands (Medisch Spectrum Twente Enschede (n = 150)) and two public hospitals of the Southern Adelaide Local Health Network in Australia (Flinders Medical Centre and the Repatriation General Hospital) (n = 150)). This study is approved by the Medical Ethical Committee Twente and the Flinders Southern Adelaide Clinical Human Research Ethics Committee and is registered in the public Australian New Zealand Clinical Trials Registry (ACTRN12612000514808). Written informed consent is requested from all patients prior to participation in this study.

Randomisation

After baseline measurements, patients who meet all study criteria will be randomly assigned to an intervention or control group (Figure 3.1) employing a minimisation program.[28] Allocation will be stratified on hospital site and balanced for potential confounders: smoking status, modified Medical Research Council (mMRC)[29] dyspnoea score, the number of diagnosed comorbidities, and whether patients are on the waiting list for pulmonary rehabilitation.

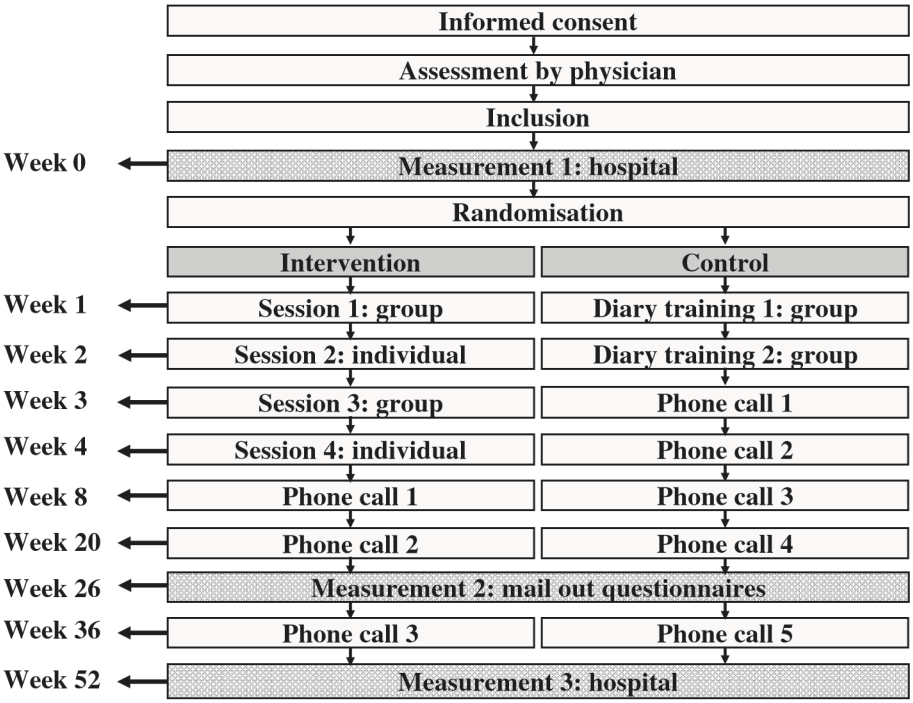


Figure 3.1. Flowchart of the COPE-III study

Inclusion criteria

Recruitment has started in June 2012 and is expected to conclude in June 2014. Researchers and the study physicians will review the eligibility of all patients. Eligible patients need to meet the following inclusion criteria:

1. a clinical diagnosis of COPD according to the GOLD criteria[30] (FEV_1 < 80% of the predicted value and $FEV_1/FVC < 0.70$);
2. ≥1 diagnostic comorbidity from the following list, selected because of their prevalence, potential for having similar symptoms as COPD exacerbations or potential to become unstable if COPD exacerbations are treated: ischaemic heart disease (history of myocardial infarction, angina pectoris), heart failure (defined

according to the ESC guidelines[31]), diabetes (steroid-induced or stable diabetes type 1 or 2); or active symptoms of anxiety and/or depression (AD) (using a cut-off score of ≥ 11 from the Hospital Anxiety and Depression Scale) (HADS)[32,33] and/or having AD symptoms that are currently being treated;

3. ≥ 3 COPD exacerbations, defined as respiratory problems that required a course of oral corticosteroids/antibiotics in the two years preceding study entry; and/or ≥ 1 hospitalisation for respiratory problems in the two years preceding study entry;
4. ≥ 40 years of age;
5. stable at the time of inclusion (at least 4 weeks post-exacerbation, 6 weeks post-hospitalisation or post-rehabilitation);
6. able to understand and read the English or Dutch language.

Exclusion criteria are:

1. terminal cancer, end stage of COPD or another serious disease with low survival rate (expected survival < 12 months);
2. other serious lung disease (e.g., α1-antitrypsin deficiency; interstitial lung diseases);
3. patients with cognitive impairment (Mini Mental State Examination (MMSE) < 24)[34]; patients who are currently enrolled in other randomised controlled trials or intensive case management programmes.

Patients who are less than 4 weeks post-exacerbation (due to COPD or any of the comorbidities) or less than 6 weeks post-hospitalisation or -rehabilitation are considered unstable and their assessment will be delayed until they reach the defined level of stability. Before inclusion, symptoms of anxiety and depression will be assessed with the HADS in all eligible patients. In case of a cut-off score of ≥ 11, we will integrate the anxiety and depression component in the patient's individual action plan. Other frequently existing comorbidities such as osteoporosis, metabolic syndrome, anaemia, and microalbuminuria are unlikely to confuse the symptomatology of COPD exacerbations as much as our selected comorbidities, so we have not included these comorbidities in our intervention. Finally, patients with cognitive dysfunction will be excluded.

Intervention

All patients will be educated in completing daily symptom diaries, and they will be asked to complete these diaries for a period of 12 months. Partners or carers of patients will be invited to participate in the sessions.

Study nurses, who are experienced senior respiratory nurses, will be trained specifically in the study methods and support of patients (e.g., recognising COPD and comorbid symptoms, the use of a diary and action plan for COPD and comorbidities, motivational

interviewing) prior to the start of the study.

Patients randomised to receive the intervention will attend four or five (depending on which comorbidities are diagnosed) weekly self-management sessions (two individual one-hour sessions and two or three two-hour group sessions) guided by study nurses and supported by cardiac, mental health and/or diabetes nurses. During the self-management sessions the nurses discuss COPD and comorbidities, inhaler techniques, breathing and relaxation exercises, physical fitness and diet. For intervention patients the diary training will be integrated in the self-management sessions. One, four, and eight months after completion of the self-management sessions, the study nurse will contact the intervention patients by phone to reinforce self-management skills by discussing the use of the diary and action plan, and the use of breathing and relaxation exercises (Figure 3.1).

Patients randomised to the control group will attend two one-hour group sessions held on two consecutive weeks, for training in diary use, and will subsequently receive 'usual care' (routine care provided at all hospitals and in primary care). During the 12 month follow-up period, the study nurse will contact them five times (3, 4, 8, 20 and 36 weeks after the first diary training) regarding the completeness of the diaries (Figure 3.1). Control patients will not receive individualised action plans.

Daily symptom diary

The daily symptom diary will be an extended version of the diary used in the COPE-II study.[21] Diaries are colourcoded and individualised. Besides COPD symptoms (breathlessness, sputum production, sputum colour, coughing, wheezing, fever), the diary includes symptoms of all relevant comorbidities (e.g. chest pains, swollen ankles, weight gain, anxiety or depressive symptoms) with which the patient is diagnosed at baseline. At the end of the month, patients will be instructed to complete additional information regarding unscheduled health care visits (e.g., GP (General Practitioner) visits, emergency department visits, hospitalisations) and information on the use of additional medication (e.g. a course of corticosteroid and/or antibiotics). If other relevant comorbidities are diagnosed during the follow-up period, patients will receive an adapted version of the diary, including these newly diagnosed comorbidities. At inclusion all patients (control and intervention) will also receive a 'what are my usual symptoms' card, which describes their individual symptom levels in a stable health state. This card is useful in completing the daily symptom diary as patients can compare the symptom levels in a stable health state with symptoms experienced in the last 24 h.

When patients have experienced no deterioration in any of the predetermined symptoms listed in the diary during the last 24 h, they will be instructed to tick the box 'no change in

symptoms'. Whenever they have experienced deterioration in any symptom listed in the diary, they will be asked to report the level of change for each symptom listed in the diary: no change, slightly increased, or clearly increased.

Patients will be asked to return their completed diary by pre-paid mail to the research office at the end of each month. All patients will be given feedback by phone if the completion of the diary is incorrect. In COPE-II, this approach resulted in a high 85% completion rate of diaries (unpublished data COPE-II study[21]). Another multicentre randomised controlled trial that used comparable diaries also reported high compliance and diary completeness.[35]

Self-treatment

The study intervention is based on a self-management course used successfully in the COPE-II project,[21] but for the first time modified to address complicated comorbidities. The expertise regarding the development of the action plan for comorbidities has been provided by disease-experts in cardiovascular disease, diabetes, and anxiety and depression. The diaries and action plans have been developed and refined prior to the start of this trial. A pilot study to evaluate the feasibility and usability was performed in six complex patients with COPD and at least one comorbidity. Compliance and completeness of diary data were as high as in previous studies using comparable diaries.[21,35] Patients completed a total of 483 diary days (94.5%). Eight symptom-based exacerbations were reported. During seven of these exacerbations, the patients acted according to the action plan. No concerning issues were reported and patients scored the readability of the action plans 9.2 (SD 1.75) and had a high confidence in completing the diary: 9.2 (SD 1.75) (0 = very poor–10 = excellent). Patients who participated in the pilot study will not be included as participants in this trial.

During the self-treatment course, intervention patients will be taught how to act when symptoms increase using the action plan that is linked to their daily symptom diary. The action plans will consist of colour-coded individualised actions for COPD and each of the relevant comorbid symptoms. Patients will be taught when to start a course of oral corticosteroids (and antibiotics) for a COPD exacerbation. Actions required for change in comorbid symptoms include e.g. taking additional diuretic treatment for increased oedema; using specific relaxation strategies for anxiety; checking blood glucose levels when using steroids; or calling an ambulance in case of severe or unresolving chest pain. In some cases the action plan will advise the patient to contact the pulmonary research office. The nurse will act as a triage nurse when the cause of the change in symptoms is unclear and additional advice is necessary. If other relevant comorbidities are diagnosed during the follow-up period, patients will receive an additional individual training session and an adapted version of the action plan, including these newly diagnosed comorbidities.

Self-management

Besides training in the use of the action plans, the content and emphasis of the self-management training will be directed towards self-management mastery of skills necessary for successful self-initiating of actions, such as adherence to regular medications, correct inhalation technique, early recognition of symptoms of an exacerbation of COPD and/or a flare-up of potential comorbidities, and self-initiating correct and expedient actions in response to increased symptoms.[21] The program will also be aimed at knowledge regarding COPD and comorbidities, immunisations, physical fitness, inhaler techniques, and relaxation and breathing exercises will be trained.

During the group sessions the study nurse will discuss the functioning of the respiratory system, COPD symptoms, medication for respiratory problems, and symptoms of anxiety and depression. In addition, a nurse from a specific comorbid discipline will address other relevant comorbidities which can occur with COPD (cardiac diseases and diabetes) only with intervention patients diagnosed with that particular comorbidity. In another group session the study nurse will discuss the importance of exercise and good nutrition. In addition, the use of breathing and relaxation exercises will be discussed. Finally, feedback will be given on the use of the diary and the action plan.

During the individual sessions, the study nurse will train patients in completing their diary and individualised action plans. In addition, the study nurse and patient will define what symptoms the patient experiences in a stable state. This information will be integrated in a "what is usual" symptom card that the patient is asked to use when completing the diary. Finally, the study nurse will check and, where necessary, reiterate correct inhalation techniques as well as medication use for comorbidities.

Behavioural change

The objective of the intervention in this study is to improve self-regulation skills using behavioural and cognitive techniques. This intervention is designed to promote uptake and optimal use of specified disease self-management behaviour patterns. Intervention components are characterised as education, training, modelling and enablement according to the behavioural change wheel, a broad taxonomy classifying interventions based on function.[36] These behaviour change components are linked with theoretical mechanisms of change in order to optimise the effectiveness of the intervention.[37] The behaviour change components of education, training, modelling and enablement embedded in the self-management sessions will target desirable and specific behaviours including individualised diary use, patient recognition of deterioration in symptoms, and the correct and timely use of an action plan. These specific behaviours will repeatedly be discussed by phone with the study nurse to reinforce self-management skills. We will document session

attendance of patients and their carers, the motivation of patients to use a diary and an action plan, the compliance and completeness of diary data, and the adherence to the action plan. So at the end of the study, we will be able to assess the fidelity of delivery of the intervention with these data. 4.9.

Outcome measures

Measurements will be performed at baseline, and after 6 and 12 months (Figure 3.1). The baseline and 12-month measurements will take place in an outpatient clinic, whereas the 6-month measurements will be collected via mailed questionnaires. Lung function measurements at follow-up will be conducted single-blind by a lung function assistant who does not know the patient's group allocation.

Baseline parameters include basic socio-demographic data, age, gender, smoking status, COPD Assessment Test (CAT) score,[38,39] COPD severity (BODE score[40]), degree of comorbidity (Charlson Index[41]), information regarding health literacy (HL)[42] and patient activation status (PAS)[43], New York Heart Association functional classification[44] for the patients with cardiac disease, HbA1c for the patients with diabetes, and self-reported immunisation status. Their COPD status will be documented by GOLD 2007 Severity Level using lung function and GOLD 2011 Grade by a combination of lung function severity, exacerbations in the previous year, mMRC score and CAT score. Some data (e.g. previous lung function tests, amount of COPD exacerbations and hospitalisations during the past two years, diagnosed comorbidities) will be extracted from the patients' medical records by research nurses, for which participant informed consent will be obtained. A six minute walking test (in duplicate)[45] will be performed at baseline to measure exercise capacity and provides one component of the index of COPD severity, the BODE score.[40] Other parameters used to calculate the BODE score are the body-mass index, the degree of airflow obstruction (FEV_1% of predicted), and dyspnoea (mMRC score).[29]

The primary outcome measure is the absolute number of COPD exacerbation days per patient per year (retrospectively defined with the daily symptom diary). In this study a COPD exacerbation is defined as 'worsening of the patient's condition from the stable state and beyond day-to-day variations, requiring treatment with a course of oral corticosteroids and/or antibiotics'. The start of a COPD exacerbation will be defined as 'a clear negative change in two major symptoms (breathlessness, sputum production, sputum colour)[46] or one major and one minor symptom (cough, wheeze, and fever (>38.5 °C))[46] from baseline, for at least two consecutive days'. The day of exacerbation resolution will be defined as the first day of: 1) three successive days that the patient has returned to his normal health state; or 2) seven consecutive days on which the patient continuously reports no or only a slight increase in symptoms compared to baseline, with no fever or change in sputum colour.[21] Secondary outcome measures and other objectives are summarised in Table 3.1.

Economic analyses will be performed separately for Australia and the Netherlands. For economic analyses, data regarding health care resource use (e.g. outpatient visits, hospitalisations and GP visits) will be retrospectively collected per individual patient. Self-reported data from diaries, a six month follow-up and a 12 month follow-up questionnaire will be cross-checked with information from GPs, pharmacists, Medical Centres and medical records. In the Netherlands medication details for all patients will be retrospectively collected from the pharmacists. In Australia, data will be obtained from Pharmaceutical Benefits Scheme (PBS) and Medicare Benefits Schedule (MBS) utilisation data. In addition, unit costs will be derived from published data sets including PBS, MBS and Australian Refined Diagnosis Related Groups (AR-DRG) cost weights. In the Netherlands, an incremental cost-effectiveness analysis will be performed with Dutch unit costs derived from an extrapolation of the Australian unit cost data to The Netherlands.

Table 3.1. Description of secondary outcome measures

Secondary outcome measure	Defined by
Number of chronic heart failure exacerbation days	Daily symptom diary
Severity of symptom scores for COPD and comorbidities	Daily symptom diary
Lung function	Spirometry (FEV_1, FEV_6, FVC)
Dyspnoea	Modified Medical Research Council (mMRC)[29]
Health-related quality of life	Chronic Respiratory Questionnaire (CRQ)[47] and EuroQol Visual AnalogueScale (EQ VAS)[57,58] recording an individual's health-related quality of life state on a vertical scale
Subjective fatigue	Identity-Consequence Fatigue Score (ICFS)[59]
Anxiety and depression symptoms	Using a cut-off score of ≥ 11 from the Hospital Anxiety Depression Scale (HADS), indicating active symptoms of anxiety and depression[32,33]
Patient's self-management behaviour and knowledge	Partners in Health scale (PIH)[60]
Confidence and competence	COPD Self-Efficacy Scale (CSES)[61] regarding ability to avoid breathing difficulty while participating in certain activities, and mastery domain of the CRQ[47] measuring the feeling of control one has over the disease and its effects
Adherence with self-treatment protocol	Retrospectively determined from the daily symptom diary (number of days between start of exacerbation/flare-up of comorbidity and the initiation of the required action)
Satisfaction and confidence of healthcare providers regarding self-treatment	Semi-structured interviews
Patient's satisfaction and confidence	Evaluation using focus groups
Cost and health care utilisation	Health care utilisations for COPD, all cause respiratory, cardiac and diabetes: GP visits, specialist consultations and other services, number of hospitalisations, number of in-hospital days, travel, costs of usual care, and EQ-5D[57,58] for the measurement of utilities

Sample size

Based on data from the COPE-II study (exacerbation rate (days/patient/year) intervention group: 0.116; baseline (control group): 0.176)[21], both with an estimated SD of 0.17 and allowing for over dispersion, 105 patients per group are needed to provide 80% power to detect an effect of this size. Allowing for an attrition rate of 30% in these severe patients with comorbidities and a possible potential reduced effect in this group of patients compared to the COPE-II population, 150 patients per study group will be included.

Safety reporting

The participating centres are responsible for reporting adverse events to the accredited medical ethical committees. Adverse events are defined as any undesirable experience occurring in a subject during the study, whether or not considered related to the intervention. Serious adverse events which are likely related to the study intervention are required to be reported within 24 h.

No interim analyses have been planned unless deemed necessary by an external Data and Safety Monitoring Board (DSMB). The DSMB will assess data integrity and adverse events after the randomisation of 100, 200 and 300 patients. For this purpose, data (hospitalisations, deaths and other serious event data) will be blinded and de-identified and sent to the DSMB members prior to the safety data review meetings. Efficacy with regard to hospitalisations or deaths will only be reviewed by the DSMB when safety concerns have risen. The DSMB will advise the investigators if the study needs to be modified or prematurely terminated.

Data analysis

All analyses will be conducted on an intention-to-treat basis (random effect negative binomial regression and random effect mixed models). If patients have less than three months of complete diary data over the course of the year they will be excluded from the analysis of the daily diaries. Differences in baseline characteristics between the intervention and control group will be analysed using common statistical procedures, such as chi-squared tests, T-tests and Mann–Whitney U tests, as appropriate.

The primary outcome will be the number of COPD exacerbation days/patient/year, which will be assessed using Poisson regression with a scale-parameter to correct for over dispersion. Secondary analyses will include between-group differences in the proportion of patients who have a total number of exacerbation days above the median, 75th, and 90th percentile of the population as a whole. Between-group differences of secondary continuous variables (e.g., CRQ[47], HADS) over the 12-month period will be assessed using a multi-level model to incorporate the repeated measurements over time. The total number of health care contacts and courses of corticosteroids/ antibiotics will be analysed using

Poisson regression.

Multivariate logistic regression will be used within the intervention group to identify independent variables predictive of patient's adherence to the intervention. Successful adherence is defined as patients acting according to their action plan in ≥80% of their exacerbations (if symptoms change). These analyses will be carried out using SPSS v 20.0 or higher with $p<0.05$ considered statistically significant.

DISCUSSION

COPD is a complex systemic disease involving more than airflow obstruction, and it often coexists with other chronic diseases that can influence patients' health status and prognosis. We have developed a novel symptom-based COPD self-treatment approach using action plans, which incorporates management of frequently existing comorbidities (cardiovascular diseases, diabetes, and anxiety and depression) that may confuse the use of COPD action plans or are known to be triggered by COPD exacerbations. A clinical trial is necessary to evaluate the effects of these individualised self-treatment action plans.

Symptoms of comorbidities can overlap symptoms of COPD and limit the applicability, effectiveness and safety of symptom-based COPD self-treatment guidelines, which have otherwise proven to be effective in patients with COPD without severe comorbidities. The use of symptom-based COPD action plans in such complex patients can therefore lead to initiation of incorrect actions and/or delay of proper treatment (e.g., dyspnoea and chest pain can relate to both COPD and cardiovascular diseases[30,31]). In addition, exacerbations of COPD per se or their treatment may also lead to flare-ups of comorbid diseases (e.g., increased anxiety during an exacerbation and steroid-induced hyperglycaemia[48]). Finally, comorbid symptoms can influence the use of action plans (e.g., depressive symptoms can recude treatment adherence[49]). For these reasons, the use of self-treatment training solely directed towards COPD is less applicable, and potentially dangerous, to the large numbers of patients with COPD and comorbidities.

Whereas COPD action plans have now become part of usual care,[50] prudence should be employed before extrapolating the use of COPD specific action plans in patients to other comorbidities. Results of most COPD self-treatment studies cannot be generalised to the whole COPD population, because often patients with (severe) comorbidities have been excluded.[21,24] In the study of Fan et al.[51] a COPD specific action plan was included in a comprehensive care management program (CCMP) based in US Veteran hospitals. The study population included, in contrast to most other studies, patients with severe comorbidities. Controversially, the CCMP group showed a higher mortality rate than the usual care

group.[51] Because of this, the study was terminated early. The role of comorbidities was evaluated, but no definite explanation for the unexpected outcomes could be provided. It is conceivable that confounding of symptoms and confusion with self-treatment actions might have contributed to the mortality excess, although there was no clear interactive effect of comorbidities found. In a second paper, published almost simultaneously from Scotland, similar outcomes were observed.[52]

The effects of our novel self-treatment training will provide new evidence for translation into practice of a self-treatment approach in the wider COPD population. Given the costs and complexity of such a study, it is important that its results are both valid and generalisable. Use of a Dutch-Australian study population will improve the generalisability of the results and facilitate future implementation of the intervention, if proven effective, in other health care systems.

An important contributor towards success of treatment is adherence,[53] defined as the patient's active role in consenting to and following prescribed treatments.[54] A recent study reported that adherence to written COPD action plans was associated with a significant reduction in exacerbation total recovery time.[55] Several factors have been reported to increase the likelihood of adherence to an action plan, including younger age, previously receiving an influenza vaccination and having a cardiac comorbidity or more severe airflow obstruction.[55] However, more information is needed to define the influence of other factors on the adherence (e.g., depressive symptoms, self-efficacy), so these factors need to be taken into account in this self-management plan to individual patients.[56]

Our study has several potential limitations, the first being the use of symptom diaries by control patients. This may increase awareness of symptoms and could therefore influence behaviour towards changing symptoms (e.g. seeking earlier contact with health care providers). We are aware that this may lead to an underestimation of the effect size, although in the COPE-II study a similar approach did not confound results in this regard. Secondly we are aware of the risk of contamination bias. Case managers and physicians will therefore repeatedly be instructed not to give control patients any information regarding the content of the study action plans throughout the trial. A final point of consideration is the frequent use of COPD actions plans in the source population. This might decrease the effect size because control patients will also be guided to act in case of respiratory symptoms change. However, as said previously, we strongly feel that the use of solely symptom-based COPD action plans can lead to initiation of incorrect actions and/or delay of proper treatment in COPD patients with comorbidities and therefore hypothesise benefits in the intervention group; we also wish to ensure that harm does not come to either group.

This international randomised controlled trial tackles the important and challenging issues

of multimorbidity in the same structured way used increasingly for COPD. COPD-specific action plans are not suitable and potentially unsafe for patients with multimorbidity, which represent the rule rather than the exception. This clinical trial broadens the scope from COPD to multimorbidity by including specific relevant comorbidities. We believe this might be a useful step providing evidence to manage all multimorbidity patients, especially because the intervention is mainly patient-centered and patient-initiated. We have imposed no upper age limit since age itself is an important risk factor for COPD and comorbidities. Our study design will provide a representative study of patient groups having moderate to severe COPD and comorbidities who experience COPD exacerbations for which it is expected that self-management and selftreatment will result in a reduction of COPD exacerbation days.

To summarise, self-management and self-treatment in patients with comorbidities will be directed towards enabling early recognition of COPD exacerbations as well as flare-ups of comorbidities, and therefore a more rapid start of the correct treatment in order to reduce the severity of both the COPD exacerbation and/or flare-up of comorbidities. Earlier intervention has the potential not only to reduce the severity and duration of exacerbations and COPD-related hospitalisations, but also to reduce all cause hospitalisations, with consequent reduction in costs. Moreover, better management of exacerbations is likely to improve patients' health status, morbidity and mortality in the medium to long term. This randomised controlled trial will identify if a selftreatment strategy as part of a self-management program makes action plans sufficiently applicable, effective and safe to use in patients with COPD and severe comorbidities.

ACKNOWLEDGEMENTS

Funding from the Netherlands Lung Foundation, the Australian Lung Foundation, and the Repat Foundation has made it possible to perform this study. We would like to thank all disease-experts in respiratory and cardiovascular disease, diabetes, and anxiety and depression for the expertise regarding the development and adjustments of the action plans: Morton Burt, Robert Minson, Debra Spicer, Malcolm Battersby, Sally Anesbury, Anne Southwell, Marie-Jose Pouwels, Elly Wajon, Hermien ten Bolscher, Clara van Ommeren, Janneke Roukema, Anna Weierink and Astrid Brilleman. We would also like to thank Stephen Quinn and Julie Ratcliffe for their input in the statistics and health economic analyses respectively. Finally we would like to thank the data managers Sylvia Punte and Anne Southwell, and the nurses Chantal Bergman, Kim Klieverik, Marin Bilgic, Alice Grooten-Nijkamp, Adrienne Beverley, Katherine Bassett, Cheryl Parton, and Toni Mazzone for their support in running the current study.

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4

The development of a self-treatment approach for patients with COPD and comorbidities

T.W. Effing
A. Lenferink
J. Buckman
D. Spicer
P.A. Cafarella
M.G. Burt
K.L. Bassett
C. van Ommeren
S. Anesbury
P.D.L.P.M. van der Valk
P.A. Frith
J. van der Palen

J Thorac Dis 2014;6(11):1597-605

ABSTRACT

Background

Patient-initiated action plans are an important component of COPD self-management (SM) interventions. When integrated into SM interventions, these action plans have proven to be effective in reducing exacerbation severity, hospitalisations, and costs and in improving health status in patients with COPD without severe comorbidities. Because of overlap in symptoms, a self-treatment (ST) approach that focuses solely on traditional symptoms of COPD is inadequate for patients with COPD and comorbidities. The COPE-III SM intervention combines (I) patient-initiated action plans that are tailored to the individual's co-morbid disease(s), and (II) ongoing nurse support. In this paper we provide information regarding the integration of information from two previous COPD SM studies (COPE I and II) in the development of the current COPE-III ST approach.

Materials and methods

COPE-III ST materials include daily symptom diaries and action plans that take patient's common comorbidities [chronic heart failure (CHF), anxiety, depression, ischaemic heart disease (IHD), and diabetes] into account. The comorbid diary and action plans components were developed in collaboration with multiple disease-experts.

Results: Previous SM studies have highlighted some essential topics that need to be considered when developing a SM or ST approach: 'when to initiate ST', 'how to optimize materials and safety', and 'how to achieve behavioural change'. In the COPE-III study, ST is initiated after a significant change in symptoms. This is consistent with the COPE-II approach and was implemented because disease symptoms are often present even when patients are stable. We have tried to ensure patient safety by providing an easily accessible case-manager to patients throughout their involvement in the study. Furthermore, a psychologist has ensured the use of behavioural change techniques throughout the intervention.

Conclusions

We should continue to learn from our experiences with SM interventions to further optimize future SM and ST interventions. The use of materials that are suitable for different levels of patient literacy and the training of health care providers are other points of improvement.

INTRODUCTION

COPD is a leading cause of death and disability internationally[1] that affects approximately 1:10 adults in the developed world and is increasing in prevalence globally.[2] High financial and social burdens have been associated with COPD in general[3,4] and COPD exacerbations in particular.[5,6] COPD exacerbations, defined by episodes of acute deterioration in respiratory health,[7] are also a major contributor to a step-wise worsening of quality of life in patients.[7]

The latest Cochrane systematic review of COPD self-management (SM) has documented that COPDspecific SM interventions are associated with a reduction in hospital admissions.[8] Patient-initiated action plans are an important component of SM interventions.[8,9] When used appropriately, they can lead to accelerated initiation of appropriate treatment[10] and therefore reduce the exacerbation severity.[11] When integrated into SM interventions, these action plans have proven to effectively reduce exacerbation severity, hospitalisations, and costs and improve health status.[11-13]

Comorbidities are the rule rather than the exception in COPD.[14,15] Over two-thirds of COPD patients (68.4%) suffer from at least one comorbidity, about 16% have at least two comorbid conditions,[15] and one third of the COPD patients admitted to hospital have at least four coded comorbidities.[16-18]

Because the symptoms of COPD and common cooccurring diseases overlap, a "one size fits all" approach that focuses solely on traditional symptoms of COPD is inadequate. For example, increased dyspnoea could relate to either a COPD exacerbation or a sudden deterioration of cardiovascular disease (e.g., heart failure).[19,20] Reliance on specifically designed for COPD symptoms and actions/ treatments could therefore lead to the initiation of incorrect or delayed treatment.

The latter is highlighted by a recent study evaluating COPD-specific action plans in a COPD population with comorbidities.[21] The study was terminated because of significantly higher mortality rates in the intervention group. No definite reason for this has emerged and the findings contrast positive outcomes of a comparable SM study.[22] Nevertheless, the study[21] has resulted in controversy regarding the effectiveness of SM interventions, especially in patients with high burden of disease and co-morbidities.[23] In these patients, SM interventions may be more challenging and not without risk of serious adverse events.[23] It underlines the need for further evaluation of action plans in COPD patients with comorbidities.

In this paper we provide an insight into how we have used our experiences with our previous SM studies to develop a novel COPD self-treatment (ST) approach for patients with COPD and co-morbidities.

The COPE studies

During the last 15 years we have performed three large randomized controlled trials to explore effects of SM: the COPE-I[24], COPE-II[11,25], and COPE-III study[26]. COPE stands for 'COPD study at Department of Pulmonology Enschede'. Whereas the COPE-I and COPE-II study were performed in the Netherlands, COPE-III is a joint Dutch - Australian research project. Experiences from COPE-I and COPE-II have been used to develop the design for the COPE-III study. Details of all three COPE studies have been summarized in Table 4.1.

COPE-I

In the COPE-I study the effects of a comprehensive SM intervention were evaluated in 248 patients with moderate to severe COPD and no severe comorbidities.[24] The intervention involved an individualized treatment plan that incorporated smoking cessation, optimisation of pulmonary status by pharmacotherapy, a standardised low-intensity exercise program, and a written ST action plan for COPD exacerbations that was based on symptom perception. If patients experienced an increase of respiratory symptoms and normally would have called their physician, they could start with a short course of oral prednisolone, and with onset of purulent sputum a course of antibiotics for which prescriptions were supplied.[24] The study results showed no effects on quality of life and exercise capacity, and an increased number of exacerbations, defined as an increase of respiratory symptoms treated with prednisolone and/or antibiotics in the intervention group. However, because daily symptoms were not recorded in either study groups, it could not be clarified whether this meant that there was an over-treatment in the intervention group or an under-treatment in the control group.[24]

COPE-II

In the COPE-II study,[11] the extra value of a COPD SM component was evaluated. A group of patients who received a SM intervention that included specific training in ST (intervention group; n=70) was compared to a group of patients who received a similar SM intervention without this specific training (control group; n=72). The ST training component incorporated training in COPD symptom recognition (with the help of a daily symptom diary) and use of an action plan. The concerns from the COPE-I study regarding over-treatment in the intervention group were taken into consideration and the start of a COPD exacerbation was defined as 'a clear negative change in two major symptoms or one major and one minor symptom from baseline, for at least two consecutive days' [major symptoms: breathlessness, sputum production, sputum color; and minor symptoms: cough, wheeze, running nose, sore throat, and fever (>38.5 °C)[27]].[11] This meant ST was only initiated 48 hours after an initial change in symptoms. Similar to the COPE-I study,[24] COPE-II data showed a significantly higher use of courses of prednisolone and antibiotics in the ST group. However, the number of reported courses in the ST group was still lower than

the actual number of exacerbations reported in the diaries, meaning that prednisolone was not used during every exacerbation. The final COPE-II study results therefore indicated that this approach did not lead to overtreatment, and indeed less COPD exacerbation days and lower costs occurred in the intervention group.[11] In summary, the COPE-II study demonstrated that specific COPD ST training within a more general COPD SM training intervention leads to less exacerbation days and lower costs.[11] However, these study results cannot be generalized to the large population of COPD patients with comorbidities.

COPE-III

The COPE-III SM intervention incorporates (I) patient-initiated action plans that are tailored to the individual's co-morbid disease(s) as well as their COPD, and (II) phone support from case-managers. The design of the COPE-III study, an international randomised controlled multi-centre trial, has previously been published and the intervention is currently under evaluation in both the Netherlands and Australia.[26] Patient recruitment takes place in five hospitals [Netherlands: Enschede (Medisch Spectrum Twente) and Nijmegen (Canisius-Wilhelmina Ziekenhuis); Australia (Adelaide: Repatriation General Hospital, Flinders Medical Centre, Royal Adelaide Hospital)]. We expect that data collection will be completed by the end of 2015. In the COPE-III study, we have incorporated at similar COPD ST component to that evaluated in the COPEII study and combined this with action plans for common comorbidities [chronic heart failure (CHF), anxiety, depression, ischemic heart disease (IHD), and diabetes]. The comorbid action plan components have been developed in collaboration with multiple disease-experts (Cardiologist, Cardiac Nurse Practitioner, Endocrinologist, Psychiatrist, and Psychologist). In COPE-III, extensive patient training directed towards individualized materials is provided.

COPE-III ST approach

The COPE-III intervention involves a total of 8-9 hours of SM session time and several additional follow-up phone calls. A more specific description of the intervention has been provided in a previous paper.[26] Because of the adjustment of intervention materials for comorbidities, materials are more complex than the ones used in previous two studies. It has therefore become necessary to deliver half the COPE-III training sessions individually instead of in a group and to allocate relatively more session time towards specific ST training compared to previous interventions. ST materials include a 'what are my usual symptoms' card, a daily symptom diary, and an action plan. During training in the use of these materials, hypothetical scenarios were incorporated to engage the patient in practicing the completion of the diaries and understanding appropriate use of the action plans.

As in previous studies, SM training is provided by casemanagers (respiratory nurses). Patients are provided with information on how to contact the case-manager if they have

any doubts or questions. Access to case-managers is available during office hours and patients are advised to contact their GP or Emergency Department during out of office hours. The case-manager also acts as a triage nurse when the cause of the change in symptoms is unclear and additional advice is necessary.[26]

COPE-III ST materials

Even when stable, many patients with COPD experience symptoms of their respiratory disease and comorbidities, especially patients with moderate to severe disease.[19] In the COPE-III intervention, the nurse and patient define together the patient's symptoms during a stable health state and summarize these findings in the patients' 'what are my usual symptoms' card. The patient is advised to use this card while completing the daily symptom diary and to indicate whether symptoms have changed compared with their stable health state. So as in COPE-II,[11] ST actions are linked to changes in symptoms rather than to existing symptoms. This approach requires that patients have skills and knowledge to recognize deterioration in their symptoms.[28]

Patients are asked to complete the symptom diary that includes respiratory symptoms and relevant comorbid symptoms, every day. When patients do not experience deterioration in any of the predetermined symptoms listed in the diary during the last 24 hours, they are instructed to tick the box 'no change in symptoms' (indicating no further actions are required). Whenever they experience deterioration in any symptom listed in the diary, they are asked to report the level of change for each of the listed symptoms and if this change is of sufficient magnitude, consult their tailored action plan.[26]

Besides the COPD component, all daily symptom diaries and action plans include one or more comorbid components in a pre-defined order: (I) CHF; (II) anxiety and/or depression (AD); (III) IHD; and (IV) diabetes. Diabetes action plans differ for patients with type 1, type 2 and prednisolone-induced diabetes. As such, there are 21 possible action plans that can be instigated.

Cardiac component

Similar action plans are provided for two cardiac comorbidities, IHD and CHF, in both Australia and the Netherlands.

For CHF three questions are included in the daily symptom diary regarding fluid retention (weight, swelling of ankles and abdomen, and waking up at night short of breath). According to the action plan, patients should increase/start their diuretic medication when they record 'a significant change' for two consecutive days for at least one of these questions. The expert team agreed that a change in weight of at least one kilogram in 24 hours should be considered a significant change. Patients are asked to contact the casemanager if symptoms do not decrease with diuretic therapy, or if they think they need more than the 3-day diuretic course as directed in the action plan. In the Netherlands patients are asked

to contact their cardiac nurse directly.
A second CHF action plan component is included for safety reasons. Patients are asked to contact the case-manager (or cardiac nurse for Dutch patients) if they become more light-headed and/or dizzy. Consequently, the case-manager contacts the cardiac nurse to see if further actions are required (possible causes for these symptoms include rhythm disorder, over diuresis or a side effect of medication).
The existing action plan for IHD, developed by the 'National Heart Foundation of Australia', is being used with minor adjustments in lay-out.[29]

Anxiety and depression

The action plan for anxiety and depression advises patients to commence relaxation exercises (which are practiced during the SM courses) if they experience increased AD. If symptoms do not improve after 5 days patients are asked to contact the case-manager (Dutch patients could directly contact the mental health worker). When necessary, their predefined 'plan' (e.g., seeing their GP to discuss their symptoms and management) is activated and/or a consult with a psychologist arranged.
Prior to inclusion patients are screened with the Hospital Anxiety and Depression Scale (HADS).[30] Patients with scores meeting recognized clinical cut-off points (exceeding 10 per subscale) of the HADS[30] are offered psychological counseling prior to the baseline measurement.
Although experiencing suicidal ideation is an exclusion criterion for the COPE-III study, standardised action plans are used if patients develop suicidal ideation during the study. For example, patients may contact nurses who conduct a risk assessment and patients are also provided with an emergency 24-hour phone number for specialised counselling for suicidal ideation.

Diabetes

Prednisolone treatment of COPD exacerbations increases blood glucose levels (BGLs), especially in patients with preexisting diabetes. Hyperglycaemia in patients treated with prednisolone predominantly occurs between midday and midnight.[31] Higher glucose concentrations are associated with increased mortality, morbidity and length of hospital stay during a COPD exacerbation.[32,33]
Separate diabetes action plan components were developed for type 1, type 2 and prednisolone-induced diabetes. In contrast with the other comorbidities, the diabetes action plans are not linked to a change in 'diabetes' symptoms, but to the start of a COPD exacerbation. When taking prednisolone, patients are advised to check their BGL four times per day (before breakfast, lunch, dinner, and bed time). Extra training on blood glucose monitoring and insulin injections is then arranged with a diabetes nurse if required.
There are differences in the action plans for diabetes used in Australia and the Netherlands,

in order to mimic as much as possible usual care in both countries and simplify possible future implementation.

In Australia, patient management plans have been developed for two main groups of patients: (I) patients with diet-controlled diabetes or taking oral hypoglycaemic agents; and (II) patients already taking insulin. If patients record one BGL above 15 mmol/liter or two measurements above 10 mmol/liter, the action plan directs them to contact the case-manager who then contacts an endocrinologist. Patients who are not already taking insulin are taught to administer insulin isophane during COPD exacerbations, with dosing adjustments by an endocrinologist based on ongoing BGL recordings. Patients who are already taking insulin have their current insulin regimen doses adjusted by the endocrinologist.

In the Netherlands, patients with diet-controlled diabetes or taking oral hypoglycaemic agents are instructed to use insulin injections temporarily if they experience a high BGL (one BGL measurement above 15 mmol/liter or three measurements above 10 mmol/liter during a 24-hour period). Insulin dosing schedules are patient-fitted by the diabetes nurse and discussed during SM training. Patients have a tailored insulin dosing schedule (as advised by the diabetes nurse) or they are instructed to administer shortacting subcutaneous insulin using a sliding scale regimen.

Optimising of the COPE-III ST intervention

Prior to the start of the randomized controlled trial, the COPE-III ST intervention was tested in six patients with severe COPD to further optimize the intervention. Recruited patients were already included in an intensive nurse-led case-management program to which the COPE-III ST intervention was added. During the pilot, study nurses and patients were asked to provide frank feedback on the materials. During and after the pilot, significant adjustments were made to the ST materials. We have summarized an overview of these adjustments in Table 4.2. The intervention materials were adjusted to ensure that the intervention could be easily implemented in different health care systems.

Training of the health care providers

Both the COPE-I and COPE-II studies were extensively piloted (by groups of health care providers and patients). Besides optimising the intervention, the goal of these pilots was to train all health care providers in 'SM'. In addition, all involved health care providers in the COPE-III study attended a half day course regarding the guidance of group sessions. The content of this course included discussion of behavioural change techniques that were embedded in the SM sessions: components of education, training, modelling, and enablement, which target desirable and specific behaviours including individualised diary use, patient recognition of deterioration in symptoms, and the correct and timely use of an action plan.[26] Ongoing, regular follow-up meetings (approximately once a month) were

planned with the health care providers involved.
The COPE-III study was also extensively piloted by patients and health care providers. The education in comorbidities was provided by disease experts in both countries (approximately 2-3 hours per comorbidity) and predominantly directed towards triaging of problems that could occur in these complicated COPD patients. Overlap in disease symptoms was discussed intensively. The training in SM and behaviour change principles was provided by an Australian psychologist during a 2-hour group meeting. This meeting was recorded, so it could also be viewed by the study nurse in the Netherlands.
Separate training in the diaries and action plans was provided by the study investigators in both countries (approximately 4 hours), with frequent follow-up meetings, that were especially important during the first year of the study.

DISCUSSION

The COPE-III study is focused on treatment of COPD and common comorbid diseases. The intervention was developed and adjusted by using experiences and knowledge learnt from two previous COPE studies and by a pilot study. Although the action plans used in COPE-III are established and cannot be changed during evaluation, we are aware that we can continue learning from our experiences with COPD ST.

In the COPE-III study, we are attempting to deal with two of the most important lingering issues within ST, namely dealing with comorbidities and ensuring patient safety. We believe that a 'one size fits all' approach that focuses solely on traditional symptoms of COPD is inadequate and in fact, potentially dangerous in patients with (numerous and severe) comorbidities. This was the rationale underpinning the COPE-III approach. We have tried to optimize patient safety by ensuring a case-manager who is accessible to patients throughout the study. This is emphasized during patient training and highlighted on all ST materials. We also incorporated fallback procedures into the action plans, such as contacting usual health care providers for unresolved or worsening breathlessness or fever (see Table 4.2). The safety of the study is monitored by a Data and Safety Monitoring Board.

Another recommendation is that ST approaches have to be included in a formal SM training intervention[10] that includes behavioural change techniques[9] and is tailored to the patient's individual needs. The COPE-III intervention meets all of these criteria. Behavioural change techniques are included in an extensive patient training intervention (e.g., education, training, modeling, individualised action plans, behavioural enablement, individualised goal setting, and feedback on behaviour). Although ST of co-morbidities is patient-tailored, the content of the SM training is part of an intervention with set components (e.g., disease education, relaxation, and breathing techniques). In COPE-III we have utilised a ST

Table 1 Characteristics of the COPE-I, COPE-II, and COPE-III study

COPE study	Methods				Participants			SM intervention group			Primary outcome	Secondary outcomes
	Design	Intervention	Control	Follow-up (months)	Numbers	Major inclusion criteria	Major exclusion criteria	Setting	Session frequency and duration	Key topics		
I	RCT	SM, ST and non-standardized low-intensity exercise	Usual care	12	127 intervention; 121 control	COPD diagnosis; (ex) smoker; age: 40-75	Medical condition with low survival, serious psychiatric morbidity; other serious lung and cardiac disease	Outpatient clinic, exercise in private practices	4 weekly 2-hour group sessions and 1 follow-up 2-hour group session given 3 months after the 4th session. Professionals: respiratory nurse, physiotherapist	COPD knowledge, symptom recognition, COPD ST action plan, inhalation technique, exercise, relaxation, nutrition, breathlessness, energy conservation, communication and social relationships	HRQoL (SGRQ)	Symptoms and exacerbation frequency of COPD, self-confidence, 6MWT, lung function, doctor consultations, hospital admissions, days lost from work
II	RCT (2-by-2 factorial design)	SM, ST and standardized exercise	SM intervention and standardized exercise	24 (published: 12 months)	70 intervention; 72 control	COPD diagnosis; ≥3 exacerbations, and/or 1 respiratory hospitalization in previous 2 years; (ex) smoker; age 40-75	Medical condition with low survival or serious psychiatric morbidity; other serious lung or cardiac disease	Outpatient clinic, exercise in private practices	4 weekly 2-hour group sessions and 5 follow-up phone calls. Professionals: respiratory nurse, physiotherapist	COPD knowledge, symptom recognition, COPD ST action plan, inhalation technique, exercise, relaxation, nutrition, breathlessness, energy conservation, communication and social relationships	Exacerbation severity—daily symptom diary (exacerbation days and severity scores)	Exacerbation frequency, hospital admissions and days, courses of oral steroids and antibiotics, lung function, CRQ, CCQ, HADS, HR-QoL, health care utilisation, costs
III	RCT (international-multisite)	SM and ST	Usual care	12	Recruitment in progress	COPD diagnosis; ≥1 comorbidity: IHD, CHF, AD, DM; ≥3 exacerbations, and/or 1 respiratory hospitalisation in previous 2 years; age ≥40	Medical condition with low survival or serious psychiatric morbidity; other serious lung disease; low cognitive functions	Outpatient clinic	4 or 5 weekly sessions (2 individual 1-hour sessions; 2 or 3 two-hour group sessions) and 3 follow-up phone calls. Professionals: respiratory, cardiac, mental health and/or diabetes nurse	COPD and comorbidity knowledge, symptom recognition, ST action plan for COPD and comorbidities, inhalation technique, exercise, relaxation, nutrition, breathlessness, energy conservation	Number of COPD exacerbation days—daily symptom diaries	Exacerbation severity (symptom score), hospital admissions and days, number of CHF exacerbation days, comorbid symptom scores, courses of oral steroids and antibiotics, lung function, CRQ, ICFS, HADS, CSES, HR-QoL, SM behaviour and knowledge, self-confidence, satisfaction, adherence with ST protocol, health care utilisation, costs

6MWT, 6-minute walking test; AD, anxiety and/or depression; ATS, American Thoracic Society; CCQ, clinical COPD questionnaire; CHF, chronic heart failure; CRQ, chronic respiratory questionnaire; CSES, COPD self-efficacy scale; DM, diabetes mellitus; ER, emergency room; FEV_1, forced expiratory volume in one second; FVC, forced (expiratory) vital capacity; GOLD, global initiative for chronic obstructive lung disease; GP, general practitioner; HADS, hospital anxiety and depression scale; HR-QoL, health related quality of life; ICFS, identity-consequence fatigue score; IHD, ischaemic heart disease; RCT, randomised controlled trial; SGRQ, St George's respiratory questionnaire; SM, self-management; ST, self-treatment.

approach that provides appropriate tools, training in necessary skills, and the possibility to incorporate the approach in existing health care support systems.[9]

Additionally, health literacy of patients should also be taken into account. Literature suggests that only a third of patients with low literacy are able to comply with simple written instruction such as 'Take two tablets by mouth twice daily' (34). We are acutely aware that our ST materials are much more complicated than this instruction, and we concede that SM is not an approach that would be suitable for all patients with chronic diseases like COPD. However, lessons were learnt during the pilot study and the patient materials were simplified. Although we exclude patients who are non-literate and those assessed as having an impaired cognitive function,[26] we have not excluded people with low health literacy in any of the COPE studies.

For ST of COPD exacerbations it is also important to keep in mind that patients should be able to use their action plans regularly. If their symptoms are not varying with some frequency, amounting to repeated exacerbations, there are no opportunities for them to refer to their action plan and therefore learn from or receive feedback on their actions. In COPE-II and COPE-III it was therefore decided to include only frequently exacerbating COPD patients (patients who had at least three exacerbations or one respiratory related hospitalization in 2-year previous to inclusion).

At present there is no general agreement on the specifics of training health care providers to deliver optimal SM interventions, although experts agree that training of health care providers is crucial. In preparation for COPE-III, a psychologist was asked to provide a discussion session regarding behavioural change techniques that could be included in the COPE-III intervention. As this is an important aspect of SM, additional follow-up meetings were organized to discuss behavioural change techniques.

Finally, little is known about the factors influencing the success and failure of SM interventions, although understanding is growing as we acknowledge the intricacies of human behaviour and what drives behaviour change. Perhaps even less is known of the factors influencing the success and failure of ST interventions, and further studies will hopefully shed more light on this in the near future.

Table 4.2. Summary of adjustments of self-treatment materials (usual symptom cards, symptom diary, action plan, course material) as a result of the pilot study

Aims	Documents	Adjustments
Simplification of education material	All materials	Comorbidity components are colour coded and numbered
	Symptom diary	Reduction of numbers of items by combining the 'minor respiratory symptoms' in one question
	All materials	Remove medical jargon and simplify text
	Symptom diary	Make more clear that the action plan needs to be consulted by using red 'marked' boxes for a change that is 'significantly more than usual'
	All materials	Consistency in wording
	All materials	Consistency in the order in which comorbidities are addressed
Better discrimination breathlessness due to COPD or due to IHD and CHF	Usual symptom cards	IHD item: record what patients normally use as IHD medication (e.g., a spray or a tablet)
	Symptom diary	between IHD item: use of 'sudden change in your breathing' instead of just 'short of breath'
	Action plan	Inclusion of a final box with the comment: 'If you have been significantly more breathless than usual (marked red boxes) for at least 2 days in a row but you did not tick any red boxes for other symptoms: please contact the study office'
	Course material	Extensively discussion of breathlessness by working through scenarios
Stimulating patients to go through the complete action plan	Action plan	Insert a clear message after every box in the action plan to go to the next part of the action plan
	Course material	Practising with the action plan and underlining to read through the complete action plan
Increasing of safety of the ST approach	Symptom diary, action plan, course material	Making clear that patients can always contact the study nurse if uncertain or having questions
	Action plan	Adding a final box to the action plan with the following messages: ➢ Contact the study office if you have been significantly more breathless than usual (ticked red boxes) for at least two days in a row but you did not tick any red boxes for other symptoms ➢ Contact your GP if you have a fever (more than 38.5 °C) for at least 2 days in a row but you did not tick any red boxes for other symptoms ➢ Please check the action plan tomorrow again and remember: you can always contact the study office during office hours if you have any doubts or questions 'phone number' (Monday-Friday: 8.00 am-4.30 pm; excluding Public Holidays) ➢ If you require assistance during out of office hours: please contact your GP or Emergency Department

IHD, ischemic heart disease; CHF, chronic heart failure; ST, self-treatment; GP, general practitioner.

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5

Construct validity of the Dutch version of the 12-item Partners in Health scale: measuring self-management behaviour and knowledge in patients with COPD

A. Lenferink
T.W. Effing
P. Harvey
M. Battersby
P. Frith
W. van Beurden
J. van der Palen
M.C.S. Paap

Plos One 2016;11(8):e0161595

ABSTRACT

Objective

The 12-item Partners in Health scale (PIH) was developed in Australia to measure self-management behaviour and knowledge in patients with chronic diseases, and has undergone several changes. Our aim was to assess the construct validity and reliability of the latest PIH version in Dutch COPD patients.

Methods

The 12 items of the PIH, scored on a self-rated 9-point Likert scale, are used to calculate total and subscale scores (knowledge; coping; recognition and management of symptoms; and adherence to treatment). We used forward-backward translation of the latest version of the Australian PIH to define a Dutch PIH (PIH(Du)). Mokken Scale Analysis and common Factor Analysis were performed on data from a Dutch COPD sample to investigate the psychometric properties of the Dutch PIH; and to determine whether the four-subscale solution previously found for the original Australian PIH could be replicated for the Dutch PIH.

Results

Two subscales were found for the Dutch PIH data (n = 118); 1) knowledge and coping; 2) recognition and management of symptoms, adherence to treatment. The correlation between the two Dutch subscales was 0.43. The lower-bound of the reliability of the total scale equalled 0.84. Factor analysis indicated that the first two factors explained a larger percentage of common variance (39.4% and 19.9%) than could be expected when using random data (17.5% and 15.1%).

Conclusion

We recommend using two PIH subscale scores when assessing self-management in Dutch COPD patients. Our results did not support the four-subscale structure as previously reported for the original Australian PIH.

INTRODUCTION

Self-management interventions aim to improve the health behaviour and self-management skills of patients with chronic and complex health conditions in order to improve the physical health and well-being of these patients.[1,2] Problem solving, decision making, resource utilisation, forming patient-provider partnerships, and patient-tailored action planning are essential parts of self-management.[2] As patient self-management skills develop, increased confidence in their own health management becomes a powerful factor in inducing and sustaining behaviours that provide perceived benefits.[2,3] This is especially important in patients with Chronic Obstructive Pulmonary Disease (COPD) who are responsible for their day-today disease management.[2] COPD self-management interventions aim to e.g., instil the confidence to recognise COPD exacerbations[1] and to take appropriate actions when COPD symptoms deteriorate. The most recent Cochrane review regarding COPD self-management interventions showed that COPD self-management interventions are associated with improved health-related quality of life (HRQoL), a reduction in the number of hospitalisations, and improved dyspnoea.[4] In COPD patients, assessments have traditionally involved objective parameters (e.g., lung function). More recently, patient-reported outcomes (PROs) have become increasingly popular. Using PROs, it is not only possible to evaluate outcomes such as COPD-specific HRQoL[5] (e.g., St. George's Respiratory Questionnaire (SGRQ)[6]) and COPD self-efficacy[7], but also perceived health outcomes. Little is known, however, about perceived health outcomes such as self-management behaviour and knowledge in COPD patients.

To facilitate the measurement of self-management behaviour and self-management knowledge of patients with chronic diseases the 12-item Partners in Health scale (PIH) was developed by an Australian research group.[8] The Australian 12-item PIH was intended to provide a first step of assessing a patient's self-management in developing a collaborative patient-clinician self-management care plan. It was designed to assist patients with chronic and complex conditions in learning how to participate more effectively in the management of their condition and to improve their self-management skills, because previous research indicated that providing coordinated care for people with chronic conditions was predominantly based on their self-management capabilities rather than on the severity and/or complexity of their illness.[9] The Australian 12-item PIH was therefore introduced as a generic self-rated clinical PRO tool suitable for: 1) assessing the effects of self-management interventions in populations with different chronic conditions; 2) comparing populations; and 3) determining changes in patient self-management knowledge and behaviour over time.[8] Subsequently, it was found to be a valid measure of patient competency in relation to the self-management of their chronic conditions.[8] Four subscales were reported based on Principal Component Analysis (PCA): knowledge, coping, recognition and management of symptoms, and adherence to treatment.[8]

Hitherto, the Australian PIH has been successfully used to evaluate (self-) management strategies for chronic disease prevention and management.[10] In addition, the PIH has also been used as a screening tool to identify patients who would most benefit from a self-management care plan.[11] The PIH has been translated into Spanish and validated among healthcare users (patients with diabetes, hypertension and cancer) of primary care in Mexico.[12] Three subscales were reported for the Spanish PIH based on exploratory factor analysis (FA).[12]

Having greater insight into COPD patient behaviour and knowledge would facilitate the identification of key COPD self-management skills that could be improved. This could help inform further improvement of patient-tailored COPD self-management interventions and may reduce the high disease burden, hospitalisations and healthcare cost in COPD patients.[13,14] The PIH has, however, not been validated for use in patients with COPD nor has it been validated in the Dutch language. The aim of the current study was, therefore, to assess the construct validity and reliability of a Dutch translation of the latest PIH version in Dutch patients with COPD. More specifically, we assessed the underlying dimensionality of the Dutch PIH using data from a Dutch COPD sample participating in the COPE-III self-management intervention study[15] to determine whether the same four-subscale solution of selfmanagement for the original Australian PIH as proposed by Petkov et al.[8] could be found for the Dutch PIH.

MATERIALS AND METHODS MEASURES

Partners in Health scale

The original PIH consists of 12 items (PIHv1), scored on a selfrated 9-point Likert scale with 0 indicating the worst and 8 the best possible patient self-management.[8] Both a total sum score and four subscale scores can be calculated for the PIHv1: knowledge (items 1, 2, 4, 8); coping (items 10–12); recognition and management of symptoms (items 6, 7, 9); adherence to treatment (items 3, 5). Reliability (estimated using Cronbach's Alpha) equalled 0.82 for the total scale.[8] The 12-item PIHv1 is based on six key principles essential for effective self-management that were transformed into 12 items assessing how well persons were self-managing. It was revised by splitting two double-barrelled items into two questions each; for instance emotional and social impacts of the condition(s) became items 10 and 11 in PIHv2. The resulting 14-item PIH version was used clinically for several years and was also included in a RCT aimed at improving patient self-management competencies.[16] After a national project to determine a consensus definition of self-management the 14-item PIH was further revised,[17] which allowed the number of items to be reduced and the time to administer and score the tool minimized, balanced against retention of items that were

clinically relevant. Therefore, item 5 from PIHv1 ('arranging and attend appointments') was changed into item 6 'attend appointments' in PIHv2. Two questions on monitoring and managing symptoms (item 6 and 8) were removed from PIHv1. In addition, an item on ability to access culturally appropriate services was added (item 5). The result was the current 12-item PIHv2 from which the Dutch version was derived. A copy of PIHv2 can be obtained from Flinders University, Australia.

Development of the Dutch PIH

For use in a Dutch speaking population the PIHv2 was translated into Dutch then back-translated into English by an independent translator (guidelines Guillemin et al.[18,19]). A Dutch PIHv2 (PIH(Du)) was defined (see S1 Table) and pretested in a qualitative evaluation with a small group of Dutch COPD patients who did not participate in the COPE-III self-management study,[15] which is an ongoing RCT regarding selfmanagement in COPD patients with comorbidities. Sampling of patients for the qualitative evaluation was continued until saturation of information was achieved. Comments on the wording, layout of the 9-point Likert scale, and issues encountered during the self-administration process were collected using the three-step test interview (TSTI).[20] Respondents completed the PIH and concurrently verbalised their thoughts ('think aloud technique'). Subsequently, they answered probes about terms or phrases in the PIH. A predefined cognitive testing protocol[21] was used for this second step. The third step elicited experiences and opinions of patients.[20,21] Non-verbal communications were documented and all verbalisations were audio recorded for further analysis. Data from the TSTI were analysed using content analysis approach,[22] in which coding categories are derived directly from the text data.

Patients

We used baseline data from Dutch COPD patients with comorbidities participating in the COPE-III study for the psychometric analyses.[15] The patient eligibility criteria have been previously described[15] and can be summarised as follows: a clinical diagnosis of COPD[23]; clinically stable at the time of inclusion; at least one clinically relevant comorbidity (ischemic heart disease, heart failure, diabetes, anxiety and/or depression); at least three COPD exacerbations and/or one hospitalisation for respiratory problems in the two years preceding study entry; and adequate Dutch language proficiency. All procedures performed in the current study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was approved by the Medical Ethical Committee at Medisch Spectrum Twente and by the Southern Adelaide Clinical Human Research Ethics Committee. The study is registered in the public Australian New Zealand Clinical Trials Registry (ACTRN12612000514808). Written informed consent was obtained from all individual participants prior to participation in this study.

Statistical analyses

Descriptive statistics were calculated using SPSS v20.0.[24] Both scale structure and item properties were analysed. The analytic strategy was defined prior to viewing the dataset. Following Paap et al.,[25] we used two complementary statistical methods to evaluate the dimensionality of the PIH(Du): 1) Mokken Scale Analysis (MSA; a non-parametric technique); and 2) common FA.

In recent years, MSA has increased in popularity in health research.[26-31] MSA identifies scales that allow an ordering of individuals on an underlying scale using unweighted sum scores.[32,33] In order to ascertain which items co-vary and form a scale, scalability coefficients are calculated on three levels: item-pairs (H_{ij}), items (H_i), and scale (H). H is based on H_i and reflects the degree to which the scale can be used to reliably order persons on the latent trait using their sum score. A scale is considered acceptable if $0.3 \leq H < 0.4$, good if $0.4 \leq H < 0.5$, and strong if $H \geq 0.5$.[32,33] MSA can be used in both a confirmatory and exploratory manner. The exploratory procedure follows a bottom-up, iterative approach. First, a start set of items is identified in one of two ways: 1) the item pair with the highest H_{ij} value is chosen (default), or 2) the researcher specifies the start set manually. Subsequently, the relationship (in terms of H coefficients) of each remaining item with the start set is evaluated one item at a time. At each step, the item that maximises H is added, but only if a) it has a positive relationship (in terms of H_{ij}) with the set of items in the current scale, and b) adding the item results in an H_i value higher than a predefined user-specified constant c (typically 0.3). When no more items can be added, a second subscale is formed. The procedure stops when no items are left, or when no other items can be assigned to subscales anymore. For more detailed information on MSA, we refer to Paap et al. (2013; online supplement[25]). MSA was applied using the R[34] package Mokken.[35] We ran the exploratory analysis several times in a row, each time increasing the lower bound scalability coefficient c.[33] The outcomes indicate whether the data set is onedimensional or multidimensional.[33]

We used Parallel Analysis (PA) based on Minimum Rank Factor Analysis (MRFA); this method will be abbreviated as PA-MRFA.[36] MRFA is a common FA method that allows one to find the "most-unidimensional" solution.[37] In PA-MRFA, for each factor the empirical value of the proportion of explained common variance (ECV) is compared to corresponding factors ECV derived from random data.[36] The random data are generated based on the sample size of the real data assuming independence among items.[38] Typically, a large number of random datasets are generated, resulting in a sampling distribution of ECV-values for each factor. To determine the optimal number of factors, for each successive factor the observed ECV can be compared to the mean or the 95th percentile of the sampling distribution associated with the respective factor. We used the software package FACTOR[39] to perform the PA-MRFA analyses. We used the standard configuration for PA-MRFA: 500 random

correlation matrices were generated based on "random permutation of sample values".[36] Usually, it is advised to use polychoric correlation-based common FA in the case of ordinal data (with five or fewer answering categories). Although the PIH items were scored with nine response options (eligible to be treated as continuous), we had to collapse categories for all items prior to the analyses, in order to ensure adequate coverage (at least 10–15 observations per item-category combination). Polychoric correlation based models would, therefore, be more appropriate. However, they are known to be more prone to convergence issues when small sample sizes are involved. It was therefore decided to run two sets of analyses; one based on polychoric correlations and one based on Pearson correlations. The 95th percentile threshold was used for the polychoric analysis and the mean threshold for the Pearson analysis.[36] Since both sets of models converged and resulted in similar factor solutions, we will only report the findings based on the polychoric correlations. An oblique factor rotation (Promin) was used to facilitate interpretation of the factors.[40]

RESULTS

Qualitative evaluation of the PIH(Du)

Qualitative data were gathered during interviews with four Dutch COPD patients. In general, the instructions were found to be clear and patients indicated that the PIH(Du) was a proper, readable, synoptic, complete and clear instrument. Critical notes were: use of long sentences; information on a time period that fits with the completion of the instrument was lacking; and it could be more COPD-specific. In addition, more specific comments on the individual items and the clarity of wordings were provided for the items 5–12 (see Table 5.1). Patients' suggestions for improvements were, for instance, adding a definition of a 'healthcare professional' and 'blood glucoses level'. Other suggestions were: delete 'culture, value and beliefs' from item 5 ("You could leave out the last part of this question (culture, values and beliefs)"); add 'life style' and rephrase item 9; and split item 12 into different items for the different healthy life styles (e.g., 'I manage to live a healthy life with no smoking', 'I manage to live a healthy life with moderate alcohol use'). The horizontal axis of the 9-point Likert scale was found acceptable and familiar ("This is quite similar to what they ask in connection with the pain threshold"). However, patients also indicated that a PIH(Du) item score of zero (lowest possible self-management) will most likely only be used by patients with an end-stage disease. Suggested improvements for the 9-point Likert scale were using fewer response options and visualising response options ("You could use it like a traffic light").

Table 5.1. Results of the qualitative evaluation of the 12-item PIH(Du) in four Dutch COPD patients

Item	Interpretation	Comments (e.g., on clarity of wordings)	Improvements
1: Knowledge of illness	"What I know in general about my health conditions" "How much you know yourself about your illness." "What the health reasons are." "Whether I have lung issues." "Whether you are well informed about your own health conditions."	-	-
2: Knowledge of treatment	"Whether I do know what the treatments and medications are for my conditions." "It is about what I know in general about the medicines I use" "The treatment with medication changes so quickly. I think, regarding the information about medicines, that it could be done better." "And I have pointed that out a few times about my treatment."	-	-
3: Taking prescribed medication	"Just whether to take the medicines and to follow the treatment instructions." "Regarding those medicines….nothing is ever said about it or how to use it." "That you take what is prescribed, as has been agreed with your healthcare provider."	-	-
4: Decision sharing	"In principle, I always take decisions together with my doctor or healthcare provider." "Actually, I haven't been informed about that yet, about what's wrong – or not wrong – with me." "I don't know what, what, what ... where I always stand." "I should talk about it with the doctor or healthcare provider then, shouldn't I? "Whether you take decisions if you do experience symptoms."	-	-

5: Services fit with culture/ value/ beliefs	"Because I do occasionally discuss this with my doctor." "Should I also arrange for a health professional? That 's what it seems to say." "That is self-evident that a healthcare provider should adapt to someone with a different cultural background"	"Yes, and just what does it all mean?" "I don't understand it very well." "But this has nothing to do with the kind of healthcare you need, I think." "The most important thing is that you are able to arrange your healthcare as much as possible yourself."	"You could leave out the last part of this question (culture, values and beliefs)."
6: Arrange and attend appoint-ments	"Then you need to go to a doctor or health professional." "An appointment where I need to go."	"I've never had contact with a health professional. Then I don't know what this health professional is supposed to do." "What do you mean by that, a health professional?" "So I'd think this word [health professional] is not appropriate this questionnaire.	"Add a definition of health professional."
7: Track of symptoms	"I understand my symptoms." "Then you need to indicate how and what then. The same goes for your medicines. If I'm breathless or something. "To act in time if you are not feeling well." "That you need to know your body well yourself." "I recognise the symptoms, but I don't take action."	"I think that this is a good question." "This is a very long sentence." "This is not applicable to me, but I do understand it." "I cannot fill in fairly well or very well, since I don't know what that is: peak flow." "Peak flow? What do they mean by that?" "For instance blood sugar levels and peak flows. I don't know what that is." "I don't know to what extent blood glu-cose levels, peak flows, weight and sleep-ing problems are related to COPD. I don't know that as a layperson, do I?"	"Add a description of peak flow and blood glucoses level to this question." "Shorten this question." "Change this question into: 'For in-stance, I watch my symptoms or early warning signs, such as breathlessness', which makes this more relevant for COPD.
8: Take action when symptoms deteriorate	"Well, then I always tell the doctor when the symptoms get worse." "Whether I do take action when there are warning signs" "I never take action when I have symptoms or something" "Yes, well, yes, I do take action. But quite late, usually." "Usually I contact the pulmonary physician then"	"Because I also think that many people will not understand this... symptoms and all those kinds of words"	"If you want to make it easier to un-derstand for everyone, then you could simplify it" "Make it more concrete"

9: Dealing with effects on physical activity	"How you function yourself." "What is possible and what is not possible." "That I have everything under control, such as performing household chores and walking." "If I do those activities, how my health will develop" "If someone leads a regular life, then you will have control over your lungs, over your walking, won't you."	"Rather a mouthful, in my opinion. And that question really depends on how your complaints are at that moment." "Short term or long term?" "Because that depends on how your physical condition is at that moment" "So I think this question is very difficult defined." "The effects will come later." "I think this it is a little bit hard to answer" "The effect of health conditions, I think that yes, that depends on the severity of your conditions, of course.	"Maybe add life style" "So, I would describe it more, like 'I can control my physical activities such as household chores, walking, in a normal way.' " "And you could put it in an even simpler way, like: 'I have control over my health conditions and over my daily activities myself. For example, walking and household chores.' "
10: Dealing with effects on emotional wellbeing	"Well, whether I have my emotions under control and that I mentally...That all is well mentally." "Whether I have control over the effects on my emotional wellbeing." "Whether I can keep my emotions under control, when I have problems." "This question is not applicable to me. Actually, I'm always in a good mood."	"Very long sentences. It's almost like two questions in one." [reads first half of question out loud] "(...) the effect of my health condition, I think that is very incomprehensible for many people." "I think the word 'effect' will be filled in differently than what is meant."	"You need to turn it around. What or with a question: 'what is the effect of my health...ehm...condition on your own emotions and whether you have it under control?' " "Start this question with 'I have insight into my health condition', because that is easier to understand."
11: Dealing with effects on social life	"I often have things that I think I love to do this or that." "How I behave and everything." "Whether I can cope with my health issues." "I'm not very sociable; I don't need to be around a lot of people. So I'll never visit a crowded place." "It does not have any effect when my symptoms change."	"Also very broad" "I think this is more about like a character trait." "It is a general list. I have trouble relating it to lung problems"	"Just like before, start this question with 'I have insight into (…)'."
12: Manage to live a healthy life	"Whether I am smoking, using alcohol or doing a lot of physical exercise."	"There are several things incorporated that I think are very difficult to answer" "It can be difficult to indicate whether you eat healthy, I don't know that." "Everything has been added to this question." "I cannot answer this question by giving one answer, since this question contains different things of a healthy life."	"Split this question into different questions for the different healthy life styles, e.g., smoking behaviour, alcohol use, sports etc."

Patient characteristics

Patient characteristics for the Dutch COPD sample used for psychometric analysis can be found in Table 5.2. The PIH(Du) (see S2 Table) was completed by 118 COPD patients (65.3% male, mean age 67.6, 19.5% smoker) diagnosed with at least one clinically relevant comorbidity (71.2% cardiovascular disease, 40.7% diabetes, 19.5% anxiety, 16.9% depression).

Table 5.2. Characteristics of Dutch COPD patients with comorbidities who completed the 12-item Dutch Partners in Health Scale

Patient characteristics	Total (n = 118)
age in years; mean (SD)	67.6 (8.9)
male; n (%)	77 (65.3)
smoker; n (%)	23 (19.5)
mMRC dyspnoea score, range 0-4; mean (SD)	1.99 (0.91)
health literacy*, range 1-5; mean (SD)	2.56 (0.92)
lung function parameters; mean (SD)	
FEV_1% predicted post-bronchodilator	52.4 (14.7)
FEV_1/FVC post-bronchodilator	51.3 (12.9)
diagnosed disease; n (%)	
COPD	118 (100)
cardiovascular	84 (71.2)
diabetes mellitus	48 (40.7)
depression	20 (16.9)
anxiety	23 (19.5)
12-item PIH(Du) total score; mean (SD)	78.1 (9.7)
PIH(Du) subscale 1**; mean (SD)	35.2 (6.9)
PIH(Du) subscale 2***; mean (SD)	42.9 (4.3)

FEV_1: Forced Expiratory Volume in one second as percent predicted for age, gender and height; FVC: Forced (expiratory) Vital Capacity; mMRC: modified Medical Research Council; PIH(Du): Dutch Partners in Health scale; SD: Standard Deviation

*Health literacy was measured by asking patients for their confidence in completing medical forms by themselves with higher scores indicating lower confidence;

**Subscale 1 was tentatively labelled as 'knowledge and coping';

***Subscale 2 was tentatively labelled as 'recognition and management of symptoms, adherence to treatment'.

Dimensionality and reliability analyses

Running exploratory MSA indicated a two-dimensional pattern for the PIH(Du) (see Table 3). The two PIH(Du) subscales were tentatively labelled as: 1) knowledge and coping (items 1, 2, 8–12) and 2) recognition and management of symptoms, adherence to treatment (items 3–7).

Table 5.3. Scale solutions for the 12-item Dutch Partners in Health scale

12-item Dutch Partners in Health scale	MSA	PA-MRFA
Item 1: Knowledge of illness	1	1
Item 2: Knowledge of treatment of illness	1	1
Item 3: Taking medication as prescribed	2	2
Item 4: Decision sharing	2	2
Item 5: Services fit with culture/value/beliefs	2	2
Item 6: Arrange and attend appointments	2	2
Item 7: Track of symptoms	2	2
Item 8: Take action when symptoms deteriorate	2	1
Item 9: Dealing with effects on physical activity	1	1
Item 10: Dealing with effects on emotional wellbeing	1	1
Item 11: Dealing with effects on social life	1	1
Item 12: Manage to live a healthy life	1	1

MSA: Mokken Scale Analysis; PA-MRFA: Parallel Analysis based on Minimum Rank Factor Analysis;
Note: The last two columns indicate whether the item was assigned to the Dutch Partners in Health subscale 1 or 2. Subscale 1 was tentatively labelled as 'knowledge and coping', subscale 2 was tentatively labelled as 'recognition and management of symptoms, adherence to treatment'.

Table 5.4. Polychoric correlations matrix for the 12-item Dutch Partners in Health scale

	I1	I2	I3	I4	I5	I6	I7	I8	I9	I10	I11	I12
I1	1.00											
I2	0.60	1.00										
I3	0.03	0.16	1.00									
I4	0.27	0.26	0.73	1.00								
I5	0.40	0.38	0.34	0.61	1.0							
I6	0.00	0.14	0.70	0.46	0.22	1.00						
I7	0.12	0.26	0.42	0.39	0.44	0.20	1.00					
I8	0.34	0.31	0.23	0.24	0.50	0.07	0.56	1.00				
I9	0.25	0.28	-0.20	-0.05	0.24	-0.04	0.33	0.32	1.00			
I10	0.32	0.26	-0.06	0.11	0.40	-0.01	0.22	0.31	0.58	1.00		
I11	0.38	0.35	0.20	0.23	0.36	0.21	0.34	0.28	0.47	0.64	1.00	
I12	0.20	0.32	0.17	0.23	0.36	0.19	0.34	0.38	0.41	0.60	0.51	1.00

The H-values of the two subscales based on the Dutch data were good (0.43, subscale 1) and acceptable (0.38, subscale 2). The correlation between the two subscales was 0.43. The lowerbound of the reliability (estimated using Cronbach's Alpha) for the total scale equalled 0.84. Cronbach's Alpha was 0.80 and 0.72 for the PIH(Du) subscales 1 and 2, respectively.

Table 5.5. Results of Minimum Rank Factor Analysis Dutch Partners in Health scale

Factor	% ECV real data	Mean % ECV random data	95th percentile % ECV random data	Eigenvalue*
1	**39.4**	17.5	20.1	4.17
2	**19.9**	15.1	16.7	2.16
3	9.6	13.4	14.9	0.98
4	8.9	11.8	12.9	0.78
5	6.2	10.3	11.4	0.51
6	5.0	8.9	9.9	0.29
7	3.9	7.5	8.6	0.20
8	3.2	6.1	7.2	0.19
9	2.4	4.6	6.0	0.11
10	0.9	3.2	4.6	0.07
11	0.6	1.8	3.1	0.00
12	0.0	0.0	0.0	0.00

ECV: explained common variance
*Based on reduced correlation matrix
Note: Standardized Cronbach's Alpha (total scale) = 0.84

Table 5.6. Factor loadings of the Dutch Partners in Health scale based on Minimum Rank Factor Analysis

	PIH(Du) subscale 1: 'knowledge and coping'	PIH(Du) subscale 2: 'recognition and management of symptoms, adherence to treatment'
Item 1: Knowledge of illness	**0.57**	0.07
Item 2: Knowledge of treatment of illness	**0.47**	0.19
Item 3: Taking medication as prescribed	-0.39	**1.05**
Item 4: Decision sharing	-0.13	**0.93**
Item 5: Services fit with culture/value/beliefs	0.39	**0.48**
Item 6: Arrange and attend appointments	-0.26	**0.74**
Item 7: Track of symptoms	0.30	**0.45**
Item 8: Take action when symptoms deteriorate	**0.49**	0.26
Item 9: Dealing with effects on physical activity	**0.80**	-0.27
Item 10: Dealing with effects on emotional wellbeing	**0.89**	-0.17
Item 11: Dealing with effects on social life	**0.65**	0.12
Item 12: Manage to live a healthy life	**0.60**	0.13

PIH(Du): Dutch Partners in Health scale
Note: To aid interpretation, the factor loadings higher than 0.40 are printed in bold.

The factor analyses resulted in a very similar scale solution to the MSA analyses (see Table 5.3). The polychoric correlations matrix can be found in Table 5.4. The first two factors explained a larger percentage of common variance (39.4% and 19.9% for factor 1 and 2, respectively) than could be expected when using random data (see Table 5.5). The estimated correlation between the factors extracted from the Dutch data was 0.41. The factor analyses for the two PIH(Du) subscales showed that the newly added item 5 showed similar factor loadings for both subscales; 0.39 for subscale 1 and 0.48 for subscale 2 (see Table 5.6).

DISCUSSION

Our dimensionality analyses showed a two-subscale solution for the PIH(Du): 1) knowledge and coping; 2) recognition and management of symptoms, adherence to treatment. Our results therefore did not support the four-subscale structure as previously reported for the original Australian PIH.[8] It is of interest that a Spanish version of the PIH was found to have a three-subscale solution.[12]

Several possible explanations have been put forward to account for different findings in factorial solutions across studies: differences in statistical methods and target populations, sample size, number of items per factor, number of factors in the model, and the size of the communalities (proportion of the variance of an item that is accounted for by the common factors in the model).[31,41,42] At the time of the original Australian PIH development,[8] its dimensionality was evaluated by using a two-stage procedure: an exploratory PCA (data reduction technique to group items into a set of new variables) and a confirmatory common FA (a mathematical model to estimate the relationship between items and latent variables[43]) was subsequently used to "validate" the structure identified by the exploratory analysis. However, PCA and common FA will only produce similar results under very specific circumstances.[38] We favoured using exploratory IRT and common FA models over PCA in this study, because they are suitable for ordinal data[44] and result in meaningful scales (e.g., Borsboom et al.[45]). It is unclear which exploratory FA was performed for the Spanish PIH validation.[12] We were therefore unable to compare our results with the three-subscale solution for the Spanish PIH.

The MRFA criteria used in our study require less interpretation in determining dimensionality and allows one to find the "most-unidimensional" solution,[37] in comparison with conclusions based on a PCA. Petkov et al. used a Cattell's Scree plot[46] as a graphical representation of the eigenvalues and suggested a cut-off of three components as defined by the 'elbow'. This choice is somewhat arbitrary and the plot can be interpreted in different ways, since the slope has flattened from two components onwards and, therefore, the

cut-off point could also be at two or one component. It has been shown that the Scree test has a tendency to overestimate the number of subscales[47] and it should be used and interpreted with care. Kaiser's criterion to retain factors with eigenvalues greater than one for interpretation is the best known and most utilised method in practice.[48] Despite its simplicity, though, this method may also lead to arbitrary decisions and be inefficient in determining the number of subscales.[48]

There is no consensus about a decision rule for the minimal sample size requirements in dimensionality analyses. In the current study, our sample size of 118 COPD patients is of a small to moderate size, with a correlation between the two PIH(Du) subscales of 0.43 and Hvalues of 0.43 and 0.38. According to the guidelines of Straat et al.[49] the sample size should be 50 to 250 to obtain 90 to 99% correct item assignment and adequate to good Per Element Accuracy in MSA. For MSA analyses the required minimal sample size is mainly dependent on the correlations between the latent variables and the H-values of the items.[49] Based on the correlations and H-values we found in the current study, our sample size should be sufficient to obtain 94–99% correct item assignment.[49] For FA the minimally required sample size depends on a complex interplay of many aspects, e.g., the estimated factor loadings and communalities.[50] When communalities are high, sample size tends to have less influence on the quality of factor solutions compared to when communalities are low.[50] In case of relatively low communalities, a larger sample size and number of items per factor are needed to obtain stable results in FA.[41] Conversely, in case of a relatively small sample size, a higher number of items per factor (4 items per factor[42]), a small number of factors and moderate to high communalities are needed to estimate a model that will give a good representation of the population factors.[41] Since the factorial solutions we found consist of a small number of well-identified factors with moderate to high communalities, we feel confident that our low-dimensional solutions for the PIH(Du) will be easy to replicate.

Cross-cultural differences and adjustments made after publication of the original PIH may also have contributed to the discrepancy in dimensionality between the original Australian PIH and the PIH(Du). For instance, item 5 ('dealing with health professionals to get services that fit with culture, values and beliefs'), which is unique to the PIHv2, was difficult to interpret for Dutch patients and most patients felt the item was not applicable to them. In addition, item 5 showed high factor loadings on both of the Dutch subscales, making it difficult to assign the item to either scale. We therefore suggest removing this item. Item 10 ('manage the effect of health condition(s) on emotional wellbeing') has recently been added by the PIH authors in an attempt to show the psychological/emotional impact of the disease(s). Their clinical experiences so far suggest that the item is powerful in 'breaking open the case' to uncover factors that can interfere with self-management. However, this

item was poorly-received by patients completing the PIH(Du); patients indicated the item was too lengthy, the formulation too complex and it was unclear what the reference time period was. We therefore suggest specifying a recall period in the PIH.

Differences in heterogeneity between the Australian and Dutch samples may also have contributed to the difference in the number of subscales found. Studies on other self-report instruments, such as the SCL-90, have indicated that the number of dimensions found can be related to for example disease severity.[31] Whereas the original Australian PIH was completed by patients with different kinds of chronic diseases, including respiratory problems, the PIH(Du) was administered exclusively to COPD patients, albeit with comorbidities and different COPD severity scores. Patients may provide different responses if multiple chronic conditions are present. For instance, 'health condition(s)', as used in the items 1, 2, 4, 9, 10 and 11 from the PIH(Du) is a broad definition and can be interpreted in different ways. Patients completing the PIH may only have considered those health conditions for which they have recently experienced symptom deterioration. Therefore, when multiple chronic conditions are present, the specific contribution and effects of each chronic condition cannot be assessed by the PIH scores. However, PIH scores were developed to enable assessment of the knowledge and behaviour of patients in general to improve self-management interventions.

Based on our findings, we feel confident that the PIH is a useful tool in assessing self-management behaviour and knowledge in COPD patients, but we do recommend some minor changes to the instrument. Obviously, the PIH requires translation if used in other than the source language, which is often the case in international research.[51-53] However, when, besides translation, other changes are made over time to further improve measurement instruments, this may negatively impact its interpretation for use in research or clinical practice. First, with regard to changes made to the Australian PIH version, clear guidelines are needed before translation and validation of the instrument for use in other settings and countries can be continued. Second, we recommend introducing a recall period. Third, we suggest avoiding the use of terms with multiple meanings and composite items (e.g., it is difficult to respond unequivocally to the question "I take medications or carry out the treatments" if patients do take their medication, but do not carry out the treatments as asked by the doctor). Furthermore, none of the Dutch patients used all nine response options. Simplifying the PIH by using fewer response options could therefore be considered, although any such change would of course require re-validation.

As a next step in our validation process, we plan to investigate the clinical relevance of the two-subscale solution by assessing the ability of both subscale scores to discriminate between patients who received benefit from the COPD self-management intervention

(e.g. better selftreatment adherence, higher quality of life scores, fewer hospitalisations and fewer exacerbation days) and those who did not, and who demonstrated a poor self-management capacity. We will also assess the associations between the subscale scores and e.g. quality of life. In addition, we have planned to assess the responsiveness of the PIH, and whether response shift occurs in COPD patients. A study by Harvey and colleagues showed that self-reported Australian PIH scores improved significantly over time when patients with chronic diseases were involved in peer-led self-management education programs. [54] Their results indicated that patients had improved understanding of their condition and the ability to manage and deal with their symptoms resulting in a positive effect on self-management skills, confidence and health-related behaviour.[54] Our ongoing RCT regarding self-management in COPD patients[15] will allow us to assess the responsiveness of the PIH in more detail.

CONCLUSION

This is the first time that a translated Dutch PIH was validated in a sample of Dutch COPD patients. Our findings indicate that most items are well-received by patients and show favourable psychometric properties. We recommend making minor changes and refinements. More importantly, however, there is need for (international) consensus on a final version of the PIH which can be validated in several settings and populations. Nevertheless, the PIH shows great promise to facilitate the identification of self-management skills needing improvement in COPD patients with other comorbid conditions. PIH scores could be used to tailor COPD selfmanagement interventions to the patient's needs and capabilities, facilitating appropriate selfmanagement of COPD exacerbations and a reduction of hospitalisations. For use in Dutch COPD patients, we recommend using two PIH subscale scores when assessing self-management knowledge and behaviour. More research is needed to evaluate whether this two-subscale solution is optimal for other populations as well.

ACKNOWLEDGEMENTS

We would like to thank the COPD patients who participated in this study. We would also like to thank Talencentrum Maastricht University for the Dutch translation of the PIH. We thank Mitzi Paap, Bachelor of Arts in English language and culture, for translating the citations of patients, and helpful discussions. This study was supported by the Lung Foundation Netherlands (grant number 3.4.11.061).

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SUPPORTING INFORMATION

S1 Table. Dutch translated 12-item Partners in Health scale (PIH(Du))

Item	Original Partners in Health scale	Dutch translation Partners in Health scale
1	Overall, what I know about my health condition(s) is:	Wat ik globaal weet over mijn gezondheidsaandoening(en) is
2	Overall, what I know about the treatment, including medications of my health condition(s) is	Wat ik globaal weet over de behandeling en medicijnen van mijn aandoening(en) is
3	I take medications or carry out the treatments asked by my doctor or health worker	Ik neem de door de arts of zorgverlener voorgeschreven medicijnen of volg de behandeling
4	I share in decisions made about my health condition(s) with my doctor or health worker	Beslissingen betreffende mijn gezondheidsaandoening(en) neem ik samen met mijn arts of zorgverlener
5	I am able to deal with health professionals to get the services I need that fit with my culture, values and beliefs	Ik ben in staat om met gezondheidsdeskundigen te regelen dat ik de zorg krijg die ik nodig heb en die past bij mijn cultuur, waarden en overtuigingen
6	I attend appointments as asked by my doctor or health worker	Ik ga naar de door de arts of gezondheidswerker verzochte afspraken:
7	I keep track of my symptoms and early warning signs (e.g. blood sugar levels, peak flow, weight, shortness of breath, pain, sleep problems, mood)	Ik houd mijn symptomen en vroege waarschuwingstekens in de gaten (bijv. bloedsuikerwaarden, piekwaarde, gewicht, kortademigheid, pijn, slaapproblemen, gemoedstoestand)
8	I take action when my early warning signs and symptoms get worse	Ik grijp in als de waarschuwingstekens en symptomen verergeren
9	I manage the effect of my health condition(s) on *my physical activity* (i.e. walking, household tasks)	Ik heb het effect van mijn gezondheidsaandoening(en) op *mijn fysieke activiteit* onder controle (d.w.z. lopen, huishoudelijke taken)
10	I manage the effect of my health condition(s) on *how I feel* (i.e. my emotions and spiritual wellbeing)	Ik heb het effect van mijn gezondheidsaandoening(en) op *hoe ik me voel* onder controle (d.w.z. mijn emoties en geestelijk welzijn)
11	I manage the effect of my health condition(s) on *my social life* (i.e. how I mix with other people)	Ik heb het effect van mijn gezondheidsaandoening(en) op *mijn sociale leven* onder controle (d.w.z. hoe ik met andere mensen om ga)
12	Overall, I manage to live a healthy life (e.g. no smoking, moderate alcohol, healthy food, regular physical activity, manage stress)	In het algemeen lukt het mij een gezond leven te leiden (bijv. niet roken, matig alcoholgebruik, gezond eten, regelmatig bewegen, omgaan met stress)

S2 Table. Observed scores of the Dutch 12-item Partners in Health scale (PIH(Du))

RANDnr	PiH 1	PiH 2	PiH 3	PiH 4	PiH 5	PiH 6	PiH 7	PiH 8	PiH 9	PiH 10	PiH 11	PiH 12
1	8	7	7	8	7	8	7	8	6	8	8	8
2	8	8	7	7	8	8	8	7	7	7	7	7
3	6	6	8	6	0	8	7	7	6	8	8	5
4	7	7	8	7	4	8	7	7	4	4	6	7
5	6	6	8	8	7	8	7	6	7	8	7	7
6	4	5	8	8	4	8	5	4	4	5	5	6
7	6	7	8	8	7	8	8	8	6	8	8	6
8	5	4	8	6	6	8	5	6	4	5	4	7
9	6	6	8	7	6	8	6	7	3	7	4	5
10	3	3	3	4	4	4	8	4	8	5	3	3
11	5	6	8	7	6	8	6	6	6	4	5	7
12	7	7	8	8	8	8	8	8	7	7	7	8
13	4	6	8	8	7	8	7	7	4	6	6	6
14	4	8	8	7	7	8	8	8	4	4	8	8
15	7	7	7	7	7	8	7	6	6	5	7	3
16	7	7	8	8	7	8	8	8	6	7	7	7
17	6	5	8	8	7	8	8	6	2	7	7	6
18	7	7	7	7	7	7	7	7	7	7	5	7
19	8	8	8	8	8	8	4	8	4	8	4	8
20	7	6	8	6	7	4	6	7	4	7	8	6
21	8	8	8	8	8	8	8	8	4	4	4	0
22	7	7	8	7	6	8	8	8	5	4	4	4
23	7	7	8	8	8	8	6	6	7	8	8	5
24	5	5	5	5	4	7	7	7	5	7	7	7
25	5	6	8	8	6	8	7	7	5	5	6	6
26	6	5	8	8	8	8	8	6	6	8	8	8
28	8	8	8	8	8	8	8	8	8	8	8	8
29	6	7	8	8	8	8	8	7	6	6	7	6
30	4	4	8	8	0	8	4	4	4	0	4	4
31	8	6	8	8	8	8	6	8	6	8	8	6
32	4	8	8	8	8	8	8	8	4	4	7	5
33	8	8	8	8	8	8	8	7	3	7	7	7
34	6	6	8	7	7	6	8	8	0	3	4	4
35	6	6	8	8	8	8	7	6	6	7	7	6
36	8	6	6	6	7	7	6	8	7	6	6	3
37	7	7	8	7	8	8	7	8	7	7	8	8

38	6	7	8	7	7	8	7	8	5	4	4	4
39	5	5	6	6	6	8	6	7	6	7	6	7
40	4	5	7	7	4	6	5	6	4	6	6	4
41	4	4	8	8	6	8	8	6	5	7	6	6
42	6	5	8	8	7	8	8	7	6	7	8	7
43	6	6	8	7	8	8	7	8	6	6	6	6
44	4	6	8	8	7	8	8	7	7	7	7	7
45	7	7	7	7	8	8	8	8	7	8	8	8
46	7	7	8	7	7	8	8	8	8	8	8	7
47	7	7	8	7	4	8	6	6	5	5	5	1
48	6	6	7	7	7	8	7	8	7	7	7	5
49	8	8	8	8	8	8	8	8	8	8	8	8
50	5	5	8	8	7	8	8	8	5	5	4	5
51	6	5	7	6	7	7	7	6	6	5	6	5
52	4	5	5	6	4	7	6	7	5	5	7	7
53	4	4	8	8	8	8	8	8	4	4	4	4
55	6	6	7	5	5	8	6	6	6	6	7	3
56	7	5	7	2	2	8	7	8	6	6	6	7
57	4	4	8	8	7	8	8	6	4	3	4	0
58	5	5	8	6	6	8	8	7	5	6	6	7
59	0	4	8	8	8	8	8	8	4	4	4	8
60	7	8	7	8	7	7	7	7	0	0	4	0
61	7	7	8	8	7	8	7	7	7	6	7	7
62	5	5	7	7	7	7	7	7	5	5	3	5
63	7	7	8	7	7	8	7	8	6	6	7	6
64	6	4	8	8	8	8	6	7	4	5	5	5
65	7	7	8	8	8	8	6	6	7	6	6	6
66	7	7	8	8	1	8	7	7	4	4	7	7
67	6	6	7	7	7	7	7	7	6	6	6	7
68	2	5	7	6	7	8	2	7	6	6	5	6
69	6	7	7	7	7	7	8	8	7	7	6	7
71	7	7	8	8	8	8	8	8	6	6	7	7
72	4	4	6	6	6	8	7	7	6	7	7	4
73	5	6	7	7	6	8	6	6	5	6	6	4
75	6	6	8	4	7	8	5	6	2	6	7	4
76	6	8	8	8	8	8	8	8	8	8	7	6
77	7	7	8	8	4	8	7	7	3	4	6	2
78	7	7	8	8	8	8	7	8	7	7	7	8
79	6	6	6	6	6	8	6	6	4	8	5	8

80	7	7	8	8	8	8	8	8	8	8	7	8
81	6	6	8	8	7	8	7	7	4	2	6	6
82	5	6	8	7	6	6	6	7	5	6	6	7
83	8	8	6	8	8	8	4	6	5	4	5	3
84	6	7	8	4	7	8	7	8	3	6	6	3
85	6	6	7	7	7	8	7	8	6	6	6	7
86	8	4	6	8	8	6	0	8	0	7	0	0
87	7	7	8	8	8	8	7	7	6	7	6	7
90	8	7	8	8	7	8	7	8	8	8	8	8
91	4	4	8	8	8	8	6	7	3	3	6	7
92	6	5	8	8	7	8	6	7	5	5	6	3
93	5	4	8	8	8	8	8	8	5	8	8	8
94	6	6	8	8	6	8	7	7	6	6	7	5
95	6	6	8	8	8	8	8	8	7	8	8	8
96	6	6	8	7	7	8	7	5	0	6	7	7
97	7	7	7	7	8	5	7	7	6	8	7	7
98	6	6	7	4	5	8	3	3	5	4	5	4
99	6	6	7	6	7	8	7	7	6	4	4	6
100	6	7	8	8	8	8	7	8	7	7	8	7
101	8	4	8	8	8	8	8	8	4	4	8	4
102	4	0	8	0	0	8	8	8	8	4	4	4
103	6	7	7	7	7	8	7	7	7	7	7	5
104	6	6	7	4	1	8	5	7	7	6	7	7
105	6	7	7	7	8	8	7	7	7	6	6	5
106	4	0	8	7	7	8	7	7	4	3	4	4
107	8	8	8	8	8	8	8	4	4	4	8	4
109	6	6	7	7	8	8	8	8	8	8	7	8
110	7	7	8	8	8	8	8	8	7	7	7	8
112	8	6	8	8	8	8	8	8	8	7	8	7
114	5	6	8	8	8	8	6	8	5	5	7	5
115	8	8	8	8	8	7	8	8	8	8	8	8
116	6	5	7	7	7	7	6	7	5	6	6	4
117	6	6	6	7	7	7	6	7	7	5	7	6
118	5	5	8	8	7	8	5	5	3	3	3	4
119	7	8	8	8	8	8	8	8	7	8	8	8
121	7	5	7	6	4	8	6	4	5	3	5	6
122	5	6	8	8	7	8	8	7	7	6	7	7
122	7	7	8	8	7	8	8	8	1	1	1	1
123	5	6	8	8	7	8	6	7	6	6	7	5

124	5	4	8	8	4	8	6	6	4	4	4	4
125	6	6	7	7	7	7	7	7	7	7	7	5
127	6	6	8	8	8	8	8	8	7	7	8	7

RANDnr = randomisation number (person index), n=118 cases.
Note: observed item scores before collapsing categories

7

General Discussion

General Discussion

The primary objective of this thesis was to evaluate the effectiveness of a self-management intervention including exacerbation action plans for patients with COPD and comorbidities. The included review provides an overview of the effectiveness of self-management interventions including action plans in patients with (relatively uncomplicated) COPD. Subsequently, we describe the development and evaluation of a self-management intervention including exacerbation action plans for COPD patients with common comorbidities – the COPE-III study. The performed international multicentre randomised controlled trial provides the first evidence that exacerbation action plans for COPD patients with comorbidities embedded in an individualised, multi-faceted self-management intervention with case-manager support represent an effective approach to reduce COPD exacerbation duration and respiratory-related hospitalisations without excess all-cause mortality.[1] Since comorbidities are common in patients with COPD, we suggest that future COPD self-management interventions should consider the self-treatment of comorbidities in the action plans as a serious treatment option for the broader range of COPD patients with the added complexity of comorbidities.

After evaluation of the Partners in Health (PIH) scale, we recommend using two subscale scores for assessment of self-management behaviour and knowledge in Dutch COPD patients. To further facilitate the identification of patients who will receive benefit from COPD self-management interventions, there is however a need for consensus on a final version of the PIH that can be used in several settings and populations.

In this final chapter we will put our findings into a wider context of self-management interventions, review methodological considerations, and provide implications for future research and clinical practice.

Multi-component self-management interventions

COPD self-management interventions are comprehensive and often multi-component. They include goals of motivating, engaging and supporting the patients to positively adapt their health behaviour(s) and develop skills to better manage their disease.[2] Case-manager support is recognised as a key component to achieve effective and safe self-management. It is targeted at behavioural change and represents a feasible form of healthcare delivery to reduce acute COPD exacerbation readmissions.[3,4] Moreover, self-management interventions including an iterative process between patient and healthcare provider(s) to reinforce patients' self-management skills are associated with improved HRQoL, reduced hospitalisations, and improved dyspnoea.[5] The self-management training should ideally include techniques directed towards behavioural change,[6] e.g., smoking behaviour, physical activity, exercise, diet, use of maintenance medication, correct device use, and

coping with breathlessness. It is important to offer effective and safe self-management interventions, applicable for each individual COPD patient. Patient-tailored action plans are especially important in patients with a chronic condition as COPD, where the patient is responsible for the day-to-day care in the continuum of the chronic care management.

Action plans for exacerbations of COPD

An action plan for the self-management of COPD exacerbations refers to specific behaviour initiated when respiratory symptoms deteriorate. It is an agreed upon strategy and it describes when, where and how a patient should act (e.g., by initiating self-treatment or contacting a healthcare provider for support if needed). Action plans for the self-treatment of COPD exacerbations are an intrinsic part of COPD self-management interventions as they reduce exacerbation duration, hospitalisations and healthcare costs.[7-9]

The Cochrane review showed that self-management interventions including action plans for COPD exacerbations are associated with improvements in HRQoL and a lower probability of respiratory-related hospitalisations compared to usual care (**Chapter 2**).[10] Subgroup analyses revealed a significant difference in HRQoL between the COPD self-management interventions that did and did not include smoking cessation; including a smoking cessation programme seemed effective to further improve HRQoL. Smoking cessation should therefore be considered for inclusion in self-management interventions to achieve an optimal improvement in HRQoL. The number of behavioural change technique clusters (intervention components designed to alter or redirect causal processes that regulate behaviour, e.g., feedback, self-monitoring, reinforcement)[6] integrated in the self-management intervention, the intervention duration, offering a standardised exercise programme, and adaptation of maintenance medication as part of an action plan did not affect HRQoL. No excess all-cause mortality was observed, but exploratory analysis showed a small significant higher respiratory-related mortality rate for self-management compared to usual care.[10] These respiratory data should however be interpreted with care as differentiating between respiratory problems as main cause or as a contributing factor is hard and misclassification is common.[11] Future studies should therefore strive to perform death classification in a similar way in all the study groups.

For future COPD self-management interventions including action plans, we would like to urge cautiously using only self-management interventions that meet the requirements of the most recent COPD self-management intervention definition.[2] Providing more uniformly reported detailed information regarding the delivered interventions (e.g., self-management intervention components, action plan components, training of case-managers, behavioural change techniques) will increase the transparency of interventions, and therefore increase the ability to provide stronger recommendations regarding

effective self-management interventions including action plans for exacerbations of COPD. The beneficial effects of COPD self-management interventions may be a result of patients' skill improvement; an early self-initiation of appropriate and timely treatment of exacerbations in COPD patients has shown to decrease the impact of exacerbations on health status, tend to accelerate recovery, and reduce healthcare utilisation.[12,13] Negative effects may, however, be a result of using COPD-specific action plans in COPD patients with serious comorbidities; an overlap of COPD and comorbid symptoms lead to incorrect or delayed proper treatment actions. Whereas we were unable to evaluate the effects of tailoring action plans for comorbidities in the review, the effectiveness of action plans may be limited if these are just supplied to patients and not incorporated in multi-component patient-tailored self-management interventions.[14] If future COPD self-management action plans will take the added complexity of comorbidities into account, this will most likely not only increase the safety of COPD self-management interventions by appropriate and timely treatment actions, but will also increase benefits on hospitalisations.

Action plans for exacerbations of COPD and comorbidities

Exacerbations and comorbidities in COPD, such as diabetes, mental health issues, and cardiac diseases contribute to the overall severity of individual COPD patients.[15,16] Comorbid symptoms may overlap with COPD symptoms (e.g., breathlessness can be caused by COPD, anxiety, heart failure, or a combination) and therefore lead to incorrect actions and to delay of proper treatment. In addition, COPD exacerbations may introduce the deterioration of comorbid symptoms (e.g., prednisolone treatment of COPD exacerbations increases blood glucose levels, especially in patients with pre-existing diabetes). Despite the huge impact that the comorbidities have on quality of life and mortality in COPD patients,[15,16] self-management interventions and self-treatment action plans are frequently not adjusted for these comorbidities. The use of symptom-based COPD action plans therefore limits the applicability, effectiveness and safety of self-treatment guidelines when serious comorbidities are present. Tailored approaches with individualised care plans are needed to reduce the treatment burden and optimise care in COPD patients with comorbid conditions.[17]

We have developed a self-management intervention including exacerbation action plans for COPD patients with comorbidities and ongoing case-manager support (**Chapter 3 and 4**). The action plans were tailored to the individual's comorbid condition(s). The COPE-III data showed that the exacerbation action plans for COPD patients with comorbidities reduced the COPD exacerbation duration and respiratory-related hospitalisations without excess all-cause mortality (**Chapter 6**).[1] Behaviour change techniques as e.g., goal setting, action planning, problem solving, review of goals, feedback, self-monitoring, instruction on how to perform behaviour, practice/rehearsal, and habit formation,[6] were used to

improve patients' self-regulation skills and targeted uptake and optimal use of appropriate self-management behaviours.[6] For the self-management group this resulted in improved patients' self-efficacy to prevent breathing difficulty. Both the self-regulation skills and improved self-efficacy may have resulted in a better control of the deteriorating symptoms, and therefore a reduction in COPD exacerbation duration.

Patients' perceptions of emotional health were worse in the self-management intervention (**Chapter 6**). This may be a result of more awareness of emotional symptoms that were associated with their health status after self-management training. More than one third of the COPD patients experience negative emotions, such as depressive symptoms, fear of breathlessness, and anxiety.[18] These negative emotions and lack of psychosocial well-being are associated with non-adherence.[19,20] Further tailoring emotional support in an individualised self-management intervention and associated case-manager support may further enhance self-efficacy, improve (mental) health status and adherence to action plans. For example, an assessment of emotional support in self-management, based on individual patient profiles (e.g., knowledge, confidence, self-efficacy, self-management skills) can be used to identify positive and negative emotions towards self-management strategies. With this information, the emotional support can then be further tailored (e.g., providing more support to patients who are unconfident in for example decion making, directing extra case-management on coping with further impairment).[21] In COPD patients the emotional intelligence – the capacity to understand and manage personal thoughts and feelings to positively influence interpersonal communication and social well-being[22] – is associated with quality of life and self-management abilities.[21] Emotional intelligence training includes components to: 1) increase awareness of and differentiation between positive and negative emotions; 2) understand interactions between emotions and thoughts; 3) manage emotions; 4) recognise the interplay between emotions and interpersonal relationschips; 5) increase motivation; 6) practice relaxation techniques (e.g., mindfulness, meditation).[21] In self-management interventions, a trained case-manager may help to improve emotional intelligence skills by further discussing the negative emotions with patients, and by reinforcing the patient's self-management skills that are needed to manage emotions. In COPD patients this can lead to improved mental and social well-being, more control during stressful situations, an increased ability to understand and regulate emotions, a prevention of negative emotions and further symptom impairment in COPD, and possibly less healthcare utilisation.[21]

Since improving a patient's psychosocial well-being requires patient adaptation and behavioural change,[22] increasing motivation to change behaviour is important. Motivational interviewing is a promising technique to increase this motivation to change behaviour in COPD to optimise adaptation to the disease.[23] This technique requires expertise and skills

from the healthcare provider to attempt to increase patients' awareness of the potential problems of their actual behaviour, and to change the thinking of this behaviour to ultimately consider what might be gained through change.[23] For COPD patients this often means that the patient has to become aware of the severity of their disease, of their problems in health status, and the negative effects of maladaptive behaviours.[22] The Nijmegen Clinical Screening Instrument (NCSI) method[22] can also be used in routine clinical care for an individual patient as an aid for the healthcare provider to formulate individualised treatment goals and help the caregiver to motivate the patient to adhere to these goals within only a few sessions. This method can also be used for evaluation of treatment effects and for automated patient monitoring.[22]

The COPE-III data showed no effect on all-cause hospitalisations, which was related to a higher cardiovascular-related hospitalisation rate in the intervention group (**Chapter 6**). Some self-management group patients experienced their first cardiovascular-related event during follow-up, and had therefore not received self-treatment action plans for cardiovascular-related symptoms. Even when cardiac complications are not clinically apparent, cardiac dysfunction and acute cardiac events often occur during COPD exacerbations and it is related to a poor prognosis.[24] Cardiovascular disease can be detected in 55% of patients hospitalised with COPD exacerbations[24] and up to 20% of the COPD exacerbations could be due to acute decompensated heart failure and cardiac arrhytmias.[25] Although cardiac comorbidities contribute to disease severity, hospitalisations and mortality in patients with COPD, they are frequently undiagnosed.[24,26] The diagnosis of cardiac comorbidity in COPD is however difficult to recognise clinically, because: 1) electrocardiographic abnormalities are common in COPD exacerbations, but frequently under-recognised or considered irrelevant in clinical practice; 2) recognition of an acute coronary syndrome is challenging because the chest pain, electrocardiographic changes, and increased troponin concentrations might be unreliable during a COPD exacerbation as these are frequently increased without other evidence of myocardial infarction; and 3) chest discomfort associated with a COPD exacerbation can be difficult to distinguish from cardiac pain.[24] Several mechanisms could plausibly contribute to cardiac dysfunction in COPD exacerbations, e.g., an acute respiratory infection, hypoxaemia, systemic inflammation, platelet activation, or lung hyperinflation.[24] In addition, due to symptom overlap the differentiation between the symptoms and signs caused by COPD, CHF, or a combination, is complicated.[26-29] Therefore, there remains a challenge for appropriate self-treatment of patients with a combination of COPD and cardiac diseases. It is therefore recommended to create more awareness among healthcare providers and patients to recognise and consider treatment of cardiac comorbidities in COPD. However, definitive guidelines for diagnosis and management are still lacking, because of limited knowledge of mechanisms of cardiac dysfunction in COPD exacerbations.[24] Because of the heterogeneity in exacerbations and

other patient characteristics, further research into the phenotyping of exacerbations (e.g., by using cardiac biomarkers)[24] and treatment of acute cardiac dysfunction in COPD exacerbations is urgently needed. In addition, patient-tailoring of existing (standardised) exacerbation action plans should be considered (e.g., by including cardiac biomarkers in action plans or directing patients to contact the case-manager if the cause of symptom deterioration is unclear).

Methodological considerations

Case-mix of patients

Whereas clinical trials often exclude COPD patients with multiple morbidities,[28] in the COPE-III study we chose to include COPD patients with the added complexity of major comorbidities (**Chapter 6**). We took into account these comorbidities in patient-tailored diaries, action plans and the associated self-management intervention sessions. Our case-mix of patients represents therefore a more real life population as COPD is a multi-component condition and most COPD patients have comorbidities. Our complex patient group, however, also hampered the recruitment process because of instability of patients due to exacerbations and hospitalisations of COPD and/or comorbid conditions; in our 4-year recruitment period we screened over 5,700 patients for eligibility and only included 201 patients in our RCT. The main reasons for exclusion were: no comorbidity (n=1,550); other serious disease (n=379); no exacerbations or hospitalisations (n=356); no COPD (n=258); other lung disease (n=255); end stage disease (n=235); cognitive impairment or dementia (n=193). Undiagnosed comorbidities are common in COPD patients,[26,31] and remain therefore often untreated. This may be a result of absence or overlap of symptoms, barriers to ask healthcare providers for support or to seek medical attention, or the patient's and healthcare provider's perception about comorbidities.[31] Since having at least one comorbidity was one of our inclusion criteria, the undiagnosed and underreported comorbidities in COPD patients further challenged our recruitment process and could also have influenced the instability of patients (e.g., undiagnosed flare-ups of heart failure or anxiety). It could be argued that in our COPE-III study highly motivated patients (e.g., patients who would like to increase their autonomy and independence) were selected, who are more willing to participate in self-management interventions. Therefore, these patients were more likely to be included than others. This has implications for the generalisability and external validity of results as ultimately self-management interventions need to be applicable for the broader range of patients with COPD. Evaluations of self-management interventions should therefore focus on the wider COPD population (e.g., including a variety of patients with regard to COPD severity, comorbid conditions) in different continents. This will provide useful information for data generalisability in different healthcare systems. Moreover, since many self-management interventions are performed in a secondary healthcare setting and focussed on a hospital setting, these interventions

may need further adaptation to be applicable to a different - often less severe – population in the primary care.

An evaluation of the adherence to action plans and the COPE-III self-management intervention will help to identify patient and intervention characteristics that may be useful to further improve and patient-tailor the action plans in self-management interventions. The level of burden of patients (e.g., disease severity, quality of life, hospitalisations, specialist visits) is one of the patient characteristics that may influence the patient's compliance and adherence to self-management interventions, and thus the effectiveness of the intervention. Further assessment of patient burden in an individual assessment is therefore recommended to reduce both the current symptoms and the future risks.[32]

Data

The COPE-III study focussed beyond the patients' COPD and provided unique insights in the daily symptoms of COPD patients with cardiac diseases (chronic heart failure, ischaemic heart disease), anxiety and depression over one year of follow-up (**Chapter 6**). Although self-reported in the diaries, these daily symptom scores prevent recall bias and yield information on day-to-day variability.[33] It enabled us to capture a near complete overview and accurate assessment of all COPD exacerbations and flare-ups of comorbid symptoms, and patients' individual symptom scores at daily level. We used adequate methods to check the validity and completeness of the diaries. All the patients were given feedback by phone if the diary completion of symptoms was incorrect and this resulted in an overall completion of 59,629 diary days (81.3%). Our data are consistent with another multicentre RCT that used comparable diaries and also reported high compliance and diary completeness.[12] These diary data can be used to obtain more insight in barriers and facilitators of action plan use by the patient. We have planned future analyses of the diary data, data on action plan use, and additionally collected qualitative information on patients' barriers and facilitators. We anticipate that the results of these future analyses will help to further optimise the COPE-III self-management intervention.

In **Chapter 5** we used a combination of quantitative and qualitative data to validate the Partners in Health Scale (PIH), an instrument to measure actual self-management knowledge and behaviour, in a sample of Dutch COPD patients. Our dimensionality analyses showed a two-subscale solution for the Dutch PIH: 1) knowledge and coping; 2) recognition and management of symptoms, adherence to treatment.[34] We have provided several explanations for this discrepancy in dimensionality between the original Australian[35] and the Dutch PIH: differences in statistical methods and target populations, sample size, number of items per factors, number of factors in the model, size of communalities, cross-cultural differences, and adjustments made after publication of the original PIH. Based

on these discrepancies we have recommended changes and refinements of the PIH (e.g., specifying a recall period). Whereas the PIH shows great promise in facilitating the identification of self-management skills needing improvement in COPD patients with comorbid conditions, there is a need for consensus on a final version of the PIH, which can be validated in several settings and populations. More research is in addition needed to evaluate whether the two-subscale solution is optimal for other populations. Furthermore, an evaluation of the clinical relevance and an assessment of the responsiveness of the PIH will further facilitate the identification of patients who may receive benefit from COPD self-management interventions (e.g., self-treatment adherence, better HRQoL) with a better self-management capacity.

Methodological limitations

Our COPE-III study (**Chapter 6**) has some methodological limitations. Because of the nature of the self-management intervention, blinding of patients to group assignment was impossible, introducing performance bias (e.g., more awareness on symptom monitoring and recognition in the self-management group compared to usual care as self-management patients know they can initiate self-treatment if symptoms deteriorate). In addition, our study was powered to identify an effect for the number of exacerbation days per patient per year. There was, however, no between-group difference observed for this number. Since the observed attrition rate (15.9%) of the randomised patients was higher than a-priori expected (10%), there were probably more patients needed to detect a significant treatment effect for the number of exacerbation days per patient per year.

A short follow-up makes it difficult to interpret the effects on behavioural change. In the Cochrane review (**Chapter 2**), six out of 22 (27%) self-management interventions had a follow-up duration less than a year. In these studies, seasonal variations might have influenced the outcomes; for example, a COPD exacerbation tends to occur more often in winter and early spring. If the individual patient follow-up was outside this period, then this might have resulted in an underestimation of the effect.

In the COPE-III study, structured templates were used for the scheduled follow-up phone calls to discuss the completion of the diaries (both groups) and to reinforce self-management skills (self-management intervention group). Our study did, however, not include a process evaluation of the case-managers and disciplines involved and no structured teaching templates were used. In addition, there is a need to assess the fidelity of delivery of the intervention. This can be done on the level of the patient (e.g., session attendance rates, adherence to action plans), but also on the level of the healthcare provider (e.g., by using a manual and checklist to compare the delivered self-management intervention to the pre-specified intervention content). For the latter, a manual containing

explicit guidelines about the content and instructions on the method of delivery of the self-management intervention will increase the likelihood of the intervention being implemented as designed.[36]

Finally, usual care might be better in practices that are regularly actively involved in RCTs. This might have led to an underestimation of the effect sizes observed in the Cochrane review (**Chapter 2**) and in the COPE-III study (**Chapter 6**). We do, however, think that this is a general methodological issue in RCTs and reviews on similar interventions (e.g., pulmonary rehabilitation, integrated care).

Implications for future research and practice

Self-management embedded in usual care

Self-management is becoming increasingly integrated in usual care. COPD patients with comorbidities are more closely reviewed and monitored as part of routine clinical care. Furthermore, as part of usual care, an increasingly number of patients will have action plans for the self-treatment of exacerbations at home. This may have led to an underestimation of the effect of self-management interventions. If the COPD management as part of usual care is optimised (e.g., medication treatment), then it will be more difficult to detect an effect of self-management interventions and a larger sample size will be needed.

Transparency by providing more uniformly presented and detailed information regarding the delivered self-management interventions will increase the reproducibility of results. We would therefore like to urge future COPD self-management interventions to use the most recent COPD self-management intervention definition. This will help further subgroup analyses and increase the ability to provide stronger recommendations for practice and future research. Since usual care differs significantly between countries and healthcare systems, and sometimes self-management will already be included as part of usual care, it is also desirable to strive for better descriptions of usual care (e.g., description of action plans that are part of usual care, provision of healthcare provider support).

Towards a holistic and patient-tailored approach

The multi-faceted management of COPD places a significant burden on patients, healthcare providers and healthcare systems, as it extends beyond the lungs and includes the challenges of a comprehensive, but patient-tailored approach. The results of the COPE-III study (**Chapter 6**) have implications for COPD care; the exacerbation action plans for COPD and comorbidities and the associated self-management training have shown to be effective and should therefore be considered as a treatment option for COPD patients with the added complexity of comorbidities. Providing an action plan for the self-treatment of COPD exacerbations will, however, not automatically lead to successful self-management.

The findings that a significant minority of patients derives benefit from an intervention with self-management components must be regarded as hypothesis generating.[37,38] As indicated before by Nici et al.[39] the key is to increase the percentage of successful self-managers. Therefore, we first need to determine who is suitable for self-management interventions by identifying patient characteristics that predict successful COPD self-management. This will not only facilitate better identification of COPD patients who will benefit, but it will also help to further improve and adapt self-management to a more patient-tailored and safe intervention.

Since self-management strategies often focus on the patient's ability to identify an exacerbation and consult the action plan, its success relies heavily on the patient's understanding and the ability to actually become an effective self-manager.[40] Health literacy is a concept of reading and quantitative ability, and an interaction between knowledge, societal and cultural influences.[41] Individuals with limited health literacy have an increased risk of healthcare utilisation, hospitalisations and mortality.[42-45] It is also associated with poorer medication adherence.[45] Health literacy influences health outcomes at least partially through its effect on patient's self-efficacy, knowledge, and health behaviors.[46] In addition, health-related perceptions and experiences, and familiarity with health concepts are influencing health outcomes.[46] Patients with chronic diseases face tremendous learning demands.[42] In the COPE-III study, information regarding health literacy was obtained by asking the patients only one question for their confidence in completing medical forms by themselves.[47] COPD patients with inadequate health literacy who have several comorbidities will be less likely to know how to manage their diseases, even if they have participated in self-management training sessions to learn how to cope with a deterioration of symptoms. Moreover, health literacy is a broad concept and there are several components that could influence health literacy in this complex group of COPD patients with comorbidities (e.g., living alone, social commitments, education level). Furthermore, the mechanisms underlying the relationship between health literacy and health outcomes are not yet fully understood.[46] For future research and clinical practice, it may therefore recommended to have a more extensive assessment of factors influencing health literacy.

Another important contributor towards success of self-treatment is adherence,[3,48] defined as the patient's active role in consenting to and following prescribed treatments.[49] Adherence to written COPD action plans is associated with a significant reduction in exacerbation total recovery time.[50] Several patient characteristics have been reported to increase the likelihood of adherence to an action plan, including younger age, living with others, previously receiving an influenza vaccination, having a cardiac comorbidity, and more severe airflow obstruction.[38,50] Furthermore, cognitive impairment and literacy are

recognised as limiting factors for using COPD self-management interventions.[2,3] More patient details (e.g., mental health status, self-efficacy, health literacy) and intervention characteristics (e.g., case-manager support, social support, resources) need to be used to define the influence of other factors on the adherence, and specifically adherence to exacerbation action plans.

Despite positive research findings on self-management interventions, the implementation of these interventions is limited. This may be due to restricted resources or budget. Economic evaluations of the benefits and costs of the implementation of self-management interventions are often lacking. Health information technology could play an important role to facilitate the implementation of self-management interventions in practice as they support patient empowerment and facilitate innovative healthcare delivery,[51,52] enabling accessible and easy provision of tailored information. In addition, health information technology has the potential to improve the health of individuals and performance of the providers, yielding improved quality, cost savings, and greater engagement by patients in their own healthcare.[51] Despite evidence of these benefits, there are challenges of implementing health information technology more specifically as there remain problems and barriers with for example electronic health records among some healthcare providers.[52]

For a beneficial self-management intervention for COPD and comorbidities and a timely, appropriate use of the exacerbation action plans we think a holistic and patient-tailored approach as the COPE-III study, is needed with the following recommended components: an individual assessment of COPD and comorbidities; information on self-management (e.g., symptom recognition, symptom treatment, exercise, diet, breathing and relaxation exercises); daily self-monitoring of symptoms; action plans (this could include automated decision-support) for the self-treatment of exacerbations of COPD and comorbidities; and case-manager and social support for personal feedback and motivation. A holistic approach, as the COPE-III study, will lead to better decision making and enables a quick start of proper treatment. In particular, this is important for the ageing population with COPD, with other chronic conditions as well.

Conclusions

Exacerbation action plans for COPD patients with comorbidities embedded in an individualised, multi-faceted self-management intervention are effective in reducing COPD exacerbation duration and respiratory-related hospitalisations without influencing all-cause mortality. The exacerbation action plans and the associated self-management training should therefore be considered as a treatment option for COPD patients with the added complexity of comorbidities. To further increase the safety and efficacy of self-management interventions, we suggest that future COPD self-management interventions

should include the self-treatment of the individual's comorbid conditions when applied in the wider population of COPD patients with comorbidities. Challenges remain to further tailor the self-management interventions to patient's needs, preferences, competences and capabilities and to implement it in the COPD healthcare. A holistic approach within a supportive healthcare system seems essential to offer optimised patient-tailored self-management interventions.

In summary, our implications for future research and clinical practice are:

- A holistic and patient-tailored approach is recommended for a self-management intervention in patients with COPD and comorbidities. Future COPD self-management interventions should consider the self-treatment of comorbidities in patient-tailored exacerbation action plans together with associated self-management training to facilitate a quicker initiation and appropriate use of these action plans in the broader range of COPD patients with the added complexity of comorbidities.
- Self-management interventions should be further tailored to the patient's needs, capabilities, preferences and competences, especially focusing on (mental health) case-manager support.
- For future studies, we recommend to cautiously only using action plans together with self-management interventions that are structured, but personalised, and often multi-component, with goals of motivating, engaging and supporting the patients to positively adapt their health behaviour(s) and develop skills to better manage their disease.
- Future studies should provide more detailed information regarding the delivered self-management intervention as this will increase the ability for authors of future reviews to provide stronger recommendations regarding effective self-management interventions that include action plans for COPD exacerbations.
- It is important to determine who is suitable for self-management interventions by identifying patient characteristics that predict successful COPD self-management, especially focusing on facilitators and barriers for adherence to exacerbation action plans.
- There is a need for consensus on a final version of the Partners in Health scale that can be used in several settings and populations. Furthermore, an evaluation of the clinical relevance and an assessment of the responsiveness of the Partners in Health scale will further facilitate the identification of patients who may receive benefit from COPD self-management interventions.

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8

Summary

Summary

Chronic Obstructive Pulmonary Disease (COPD) is a chronic progressive lung disease. It is characterised by symptoms of dyspnoea, sputum purulence, wheezing and cough, with distressing exacerbations - acute deteriorations in respiratory health - that contribute to impaired quality of life and increased hospitalisations, mortality and healthcare costs. COPD is considered to be a complex, heterogeneous, and multi-component condition. Frequently existing comorbid conditions in COPD, such as cardiovascular diseases, mental health issues, and diabetes, have an important impact on disease severity, hospital admission rate, and survival. These comorbidities share common risk factors with COPD, such as ageing, smoking and inactivity. In addition, COPD and comorbidities have overlap in symptoms, e.g., breathlessness, fatigue. In COPD patients with the added complexity of comorbidities a "one size fits all" approach that focuses solely on COPD symptoms may be inadequate and could lead to the initiation of incorrect or delayed treatment. Multi-component COPD self-management interventions, targeted at behavioural change, are important in the management of COPD patients. Exacerbation action plans are an intrinsic part of these COPD self-management interventions.

In **Chapter 2** we evaluate 22 studies in a Cochrane review comparing the effectiveness of COPD self-management interventions including an action plan for acute exacerbations of COPD with usual care. We observed that self-management interventions including a COPD exacerbation action plan are associated with improvements in health-related quality of life and a lower probability of respiratory-related hospital admissions, without excess all-cause mortality. For future studies, we recommend to cautiously only using action plans together with self-management interventions that are structured, but personalised, and often multi-component, with goals of motivating, engaging and supporting the patients to positively adapt their health behaviour(s) and develop skills to better manage their disease. To increase transparency, providing more detailed information regarding the delivered interventions will help increase the ability to provide stronger recommendations regarding effective self-management interventions that include action plans for COPD exacerbations. Safety of self-management interventions can be expected to increase further if COPD self-management action plans take into account comorbidities when used in the wider population of COPD patients with comorbidities. We were, however, unable to evaluate this strategy in the review.

In **Chapter 3** we report the design of the COPE-III self-management intervention, that combines self-initiated patient-tailored action plans for COPD and comorbidities (chronic heart failure, ischaemic heart disease, anxiety, depression, diabetes mellitus) with ongoing case-manager support. In collaboration with multiple disease experts, we developed daily symptom diaries for the symptom monitoring and action plans for self-treatment of

individual's COPD and comorbid condition(s).

In **Chapter 4** we provide information regarding the integration of information from two previous COPD self-management interventions (COPE-I and COPE-II) in the development of our COPE-III self-treatment approach. Consistent with the COPE-II approach, the COPE-III intervention initiates treatment after a significant deterioration of symptoms that is beyond the individual's level of symptoms in a stable health state. Similar to the COPE-I and COPE-II study, we have tried to ensure patient safety by providing easily accessible ongoing case-manager support.

In **Chapter 5** we present a validation of the Partners in Health (PIH) scale to measure self-management behaviour and knowledge in Dutch COPD patients. Two subscales were found for the Dutch PIH data: 1) knowledge and coping; 2) recognition and management of symptoms, adherence to treatment. We recommend using these two subscale scores when assessing self-management in Dutch COPD patients. In addition, based on the discrepancies between the original Australian PIH and the Dutch PIH, we recommend changes and refinements of the PIH. We think that the PIH shows great promise in facilitating the identification of self-management skills needing improvement in COPD patients with comorbid conditions. There is however more research needed to evaluate whether the two-subscale solution is optimal for other populations and consensus is needed on a final version of the PIH, that can be validated in several settings and populations. Furthermore, an evaluation of the clinical relevance and an assessment of the responsiveness of the PIH will further facilitate the identification of patients who will receive benefit from COPD self-management interventions.

In **Chapter 6** we demonstrate that our international multicenter randomised controlled trial is the first to test and confirm that patients with COPD and important comorbidities have better outcomes if they receive a self-management intervention that addresses their multiple conditions compared to usual care. We observed that exacerbation action plans for COPD patients with comorbidities embedded in an individualised, multi-faceted self-management intervention are effective in reducing the COPD exacerbation duration and respiratory-related hospitalisations without excess all-cause mortality. It also improved patients' self-efficacy to prevent breathing difficulty. The self-management group reported a higher cardiovascular-related hospitalisation rate. However, there was no significant difference on cardiovascular-related hospitalisations when excluding the patients from the self-management group who experienced their first cardiovascular-related event during study follow-up, and had therefore not yet received an action plan for their cardiovascular problems. In addition, the self-management group reported lower emotional function scores, possible reflecting more symptom awareness due to self-management training. We

used education, training, modelling and enablement to improve patient' self-regulation skills and target uptake and optimal use of appropriate self-management behaviours. The exacerbation action plans for COPD and comorbidities and the associated self-management training should be considered as a treatment option for COPD patients with the added complexity of comorbidities. These self-management interventions should be further tailored to the patient's needs and capabilities, especially focusing on case-manager support to enhance self-efficacy and (mental) health status.

In **Chapter 7**, the major results of the studies in this thesis are discussed and our findings are put into a wider context of self-management interventions. Some methodological considerations are provided, such as a selection of highly motivated patients in our study sample and a lack of process evaluation of our case-managers.

In summary, our implications for future research and clinical practice are:

1. consider the self-treatment of comorbidities in patient-tailored exacerbation action plans together with associated self-management training for patients with COPD and comorbidities, especially focusing on (mental health) case-manager support;
2. cautiously only using action plans together with self-management interventions that are structured, but personalised, and often multi-component, with goals of motivating, engaging and supporting the patients to positively adapt their health behaviour(s) and develop skills to better manage their disease;
3. provide more detailed information regarding the delivered self-management intervention;
4. identify patient characteristics that predict successful COPD self-management; and
5. reach consensus on a final version of the Partners in Health scale, that can be used in several settings and populations.

SAMENVATTING
(Dutch Summary)

Samenvatting

Chronic Obstructive Pulmonary Disease (COPD) is een chronische progressieve longaandoening. Deze longziekte wordt gekenmerkt door klachten van kortademigheid, slijmproductie, hoesten en een piepende ademhaling, met exacerbaties – longaanvallen, acute verergering van longklachten - welke bijdragen aan verminderde kwaliteit van leven en meer ziekenhuisopnames, mortaliteit en zorgkosten. COPD wordt beschouwd als een complexe, heterogene en multi-componente ziekte. Veelvoorkomende comorbiditeiten bij COPD, zoals cardiovasculaire ziekten, psychische klachten en diabetes, hebben een belangrijke impact op de ernst van de ziekte, ziekenhuisopnames en overleving. Deze comorbiditeiten delen dezelfde algemene risicofactoren als COPD, zoals veroudering, roken en inactiviteit. Daarnaast kennen COPD en comorbiditeiten een overlap van klachten, bijvoorbeeld kortademigheid of vermoeidheid. Bij COPD patiënten met daarnaast de complexiteit van comorbiditeiten zal een 'one size fits all' benadering, die zich enkel richt op COPD klachten, inadequaat zijn. Dit kan namelijk leiden tot een vertraagde of verkeerde (zelf)behandeling. Multi-componente COPD zelfmanagement interventies, die zich richten op gedragsverandering, zijn belangrijk in de management van COPD patiënten. Exacerbatie actieplannen zijn een essentieel onderdeel van deze COPD zelfmanagement interventies.

In **Hoofdstuk 2** hebben we 22 studies geëvalueerd in een Cochrane review. In dit review hebben we de effectiviteit van COPD zelfmanagement interventies met een actieplan voor acute COPD exacerbaties vergeleken met reguliere zorg. De resultaten lieten zien dat zelfmanagement interventies met COPD exacerbatie actieplannen zijn geassocieerd met een verbetering van de kwaliteit van leven en een lagere kans op respiratoir-gerelateerde opnames, zonder buitensporige mortaliteit. Voor toekomstige studies adviseren we om alleen actieplannen te gebruiken als deze onderdeel zijn van zelfmanagement interventies, welke gestructureerd en gepersonaliseerd zijn en bestaan vaak uit meerdere componenten. Deze interventies hebben als doel om de patiënten te motiveren, te betrekken en te ondersteunen om positieve gedragsverandering te bewerkstelligen en om vaardigheden te ontwikkelen om beter te kunnen omgaan met hun ziekte. Als studie auteurs meer gedetailleerde informatie geven over de aangeboden interventies, dan zal de transparantie over de zelfmanagement interventie componenten, de actieplan componenten en de technieken voor gedragsverandering vergroot kunnen worden. Hierdoor zullen betere aanbevelingen gegeven kunnen worden omtrent effectieve zelfmanagement interventies met actieplannen voor COPD exacerbaties. De veiligheid van zelfmanagement interventies zal kunnen worden verbeterd als in COPD zelfmanagement actieplannen rekening wordt gehouden met comorbiditeiten. Wij hebben deze strategie echter niet kunnen evalueren in ons review.

In **Hoofdstuk 3** beschrijven we het ontwerp van de COPE-III zelfmanagement interventie,

waarin zelf-geïnitieerde persoonlijke actieplannen voor COPD en comorbiditeiten (chronisch hartfalen, ischemische hartziekten, angst, depressie, diabetes mellitus) worden gecombineerd met doorlopende casemanager ondersteuning. In samenwerking met multi-disciplinaire ziekte-experts hebben we een dagelijks klachtendagboek voor klachtenmonitoring ontwikkeld en hieraan gelinkte actieplannen voor de zelfbehandeling van de individuele COPD en comorbide aandoening(en).

In **Hoofdstuk 4** geven we informatie over de integratie van informatie van twee voorgaande COPD zelfmanagement interventies (COPE-I en COPE-II) voor de ontwikkeling van onze COPE-III zelfmanagement interventie. Geadviseerd wordt om het COPE-III actieplan te raadplegen zodra er een duidelijke verergering van klachten optreedt, welke afwijken van de individuele klachten in een stabiele gezondheidstoestand. Dit is vergelijkbaar met de benadering in de COPE-II studie. We hebben geprobeerd om, net zoals in de COPE-I en COPE-II studie, de patiëntveiligheid te waarborgen door makkelijk toegankelijke doorlopende casemanager ondersteuning te bieden.

In **Hoofdstuk 5** presenteren we een validatie van de Partners in Health (PIH) schaal om zelfmanagement gedrag en kennis van Nederlandse COPD patiënten te meten. Er zijn twee subschalen gevonden voor de Nederlandse PIH data: 1) kennis en omgaan met de aandoening; en 2) herkenning en management van klachten, therapietrouw. We adviseren om deze twee subschaalscores te gebruiken om zelfmanagement in Nederlandse COPD patiënten te beschrijven. Op basis van de gevonden discrepanties tussen de originele Australische PIH en de Nederlandse PIH adviseren we daarnaast om enkele wijzigingen en verfijningen van de PIH door te voeren. We denken dat de PIH veelbelovend is in het identificeren van de (te verbeteren) zelfmanagementvaardigheden in COPD patiënten met comorbiditeiten. Er is echter meer onderzoek nodig om te evalueren of het gebruik van twee subschalen optimaal is in andere populaties. Daarnaast is consensus nodig over een definitieve versie van de PIH, die kan worden gevalideerd in verschillende settings en populaties. Tevens zal een evaluatie van de klinische relevantie en een beschrijving van de responsiviteit van de PIH kunnen helpen om patiënten te identificeren die baat zullen hebben van de COPD zelfmanagement interventies.

In **Hoofdstuk 6** beschrijven we de resultaten van onze internationale multi-center gerandomiseerde gecontroleerde studie. Dit is de eerste studie die bevestigt dat patiënten met COPD en belangrijke comorbiditeiten betere uitkomsten hebben als ze een zelfmanagement interventie ontvangen welke rekening houdt met comorbiditeiten. De exacerbatie actieplannen voor COPD patiënten met comorbiditeiten - aangeboden in een geïndividualiseerde zelfmanagement interventie, bestaande uit meerdere facetten - bleken effectief in het verminderen van de duur van een COPD exacerbatie en respiratoir-

gerelateerde ziekenhuisopnames, zonder buitensporige mortaliteit. Daarnaast was er bij de patiënten in de zelfmanagementgroep ook een verbetering van het vertrouwen in eigen kunnen om ademhalingsproblemen te voorkomen. De zelfmanagementgroep rapporteerde meer cardiovasculair-gerelateerde opnames. Er was echter geen significant verschil in cardiovasculair-gerelateerde opnames zodra er enkele zelfmanagementgroep patiënten werden geëxcludeerd, die tijdens de follow-up hun eerste cardiovasculair-gerelateerde event ervoeren. Zij hadden daarom geen actieplan ontvangen voor hun cardiovasculaire problemen. Verder rapporteerde de zelfmanagementgroep lagere scores voor emotioneel functioneren, welke mogelijk een weerspiegeling zijn van meer bewustzijn van klachten door de zelfmanagementtraining. We hebben educatie en training gebruikt om de zelfregulatievaardigheden van patiënten te verbeteren en om te richten op optimaal passend zelfmanagementgedrag. Het aanbieden van exacerbatie actieplannen voor COPD en comorbiditeiten samen met zelfmanagementtraining moet in acht worden genomen als een behandelingsmogelijkheid voor COPD patiënten met daar bovenop de complexiteit van comorbiditeiten. Deze zelfmanagement interventies moeten verder worden aangepast aan de behoeften en mogelijkheden van de individuele patiënt. Ook moet worden gefocust op casemanager ondersteuning om het vertrouwen van patiënten in hun eigen kunnen en de mentale gezondheidstoestand van patiënten te verbeteren.

In **Hoofdstuk 7** worden de belangrijkste resultaten van de studies in dit proefschrift bediscussieerd en worden de bevindingen in een bredere context van zelfmanagement interventies geplaatst. Er worden methodologische overwegingen gegeven, bijvoorbeeld de selectie van sterk gemotiveerde patiënten in onze studie sample en een gebrek aan procesevaluatie van de interventie door casemanagers.

Samenvattend zijn onze implicaties voor verder onderzoek en de klinische praktijk:

1. zelfbehandeling van comorbiditeiten overwegen in op de patiënt aangepaste exacerbatie actieplannen voor COPD patiënten met comorbiditeiten, en deze aanbieden met zelfmanagementtraining en doorlopende casemanager ondersteuning;
2. alleen actieplannen gebruiken in zelfmanagement interventies welke gestructureerd, persoonlijk en vaak multi-component zijn, met als doel om de patiënten te motiveren, te betrekken en te ondersteunen om positieve gedragsverandering te bewerkstelligen en om vaardigheden te ontwikkelen om beter te kunnen omgaan met hun ziekte;
3. studie auteurs moeten meer gedetailleerde informatie geven over de aangeboden zelfmanagement interventie;
4. patiëntkarakteristieken identificeren welke succesvol COPD zelfmanagement kunnen voorspellen; en
5. consensus bereiken over een definitieve versie van de Partners in Health schaal, die kan worden gebruikt in meerdere settings en populaties.

SAMENVATTING IN LEKENTAAL
(Dutch Lay Summary)

Samenvatting in lekentaal

Chronic Obstructive Pulmonary Disease (COPD) is een met name door roken veroorzaakte longziekte. COPD wordt ook wel chronische bronchitis en rek uit de long (emfyseem) genoemd. Deze longziekte wordt gekenmerkt door klachten van kortademigheid, hoesten met opgeven van slijm, en een piepende ademhaling. Patiënten met COPD hebben regelmatig een acute verergering van longklachten, ook wel longaanval of exacerbatie genoemd. Deze longaanvallen zorgen voor minder kwaliteit van leven en meer ziekenhuisopnames, meer kosten en zelfs een hogere kans op overlijden. COPD komt vaak voor samen met andere ziekten. Voorbeelden hiervan zijn hartziekten, suikerziekte, angst en depressie. Deze andere ziekten kunnen zorgen voor nog meer ziekenhuisopnames. Ook verhogen ze de kans op overlijden. Die andere ziekten hebben vaak dezelfde risicofactoren als COPD. Je kunt hierbij denken aan een hogere leeftijd, roken en minder actief zijn. De klachten van COPD en de andere ziekten overlappen elkaar vaak. Zo kan bijvoorbeeld kortademigheid of vermoeidheid zowel veroorzaakt worden door COPD, als door hartklachten of door angst. Bij COPD patiënten die ook andere ziekten hebben, zal een behandeling die zich alleen maar richt op COPD vaak niet passend zijn. Dit kan bijvoorbeeld leiden tot een vertraagde of verkeerde behandeling. Een COPD zelfmanagementprogramma is belangrijk voor de behandeling van COPD. Zo'n programma leert de patiënten wat ze zélf kunnen doen in verschillende situaties. Het doel is om patiënten te motiveren, te betrekken en te ondersteunen om gedrag te veranderen (bijvoorbeeld stoppen met roken, meer gaan bewegen). Daarnaast leren patiënten in zo'n programma om beter om te gaan met de ziekte. Een zelfmanagementprogramma bevat meerdere onderdelen. Voorbeelden zijn kennis krijgen over de ziekte, het leren herkennen van een longaanval en het zelf leren behandelen van zo'n aanval. Wat patiënten zelf kunnen doen (zelf actie nemen) bij een longaanval wordt beschreven in een zogenaamd actieplan.

In **Hoofdstuk 2** hebben we 22 studies met een COPD zelfmanagementprogramma én een actieplan voor longaanvallen op een rij gezet. Hierin hebben we alle studiegroepen die een COPD zelfmanagementprogramma en een actieplan voor longaanvallen hebben gebruikt, vergeleken met standaard zorg. Het gebruik van zelfmanagementprogramma's mét actieplannen voor longaanvallen zorgde voor een betere kwaliteit van leven en een lagere kans op ziekenhuisopnames voor longklachten. De veiligheid en werkzaamheid van zelfmanagementprogramma's zal waarschijnlijk verder verbeteren als de actieplannen ook rekening gaan houden met andere ziekten, als die aanwezig zijn.

In **Hoofdstuk 3** beschrijven we het ontwerp van de COPE-III studie. Hierin hebben we 145 Nederlandse en 56 Australische COPD patiënten die ook andere ziekten hadden een jaar lang gevolgd. De helft van de patiënten heeft een zelfmanagementprogramma aangeboden gekregen en de andere helft standaard zorg. Voor de patiënten in het

zelfmanagementprogramma hebben we voor iedere patiënt een actieplan op maat gemaakt voor zowel COPD als voor de andere ziekten (hartziekten, angst, depressie, diabetes). Daarnaast hebben we een dagelijks klachtendagboek gemaakt zodat alle 201 patiënten een verandering van klachten konden opschrijven.

In **Hoofdstuk 4** geven we aan hoe we de informatie van twee voorgaande COPD zelfmanagementprogramma's (COPE-I studie en COPE-II studie) hebben gebruikt voor het maken van het COPE-III zelfmanagementprogramma. In de COPE-III studie heeft iedere patiënt op een 'wat is normaal voor mij' kaart in zijn of haar eigen woorden opgeschreven wat de 'normale klachten' waren (in de situatie dat de patiënt zich goed voelt). Zodra er een duidelijke verergering van klachten was (dus deze klachten weken af van de 'wat is normaal voor mij' kaart), kon de helft van de patiënten volgens het actieplan zelf starten met het behandelen van klachten (bijvoorbeeld door het gebruik van een kuur Prednisolon voor COPD klachten of een ontspanningsoefening voor meer angst). We hebben in de COPE-III studie, net zoals in de COPE-I en COPE-II studie, doorlopende ondersteuning van een verpleegkundige aan de patiënten aangeboden. Bij deze verpleegkundige konden de patiënten terecht met vragen of onduidelijkheden over het dagboek of het actieplan.

In **Hoofdstuk 5** laten we zien hoe je de Nederlandse 'Partners in Health' (PIH) vragenlijst kunt gebruiken om gedrag en kennis over zelfmanagement te meten bij Nederlandse COPD patiënten. De Nederlandse PIH vragenlijst meet twee dingen: 1) kennis van en omgaan met de ziekte; en 2) herkenning en management van klachten, opvolgen van adviezen voor de behandeling. Aan tien Nederlandse COPD patiënten hebben we gevraagd of er dingen onduidelijk waren over de Nederlandse PIH vragenlijst. Bijvoorbeeld of de gebruikte woorden in de vragenlijst duidelijk waren. Op basis van de meningen van deze patiënten en door de gevonden verschillen tussen de originele Australische PIH vragenlijst en de Nederlandse PIH vragenlijst, adviseren we om de PIH vragenlijst op enkele punten aan te passen. Bijvoorbeeld door in de PIH vragenlijst aan te geven over welke tijdsperiode de vragen gaan. We denken dat de PIH vragenlijst kan helpen bepalen welke vaardigheden van patiënten nog verbeterd kunnen worden voor zelfmanagement.

In **Hoofdstuk 6** laten we de resultaten van de COPE-III studie zien. Dit is wereldwijd de eerste studie die laat zien dat patiënten met COPD en daarnaast belangrijke andere ziekten betere uitkomsten hebben als ze een zelfmanagementprogramma volgen met een op maat gemaakt actieplan voor COPD en hun andere ziekten. Deze actieplannen zorgden voor een kortere duur van een longaanval en voor minder ziekenhuisopnames voor longklachten. Er is geen verschil in overlijden tussen de groep met en de groep zonder actieplan. Daarnaast hadden de patiënten met een actieplan meer vertrouwen in zichzelf om problemen met de ademhaling te voorkomen. De zelfmanagementgroep had meer emoties.

Mogelijke kwam dit omdat deze groep de klachten beter herkent en zich meer bewust is van de klachten, doordat ze dit hebben geleerd in het zelfmanagementprogramma. Het zelfmanagementprogramma kan nog verder aangepast worden aan de wensen en mogelijkheden van elke individuele patiënt. Daarnaast kan er meer aandacht worden besteed aan de ondersteuning door een verpleegkundige om zo het vertrouwen van patiënten en de algemene gezondheid te verbeteren.

In **Hoofdstuk 7** worden de belangrijkste resultaten van de studies in dit proefschrift samengevat en worden de resultaten in een breder kader van zelfmanagementprogramma's geplaatst. Er worden enkele beperkingen van ons onderzoek gegeven. Bijvoorbeeld dat de patiënten die meer gemotiveerd zijn, eerder zullen meedoen aan een zelfmanagementprogramma.

Kort samengevat zijn onze adviezen voor verder onderzoek en de praktijk:

1. Gebruik op maat gemaakte actieplannen in zelfmanagementprogramma's voor patiënten met COPD en andere ziekten. Biedt hierbij ondersteuning van een verpleegkundige aan;
2. Gebruik alleen actieplannen voor longaanvallen en opvlammingen van andere ziekten die worden aangeboden samen met een zelfmanagementprogramma. Het zelfmanagementprogramma heeft als doel patiënten te trainen, te motiveren, te betrekken en te ondersteunen om hun gedrag te veranderen om beter te kunnen omgaan met hun ziekte;
3. Onderzoeken moeten meer informatie geven over het aangeboden zelfmanagementprogramma;
4. In verder onderzoek kan men op zoek gaan naar eigenschappen van patiënten die voordeel hebben van een zelfmanagementprogramma. Hierdoor wordt het duidelijk wie wel of niet geschikt is voor een zelfmanagementprogramma;
5. Onderzoekers en artsen moeten het eens worden over een definitieve versie van de Partners in Health vragenlijst, zodat die kan worden gebruikt in verschillende landen.

DANKWOORD
(Acknowledgements)

Dankwoord

Mijn dankwoord, oftewel mijn allerlaatste woorden van dit proefschrift. Er zijn zoveel mensen die ik wil bedanken. Niet alleen voor de totstandkoming van dit proefschrift, maar ook voor alle support gedurende mijn periode als promovenda op de afdeling Longgeneeskunde van Medisch Spectrum Twente (MST).

Allereerst wil ik mijn promotor Job van der Palen bedanken. Bedankt voor jouw enthousiaste en positieve kijk op (COPD) onderzoek, de tweewekelijkse overleggen waarin ik alle lopende zaken met je kon bespreken, maar ook bedankt voor alle kansen die je me hebt geboden om me verder te ontwikkelen als onderzoeker. Ik ben blij dat ik als junior epidemioloog veel van jouw methodologische kennis en kunde heb mogen opsteken. Dank dat ik onderdeel heb mogen uitmaken van een leuke en inspirerende onderzoeksgroep. Hopelijk kunnen we in de toekomst leuke nieuwe projecten opstarten, maar gelukkig blijven we voorlopig nog samenwerken in een vervolgproject van de COPE-III studie.

Dan mijn co-promotor Tanja Effing, wat ben ik jou dankbaar voor alle leuke kansen die je me geboden hebt. Door jouw expertise op het vlak van COPD zelfmanagement interventies ben ik goed geïntroduceerd met het onderwerp. Daarnaast heb je me in contact gebracht met vele andere experts op dit gebied, bijvoorbeeld tijdens het congres in Perth (heel vervelend met een festival naast het congres). We hebben veel skype overleggen gehad, maar dankzij jou had ik ook een goed excuus om een kijkje te nemen in de Australische keuken. Naast onderzoek was er ook tijd voor een surfles, een gig van de Mighty Night Owls, een potje bowls, Ozzie bbq, WK voetbal NL-AUS kijken in de lokale sportkroeg van Adelaide, tour Down Under, wijnproeverij, enzovoorts. Heel erg bedankt voor de gastvrijheid en alle leuke activiteiten die jij, maar ook Bas en Liv, aan mij en Nick hebben geboden tijdens de twee onderzoeksperiodes in Adelaide. Een unieke ervaring die ik nooit zal vergeten!

Mijn andere co-promotor Paul van der Valk, ook wel (C)OP(E)A van de COPE studies. Dank dat je als longarts zorgde voor een kritische klinische blik op de stukken, die je tot in de late uurtjes hebt gelezen. Daarnaast was het leuk om in Wenen een opera met je mee te maken, al was het alleen al goed voor mijn conditie (jij vloog over de perrons!).

Also many grateful thanks to Peter Frith. It is an honour to have you on the graduation committee. Your expertise in COPD and research have contributed to the optimisation of the design and conduction of the COPE-III study. You have also been very helpful in seeking for funding opportunities and have actively participated in the interpretation of results and the writing. Thank you!

Dan de belangrijkste groep: alle patiënten die hebben deelgenomen aan de COPE-III studie, ontzettend bedankt! Zonder uw inzet zou dit onderzoek niet mogelijk zijn geweest. In totaal hebben we bijna 60.000 dagboekdagen volledig ingevuld mogen

ontvangen, dank daarvoor! Ook bedankt voor de enthousiaste opkomst tijdens de zelfmanagementbijeenkomsten. Dit alles heeft tot geweldige COPE-III resultaten geleid, waarvoor we dit jaar met trots een Longfonds publieksprijs in ontvangst hebben mogen nemen. Hopelijk lukt het ons om in de nabije toekomst de zelfmanagement van COPD en comorbiditeiten verder te verbeteren, zodat nog meer patiënten ervan kunnen profiteren.

Natuurlijk wil ik de COPE-III onderzoeksgroep bedanken voor de bijdrage aan de studie opzet, patiënteninclusie, uitvoering, data analyses en/of het schrijven. In MST: Job van der Palen, Paul van der Valk, Sylvia Punte, Clara van Ommeren, Chantal Wassink-Bergman, Kim Klieverik, Anna Weierink, Astrid Brilleman, Janneke Roukema, Judith Grooters, Alice Grooten-Nijkamp, Marie-Jose Pouwels, Elly Wajon, Hermien ten Bolscher, en alle longartsen. Clara, dank dat jij als casemanager in het MST heel nauw betrokken was bij de COPE-III studie. Jij verzorgde de zelfmanagementbijeenkomsten, de telefonische follow-up en bood de zelfmanagementgroep doorlopende ondersteuning. Dank dank dank! Saskia van Diepenbeek, ontzettend bedankt voor jouw inzet als casemanager in het Canisius-Wilhelmina Ziekenhuis (CWZ) Nijmegen. Daarnaast wil ik het CWZ bedanken voor de leuke samenwerking: Anneke van Veen, Wilma van Tuijl, Diana Verstralen, Jacqueline Kloek-Verweij, Ilse Bosman, Marijke van de Pavert, en alle longartsen. Ook de collega's in Adelaide bedankt voor jullie bijdrage aan de COPE-III studie: Tanja Effing, Peter Frith, Paul Cafarella, Stephen Quinn, Morton Burt, Anne Southwell, Adrienne Beverley, Cheryl Parton, Katherine Bassett, Robert Minson, Malcolm Battersby, Deborah Spicer, Sally Anesbury, Julie Buckman en Mary Young. Ik wil daarnaast de co-auteurs Marjolein Brusse-Keizer, Marlies Zwerink, Evelyn Monninkhof, Ruth Sladek, Peter Harvey, Malcolm Battersby, Wendy van Beurden, Muirne Paap en Karin Groothuis-Oudshoorn bedanken voor hun input.

Dank voor de financiële support van de COPE-III studie: Longfonds (voorheen Astmafonds), Stichting Astmabestrijding, GlaxoSmithKline, Lung Foundation Australia, the Repat Foundation. Daarnaast wil ik Flinders University Adelaide en Universiteit Twente bedanken voor het toekennen van een Cotutelle agreement. Het Longfonds en Medical School Twente wil ik bedanken voor hun financiële bijdrage aan de drukkosten van dit proefschrift.

De leden van de promotiecommissie, Prof. dr. ir. H.J. Hermens, Dr. C.J.M. Doggen, Prof. dr. M.A. Spruit, Prof. dr. P.A. Frith, en Prof. dr. H.A.M. Kerstjens, wil ik bedanken voor het kritisch beoordelen van mijn proefschrift.

Mijn speciale dank gaat uit naar Sylvia Punte. Dank dat jij een van mijn paranimfen wilt zijn. Jij rent en vliegt om alle onderzoeken met patiënten goed te laten verlopen. Dank voor alle COPE-III metingen en voor de gezellige fietsritten tot aan café Halfweg. Je bent een topper!

Alle andere (ex-)medewerkers van Onderzoeksbureau Longgeneeskunde MST (Tanja, Joyce, José, Irma, Elise, Ad, Marcel, Linnea, Marieke, Ellen, Brigitte, Wendy, Michiel) bedankt

voor de gezellige tijd tijdens de uitvoering van de COPE-III studie. Tanja, ontzettend bedankt voor jouw hulp bij het printen van de 1.885 Nederlandse dagboeken (oefendagboeken niet eens mee gerekend) en bij de invoer van de dagboekgegevens. Andere 'invoerders' of 'screeners' (Marloes, Sharina, Magda, Nina, Xin, Petra de Graaf) ook bedankt voor jullie hulp! Verder dank aan Protopics voor de verzameling van huisartsenpostgegevens (speciale dank aan Renate Haakmeester).

Ik wil mijn ex-kamergenoten Marlies en Maaike bedanken voor de gezelligheid gedurende de eerste jaren van mijn promotieonderzoek. Marlies, ondanks dat ik alvast van een afstandje mocht meekijken met jouw review, is het maar goed dat ik niet wist hoe groot mijn reviewklus uiteindelijk zou zijn. De collega-promovendi in het 'nieuwe MST' (Timon, Kirsten en Petra Hagens) bedankt voor de leuke tijd in het MST en de leerzame, gezellige Europese congresbezoeken. Ik wil Joanne Sloots veel succes wensen met de MATCH studie; een evaluatie van een zelfmanagement telemedicine platform voor COPD patiënten met hartfalen. Leuk dat we in dit project samenwerken!

Mijn nieuwe collega's van de vakgroep Health Technology Services and Research, Universiteit Twente, bedankt voor het warme welkom. Ik heb al veel kennis mogen opdoen over onderwijs en onderzoek binnen kwaliteit van zorg. Daarnaast bedankt dat jullie mij de tijd en ruimte hebben gegeven om dit proefschrift af te ronden.

Dan natuurlijk Jorien, Melissa, Wendy en Tanja (BFFs), bedankt voor alle leuke borrels, van trouwfeesten tot de Toppers, van een bbq tot weekend weg. Ik ben weer volop beschikbaar voor het volgende feest! Nicolien, al daten we niet dagelijks in het mooie Nimwèège, het is altijd gezellig om bij te kletsen! De Bennies & Annies (en Wannies), bedankt voor alle leuke afleidingen: de Boeskool, carnaval, de Annieweekenden met foute hits of een Dutch Oktoberfest, skivakantie of gewoon 'de stad in'.

Pap en mam, bedankt voor jullie steun en belangstelling voor mijn onderzoek. Ik vond het heel erg bijzonder dat jullie samen met Henk en Gerdy mijn werkplek in Adelaide hebben bezocht en dat we Down Under een weekje samen hebben kunnen optrekken. Sander en Korrie, bedankt dat ik af en toe in Nijmegen kon overnachten, zodat ik op tijd aan de slag kon in het CWZ. Krijn en Linda, bedankt voor jullie taxi naar Eindhoven airport voor een afleidend weekend weg. En natuurlijk Merle, dank dat je mijn paranimf wilt zijn en dat je altijd te vinden bent voor een shopdag, film, een potje beachvolleybal of een festival.

Tenslotte, Nick, bedankt voor je onvoorwaardelijke steun en het aanhoren van mijn verhalen over mijn (soms wat té lange) werkdag na mijn dagelijkse fietstochten tussen Oldenzaal en Enschede. Jij bent mijn topper en ik ben erg blij dat ik dit hele project, maar met name de twee onderzoeksperioden in Adelaide, met jou heb mogen delen. Hopelijk volgen er nog vele mooie andere reizen en projecten!

CONFERENCE PROCEEDINGS

Conference proceedings

Anke Lenferink, Peter Frith, Paul van der Valk, Julie Buckman, Ruth Sladek, Paul Cafarella, Job van der Palen, Tanja Effing. An innovative self-management approach in COPD patients with comorbidities. Poster presentation. In: Longdagen, Utrecht, the Netherlands, April 2013.

Anke Lenferink, Peter Frith, Paul van der Valk, Julie Buckman, Ruth Sladek, Paul Cafarella, Job van der Palen, Tanja Effing. An innovative self-management approach in COPD patients with comorbidities. Poster presentation. In: Ketenzorgdag, Utrecht, the Netherlands, October 2013.

Anke Lenferink. Successful COPD self-management. Workshop. In: V&VNVS congress, Arnhem, the Netherlands, October 2013.

Anke Lenferink, Job van der Palen, Peter Frith, Paul van der Valk, Tanja Effing. Associations between comorbid load and baseline characteristics in COPD patients with comorbidities: preliminary results. Poster presentation. In: European Respiratory Society (ERS) 2014 – Munich, Germany, September 2014.

Anke Lenferink, Job van der Palen, Peter Frith, Paul van der Valk, Tanja Effing. Associations between comorbid load and baseline characteristics in COPD patients with comorbidities: preliminary results. Poster presentation. In: Longdagen, Utrecht, the Netherlands, October 2014.

Anke Lenferink, Job van der Palen, Peter Frith, Paul van der Valk, Tanja Effing. Associations between comorbid load and baseline characteristics in COPD patients with comorbidities: preliminary results. Poster presentation. In: Ketenzorgdag, Utrecht, the Netherlands, January 2015.

Anke Lenferink, Job van der Palen, Peter Frith, Paul van der Valk, Tanja Effing. Associations between comorbid load and patient characteristics in COPD patients with comorbidities: preliminary results. Oral presentation. In: Thoracic Society of Australia and New Zealand (TSANZ) 2015, Gold Coast, Queensland, Australia, April 2015.

Anke Lenferink, Job van der Palen, Tanja Effing. The future of COPD self-management care. Oral presentation. In: Dr G.J. van Hoytema Stichting, Almelo, the Netherlands, June 2015.

Anke Lenferink, Muirne Paap, Peter Harvey, Malcolm Battersby, Peter Frith, Paul van der Valk, Wendy van Beurden, Job van der Palen, Tanja Effing. Validation of the 12-item Partners in Health scale to measure patient self-management behaviour and knowledge in Dutch patients with COPD. Poster presentation. In: European Respiratory Society (ERS) 2015 – Amsterdam, the Netherlands, September 2015.

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Anke Lenferink, Job van der Palen, Peter Frith, Paul van der Valk, Tanja Effing. Differences in patient characteristics and associations with comorbid load in Dutch and Australian patients. Poster presentation. In: European Respiratory Society (ERS) 2016, London, United Kingdom, September 2016.

Anke Lenferink, Marjolein Brusse-Keizer, Paul van der Valk, Peter Frith, Marlies Zwerink, Evelyn Monninkhof, Job van der Palen, Tanja Effing. Self-management interventions that include COPD exacerbation action plans improve health-related quality of life – a Cochrane review. Poster presentation. In: European Respiratory Society (ERS) 2016, London, United Kingdom, September 2016.

Anke Lenferink, Job van der Palen. Self-management in COPD. Oral presentation. In: Nederlandse Vereniging van Longfunctieanalisten (NVLA) Thorax Academy, Breukelen, the Netherlands, October 2016.

Anke Lenferink, Gerard Linssen, Hermie Hermens, Paul van der Valk, Monique Tabak, Martijn Grinovero, Miriam Vollenbroek-Hutten, Job van der Palen, Tanja Effing. Self-management and telemedicine in patients with COPD and chronic heart failure. Oral pitch. In: Pioneers in Health Care, Enschede, the Netherlands, November 2016.

Awarded a Pioneers In Health Care Innovation Fund 2016.

Anke Lenferink, Marjolein Brusse-Keizer, Paul van der Valk, Peter Frith, Marlies Zwerink, Evelyn Monninkhof, Job van der Palen, Tanja Effing. Self-management interventions including COPD exacerbation action plans improve hospitalisation rate and health-related quality of life – a Cochrane review. Oral presentation. In: Thoracic Society of Australia and New Zealand (TSANZ) 2017, Canberra, Australia, March 2017.

Awarded a Lung Foundation Australia / Cochrane Airways Australia Scholarship 2016.

Anke Lenferink, Job van der Palen, Paul van der Valk, Anneke van Veen, Karin Groothuis-Oudshoorn, Peter Frith, Tanja Effing. The effects of individualised action plans for the self-treatment of exacerbations in patients with COPD and comorbidities. Oral presentation. In: Longdagen 2017, Ermelo, the Netherlands, April 2017.

Awarded a Lung Foundation Netherlands Audience Award 2017.

Anke Lenferink, Job van der Palen, Paul van der Valk, Paul Cafarella, Anneke van Veen, Steve Quinn, Karin Groothuis-Oudshoorn, Morton Burt, Mary Young, Peter Frith, Tanja Effing. Self-management action plans for COPD patients with comorbidities reduce exacerbation duration and respiratory-related hospitalizations – the COPE-III study. Oral presentation. In: American Thoracic Society (ATS) International Conference 2017, Washington DC, United States of America, May 2017.

Awarded an American Thoracic Society (ATS) International Trainee Scholarship Award 2017.

Anke Lenferink, Job van der Palen, Paul van der Valk, Paul Cafarella, Anneke van Veen, Steve Quinn, Karin Groothuis-Oudshoorn, Morton Burt, Mary Young, Peter Frith, Tanja Effing. Effects of self-management action plans for COPD patients with comorbidities on health status and self-efficacy. Poster presentation. In: European Respiratory Society (ERS) 2017, Milan, September 2017.

CURRICULUM VITAE

Curriculum Vitae

Anke Lenferink was born in Tubbergen, the Netherlands, on the 17th of November 1985. She graduated from secondary school in 2004 at the St. Canisius college in Almelo. From 2005 to 2011, she studied Biomedical Sciences at the Radboud University, Nijmegen, where she graduated with majors in Epidemiology, and Health Technology Assessment in December 2011. She performed her master thesis on screening tools for diabetic retinopathy at the Eye and Ear hospital in Melbourne, Australia.

After her graduation, she commenced her PhD candidature at the Department of Pulmonary Medicine, Medisch Spectrum Twente, the Netherlands, in 2012. Her PhD project was concerning the effectiveness of a self-management intervention in patients with Chronic Obstructive Pulmonary Disease (COPD) and comorbidities: the COPE-III study. This study was performed in two hospitals in the Netherlands (Medisch Spectrum Twente Enschede, Canisius-Wilhelmina Ziekenhuis Nijmegen) and three hospitals in Adelaide, Australia (Repatriation General Hospital, Flinders Medical Centre and Royal Adelaide Hospital). She obtained a Cotutelle agreement between the University of Twente, Enschede, and the Flinders University, Adelaide, for cooperation between the Dutch and Australian research groups on the self-management of patients with COPD. In 2014 and 2016, she visited Adelaide for two four-month research periods as part of her Cotutelle agreement. The results of her PhD project are described in this dissertation.

Combined with her PhD project, she was also trained as an epidemiologist B at the Radboud University Nijmegen. Therefore, she has weekly reviewed articles on methodological issues and followed courses and conferences about epidemiology and methodology. In addition, she has reviewed multiple papers for several peer-reviewed journals. Next to her PhD project, she was also involved in work of another Australian research group on an Australian and Netherlands Consumer Delphi study to obtain consensus about essential factors to adopt and maintain optimal activity patterns in COPD patients.

Currently, Anke is employed as an assistant professor at the University of Twente, Enschede, where she is involved in education and research on quality in healthcare. She has recently started further research on the development of a self-management telemedicine platform for patients with COPD and chronic heart failure. Anke hopes to continue and expand her collaboration with different (international) disciplines and institutions to contribute to further improvement of self-management interventions.