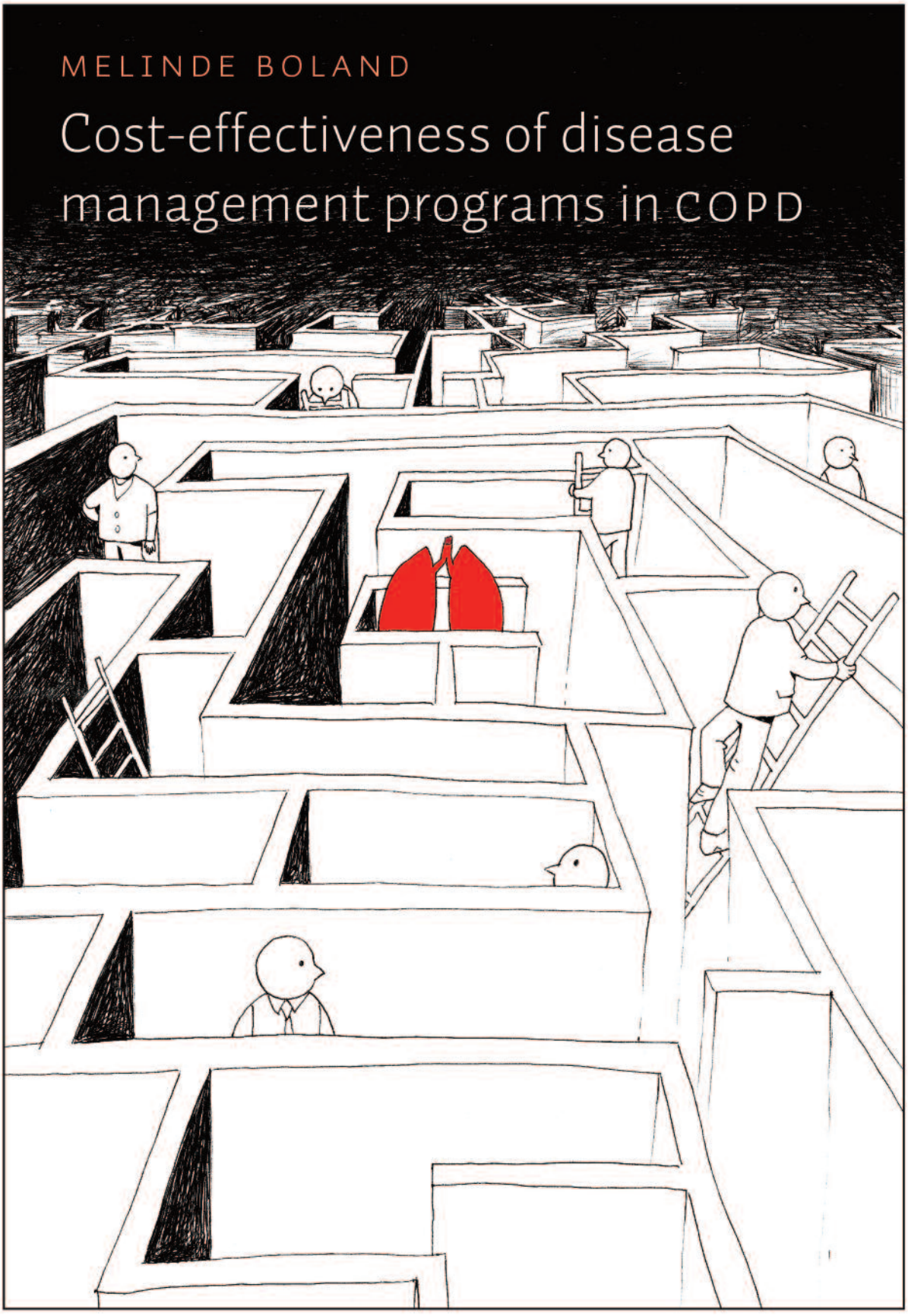
MELINDE BOLAND

Cost-effectiveness of disease management programs in COPD



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FUNDING

The RECODE trial was funded by Stichting Achmea Gezondheidszorg (SAG) and the Netherlands Organisation for Health Research and Development (ZonMW). The supplementary funding for providing a COPD specific exercise training for the RECODE study was provided by two local Dutch healthcare insurers 'Centraal Ziekenfonds (CZ) Zorgverzekeringen' and 'Zorg en Zekerheid.' The mapping study (chapter 9) was funded by Boehringer Ingelheim.

Cover design and layout: Marc Suvaal
Printing: Wilco, Amersfoort

Cost-effectiveness of disease management programs in COPD

Kosteneffectiviteit van disease management programma's voor COPD

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. H.A.P. Pols

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op

donderdag 12 november 2015 om 15:30 uur

door
Melinde Rosanne Sorayah Boland
geboren te Rotterdam

Erasmus University Rotterdam

Erasmus

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CHAPTER 1

General introduction

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a complex and heterogeneous respiratory disease with many different clinical phenotypes.[1] Among the essential determinants of improved health outcomes of COPD patients are behavioural changes in smoking, physical activity, and diet. Thus, assessment and treatment of the airways alone is evidently insufficient in the care of COPD patients.[2,3] COPD requires an integrated care approach that is tailored to the characteristics of an individual patient. Such an integrated care approach calls for a transformation of the healthcare delivery system from acute and reactive to proactive and planned healthcare. The behavioural and organizational changes that are part of such an approach require time and cannot be reached by implementing a single intervention. Instead, a set of patient-oriented, professional-oriented and organizational interventions is required.[4] Disease management (DM) is such an integrated care approach and is seen as a potentially powerful means to increase health outcomes, improve patients' experience with care and slow down the growth in healthcare expenditure. Favourable effects of these integrated care programs in COPD patients have been shown in some clinical studies[5–11], but not in others.[12,13] The growing worldwide burden and costs of COPD, to patients, their families, the healthcare sector, and society at large[14] emphasizes the needs for further justification of these programs in terms of cost-effectiveness. This thesis aims to investigate the cost-effectiveness of DM programs for COPD (herein, COPD-DM) patients as well as issues related to the mechanism of action of these programs. This introduction describes the disease characteristics, the prevalence and (economic) burden of COPD, as well as the characteristics of COPD-DM programs and cost-effectiveness analyses of these programs.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is characterized by persistent, often progressive, airflow limitation that is associated with a chronic inflammatory response in the airways and lungs to noxious particles and gases.[14,15] Symptoms of COPD are breathlessness on exertion, chronic cough with or without sputum production, wheezing, chest tightness, and many patients experience fatigue.[14,15] Weight loss, loss of muscle mass, and anorexia are additional features in severe COPD stages.[14,15] Exacerbations of COPD are important events in the progression of the disease.[15] A COPD exacerbation is defined as "a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations that is acute in onset and may warrant additional treatment in a patient with underlying COPD".[16] Exacerbations are associated with worsening symptoms[17], worsening qual-

ity of life[18], acceleration of the lung function decline[19], increasing healthcare costs[19,20], and mortality.[21]

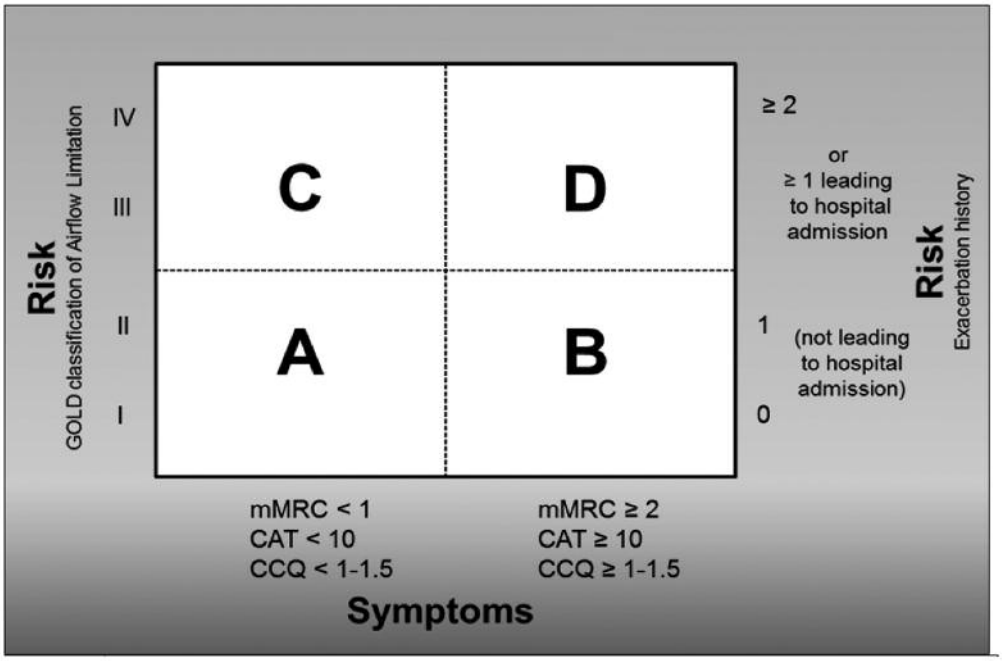
The clinical diagnosis of COPD should be considered in any patient who has a clinical history suggestive of COPD, i.e. dyspnoea, chronic cough or sputum production, and an exposure to risk factors for the disease (smoking, occupational exposure, indoor and outdoor pollution).[15] The diagnosis is based on lung function tested by spirometry; a post-bronchodilator forced expiratory volume in one second (FEV_1) / forced vital capacity (FVC) ratio below 0.7 confirms the presence of airflow limitation and COPD.[15] However, using a fixed ratio (FEV_1/FVC) to define COPD generally leads to over-diagnosis of COPD in older adults and under-diagnosis of COPD in adults aged < 45 years, because physiologically the FEV_1 decreases faster with age than FVC.[15,22] For a more accurate interpretation of the spirometry results, the Global Lung Function Initiative (GLI) developed new predicted values and age-appropriate 'lower limit of normal' (LLN) values to define airflow obstruction.[23] The European Respiratory Society (ERS) and American Thoracic Society (ATS) recommend the use of the predicted values of the GLI. Consequently, the 2015 version of the Dutch Care Standard for COPD replaced the cut-off ratio FEV_1/FVC < 0.7 with the LLN and replaced the old predicted values with the new predicted values from the GLI.[24]

Currently it is widely recognized that lung function not fully reflects the totality of disease burden experienced by the patient. Like previous studies, the ECLIPSE study showed that symptoms, health status, exacerbation frequency, and exercise capacity varied substantially between COPD patients and were often poorly related to FEV_1.[3,25] Furthermore, the course of the disease was highly variable, with close to a third of patients not progressing at all.[26] The recognition that COPD is a multicomponent disease requires a much broader definition of the severity of COPD than the traditional lung-function based definition of COPD.[26] This led to the development of multiple COPD indices[27] and subsequently, the revision of the strategy document of the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[1] In the revised GOLD strategy COPD is not only classified by the severity of airflow limitation as determined by spirometry (grade I, II, III, IV) (Table 1.1), but also by symptom level and exacerbations risk (group ABCD) (Figure 1.1).[1]

Table 1.1 GOLD I-II-III-IV grades assessment

GRADE	VALUES
GOLD-I (mild COPD)	Post-bronchodilator $FEV_1 \geq 80\%$ predicted
GOLD-II (moderate COPD)	$50\% \leq$ post-bronchodilator $FEV_1 < 80\%$ predicted
GOLD-III (severe COPD)	$30\% \leq$ post-bronchodilator $FEV_1 < 50\%$ predicted
GOLD-IV (very severe COPD)	Post-bronchodilator $FEV_1 < 30\%$ predicted

Figure 1.1 GOLD ABCD groups assessment



GOLD-A Less symptoms (CAT<10 OR mMRC<2 OR CCQ<1-1.5)
Low risk (FEV1 ≥ 50% and ≤1 exacerbation not leading to hospital admission)
GOLD-B More symptoms (CAT≥10 OR mMRC≥2 OR CCQ≥1-1.5)
Low risk (FEV1 ≥ 50% and 0-1 exacerbation not leading to hospital admission)
GOLD-C Less symptoms (CAT<10 OR mMRC<2 OR CCQ<1-1.5)
High risk (FEV1 > 50% and/or ≥1 exacerbation leading to hospital admission)
GOLD-D More symptoms (CAT≥10 OR mMRC≥2 OR CCQ≥1-1.5)
High risk (FEV1 > 50% and/or ≥1 exacerbation leading to hospital admission)

The classification of the GOLD I-II-III-IV grades is based on the severity of airflow limitation. The classification of the GOLD ABCD groups is based on symptoms and the risk of adverse health events.1 A high symptom burden can be determined using the modified British Medical Research Council (mMRC) dyspnoea scale28 (mMRC≥2), the COPD Assessment Test (CAT) (CAT≥10)29, or the Clinical COPD Questionnaire (CCQ) (cut-off has yet to be finally determined, but appears to be in the range 1 and 1.5).30 A high risk is based on the history of exacerbations in the previous year (≥2 exacerbations or ≥1 exacerbation(s) leading to hospital admission) or the FEV1 as a percentage of the predicted value (<50%), whichever results in a higher estimated risk. Based on this information the patient is allocated to one of the four groups ABCD, which intends to support the healthcare professionals in determining the severity of the disease, the impact on the patient's health status, the risk of future events and in guiding therapy.1

COPD is often accompanied by cardiovascular, metabolic, musculoskeletal, mental health conditions and (lung) cancer.15,31 On average, patients with COPD host 1.5-2 times more comorbidities compared to age-matched subjects without COPD.31 It is difficult to determine whether these are the consequences of COPD itself (comorbidity) or if these result from shared risk factors, such as smoking (multimorbidity).32 Several COPD phenotypes are currently acknowledged such as frequent exacerbators33, patients with asthma-COPD overlap syndrome (ACOS)34, and patients with an accelerated decline in FEV1.35

PREVALENCE

The Global Burden of Disease study reported that worldwide almost 33 million people suffer from COPD.[36] This likely reflects the under-diagnosis of COPD, because the World Health Organization (WHO) estimated that worldwide 65 million people suffer from COPD.[37] Differences in estimations are predominately due to differences in methods and criteria used. In practice, only a minority of the COPD diagnoses are confirmed by spirometry,[38,39] which leads to considerable mislabelling.[40] A systematic review demonstrated that among adults aged >40 years spirometric criteria resulted in a higher estimate of the prevalence than patients' self-report of COPD (9.2% versus 4.9%).[41] The Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) found that the under-diagnosis of new COPD cases at the end of the nine-year follow-up period was 70%.[42] This is in line with previously found underestimations between 60-78%.[43–45] However, over-diagnosis is also present. A study from Johannesson[46] showed that the classification using pre-bronchodilator spirometric values overestimated the presence of COPD with

27%.[46] The prevalence of COPD aged ≥ 40 in Maastricht, the Netherlands, was 8.8% using doctor-diagnoses, 18.7% using the LLN as cut-off value for the FEV_1/FVC ratio and 23.7% using the fixed cut-off ratio FEV_1/FVC ratio<0.7.[47]

Using the same classification and standard post-bronchodilator spirometric values, the PLATINO and Burden of Lung Disease (BOLD) studies demonstrated a considerable variation in prevalence from 5-20% across 17 countries.[48,49] The prevalence of COPD is mostly higher among men than among women, although this difference is rapidly disappearing in countries where the effects of the later smoking uptake among women are now fully visible. Prevalence of COPD increases with age.[31,47–49] However, variation in prevalence is also associated with geographic altitude[49], other environmental factors, exposures, and socioeconomic status.[31]

BURDEN

In 2010 COPD was the third leading cause of death, the fifth cause of disability and the ninth cause of DALYs lost (combining premature deaths and disability), in the world.[50] In Western Europe, COPD was the fourth leading cause of death, the ninth cause of disability and the seventh cause of DALYs lost in 2010.[50] Worldwide, COPD will account for about 8.6% of all deaths by 2030, compared to 5.8% in 2008.[14] Within the WHO European region, the percentage of deaths also grows about 30% from 2008 to 2030, with COPD causing 2.5% and 3.2% of deaths, respectively.[14]

The economic burden of COPD can be expressed in terms of direct and indirect costs. Direct costs are costs related to diagnosis and treatment of COPD, such as costs of medication, hospitalisation, and consultations with care providers. Indirect costs are not directly related to diagnosing and treating COPD, such as costs of productivity loss due to absence from paid work. Costs can be calculated from different perspectives. The healthcare perspective includes all costs covered by the healthcare budget while the societal perspective captures all costs (including travel costs, costs of productivity loss, costs of informal care) irrespective of who actually bears them. In Europe, the direct and indirect annual costs were estimated to be €23.3 and €25.1 billion, respectively.[14] However, it is likely that the indirect costs are overestimated, because the productivity costs were estimated with the Human Capital approach instead of the Friction Cost approach which takes into account that employees can be replaced, i.e. the Human Capital approach counts the total number of sick-days as lost while the Friction Cost approach only counts those days during the time it takes to replace a sick employee (the friction period).[51] The cost due to disability and loss of life-years (DALYs) were about €93.0 billion, resulting in total COPD costs of €141.4 billion.[14] The

underestimation of COPD prevalence results in an underestimation of COPD costs. However, the majority of undiagnosed COPD patients have mild disease severity[52] and probably have few treatment costs or indirect costs.[14]

There were significant differences in the estimated annual costs per case. A review of cost-of-illness studies from 10 European countries found that the total costs (direct and indirect costs) of a COPD patient differed from €323 in Norway to €3,647 in Italy in 2011.[53] Major variations were due to differences in unit costs, healthcare settings, perspective, type of patients included and cost categories included.[14] When using the same method, perspective and including the same cost categories in 28 European countries, the average annual costs per case were estimated to be about €6,147 in 2011; the direct, indirect costs and costs due to DALY lost were €1,013, €1,091 and €4,043, respectively.[14] Costs are strongly related to lung function and the main cost drivers were COPD exacerbations and medication costs.[54,55] Interventions preventing COPD exacerbations, stimulating appropriate use of medications and reducing lung function decline have large potential to decrease the economic burden of COPD. It has been predicted that the costs of COPD will be tripled in the 25 years following 2007.[56] This increase is due to continued exposure to COPD risk factors and aging of the population.[57]

DISEASE MANAGEMENT IN COPD

In the past, COPD treatment was primarily based on the severity of the airflow limitation, but the acknowledgement of the heterogeneity of the disease has created a worldwide movement towards a more personalized, holistic and integrated approach. According to the recent COPD guidelines, treatment objectives should be directed towards immediate relieving and reducing the impact of symptoms, and reducing the risk of adverse health events that may affect the patient at some point in the future.[1] A personalized multidisciplinary approach has traditionally been used in pulmonary rehabilitation programs,[58] which have been proven effective in severe and very severe COPD patients.[59,60] In the past few years, elements of pulmonary rehabilitation have been applied in COPD-DM programs that aim to change the routine of care delivery for a prolonged period of time.[61] COPD-DM consists of a combination of different pharmacological and non-pharmacological interventions (e.g. structural follow-up system of the COPD patients, physical activation, education, nutritional counselling, exacerbation management, smoking cessation support, and optimizing medication adherence) delivered by a multidisciplinary team of healthcare professionals. These programs are also accessible for mild to moderate COPD patients, a substantially larger part

(80%) of the COPD population than the patients with severe and very severe COPD.[62]

Providing adequate financial incentives to professionals can stimulate the structural implementation of DM programs. Currently, many countries have introduced performance- based payments schemes,[63] meaning that healthcare providers are rewarded for providing/improving quality of care as measured by certain performance indicators. In the Netherlands, performance indicators for COPD are mainly process indicators and there is a growing tendency towards using performance indicators structurally to contract integrated care. The justification for incentivizing healthcare providers to improve processes is the assumption that improved quality of care leads to improved health outcomes. A key assumption on the causal pathway is that improvements in indicators indeed alter the decision-making process of the healthcare providers, especially regarding treatment decisions.[64–66] Review studies have shown that performance based financial incentives may be effective in improving quality of care. However, the impact on patient's outcomes remains largely uncertain.[67–69]

COST-EFFECTIVENESS OF DISEASE MANAGEMENT IN COPD

In cost-effectiveness analysis (CEA) the incremental costs of a treatment are compared to the incremental health effects of the treatment, where the health effects are measured in natural units, like lung function, COPD exacerbations or disease-specific HRQoL.[70] Taking such a multidimensional approach towards outcome measurement is in line with COPD treatment guidelines.[71] However, to compare the cost-effectiveness of different treatments for different diseases, effects of an intervention need to be expressed in terms of costs per Quality Adjusted Life Year (QALY) gained. A QALY comprises both length and quality of life. The quality of life (utility value) of a certain health state can be derived from for example the EuroQoL-5 dimensions (EQ-5D)[72], the Short-form 36 (SF-36)[73] or the Health Utility Index questionnaire (HUI).[74]

DM programs are generally assumed to be cost-effective, because proactive and preventive care might reduce complications and the utilization of expensive hospital resources. However, there is still debate about the large-scale implementation of COPD-DM programs and some insurers in the Netherlands are more reluctant to do so than others. One of the reasons for the debate is that the available evidence is inconclusive. At the start of this PhD trajectory, several systematic reviews had evaluated the effects of COPD-DM.[4,75–79] However, they gave little insight into the economic consequences. In fact, there were only two studies reporting

cost-effectiveness ratios of a COPD-DM program with ≥12 months follow-up.[80,81] Monninkhof and colleagues[80], concluded that the COPE self-management program was not an efficient treatment option for moderate to severe COPD patients who rated their HRQoL relatively high; the program was twice as expensive as usual care and had no measurable beneficial effects on QALYs or HRQoL. More recently, the INTERCOM trial demonstrated that a COPD-DM program was moderately cost-effective in patients with less advanced airflow limitation and an impaired exercise performance.[81] The great variation in DM interventions, study characteristics, patient characteristics, and the limited recognition of the impact of these differences on the outcomes are contributing to the inconclusive evidence on DM.[82] In recent years, the debate in the Netherlands seems to be shifting from a debate about the need of COPD-DM programs per se to a debate about which type of program is most optimal. This shift is a consequence of the policy decision to stimulate the implementation of COPD-DM by the introduction of a bundled payment system for integrated care programs for COPD patient in 2010.[83]

RESEARCH QUESTIONS

The main aim of this thesis was to investigate the cost-effectiveness of COPD-DM. Therefore, we performed a systematic review of the literature, which is presented in chapter 2. Furthermore, as general practitioners treat the majority of COPD patients, it is of utmost importance to test the cost-effectiveness of these programs in primary care. Hence, we conducted a large cluster randomised trial (the RECODE trial) with a long-term follow-up (24 months) in which general practices were randomised to disease management or usual care (chapter 3 and 4). The design of the RECODE trial was inspired by the positive findings of two studies. One was the Bocholtz study, a controlled clinical trial, the other was an implementation project (Kroonluchter program) that was based on the experiences of the Bocholtz study.[5,6] These studies found that COPD-DM improved and sustained health status and exercise capacity in primary care COPD patients during two-years follow-up.[5,6] Because the level of implementation of a planned integrated care program is crucial for its success, we also investigated the implementation of the RECODE program in detail (chapter 5). Furthermore, we investigated the association between level of implementation and health outcomes. To summarize, the main research questions of the first part of this theses were the following:

- What is the evidence of the economic impact of a COPD-DM programs in the literature?

- Is the RECODE COPD-DM program in primary care cost-effective for patients with COPD?
- What was the level of implementation of the planned interventions in the RECODE program and what were the facilitators and barriers to implementation?
- What is the association between the level of implementation and health outcomes?

MECHANISMS OF ACTION OF COPD-DM

Because the RECODE cluster randomized controlled trial is the largest trial of a COPD-DM program to date, it provided a unique opportunity to investigate issues related to the mechanism of action of COPD-DM in more detail.

We first concentrated on the performance indicators of the COPD care process (chapter 6) because the measurement of these indicators is based on the assumption that there is a positive association between these indicators and health outcomes. We investigated if the RECODE integrated care program improved performance indicators and we investigated the impact of performance indicators on health outcomes. This chapter does have some relationship to chapter 5, because the change in performance indicators of the COPD care process could be seen as an indicator of the level of implementation of the intervention.

Next, we addressed adherence to medication. Because COPD medication is proven to be effective in reducing symptoms, reduce the frequency and severity of exacerbations, and improving health status and exercise tolerance[15], stimulating appropriate use of medications is an important element of COPD-DM programs. Unfortunately, low medication adherence in routine daily practice is common and the impact of non-adherence on HRQoL remains poorly understood.[84–86] In chapter 7 we investigated the association between adherence and health outcomes, thereby addressing a number of methodological challenges that have probably contributed to the conflicting results about this association in the literature.[87–92]

The large number of patients in the RECODE trial also provided a unique opportunity to compare the 2007 GOLD classification of COPD with the 2011 GOLD classification with respect to their association with HRQoL and costs (chapter 8). This is not only relevant from an epidemiological and clinical perspective but also from an economic perspective, because most decision-analytic models that estimate the cost-effectiveness of COPD-interventions are Markov models in which patients move through particular health states over time and in which utilities and costs are assigned to each state.

Finally, in chapter 9 we investigate the possibility to predict EQ-5D utilities from scores on the Clinical COPD Questionnaire (CCQ)[30], which is a widely-used disease-specific questionnaire to assess the effectiveness of COPD treatments. It was the primary outcome measure in the RECODE trial, whereas the EQ-5D was a secondary outcome measure. Many clinical trials include the CCQ , not only because it is brief and takes little time to complete[93], but also because the GOLD committee recommends the CCQ as one of the options to define COPD symptom level.[15] Hence, a successful mapping of the CCQ to the preference-based EQ-5D would facilitate performing economic evaluations using CCQ data in situation where there is no preference-based utility questionnaire used.

To summarize, for the second part of the theses we formulated two questions related to the mechanism of action and addressed two methodological topics that could facilitate future (model-based) cost-effectiveness studies:

- Did the RECODE program improve performance indicators of COPD care and was there a positive association between performance indicators and changed HRQoL?
- What is the association between medication adherence and HRQoL and what are the methodological challenges that need to be addressed to study this association?
- What is the association of the GOLD ABCD groups classification with a wide range of HRQoL outcomes and costs and how does it compare to the GOLD 1234 grades classification, which is based on lung function only.
- Can the CCQ scores obtained in a clinical trial be used to predict EQ-5D values?

NOTE TO THE READER

Because the chapters 2, 3, 4, 5, 6, 7, 8, and 9 of this thesis are written as separate articles for publication in international journals, they can be read independently.

CHAPTER 2

The health economic impact of disease management programs for COPD: a systematic literature review and meta-analysis

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BMC Pulmonary Medicine 2013; 13(1):40

ABSTRACT

Background: There is insufficient evidence of the cost-effectiveness of Chronic Obstructive Pulmonary Disease (COPD) Disease Management (COPD-DM) programs. The aim of this review is to evaluate the economic impact of COPD-DM programs and investigate the relation between the impact on healthcare costs and health outcomes. We also investigated the impact of patient-, intervention, and study-characteristics.

Methods: We conducted a systematic literature review to identify cost-effectiveness studies of COPD-DM. Where feasible, results were pooled using random-effects meta-analysis and explorative subgroup analyses were performed.

Results: Sixteen papers describing 11 studies were included (7 randomized control trials (RCT), 2 pre-post, 2 case-control). Meta-analysis showed that COPD-DM led to hospitalization savings of €1060 (95% CI: €2040 to €80) per patient per year and savings in total healthcare utilization of €898 (95% CI: €1566 to €231) (excl. operating costs). In these health economic studies small but positive results on health outcomes were found, such as the St Georges Respiratory Questionnaire (SGRQ) score, which decreased with 1.7 points (95% CI: 0.5-2.9). There was great variability in DM interventions-, study- and patient-characteristics. There were indications that DM showed greater savings in studies with: severe COPD patients, patients with a history of exacerbations, RCT study design, high methodological quality, few different professions involved in the program, and study setting outside Europe.

Conclusions: COPD-DM programs were found to have favourable effects on both health outcomes and costs, but there is considerable heterogeneity depending on patient-, intervention-, and study-characteristics.

Acknowledgements: The authors acknowledge P. Poole (University of Auckland, Auckland, New Zealand), J. Rich (HealthCare Partners Institute for Applied Research and Education, Torrance, California, USA), C. Chuang (HealthCare Partners Medical Group, Costa Mesa, California, USA) M. Hoogendoorn (Erasmus University Rotterdam, the Netherlands) and E. Monninkhof (Medical Spectrum Twente, Enschede, the Netherlands) for clarification and additional information on their COPD-DM programs.

BACKGROUND

Traditional healthcare for Chronic Obstructive Pulmonary Disease (COPD) focuses on pharmacotherapy to reduce symptoms and prevent exacerbations whereas patients are usually treated by a single healthcare professional, commonly the general practitioner or the respiratory

physician. However, COPD is a multi-component disease with a wide range of comorbidities.[1] Essential determinants in improving health outcomes of COPD patients are behavioural changes in physical activity, diet and smoking. Thus, assessment and treatment of the airways alone is evidently insufficient in the care of COPD patients.[2,3] COPD requires an integrated, tailor-made approach. Such integrated approach mostly asks for a transformation in the healthcare organization from acute and reactive to proactive and planned healthcare. However, these behavioural and organizational changes require time and cannot be reached by implementing a single intervention. Instead, a set of organizational, professional-, and patient-oriented interventions is required for a successful change in organizational structure and processes as well as patient lifestyle and behaviour.[4] Disease management (DM) is such an approach and is seen as a solution to tackle the challenges posed by COPD.

Although DM programs are generally believed to be cost-effective, the available evidence is inconclusive. Several systematic reviews have evaluated the effects of COPD-DM.[4,75–79] However, they gave little insight into the economic consequences. Only the review of Steuten et al.[78], which searched studies between 1995 and 2007, included 3 studies which evaluated cost data. Since then, several studies focusing on DM and cost-effectiveness have been published. Furthermore, the review of De Bruin et al.[79], which searched for DM studies between 2007 and 2009, included 5 studies which evaluated cost data of COPD-DM programs, but did not include the studies before 2007 and after 2009. Furthermore, these two systematic reviews did not perform a meta-analysis on costs and effects.[4,75–79] In addition, little is known on the key elements of DM programs that are able to affect the outcomes and cost of COPD in a particular setting.[75,82] The great variation in DM interventions, study characteristics, patient characteristics, quality of study and a limited recognition of the impact of these differences on the outcomes are the reasons that evidence on cost-effectiveness of the DM programs provides limited support to decision makers.[82] The aim of this review is to evaluate the economic impact of COPD-DM programs and investigate the relation between the impact on healthcare costs and health outcomes. We also investigate whether this impact depends on intervention-, study-, and patient-characteristics.

METHODS

Search strategy and selection criteria

A systematic electronic literature search for economic evaluations of COPD-DM was performed in Medline, the economic evaluation database of the UK National Health System (NHS-EED) and the EUROpean Net-

work of Health Economic Evaluation Database (EURONHEED). The search was restricted to the English, German and Dutch language, but there were no restrictions to dates. All databases were searched on *21 July 2011*.

For the selection of the search terms, we firstly identified the key elements of DM. There are several definitions of DM available in the literature.[94] A short overview of definitions published in the last decade is shown in Appendix 2.1. Most definitions have eight elements in common that characterize DM, which are: 1) focusing on a target group of patients with a chronic condition, 2) multi-interventions developed for patient, healthcare provider and/or organization, 3) pro-active, planned healthcare, 4) evidence based/according to guideline, 5) self- management, 6) multidisciplinary team, 7) monitoring of performance and 8) supporting clinical information systems.[94–101] Furthermore, DM programs are often based on Wagner's Chronic Care Model (CCM)[102], especially in Europe (EU). The CCM includes six interrelated components that are essential for improving chronic care. There are four elements at the micro level emphasizing interactions between patients, providers and community: 1) self-management, to empower and prepare patients to manage their disease (e.g. patient education, counselling to improve self-efficacy); 2) delivery system design, that assures the delivery of effective and efficient clinical and behavioural care (e.g. systematic and pro-active follow-up of patients); 3) decision support, to promote the use of evidence-based clinical care (e.g. electronic guidelines incorporated in information system); and 4) clinical information system, to assure access to timely, relevant data about patients (e.g. electronic patient record). One element at the meso level: 5) community, to link community and healthcare delivery. And one element at the macro level: 6) organizational support, to consider the policy and financing context. An indicated list with DM interventions grouped per CCM component is presented in Appendix 2.2. Overall, DM requires a change in routine care delivery for a prolonged period of time and DM programs often focus on the entire spectrum of severity of a disease and its complications, including often (secondary) prevention as well.

Besides the elements of DM, the search terms included descriptions of COPD, cost(s) and economic evaluation. The complete search strategy can be found in Appendix 2.3. Additional studies were sought by hand searching the reference list of reviews on economic evaluation of DM found in the literature search. The titles, keywords, abstracts and papers were screened to assess whether the study met the following inclusion criteria:

- at least some of the patients had COPD and the results of the subgroup of COPD patients were presented separately;
- the study included at least two DM interventions from the list presented in Appendix 2.2;
- the study was an original empirical research paper excluding therefore, review, methodological and modelling studies;
- the study reported both costs and effects;
- the DM program had a minimum duration of 12 months (intensive + maintenance phase);
- the comparator was usual care or no-intervention.

Potentially relevant studies retrieved from the electronic searches were identified by two reviewers (MB and AT) based on the predetermined inclusion criteria in a two-step procedure: 1) title, keywords, and abstract, 2) a brief screening of intervention, outcomes and costs. When disagreement of the two researchers could not be resolved by discussion, a third reviewer (MR) was consulted to reach consensus.

Quality assessment, risk of bias and data analyses

We developed a check-list to assess the methodological quality of the studies based on the check-list of Drummond et al.[70] and the health technology assessment disease management instrument of Steuten et al.[103] The former is used to assess the quality of economic evaluation studies in general and the latter is used to assess the methodological quality of DM evaluations specifically. The combined list assessed the strength and weaknesses of the studies on 7 key elements, each of which contains three or more items (see results section for the entire list) with a yes/no response option. The total quality score of a study is calculated as the sum of items with a positive assessment as a percentage of the number of applicable items. Hence, the maximum score is 100%.

We assessed the risk of bias of the individual studies according to the Cochrane Handbook for Systematic Reviews of Interventions[104] on five items of bias: (1) selection, (2) performance, (3) detection, (4) attrition, and (5) reporting. In order to prevent potential reporting bias, emails and telephone calls were made to the authors of the studies for additional information on the DM program, were necessary.

Given the likely heterogeneity between studies, we started with a descriptive analysis of the design, methods, quality, and results of the studies. A reviewer (MB) extracted data on study characteristics (sample size, setting, country, follow-up duration and study design), patient characteristics (age, gender, forced expiratory volume in one second as percentage of the predicted value (FEV_1% pred), history of exacerbations and

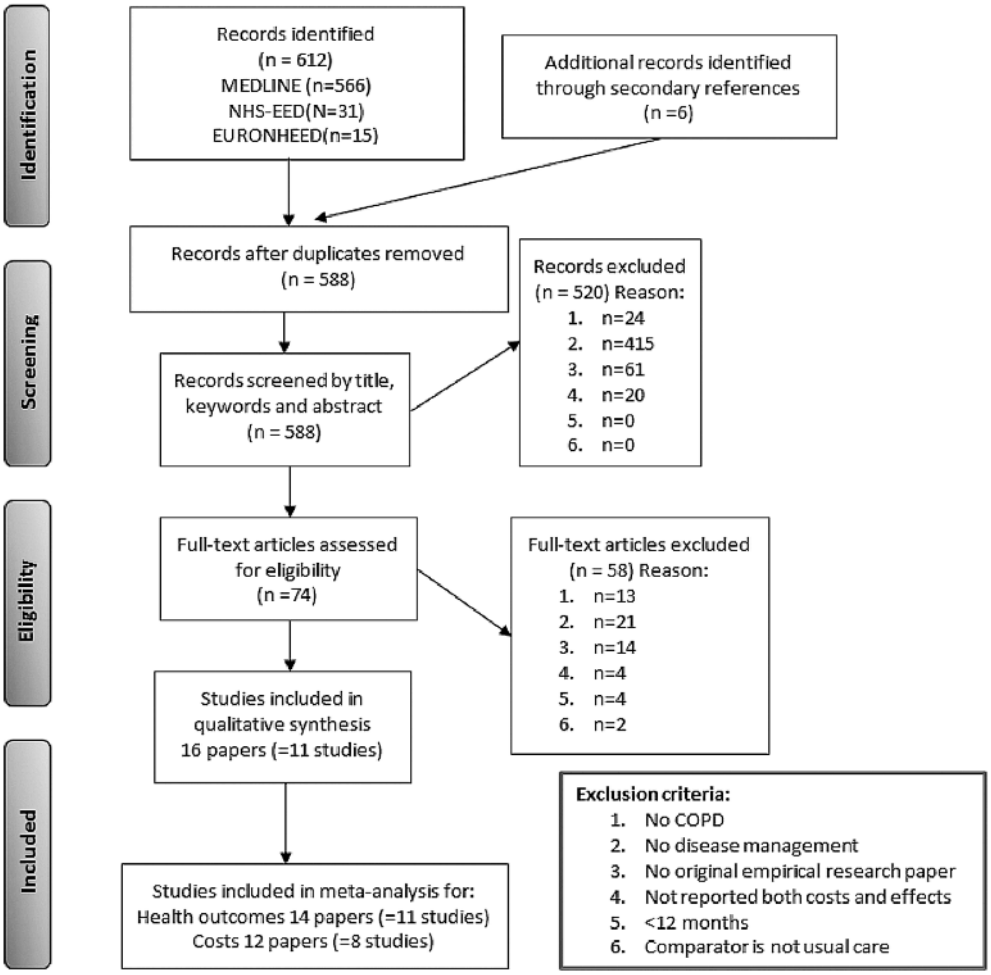
smoking status), type and number of interventions according to the CCM (i.e. self-management), type and number of healthcare provider(s) involved. Furthermore, the difference in cost per patient between the DM program and the comparator were reported according to the following categories: 1) DM development, implementation & operating costs, 2) direct costs of healthcare utilization, 3) direct costs of informal care, 4) direct non-medical costs borne by patients/families, and 5) costs of productivity loss. These were checked by a second reviewer (AT). The costs were inflated to 2010[105] and were converted to Euros (€) by using Dutch purchaser power parities.[106] In addition, we reported the difference in outcomes which were grouped into the following categories: 1) care delivery process, 2) patient behaviour, 3) biomedical, physiological outcomes (e.g. lung function, body mass index (BMI)), 4) COPD-exacerbations, 5) health related quality of life and 6) mortality. Were possible, we have calculated relative risks for dichotomous outcomes and relative differences (RD), rate ratio (RR) or standardized mean differences (SMD) for continuous outcomes. To calculate a weighted average treatment effect, the data were pooled using a random-effects meta-analysis model based on the DerSimonian-Laird method[107] and the example of Linden and Adams.[108] Heterogeneity in the results was visually displayed using forest plots grouped into 1) intervention-, 2) study- and 3) patient characteristics.

RESULTS

Description of studies

The literature search identified 612 potentially eligible papers and the screening of their references resulted in 6 additional papers. After the first step of selection (based on title, keywords and abstract) 544 papers were rejected. Examining the full text of the remaining papers led to the exclusion of 56 additional studies. The main reason for excluding were "no DM program" (n=436). Lastly, two additional papers were excluded because the comparator was not usual care or no-intervention. This resulted in the inclusion of 16 papers reporting 11 different studies. The reasons for excluding initially selected papers at various stages are presented in a PRISMA diagram[109] (Figure 2.1).

Figure 2.1 In- and exclusion of papers at various stages



The selected studies included 7 randomized control trials (RCT), 2 pre-post and 2 case-control studies (Table 1). Six studies were conducted in Europe (the Netherlands (n=3), UK (n=1), France (n=1), Norway (n=1)) and five studies originated from non-European countries including USA (n=3), Canada (n=1), New Zealand (n=1). The duration of the DM program varied from 12 to 24 months. Some programs include an intensive phase followed by a maintenance phase; others do not make this distinction. In those that do, the minimum duration of the intensive phase was 3

weeks.[80,81,110,111] The sample size of the intervention group varied from n=16[112] to n=524[113], with a mean sample size of 160 (±168). The sample size of the control group varied from n=16[112] to n=371[114], with a mean sample size of 95 (±110). The average proportion of drop-out was 14% (±11).

The average age at baseline was 66(±4) for the intervention and 67(±6) for the control group (Table 2.1). The proportion of males varied more widely between studies with a mean proportion of males of 66% (±19) in the intervention group and 68% (±17) in the control group. The mean FEV_1% of predicted was 47(±10) in the intervention group and 50(±7) in the control group, which indicates mild to moderate airflow obstruction according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.[115] More than one fourth of the patients in the studies are smokers, with a mean proportion of 28 (±10) in the intervention and 26 (±6) in the control group. Determining the specific comorbidities of the patients was impossible. However, virtually all studies excluded patients with significant comorbidities. The study and patient characteristics per study are presented in Table 2.1.

Various DM interventions were evaluated in the studies (Table 2.1). All studies included interventions of the CCM component self-management support (SMS). Eight studies evaluated interventions of the component delivery system design (DSD), followed by decision support (DEC) (n=7) and clinical information system (CIS) (n=1). No study included interventions based on the CCM components organizational support (ORG) or community (COM). Two studies included multiple interventions in one CCM component, three studies included interventions covering two CCM components, five studies[81,114,116–118] covered three components and one study[9] included interventions from 4 CCM components. Frequently applied interventions were (1) patient education on psychosocial effects of COPD (e.g. dealing with stress arising from living with a chronic disease, improving self-efficacy), knowledge of COPD and/or self-management skills (e.g. coping with breathlessness, exercise, encouragement of self-treatment), (2) stimulation of physical activity (e.g. fitness program in a small group), (3) changes in visits structure and organization (e.g. follow-up calls in response to exacerbation), (4) individual treatment plan, and (5) exacerbation management (e.g. patient training in recognizing early symptoms of exacerbation, discussion of individual causes of exacerbations, guidelines for self-treatment of exacerbations). The frequency of the interventions used in the included DM programs per CCM component can be found in Appendix 2.2.

The number of different professions involved in delivering of the DM program varied from two to five. One study did not report which healthcare providers were involved.[8] The most frequently involved healthcare

providers of the DM programs were respiratory/chest specialist (RS) (90%), respiratory nurse (RN) (90%), general practitioner (GP) (70%) and physiotherapist (PHY) (40%). The intervention characteristics are shown in Table 2.1.

The quality of studies and risk of bias

The quality score of the 11 selected studies varied between 29% and 80%. The mean score was 59% with a standard deviation of 16% (see Table 2.2). Most studies (82%) did not report detailed characteristics of institution(s) or region in which the intervention is implemented, e.g. size of the region and rural or urban environment. Only the setting of recruited institution(s) is known of all studies: 7 in a hospital setting,[8,80,81,110–112,117] 1 in a primary care setting[9] and 3 in a combination of a hospital and primary care setting.[114,116,118]

Only one study[9] reported a plan to avoid contamination by other interventions and only three studies clearly provided details of the comparator.[8,81,117] Although all studies scored well on including intermediate and final health outcomes and costs of healthcare utilization, the lack of measurement of all relevant costs and outcome categories decreased the quality score of most studies.

Selection bias was likely in two studies[112,116] (see Appendix 2.4). One study[116] did not report patient-characteristics, which made it impossible to verify if the baseline characteristics were comparable. Both studies[112,116] did not randomly allocate patients. All studies had a high risk of performance, because blinding of the intervention for caregivers and patient is impossible. Although blinding of outcome assessors is possible, only 5 studies reported to have done so.[8,81,110,114,117] Four studies were at risk for attrition bias.[9,112,116,118] These four studies did not clearly describe the patients that dropped out from the study in a flow-chart or in the text. Moreover, one study[118] had a drop-out rate of 33%. Six studies were at risk of selective reporting, because they did not report statistical difference in costs and/or outcome.[80,111,112,114,117,118]

Table 2.1 Study-, patient- and intervention characteristics

	Study characteristics							Patient characteristics										Intervention characteristics											
				Sample size at baselinec		No of patients who completed study [c]		Mean age		Sex (% male)		FEV1% predicted		% with a history of ≥ 1 exacerbation in year prior to study		Smoking status (%smokers)		Interventions categories according to CCM components*					Professions involved in delivering of the DM program**							
	Country [a]	Follow-up (months)	Study design [b]	I	C	I	C	I	C	I	C	I	C	I	C	I	C	SMS	DEC	DSD	CIS	total	RS	RN	GP	PHY	DIE	PHA	SW	total
[9]	NL	12	Pre-post	317	NA	222	NA	61	NA	56	NA	56	NA	NS	NS	40	NA	✓	✓	✓	✓	**4**	✓	✓	✓					**3**
[81]	NL	24	RCT	102	97	77	81	66	67	71	71	49	51	1.2	1.0	33	24	✓	✓	✓		**3**	✓	✓		✓	✓			**4**
[8]	FR	12	RCT	23	22	20	18	65	61	90	78	56	54	NS	NS	25	28	✓				**1**	NS	NS	NS	NS	NS	NS	NS	**NS**
[116]	USA	12	Case-control	94	47	NA	NA	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	✓	✓	✓		**3**	✓	✓	✓					**3**
[110]	NOR	12	RCT	31	31	26	27	57	58	48	52	52	55	NS	NS	39	39	✓	✓			**2**	✓	✓	✓	✓		✓		**5**
[117]	CAN	12	RCT	96	95	86	79	70	69	52	59	45	46	NS	NS	25	26	✓	✓	✓		**3**	✓	✓	✓					**3**
[80]	NL	12	RCT	127	121	122	114	65	65	85	84	56	58	1.4	1.3	28	26	✓				**1**	✓			✓				**2**
[111]	UK	24	RCT	61	61	55	49	70	70	49	49	43	49	100[e]	100	30	20	✓		✓		**2**		✓	✓					**2**
[114]	USA	12	RCT	372	371	336	323	69	71	98	98	36	38	100	100	22	23	✓	✓	✓		**3**	✓	✓		✓				**3**
[112]	NZ	12	Case-control	16	16	NA	NA	70	75	63	56	26	NS [d]	100	100	13	19	✓		✓		**2**	✓	✓	✓				✓	**4**
[118]	USA	12	Pre-post	524	NA	349	NA	64	NA	51	NA	NS	NA	NS	NA	NS	NA	✓	✓	✓		**3**	✓	✓	✓					**3**
																Total (%)		100	64	73	9		90	90	70	40	10	10	10	

[a] *NL* Netherlands, *FR* France, *USA* United States of America, *NOR* Norway, *CAN* Canada, *UK* United Kingdom, *NZ* New Zealand, [b] *RCT* Randomized Control Trial, [c] *I* intervention, *C* comparison, [d] FEV_1 control group 0.72 ± 0.22L, [e] in the last 4 years, *NS* not stated, *NA* not applicable, * *SMS* Self-management support, *DEC* decision support, *DSD* delivery system design, *CIS* clinical information system, ** *RS* respiratory/chest specialist, *RN* respiratory nurse, *GP* general practitioner, *PHY* physiotherapist, *DIE* dietician, *PHA* pharmacist, *SW* social worker

Table 2.2 Quality of Study

Characteristic	Type	9	81	8	116	110	117	80	111	114	112	118	%
Study population	1. Clear description of in- and exclusion	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	-	91
	2. Clear description of drop-outs	-	✓	✓	-	✓	✓	✓	✓	✓	-	-	64
	3. The study population consist of an intervention and control group	-	✓	✓	✓	✓	✓	✓	✓	✓	✓	-	82
	4. Relevant baseline characteristics are comparable	NA	✓	✓	-	✓	✓	✓	✓	✓	✓	NA	89
Intervention	5. Random allocation	NA	✓	✓	-	✓	✓	✓	✓	✓	-	NA	78
	6. Clear description of type of intervention	✓	✓	-	✓	✓	✓	✓	✓	✓	✓	✓	91
	7. Clear description of the comparator	-	✓	✓	-	-	✓	-	-	-	-	-	27
	8. Detailed characteristics of institution(s)/region in which the intervention is implemented are described	✓	-	✓	-	-	-	-	-	-	-	-	18
	9. Co-interventions are avoided	✓	-	-	-	-	-	-	-	-	-	-	9
Measurement of all relevant cost categories	10. Inclusion of development /implementation /operating costs	-	-	-	✓	✓	✓	✓	✓	✓	✓	-	64
	11. Inclusion of healthcare utilization costs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100
	12. Inclusion of direct non-medical and non-direct costs	-	✓	-	-	✓	-	✓	-	-	-	-	27
	13. Justification for omitting costs categories	-	-	-	-	NA	✓	NA	-	-	-	-	11
Measurement of all relevant outcome categories	14. Healthcare delivery process	✓	-	-	-	✓	-	-	-	-	-	-	18
	15. Patient behaviour	✓	✓	✓	-	-	-	✓	-	-	-	-	36
	16. Biomedical and physiological health outcomes	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100
	17. Health related quality of life and/or mortality and/or (quality) adjusted life years	✓	✓	✓	-	-	✓	✓	✓	✓	✓	✓	82
	18. Justification of omitting outcome categories	NA	-	✓	-	-	-	-	-	-	-	-	10
Measurement and valuation of data	19. Perspective explicitly mentioned	✓	✓	-	-	✓	✓	✓	-	✓	-	-	55
	20. The sources of resource utilization are described and justified	✓	✓	✓	-	✓	✓	✓	✓	✓	✓	✓	91
	21. The resource use and costs are reported separately	-	✓	-	✓	✓	✓	-	✓	✓	✓	✓	73
	22.The effects are measured in appropriate units	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100
	23. Data analysis is performed according intention-to-treat principle	✓	✓	-	-	-	✓	✓	-	✓	-	-	45
Presentation of data	24. Allowance made for uncertainty in the estimates of the costs	✓	✓	✓	-	✓	-	✓	-	✓	-	-	55
	25. Allowance made for uncertainty in the estimates of the effects	✓	✓	✓	✓	✓	-	✓	-	✓	-	-	64
	26. Incremental analysis of costs and effects are performed	-	✓	-	-	-	-	✓	-	-	-	-	36
Discussion of the study results	27. The results are interpreted adequate	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100
	28. The results are compared with other studies and allowances are made for potential differences in study methodology	✓	✓	✓	-	✓	✓	✓	✓	✓	✓	-	82
	29. The study discusses the generalizability of the results to other settings and patient groups	✓	✓	-	✓	-	✓	✓	-	✓	-	-	55
	30. The study discusses issues of implementation of the intervention	✓	✓	-	✓	-	✓	-	-	-	-	-	36
Total quality of study (%)		70	80	60	40	66	70	76	50	67	43	29	

NA not applicable

Results on costs

Various DM costs were included in the studies. Table 2.3 shows the results on difference in costs per patient (PP) between the DM program and the comparator. Of the 11 studies, 5 did not report statistical testing of the cost difference[80,111,112,117,118] and 1 study[114] reported only partly which costs differed significantly.

The total difference in costs between the COPD-DM program and the control group ranged from -€1689[110] to €2856[81], with a mean (±standard deviation (SD)) cost increase of €88 (±€1214). These total costs included the development, implementation and operating costs, where reported. Six of the eleven studies (55%) reported savings in total costs; however no study demonstrated a significant reduction of the total costs. On the other hand, no study demonstrated a significant increase of the total costs either.

The development, implementation and operating costs varied between €94[114] and €2976,[117] with a mean (±SD) costs of €1139 (±€1022). The difference in healthcare costs PP varied between a cost reduction of €2672 [112] and a cost increase of €2229 [81]. Nine of the eleven studies (82%) reported healthcare costs savings, although the costs significantly decreased in only one of these studies.[116] The total healthcare costs were mainly driven by the hospitalization costs. All but one study[8] reported a reduction in hospitalization costs in favour of the DM programs. No study estimated the costs of informal care. Direct-non-medical costs borne by patients/family were included in two studies. One study[81] found a decrease in this type of costs of €65 and the other study[110] found a statistically significant increase in these costs of €47. The productivity costs were included in three studies: one study[110] showed a cost reduction of €944 and two studies[80,81] showed a cost increase of €693 and €280, respectively. These differences in productivity costs were not statistically significant.

In total 11 and 9 studies reported total healthcare utilization and hospital costs, of which 8 and 6 studies provided enough data to be pooled in a meta-analysis, respectively. Figure 2.2a shows the results of the meta-analysis on healthcare utilization costs. COPD-DM programs were found to result in average healthcare savings of €898 PP (95% CI €231-€1566). The heterogeneity in healthcare costs across studies is large (I^2= 93.0%). The pooled results from the 6 studies that included hospitalization costs demonstrated a reduction of €1060 PP (95% CI €80- €2040) (Figure 2.2b). However, the heterogeneity between studies in hospital costs is large (I^2= 69.5%).

Table 2.3 Results on difference in costs per patient (¤ 2010)

	Healthcare utilization												Total
	Development , implementation, operating	Medication		Physician visits	Specialist visits	Other outpatient	ED visits	Hospitalization	Total healthcare utilization	Informal care	Direct-non medical costs	productivity loss	
[9]									-47				**-47**
[81]			668[1]	-12	-42	2038[1]		-424	2229[1]		-65	693	**2856**
[8]			-507*					1150	652				**652**
[116]	2007		79					-2098	-2019*				**-13**
[110]	200		-182	-145*	-13			-708	-999		47*	-944	**-1689**
[117]#	2976			-22	-2		-158	-2448	-2630				**347**
[80]#	728		42	-6				-92	-56			280	**950**
[111]#	94			-79					-79				**15**
[114]#	545		13				-118	-936*	-1042				**-497**
[112]#	1850							-2004	-2004				**-154**
[118]#	712						-357	-1804	-2160				**-1448**

* Significant (p<0.05) *ED visit* emergency department visit, # no information of significance level available (n=5 studies), Dewan e.a. 2010 [34] reported only information on significance level of hospitalization and total costs - [1] significantly higher cost: diet nutrition, physiotherapist, dietician, respiratory nurse

Table 2.4 shows the results of the meta-analysis of the COPD-DM programs by intervention-, study-, and patient-characteristics. Three intervention-characteristics were used to define subgroups for the meta-analysis: CCM components, number of different types of healthcare providers involved in the intervention and duration of the intervention. When data were pooled by the number of CCM components, the savings of programs covering 3 or more CCM components where greater than those of the programs covering 2 or less components. This difference was statistically significant for the hospital costs, but not for the total healthcare costs. Likewise, greater savings were found for studies with a long intervention duration (> 12 months), than for studies with a short intervention duration (< 12 months). These savings for studies with a long intervention duration were significant for the hospitalization costs, but not for the total healthcare costs. Subgroup analysis by number of professions involved in delivering of the DM program showed that interventions delivered by 2 or 3 disciplines of healthcare providers found significant savings in hospital costs as well as total healthcare costs but this was not found for interventions including 4 or more disciplines of healthcare providers.

Three study-characteristics were used to define subgroups: design, region and quality of study. Savings in hospital costs as well as total healthcare costs were found for non-EU countries but not for EU coun-

tries. COPD-DM programs with a non-RCT study design had on average greater healthcare savings than COPD-DM programs with a RCT study design. However, the savings were non-significant for non-RCT studies, whereas there were significant for RCT studies. Similarly, COPD-DM programs with a higher quality score found significant savings in total healthcare costs as well as hospital costs, whereas studies with a lower quality score did not.

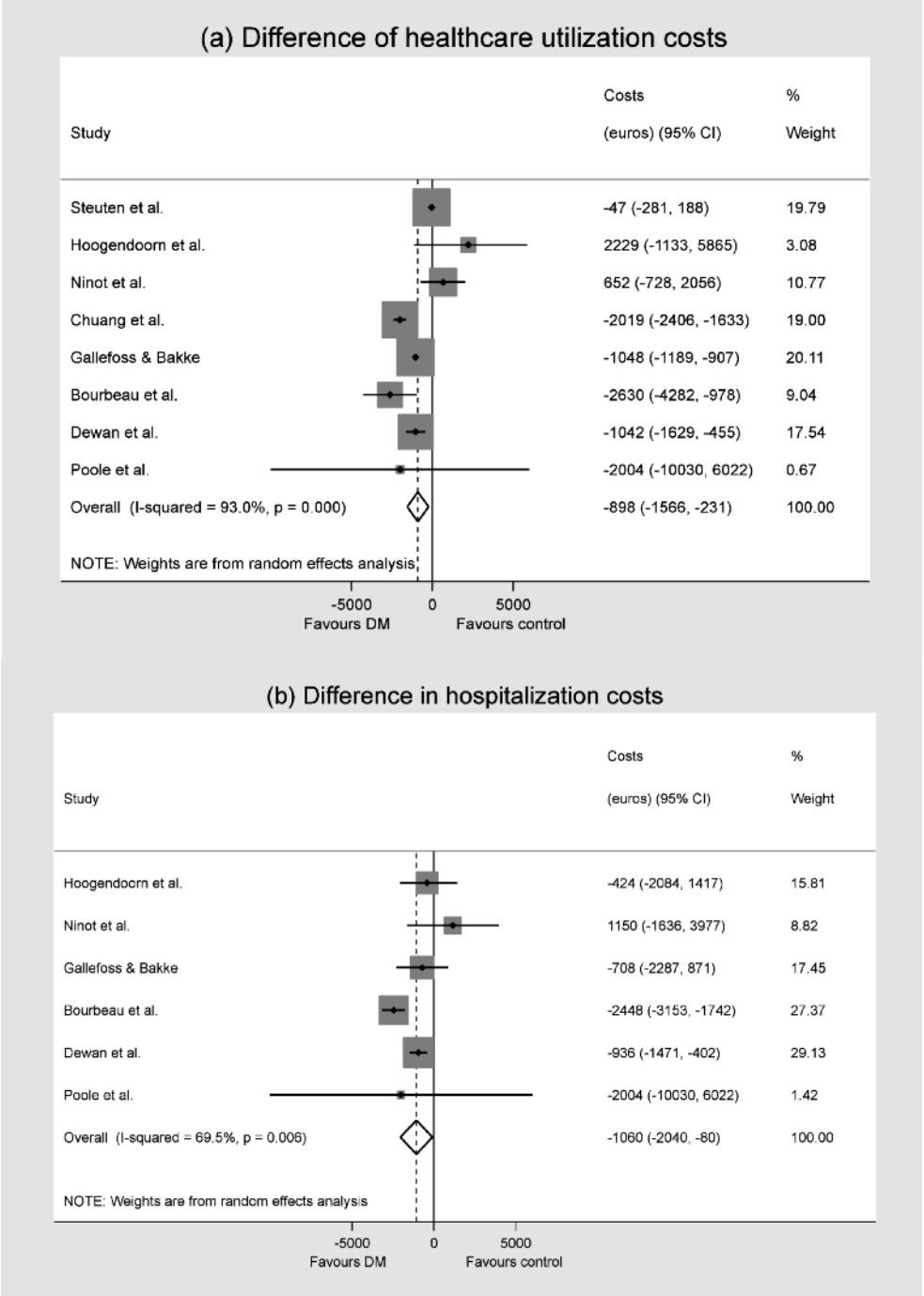
Five patient-characteristics were used to define subgroups: age, percentage male, GOLD stage, a history of exacerbation as inclusion criteria and percentage smokers. Greater savings were found for COPD-DM programs with older patients, compared to younger patient. Finally, savings in healthcare costs as well as hospital costs were higher, when patients were more severely ill, i.e. had a higher GOLD stage and a history of exacerbations.

Table 2.4 Pooled results of the meta-analysis of healthcare costs and hospitalization costs by subgroups

Characteristics	Subgroup*		Healthcare utilization costs		Hospitalization costs	
			Study (N)	Mean difference (min-max)	Study (N)	Mean difference (min-max)
Intervention	CCM	1-2	3	-428 (-1875 to 1018)	3	-311 (-1667 to 1045)
		3+	5	-1047 (-2230 to 137)	3	**-1378 (-2609 to -164)**
	Number of involved healthcare provider disciplines	2-3	4	**-1328 (-2554 to -101)**	**2**	**-1674 (-3155 to -192)**
		4+	3	-282 (-2510 to 1945)	3	-610 (-1770 to 550)
	Intervention duration (months)	0-12	2	-345 (-1986 to 1296)	2	-156 (-1820 to 1508)
		12+	6	-1066 (-2232 to 99)	4	-1406 (-2566 to -246)
Study	Design	RCT	5	**-866 (-1550 to -183)**		
		Non-RCT	3	-1074 (-2945 to 797)		
	Region	EU	4	-168 (-1043 to 706)	3	-323 (-1405 to 758)
		Non-EU	4	**-1731 (-2507 to -955)**	**3**	**-1681 (-3070 to -293)**
	Quality of study	0-60	3	-872 (-3253 to 1509)	2	806 (-1843 to 3456)
		60+	5	**-816 (-1543 to -89)**	**4**	**-1266 (-2283 to -250)**
Patient	Age	0-65	3	-307 (-1195 to 581)	2	-156 (-1820 to 1508)
		65+	4	-1128 (-2694 to 437)	4	**-1406 (-2566 to -246)**
	% male	0-60	4	**-929 (-1829 to -29)**	3	**-1790 (-3180 to -401)**
		60+	3	98 (-1568 to 1764)	3	**-738 (-1437 to -39)**
	GOLD	2	4	-168 (-1043 to 706)	3	-323 (-1405 to 758)
		3+	3	**-1558 (-2740 to -375)**	3	**-1681 (-3070 to -293)**
	Exacerbation	Yes	2	**-1047 (-1633 to -462)**	2	**-941 (-1474 to -407)**
		No**	6	**-850 (-1626 to -74)**	4	-920 (-2441 to 601)

*If subgroup assignment was impossible, the study was excluded in the meta-analyses.
** Having a history of one or more exacerbations was not stated in the inclusion criteria
CCM Chronic Care Model, *RCT* Randomized Control Trials, *EU* European Union, *GOLD* Global Initiative for Chronic Obstructive Lung Disease

Figure 2.2 Pooled results of the meta-analysis of healthcare utilization costs (a) hospitalization costs (b)



Results on effects

Various DM effects were evaluated in the studies that reported costs. Of the 11 studies, 1 did not report statistical testing of the effects.[112] Changes in the process of care delivery were measured in one study, Steuten et al.[9], which demonstrated a significantly increased patient satisfaction with a RD of 0.13, indicating that the patient satisfaction increased by 13%. Changes in patients' behaviour (e.g. physical activity, smoking behaviour) were measured in five studies. However, it was not possible to calculate the RR, RD or SMD due to a lack of information.[8,80,81,103] The only study[111] with complete information on change in patients' behaviour showed positive results in favour of DM. In details, the RD in percentage of smokers was 0.01 and the self-use of antibiotics and steroids significantly increased with a RD in percentage of 17.92. Table 2.5 shows the results on effects of DM programs in RR, RD or SMD for the other outcomes.

All studies measured changes in biomedical, physiological health outcomes or exacerbations. Hospitalizations as a proxy of severe COPD exacerbations were frequently reported. Two of the three studies that measured six-minute walk distance (6MWD)[8,81] showed an increased walking distance in the DM group compared to the usual care group, with the results being statistically significant in one of these two.[8] Three studies measured COPD exacerbations: two studies showed an increase of exacerbations,[80,81] which was statistically significant in one study[81], but not in the other.[111] An exacerbation was defined differently across the three studies: "*an unscheduled need for healthcare, or need for steroid tablets, or antibiotics for worsening of their COPD*,[111] *a visit to the general practitioner or respiratory physician in combination with a prescription of antibiotics and/or prednisolone or a visit to the emergency department or day care of a hospital, which according to the patient, was related to a COPD exacerbation*,[81] *worsening of respiratory symptoms that required treatment with a short course of oral corticosteroids or antibiotics, as judged by the patient in the self-treatment group or by the study physician in the intervention and control groups.*"[80] Complete information on the RR of hospitalization was available for 6 of the 11 studies. Meta-analysis shows that DM programs decreased hospitalizations, but the RR was not significant (RR, 0.75, 95%CI, 0.54-1.03) (Figure 2.3a).

Changes in health related quality of life were described in 6 studies, which all used the SGRQ. Five of the six studies (83%) demonstrated an improved quality of life in favour of DM (Figure 2.3b), which was statistically significant in two studies.[78,81,117] The pooled results of the SGRQ showed a small significant reduction of the SGRQ in favour of DM (1.7 95%CI: 0.5 to 2.9). This reduction does not exceed the clinical relevant

improvement of four points.[119] In addition to the SGRQ_, three studies measured the health-related quality of life on a Visual Analogue Scale (VAS) and one study measured the EuroQol 5 dimensions (EQ-5D). Two studies[9,81] reported an increase in VAS in favour of DM and one study[8] showed a small decrease in VAS in favour of usual care. The one study[9] with significantly different results in the VAS showed a small increase (RD=0.03).

The number of patients that died during the study was described in 6 studies. Mortality never differed significantly between groups in individual studies, however the pooled Relative Risk showed a small significant reduction in all-cause mortality (0.70, 95%CI 0.51-0.97) (Figure 2.3c).

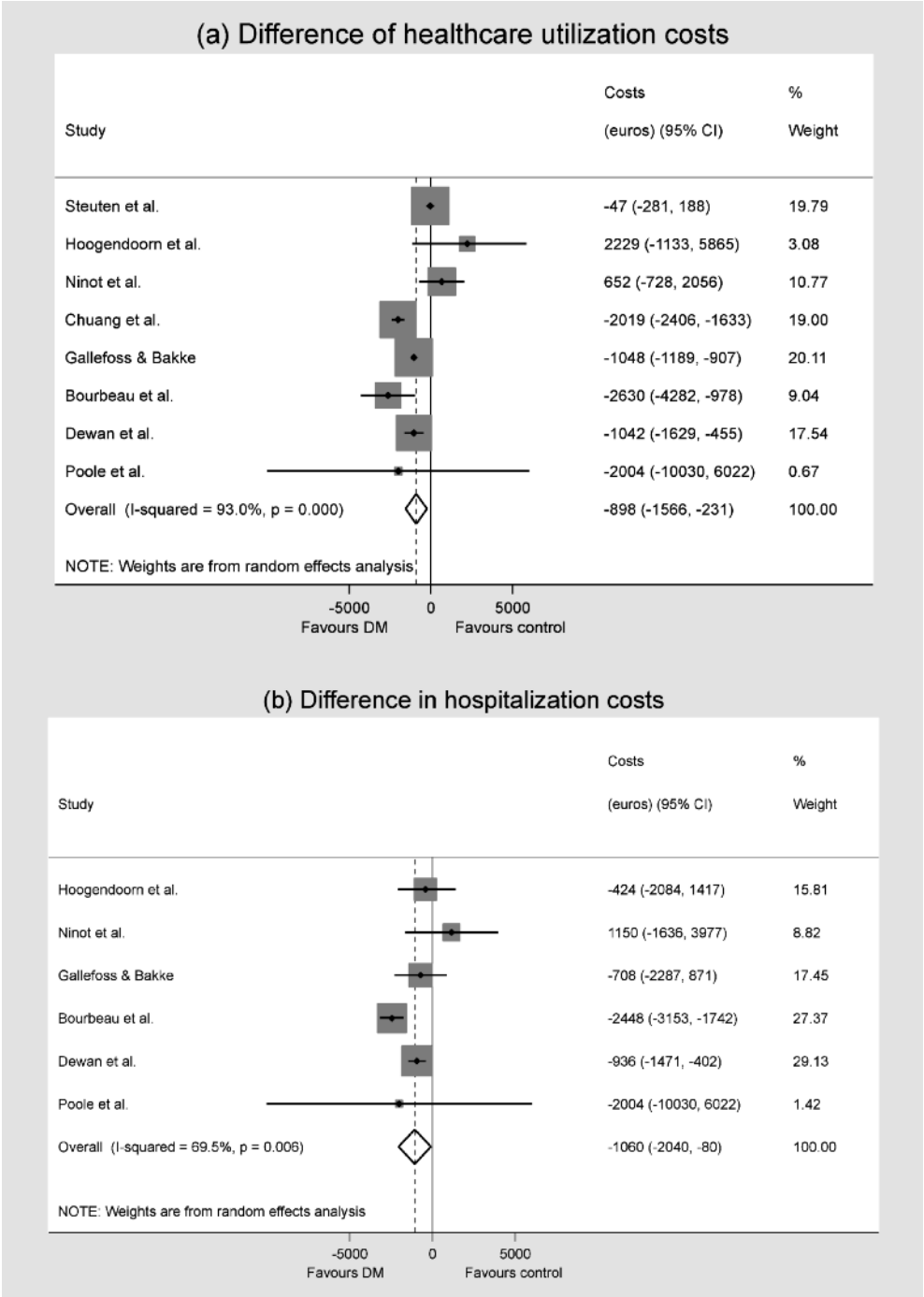
Table 2.5 Results of effects of DM programs

	BIOMEDICAL, PHYSIOLOGICAL HEALTH OUTCOMES AND EXACERBATIONS	HEALTH RELATED	RELATIVE RISK OF MORTALITY QUALITY OF LIFE
9	RD	RD	
	Fev_1% predicted= -0.02	SGRQ= -0.03	
	Fev_1 reversibility= -0.27	VAS= 0.03*	
	Tiffeneau index= 0.02		
81	RR	SMD	1.01(0.30-3.37)
	Hospitalization= 0.78 (0.69-0.89)		
	Exacerbations= 1.39 (1.10-1.74)		
	SMD		
	MRC= 0.58*		
	6MWD= 0.30		
	Endurance time=0.37*		
	Handgrip force= 0.24		
	PI max= 0.29		
	BMI= -1.22		
	Fev_1% predicted= -0.13		
	SGRQ=-0.15*		
	VAS= 1.01		
	EQ-5D= 0.17		
8	SMD	SMD	
	6MWD= 0.99*	SGRQ= 0.01	
	Peak work rate=-0.88	VAS=-0.07	
	Peak V02= -0.06		
	Energy= -0.30*		
	Pain= 0.20		
	Emotional reaction= -0.90*		
	Sleep= 3.62		
	Isolation= -0.40		

	Physical mobility=0.18		
	Voorrips total= 1.27*		
[116]	RR		
	Hospitalization= 0.35 (0.29-0.43)		
	ED visits= 0.39 (0.33-0.45)		
[110]	RR		
	Days in hosp= 0.28 (0.24-0.32)		
	Absenteeism from work= 0.05 (0.03-0.09)		
[117]#	RR	SMD	0.55 (0.19-1.58)
	Hospitalization= 0.54(0.48-0.61)*	SGRQ= -0.29*	
	Hospitalization 1 or more= 0.64(0.45-.91)*		
	ED visits=0.64 (0.53-0.78)*		
	ED visit 1 or more= 0.64(0.48-0.86)*		
	SMD		
	Fev1=0.00		
	FVC=0.00		
[80]#	SMD		
	6MWD= -0.09	SMD	0.95 (0.20-4.63)
		SGRQ= -0.03	
[111]#	RR		0.50 (0.20-1.25)
	Hospitalization= 1.20 (1.04-1.38)		due to COPD=0.13 (0.02-0.97)*
	Hospitalization 1 or more= 1.08 (0.74-1.57)		
	Exacerbation 1 or more= 1.00 (0.87-1.15)		
[114]#	RR		0.75 (0.50-1.13)
	Hospitalization= 0.72 (0.65-0.79)*		
	ED visits=0.73 (0.68-0.79)*		
[112]#	RR		0.33 (0.04-2.87)
	Hospitalization= 1.72 (1.02-2.90)		
	Hospitalization 1 or more = 1.08 (0.75-1.57)		
[118]#	RD	RD	
	Hospitalization=-0.53	SGRQ=-0.04	
	ED visits=-0.66		
	ICU admission=-0.57		
	Absenteeism from work= -0.77		

* Significant (p<0.05), *SGRQ* St. George's Respiratory Questionnaire, *VAS* Visual Analogue Scale, *FEV1%pred* % predicted Forced expiratory volume in 1 second, *FEV1 Rev* Forced expiratory volume in 1 second reversibility, *MRC* Medical Research Council Dyspnoea scale, *6MWD* Six-minute walk distance, *EQ-5D* EuroQoL 5 dimensions, *PImax* maximal inspiratory mouth pressure, *peak VO2* peak oxygen uptake $mL^{-1}kg^{-1}min^{-1}$, *BMI* body mass index, *ED visits* emergency department visits, *FVC* Forced vital capacity, *days in hosp* days in hospital, *ICU admission* intensive care unit admission

Figure 2.3 Pooled results of the meta-analysis of Risk Ratio of hospitalization (a) difference in SGRQ (b) Rate Ratio of mortality (c)



DISCUSSION

We systematically reviewed the impact of COPD-DM programs on both healthcare costs and health outcomes and highlighted the variations in intervention-, study-, and patient-characteristics.

The meta-analysis showed that DM led to average savings in healthcare costs of €898 PP (95% CI: €231 to €1566), hospitalization costs of €1060 PP (95% CI: €80 to €2040) and a decreased rate ratio of hospitalizations (0.75, 95%CI, 0.54-1.03). The costs of developing, implementing and operating the program were excluded from this estimate. Therefore, the results need to be interpreted with caution as the inclusion of all relevant costs could result in much lower cost savings, or even a total cost increase. Overall, six of the eleven studies reported savings on the total costs (including operating costs and non-medical costs), with a mean (±SD) costs increase of €88 (±1214). Interestingly, 6 studies did not report significance testing for the total costs and the remaining 5 studies did not demonstrate a significant reduction of the total costs.

The meta-analysis showed that the mean hospital costs savings (€1060 PP) were larger than the mean healthcare utilization savings (€898 PP). This is not caused by including different studies in the meta-analyses. It is also not unusual because a DM program initiates a more intensive treatment of the patient, often in primary or outpatient clinic care, in order to prevent hospital admissions or reduce the length of hospital stay. The more intense treatment leads to a cost increase, the prevention of admissions to cost savings, so overall savings in total healthcare costs are lower than savings in hospital costs.

Results of the quality assessment showed that the studies scored between 29 and 80, with a mean of 59. The studies that scored the lowest on our quality-instrument also had a substantial risk of bias.[112,116,118] Only 6 of the eleven studies (55%) scored more than 60 points. Studies with a lower quality score showed smaller savings in healthcare costs. This is related to the difference between RCTs and non-RCTs, where the first showed smaller but significant savings, whereas the latter showed greater but non-significant changes. The main problem in the methodological quality of the studies seems to be the lack of measuring all relevant costs and outcome categories, no clear description of the comparator or a description of the institution(s)/region in which the intervention was implemented. This complicates the interpretation of the study results. When trying to explain why results are different across studies, differences in patient characteristics are important. We found indications that DM led to greater savings in older patients, patients with a higher GOLD stage of airflow obstruction, and patients with a history of exacerbations. As these patients make more use of health care services, there is more room for cost savings.

Differences between intervention characteristics were also important. In line with previous reviews we found that patients who received 2[76] or even 3 or more[4,78] interventions within different CCM components in DM programs for COPD had lower rates of hospitalizations. Consequently, savings in healthcare costs were also greater. Similarly, studies with a longer duration of follow-up showed greater reductions in hospital costs, because the relatively low frequency of hospital admissions requires a sufficiently long follow-up time to detect a reduction.

The aim of this review was to investigate the relation between the impact of COPD-DM programs on costs and their impact on health outcomes. Because costs and outcomes can only be related when they are obtained within the same study, we investigated the health outcomes that were reported in the papers reporting cost consequences of DM programs. Cost-effectiveness studies commonly relate costs to effects and calculate the addition costs per unit of additional effect (incremental cost-effectiveness ratio). However, there were only two studies reporting cost-effectiveness ratios.[80,81] Therefore, we had to review costs separately from the effects that were reported in the same studies.

There was a great variability in the type of outcome measures that were reported. Most DM programs led to changes in care delivery, as interventions to promote evidence based clinical care (e.g. education of healthcare provider, integration of specialist expertise in primary care) and interventions to promote effective, efficient care (e.g. systematic and pro-active follow-up of patients) were frequently provided as part of the DM program. Biomedical or physiological health outcomes and health related quality of life have shown small but positive changes in favour of DM. The quality of life results are in line with previous reviews. Niesink et al.[77] also demonstrated positive results of DM on quality of life in people with COPD. There was a lack of evidence on whether DM programs lead to changes in patient behaviour, although all studies provided interventions to empower and prepare patients to manage their disease (e.g. exacerbation management, individual treatment plan). This was also found in previous reviews.[76,78]

Contrary to the positive biomedical or physiological outcomes, it is somewhat surprising that some studies found comparable[111] or even higher exacerbation rates for DM than for usual care.[80,81] Self-management training of the patients could have reduced the problem of underreporting of exacerbations due to an improved ability of patients to recognize an exacerbation. DM programs could also have led to earlier detection of an exacerbation because of more frequent scheduled caregivers contacts.[80,81]

Five previous systematic reviews investigated the effects of COPD-DM

programs on health outcomes.[4,75–78] The results of COPD-DM programs on quality of life in these reviews were similar to our study. In more detail, 50% of the studies in the review of Niesink et al.[77], 67% of the studies in the review of Peytemann-Brideveaux[75] and 53% of the studies in the review of Steuten et al.[78] have shown statistically significant positive outcomes of COPD-DM on one or more domains of the quality of life instruments. The two studies that pooled data on the SGRQ demonstrated small but positive results in the DM group as compared to the control group. These results were statistically significant in the review by Lemmens et al.[4] (-2.52, 95% CI: -5.00, -0.05) and not statistically significant in the review by Adams et al.[76] (-0.25, 95% CI: -1.74, 1.24). Our pooled estimate of the improvement in SGRQ due to DM was -1.7 (95% CI: -2.9, -0.5). The effects of COPD-DM programs on mortality were estimated in two meta-analyses.[75,76] Both studies found lower mortality rates in the DM group, but the difference with the control group was not statistically significant. Our RR of 0.7 (95% CI: 0.51, 0.97) further supports the positive results of COPD-DM on all-cause mortality. Furthermore, the effect of COPD-DM on hospitalization was examined in two reviews. The odds ratio of hospitalization in the study of Lemmens et al.[4] was 0.58 (95% CI: 0.40-0.83) and the relative risk in the study of Adams et al.[76] was 0.79 (95%CI: 0.66-0.94) which are comparable to the RR of 0.75 (95% CI, 0.54-1.03) found in our study.

All studies in our review evaluated a mixed package of interventions. Determining the contribution of individual components of this package is impossible. Patient education on self-management was frequently included in the DM programs, most often in combination with changes in visit structure and stimulation of physical activity. Surprisingly few DM programs focused on structural smoking cessation support or nutritional therapy, i.e. only one DM program involved dieticians.[81] Overall, the categorization of the DM interventions based on the CCM components showed that all studies included interventions within the self-management support (SMS) component and none within the organizational support (ORG) or community (COM) components. However, these components are essential to support the structural implementation of a large DM program. It is likely that these studies did not explicitly address these components because of the relatively small-scale on which the programs were implemented or because the organizational, financial and societal conditions necessary to implement disease management were already in place.

COPD-DM programs have much in common with rehabilitation programs. We avoided the inclusion of these programs by excluding all studies that evaluated a short (usually 1-4 months), intensive, multi-

disciplinary program, in which exercise training (both muscle training and endurance training) was the main component, because DM aims to change the routine of care delivery for a prolonged period of time. However, stimulating physical exercise is an element of many DM programs and some programs e.g.[8,80] pay more attention to this than others. Also, some interventions start with a short intensive intervention phase, followed by a longer and less intensive maintenance phase e.g..[81,111] The first part may resemble pulmonary rehabilitation whereas the latter part is clearly long-term DM. Because of this sliding scale it is sometimes difficult to make a clear distinction between a low-intensity community-based pulmonary rehabilitation program and an intensive DM program.

There are several limitations of this study. Firstly, most studies demonstrate a lack of data on other cost then the cost of healthcare utilization. The importance of these other costs is shown in the study of Hoogendoorn et al.[81] and Monninkhof et al.[80] where including productivity costs led to increased costs for the DM program. The study by Hoogendoorn et al.[81] also was the only study that included total healthcare costs irrespective of the reason of resource use whereas other studies included COPD-related healthcare costs. In addition, only two studies reported the incremental cost-effectiveness ratio of the DM program.[80,81]

Secondly, we pooled the results of the DM programs despite the large heterogeneity. This heterogeneity is primarily due to the variety of different interventions included in a DM programs, the variety of study designs and the quality of the studies, and the variety of patient characteristics. We address this by conducting subgroup analysis by study-, intervention-, and patient characteristics. All across Europe, reimbursement decision makers face the difficult question whether or not to reimburse such programs on a wide scale. Theoretically, the potential savings of these DM programs are great, but the evidence for this is still quite sketchy. We believe we can give some guidance by bringing all this evidence together, discuss its quality, combine it into the best possible estimate of potential savings we can currently get, and try to identify patient- and intervention-characteristics that may contribute to greater savings.

Finally, the generally small proportion of COPD patients that was included in COPD-DM programs[62,120] may jeopardize the generalizability of the costs and effects of DM programs. The exclusion of COPD patients with multi-comorbidities will decrease the generalizability of the results to the entire population of COPD patients in which comorbidity is frequent. For instance, studies excluded patients suffering from any "serious",[8,80] "overwhelming"[112] or "significant"[111] comorbidities.

Conclusions

This systematic review of the literature suggests that COPD-DM programs reduce hospital admissions and decrease hospital and total healthcare costs (excluding development and management costs of DM programs). They also improve health outcomes, including health-related quality of life. Results are however quite heterogeneous, varying by study-, intervention-, and disease-characteristics. Designers and managers of DM programs for chronic diseases can use this information to develop and target DM programs to maximise their cost-effectiveness. Future economic evaluations of DM programs should target a wider population of COPD-patients and be of higher methodological quality.

APPENDIX

Appendix 2.1 A short overview of Disease Management definitions from the last decade

STUDY	DEFINITION
95	"a combination of patient education, provider use of practice guidelines, appropriate consultation, and supplies of drugs and ancillary services"
96	"an organized, proactive, multi-component approach to healthcare delivery that involves all members of a population with a specific disease entity; care is focused on and integrated across i) the entire spectrum of the disease and its complications, ii) the prevention of comorbid conditions, and iii) the relevant aspects of the delivery system"
97	"an intervention designed to manage or prevent a chronic condition using a systematic approach to care and potentially employing multiple treatment modalities"
98	"a systematic and multidisciplinary approach to care for chronic conditions including a patient education component"
99	"multidisciplinary efforts to improve the quality and cost-effectiveness of care for selected patients suffering from chronic conditions"
94	"a group of coherent interventions designed to prevent or manage one or more chronic conditions using a systematic, multidisciplinary approach and potentially employing multiple treatment modalities"
100	"a group of coherent interventions, designed to prevent or manage one or more chronic conditions using a community wide, systematic and structured multidisciplinary approach potentially employing multiple treatment modalities. The goal of chronic disease prevention and management is to identify persons with one or more chronic conditions, to promote self-management by patients and to address the illness or conditions according to disease severity and patient needs and based on the best available evidence, maximizing clinical effectiveness and efficiency regardless of treatment settings) or typical reimbursement patterns. Routine process and outcome measurements should allow feedback to all those involved, as well as to adapt the programme"
101	"a system of coordinated healthcare interventions and communications for populations with conditions in which patient self-care effort are significant"

Appendix 2.2 Interventions used in the included DM programs per CCM component

	N	%
ORGANISATIONAL SUPPORT		
Integrated financing		
Specific subsidies for foreign population		
Sustainable financing agreements with health insurers		
COMMUNITY		
Cooperation with external community partners		
Treatment and care pathways in outpatient and inpatient care		
Involvement of patient groups and patient panels in care design		
Discussion panel for community partners related to chronic care		
Regional training course		
SELF-MANAGEMENT		
Individual treatment plan	6	55
Patient education on psychosocial effects of COPD (e.g. dealing with stress arising from living with a chronic disease), knowledge of COPD and/or self-management skills (e.g. coping with breathlessness, exercise, encouragement of self-treatment)	11	100
Smoking cessation counselling, tobacco weaning	4	36
Stimulation of physical activity (e.g. fitness program in a small group)	8	73
Nutritional therapy	3	27
Exacerbation management: patient training in recognize early symptoms of exacerbation, discussion of individual causes of exacerbations guidelines for self-treatment of exacerbations	5	45
Promotion of disease specific information		
Support of self-management e.g. internet, email or sms, e-consultation, 24-h nursing helpline)	1	9
Tele-monitoring		
Personal coaching		
Motivational interviewing		
Informational meetings		
Mirror interviews		
Education for patient and family	1	9
Regulatory skills		
Proactive coping		

	N	%
DECISION SUPPORT		
Evidence-based approach to care e.g. care standards, clinical pathways)		
Uniform treatment protocol in outpatient and inpatient care		
Training and independence of practice assistants		
Professional education and training for care providers	2	18
Education of case manager	1	9
Audit and feedback to care providers	1	9
Reminders		
Development and implementation of care protocols for immigrants		
Structural participation in training sessions		
Quality of Life questionnaire		
Registration of process and outcome indicators		
Qualitative evaluation of healthcare via focus-groups with patients		
Periodic evaluation of DM interventions and feedback		
Measurement of patient satisfaction		
Multidisciplinary protocol	1	9
Encouragement of healthcare providers to adhere the guidelines	1	9
Integrate specialist expertise in primary care	3	27
DELIVERY SYSTEM DESIGN		
Multidisciplinary cooperation between outpatient and inpatient care		
Development of health pathways and protocols		
Substitution of inpatient with outpatient care		
Specific plan for immigrant population		
Meetings of different disciplines for exchanging knowledge/information		
Monitoring of high-risk patients		
Board of clients		
Periodic discussion sessions between care professionals and patients		
Stepped care method		
Delegation of care from specialist to nurse/care practitioner	1	9
Changes in visits structure and organisation (e.g. regularly telephone call to address self-management items, follow-up calls in response to exacerbation)	7	64
Central coordination / case manager	2	18

	N	%
CLINICAL INFORMATION SYSTEMS		
Electronic Patient Records system (with/without patient portal)		
Hospital Information System		
Integrated Information System		
Use of ICT for Internal and/or regional benchmarking		
Systematic registration by every caregiver		
Exchange of information between different care disciplines		
Steering information to manage the programme	1	9

Adjusted from: [102]

Appendix 2.3 Search terms

THE SEARCH STRATEGY USED IN MEDLINE WAS AS FOLLOWS:

1 "Pulmonary disease, chronic obstructive"[MeSH Terms]
2 "Pulmonary"[All Fields] AND "disease"[All Fields] AND "chronic"[All Fields] AND "obstructive"[All Fields]
3 "chronic obstructive pulmonary disease"[All Fields]
4 "COPD"[All Fields]
5 "Chronic obstructive airway disease"[All Fields]
6 "Chronic obstructive lung disease"[All Fields]
7 "Pulmonary emphysema"[All Fields]
8 "Chronic bronchitis"[All Fields]
9 "Chronic airflow obstruction"[All Fields]
10 "COAD"[All Fields]
11 OR 1-10
12 Cost-benefit analys*[MeSH Terms]
13 "Cost-benefit"[All Fields] AND analys*[All Fields]
14 "Cost"[All Fields] AND "benefit"[All Fields] AND analys*[All Fields]
15 "Cost"[All Fields]
16 "Economic"[All Fields] AND "evaluation"[All Fields]
17 Cost-effectiveness analys*[All Fields]
18 "Cost"[All Fields] AND "effectiveness"[All Fields] AND analys*[All Fields]
19 Health AND expenditure*
20 Healthcare AND expenditure*
21 "Health"[All Fields] AND "costs"[All Fields]
22 "Healthcare"[All Fields] AND "costs"[All Fields]
23 OR 12-22

24 "Disease management" [MeSH Terms]
25 "Disease management" [All Fields]
26 "Disease state management" [All Fields]
27 "Delivery of Health Care, Integrated"[MeSH]
28 "Case management" [All Fields]
29 "Comprehensive health care" [All Fields]
30 "Patient care management"[All Fields]
31 "Managed care"[All Fields]
32 "Managed care programs"[All Fields]
33 "Integrated"[All Fields] AND ("care"[All Fields] OR "health"[All Fields] OR "delivery "[All Fields] OR system*)
34 "Patient-Centered Care"[All Fields]
35 ("Clinical"[All Fields] OR "critical"[All Fields]) AND pathway*)
36 "Care paths"[All Fields]
37 Guideline*
38 Practice guideline*
39 "Clinical protocol"[All Fields]
40 "Performance measurement"[All Fields]
41 ("Patient"[All Fields] OR "provider"[All Fields]) AND "Feedback" [All Fields]
42 ("Patient"[All Fields] OR "provider"[All Fields]) AND "Reminder" [All Fields]
43 ("Patient"[All Fields] OR "provider"[All Fields]) AND "Monitor"[All Fields]
44 "Reminder system" [All Fields]
45 "Decision support" [All Fields]
46 "Self-management"[All Fields]
47 "Self care" [All Fields]
48 ("Health"[All Fields] OR "patient"[All Fields] OR "provider"[All Fields]) AND "education" [All Fields]
49 "Health promotion" [All Fields]
50 "Community health planning" [All Fields]
51 "Planned health care"[All Fields]
52 "Pro-active"[All Fields]
53 "Continuity of patient care"[All Fields]
54 "Patient care planning" [All Fields]
55 Nursing care plan*
56 "Multiple interventions"[All Fields]
57 "Multiple"[All Fields] AND "interventions"[All Fields]
58 (Multidisciplin* OR interdisciplin*) AND ("care"[All Fields] OR "health" [All Fields] OR "delivery"[All Fields] OR "system"[All Fields])
59 "Central"[All Fields] AND "care"[All Fields] AND "giver"[All Fields]
60 "Patient care team"[All Fields]
61 "Patient tailored"[All Fields]
62 "Individual"[All Fields] AND "health plan"[All Fields]

63 "Patient care plan"[All Fields]
64 "Goals of care"[All Fields]
65 "Care goal"[All Fields]
66 "Pulmonary rehabilitation"[All Fields]
67 OR 24-65
68 English[lang] OR German[lang] OR Dutch[lang]
69 11 AND 23 AND 67 AND 68

The search strategy used in NHS-EED and in Cochrane was as follows: "COPD in Title, Abstract or Keywords OR Chronic Obstructive Pulmonary Disease in Title, Abstract or Keywords AND Disease management in Title, Abstract or Keywords
The search strategy used in EURONHEED was as follows: "respiratory tract diseases" as disease and "COPD" as keyword.

Appendix 2.4 Risk of bias

RISK OF BIAS

	Selection	Attrition	Performance	detection	Selective reporting
9	+	NA	NA	NA	+
81	+	+	–	+	+
8	+	+	–	+	+
116	–	–	–	–	+
110	+	+	–	+	+
117	+	+	–	+	–
80	+	+	–	–	–
111	+	+	–	–	–
114	+	+	–	+	–
112	–	–	–	–	–
118	–	NA	NA	NA	

-+ = high risk of bias - = low risk of bias NA= not applicable

CHAPTER 3

RECODE: Design and baseline results of a cluster randomized trial on cost-effectiveness of integrated COPD management in primary care

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BMC Pulmomary Medine 2013; 13:17.

ABSTRACT

Background: Favourable effects of formal pulmonary rehabilitation in selected moderate to severe COPD patients are well established. Few data are available on the effects and costs of integrated disease management (IDM) programs on quality of care and health status of COPD patients in primary care, representing a much larger group of COPD patients. Therefore, the RECODE trial assesses the long-term clinical and cost-effectiveness of IDM in primary care.

Methods/design: RECODE is a cluster randomized trial with two years of follow-up, during which 40 clusters of primary care teams (including 1086 COPD patients) are randomized to IDM or usual care. The intervention started with a 2-day multidisciplinary course in which healthcare providers are trained as a team in essential components of effective COPD IDM in primary care. During the course, the team redesigns the care process and defines responsibilities of different caregivers. They are trained in how to use feedback on process and outcome data to guide implement guideline-driven integrated healthcare. Practice-tailored feedback reports are provided at baseline, and at 6 and 12 months. The team learns the details of an ICT program that supports recording of process and outcome measures. Afterwards, the team designs a time-contingent individual practice plan, agreeing on steps to be taken in order to integrate a COPD IDM program into daily practice. After 6 and 12 months, there is a refresher course for all teams simultaneously to enable them to learn from each other's experience. Health status of patients at 12 months is the primary outcome, measured by the Clinical COPD Questionnaire (CCQ). Secondary outcomes include effects on quality of care, disease-specific and generic health-related quality of life, COPD exacerbations, dyspnea, costs of healthcare utilization, and productivity loss.

Discussion: This article presents the protocol and baseline results of the RECODE trial. This study will allow to evaluate whether IDM implemented in primary care can positively influence quality of life and quality of care in mild to moderate COPD patients, thereby making the benefits of multidisciplinary rehabilitation applicable to a substantial part of the COPD population.

Trial registration: Netherlands Trial Register (NTR): NTR2268

BACKGROUND

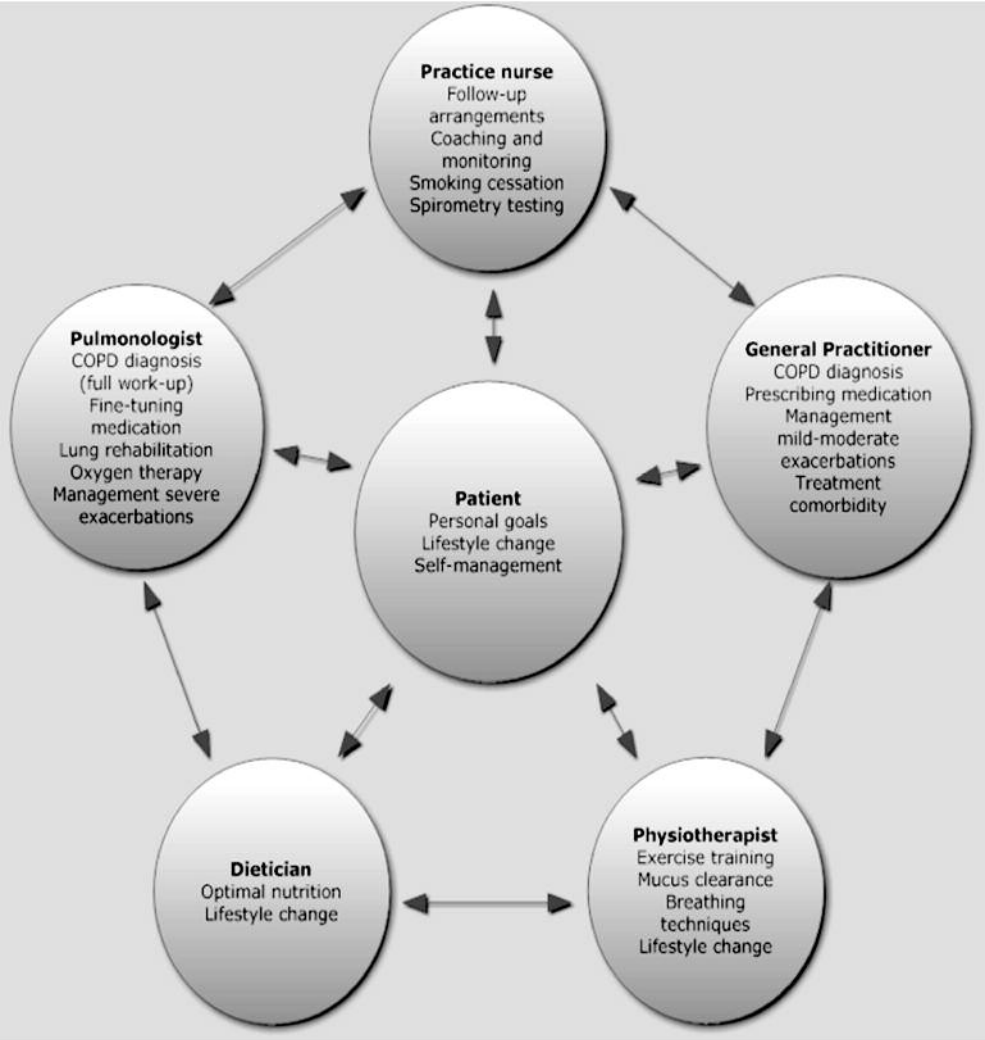
Chronic obstructive pulmonary disease (COPD) is a smoking-related pulmonary disorder, characterized by largely irreversible airflow obstruction, multisystemic manifestations and frequent co-morbidities. According to current guidelines, stable COPD is managed with a combination of different treatment components (e.g. smoking cessation, physiotherapeutic reactivation, self-management, optimization of medication adherence)[115], involving different healthcare providers. Currently, treatment is mostly guided by the severity of airflow limitation.[121] However, COPD is a complex disease, with great variation in symptoms, functional limitations and co-morbidities as well as in progression towards more severe stages.[3] Therefore, the existence of several clinically relevant phenotypes calls for a more personalized approach.[122] Ideally, optimal care of COPD patients requires an individualized, patient-centered approach that recognizes and treats all aspects of the disease, addresses the systemic effects and co-morbidities, and integrates medical care among healthcare professionals and across healthcare sectors.[123] Since professional treatment, hospital admissions and loss of work contribute to the economic burden of disease worldwide, there is much interest in systematically improving the quality of care, while reducing total costs for patients with COPD and other chronic illness. Integrated Disease Management (IDM) programs have proliferated as a means of improving the quality and efficiency of care.[97]

The most frequently applied IDM programs in COPD patients are pulmonary rehabilitation (PR) programs. According to a Cochrane systematic review, the effectiveness of PR on exercise tolerance and quality of life is well established.[59] In international reports and guidelines, it is acknowledged that PR is indicated for all individuals with COPD who have decreased exercise tolerance, exertional dyspnea or fatigue, and/or impairment of activities of daily living.[115,124,125] However, widespread access is restricted, due to limited availability of resources and high costs.[126–128] Furthermore, PR programs usually include only the more severe patients and last only for a limited period of time[129], while initial benefits seem to decline over time.[130–134] After returning home, patients are frequently insufficiently motivated to continue a more physically active and healthy lifestyle. Unfortunately, general practitioners (GPs) are rarely involved in PR programs and, as a consequence, are often unable to support program methods after a rehabilitation phase has formally been concluded.[129]

We previously argued that when components of PR are integrated into a primary care IDM program, patients can be treated in their home environment. Primary care providers can then be (more) involved as direct coaches of this process.[5,62] To establish such a program of combined in-

terventions, the set-up of a multidisciplinary team is vital, in which different healthcare professionals participate and provide their share in the spectrum of the required care (Figure 3.1). Ideally, patients and healthcare providers are close partners in IDM, in order to better control daily symptoms and promote self-management. Furthermore, strong cooperation between several disciplines in primary care and mutually agreeable collaboration with secondary and tertiary care are prerequisites for integrated chronic care.[62]

Figure 3.1 Components of an Integrated Disease Management program for COPD patients in primary care



Systematic reviews of disease management for COPD patients emphasise the need for well-designed, practical multicenter trials[4,76], including broad representative patient samples[78], with a wide range of physicians and settings to improve external validity.[4] Furthermore, authors of systematic reviews advocate studies designed to evaluate the long-term effectiveness of IDM,[4] and advise more health economic studies across different care settings.[78] When considering the large number of eligible patients for IDM in the community, the potential impact is high. However, no trials have been published that are specifically targeted to measure the cost-effectiveness of IDM in patients recruited in primary care.

Therefore, the aim of the current RECODE (acronym for Randomized Clinical Trial on Effectiveness of integrated COPD management in primary care) cluster randomized clinical trial (NTR 2268) is to assess the cost-effectiveness of an IDM program for COPD patients in primary care in the Netherlands. Based on an earlier controlled clinical trial evaluating the effect of an IDM program in mild to moderate COPD, we found the greatest improvements on quality of life in patients with a MRC dyspnea score >2.[6] As a result, we based our sample size estimates on the a priori planned subgroup of patients with MRC dyspnea score >2. This article describes the design, rationale and baseline results of this trial.

METHODS

Study objective and design

The RECODE trial is a two-group parallel cluster-randomized clinical trial with a two-year follow-up, conducted in the primary care setting. Our objective is to evaluate the clinical and cost-effectiveness of IDM for COPD patients in primary care. The intervention is delivered by the primary care team, including a GP, practice nurse, physiotherapist and dietician, with a consulting pulmonary physician at hand. To avoid contamination between treatment groups within practices, primary care practices are randomized rather than patients. The Medical Ethics Committee of the Leiden University Medical Centre approved the trial.

Participants

GPs

Inclusion of GPs and patients started in September 2010 and was finished in September 2011. Practices were considered as candidates if they were willing to create an integrated COPD management team, in which each member has responsibility for their respective areas of expertise. The practices had to include at least one GP, one practice or extramural respiratory nurse, and one physiotherapist specialized in COPD care. If multiple practices were collaborating (for example with one practice nurse),

they formed one cluster which was used for randomization. Our recruitment goal was to enrol representative groups of primary healthcare providers from a broad spectrum of practices in order to enhance external validity. This study was embedded in the Leiden Primary Care Research Network (LEON), which is managed by the department of Public Health and Primary Care of the Leiden University Medical Center. This multi-center research network consists of some 100 general practices in the western region of the Netherlands, in which these practices signed an agreement to collaborate in scientific research.

Patients

We included all patients who were diagnosed with COPD by their treating physician. We selected patients from electronic medical records (EMRs) of general practices. For all included patients, we attempted to verify the diagnosis by lung function according to the GOLD criteria 1. If spirometry data were not available, patients were invited to participate for a formal lung function assessment, according to the ATS/ERS guidelines for spirometry.[135] Exclusion criteria consisted of terminally ill patients, dementia or cognitive impairment, inability to fill in Dutch questionnaires, and hard drug or alcohol abusers. We did not exclude patients if a pulmonary physician was considered the main healthcare provider. The GPs checked the selected patients against the formal inclusion and exclusion criteria before the recruitment procedure started. All patients provided written informed consent before participation in the study.

Intervention

The intervention consists of an IDM program, which is implemented by a multidisciplinary team in general practice. The team consists of at least three members: the GP, the practice nurse, and a cooperating physiotherapist with specific certified training in COPD care. Depending on the team needs, a collaborating pulmonary physician and dietician were added to the intervention team.

We trained the multidisciplinary teams of intervention practices in a two-day course during 2010-2011. During this course, essential components of IDM for effective integrated COPD care in primary care were explained, trained and rehearsed and supervised. Elements of this course are further outlined in Table 3.1 and included a review of the advice from international guidelines, performing/interpreting spirometry and assessment of disease burden, and motivational interviewing to stimulate a healthier lifestyle including more physical activity and smoking cessation. Furthermore, the healthcare providers were trained in adopting self-management action plans, including early recognition and treat-

ment of exacerbations, encouragement of regular exercise and guideline-based physical reactivation, cooperation and collaboration with secondary care, and instructions in dietician support for nutritionally depleted patients. In addition, they were trained in how to use feedback on process and outcome data to guide and implement guideline-driven integrated healthcare. This CME course was developed according to recent national and international guidelines[115,136] and was provided by teachers with hands-on experience with the program. At the end of the course, the team designed a time-contingent individual practice plan, agreeing on steps to be taken in order to integrate a COPD IDM program into daily practice. Intervention practices were free in the fulfilment of their individual plans, as long as they were feasible and relevant for the practice. After 6 and 12 months, there was a refresher course for the intervention practices.

Table 3.1 Components of IDM included in the RECODE course for multidisciplinary teams in primary care

DM INTERVENTIONS	EXAMPLE
Optimal medication adherence	Tailoring of advices from international guidelines, e.g. frequent exacerbations necessitate inhaled corticosteroids; daily respiratory complaints necessitate long-acting bronchodilators
Proper diagnosis	Performing and interpreting spirometry, assessment of disease burden using MRC and CCQ
Motivational interviewing	Understanding and making use of patients' personal goal in physical reactivation and lifestyle changes
Smoking cessation counselling	Review of the recent literature, discussion of bottlenecks, applying behavioural techniques and drug therapy for smoking cessation
Applying self-management plans	Teaching self-management techniques, including early recognition and treatment of exacerbations
Guideline based physiotherapeutic reactivation	Using a patients' personal goal, referral for physiotherapeutic reactivation in patients with MRC score >2.
Dietary interventions	Early recognition and treatment of nutritionally depleted patients

Web-based disease management application

During the course, the team learned the details of an ICT program that supports recording of process and outcome measures by access to a flexible web-based IDM application, named Zorgdraad (in English 'Care Ties'). This application combined a patient and a healthcare provider portal. The patient portal provided patients with disease-specific easy written education, and allows personal goals and personal notes. The healthcare portal left space for a protocol for COPD follow-up guidance, quality of life scores, physiotherapy follow-up and examination, smoking cessation, medication records, and facilitates tailored benchmark reports at 6 and 12 months. These reports were generated by the researchers and sent to the practices to support prioritizing the healthcare needs. An experienced instructor provided the practices during the course with all information about Zorgdraad. An account manager supported the practice nurse and GP on individual use of the program in daily practice. It was intended that practice nurses give the COPD patients directions for use on the patient-portal of Zorgdraad.

All practices were in essence free in the usage of Zorgdraad, and in the fulfilment of their plans. Therefore, not all patients received all components of the program, but individual patient-specific care plans are negotiated by the team, in collaboration with the patient. The intensity of the IDM program depended upon the health status and needs of the patient, resulting in some patients receiving all interventions (e.g. smoking cessation, physiotherapy, nutritional support), while stable patients only had regular 6-monthly or 12-monthly follow-up by nurses. Implementation of the intervention was assessed at 24 months (see "Outcomes").

Financial coverage of the intervention

We arranged with the local healthcare insurer that all RECODE patients with dyspnea on moderate or worse exertion (indicated by a Medical Research Council (MRC) score of >2) would be totally reimbursed for the intervention, including physiotherapy.

Usual care group

The control group consists of 'usual care'[137], which is based on the 2007 national primary care COPD guidelines.[136] Instead of the multidisciplinary RECODE course, the practice nurse received a course on technical performance of spirometry in primary care only, in order to divert attention from any of the IDM topics mentioned in Table 3.1. If the results of our study show that the IDM program could substantially improve the health-related quality of life of COPD patients, we will make the entire set of interventions available to the control group after the study has been completed.

OUTCOMES

Time points

We follow patients at baseline, and at 6 and 12 months with a face-to-face interview. Blinded research nurses administer the questionnaires (Table 3.2) at specific time points. These interviews take place at the general practice or at the patients' homes, using the web-based application Zorgdraad. At 9, 18 and 24 months we sent questionnaires by post. In addition, retrospectively the researchers extract data from the patients' EMRs at 24 months over the complete trial period, regarding prescribed medication. Primary endpoint is at 12 months, when we expect to detect the clinically relevant effect of the intervention.[5,6] Total study duration provides 24 months of follow-up, to assess whether benefits can be maintained.

A. Patients

At baseline, we assessed socio-demographic factors (age, gender, socioeconomic status measured through level of education), marital status, lung function and co-morbidity.

Table 3.2 Overview of measurements per time point in the RECODE study

Outcomes	**Baseline**	**6 m**	**9 m**	**12 m**	**18 m**	**24 m**
Participants						
Demographic characteristics	X					
Lung function	X					
Co-morbidity	X					
CCQ	X	X	X	X	X	X
SGRQ-C	X	X	X	X	X	X
EQ-5D	X	X	X	X	X	X
SF-36	X	X	X	X	X	X
Smoking behavior, guided smoking attempts	X	X	X	X	X	X
IPAQ	X	X	X	X	X	X
SMAS-30	X	X	X	X	X	X
MRC-Dyspnea scale	X	X	X	X	X	X
Exacerbations	X					X
Costs of health care utilization by patients, part A: Healthcare use Questionnaire, including direct non-medical costs borne by patients/families	X	X	X	X	X	X
Costs of productivity loss: Absence from work Questionnaire	X	X	X	X	X	X

Outcomes	Baseline	6 m	9 m	12 m	18 m	24 m
Costs of health care utilization by patients, part B:						
Data extraction from medical records						
(health care utilization, medical treatment)						X
PACIC	X	X	X	X	X	X
Healthcare providers						
ACIC	X			X		
Satisfaction, involvement and implementation						
of the IDM program				X		
(IG)						
IDM program information						
Development costs of the IDM program						X (IG)
Implementation costs of the IDM program						X (IG)
Performance indicators of practices						
(see Table 3.4)	X					X

ACIC: Assessment Chronic Illness Care; *CCQ*: Clinical COPD Questionnaire; *EQ-5D*: EuroQol-5D; *IPAQ*: International Physical Activity Questionnaire; *MRC*: Medical Research Counsil scale; *PACIC*: Patient Assessment Chronic Illness Care; *SF-36*: ShortForm-36; *SGRQ-C*: Saint Georges Respiratory Questionnaire; *SMAS-30*: Self- Management Scale-30

Primary outcome

The primary outcome measure in this study is health status as measured by the Clinical COPD Questionnaire (CCQ) at 12 months. This questionnaire is a disease-specific, 10-item questionnaire that calculates an overall score and three domain scores: symptoms, functional state and emotional state. Patients are required to respond to each item on a 7-point scale with 0 representing the best possible score and 6 representing the worst possible score. This instrument is proven to be sensitive and valid, and easy to administer in primary care. The minimal clinical important difference (MCID) is -0.4 points.[30,138]

Secondary outcomes

Secondary outcome measurements at 6, 9, 12, 18 and 24 months include (the questionnaire for each outcome is provided in brackets):

1 Measures of changes in health-related quality of life (disease-specific as well as generic), measured by:
   - A CCQ
   - B St. George Respiratory Questionnaire (SGRQ); designed to measure health impairment in patients with asthma and COPD. The first part produces the symptom score and the second part the activity

and impact score. A total score can also be calculated. We use a Dutch version of the SGRQ , and consider a -4 unit change as the MCID for within-group comparison.[119]

C The Euro Qol-5D-3L is a generic, preference-based health-related quality of life questionnaire, with many applications in respiratory disease. It consists of 5 dimensions to describe health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each item with three levels of functioning (e.g., no problems, some problems, and extreme problems). We used the value set derived from the Dutch general population that, when applied to the dimensions of the health state, result in a preference-based utility score that typically ranges from states worse than dead (<0) to 1 (full health), anchoring dead at 0. Besides the descriptive system and the off-the-shelf value sets, the EQ-5D includes a visual analog scale (VAS) where an individual rates his own health on a scale from 0 (worse imaginable health) to 100 (best imaginable health).[72,139]

D Short-Form Health Survey (SF-36) is a 36-item questionnaire that measures two components (physical and mental component). The physical component consists of four domains of health: physical functioning, role limitations due to physical health, bodily pain and general health perceptions. The mental component consists of role limitations due to emotional problems, vitality, social functioning and mental health.[73]

2 Measures of change in patients' lifestyle, illness behavior and knowledge:

A Smoking behavior, guided smoking attempts;

B Taking initiatives, investment behavior and level of self-efficacy, as measured by the Self-Management Scale-30 (SMAS-30)[140];

C Physical activity, as measured by the International Physical Activity Questionnaire (IPAQ) short form. This is an instrument designed primarily for population surveillance of physical activity among adults. The items in this short form are structured to provide separate scores on walking, moderate-intensity and vigorous-intensity activity. The total score is computed by multiplying the duration (in minutes) and frequency (days) of walking, moderate-intensity and vigorous-intensity activities by its energy requirement to yield a score in Metabolic Equivalent Time (MET) minutes.[141]

3 Measures of change in intermediate patient-related outcomes:

A Dyspnea, measured by the MRC Dyspnoea Scale;[28]

B Exacerbations: moderate (oral prednisone and/or antibiotic courses), severe (hospitalizations). These data were retrospectively extracted from EMRs at 24 months, over the entire follow-up period.

4 Measures of change in healthcare utilization and costs:
   A Development and implementation costs of the program: time and material resources associated with the training of the healthcare providers and the ICT support (measured at 24 months).
   B Costs of healthcare utilization by patients: including all COPD and non-COPD related cost of a) hospitalization, b) medication, c) caregiver contact, and d) revalidation.
   C Retrospectively we extract data from EMRs at 24 months over the complete trial period, regarding prescribed medication.
   D Direct non-medical costs borne by patients/families, e.g. travel costs. Costs of productivity loss due to absenteeism/presenteeism at work. This was measured at baseline, and at 6, 9, 12, 18 and 24 months.
5 Measures of change in care delivery process: level of care integration according to patients, measured by the Patient Assessment Chronic Illness Care (PACIC).[142] This questionnaire was self-reported by patients in both groups and was administered at baseline, and at 6, 9, 12, 18 and 24 months.

B. Healthcare providers

The Assessment Chronic Illness Care (ACIC) questionnaire, which is a tool to measure the level of care integration according to healthcare providers[143], was sent to primary care providers at baseline and is evaluated at 12 months. Furthermore, we use a self-designed questionnaire at 12 months ("Satisfaction, involvement and implementation of the IDM program") for the primary care team, to measure the level of involvement and implementation of the practice teams with the RECODE intervention at 12 months. This questionnaire comprises questions on the number and type of healthcare providers which were involved in the program, the types of team meetings and local appointments, and the usage of tailored benchmark reports. Furthermore, we requested the number of patients involved in the intervention, and the numbers of components implemented in daily practice. Overall, the healthcare providers are asked to rate the intervention on a 5-point scale, and we ask for details on possible bottlenecks and problems regarding implementation.

C. Current level of care of the practices at baseline

The current level of COPD care was assessed at baseline in all general practices to be able to report any difference in quality of care at 12-months follow-up. Therefore, from the EMRs we extracted the following performance indicators: registration of smoking status and stop-smoking advice, registration of body mass index, assessment of spirometry

and inhalation technique in the last year, the number of patients with monitored functioning by means of the CCQ , MRC, or the number of patients with controlled physical activity in the last year.

Sample size calculation

The primary outcome is the difference in change in the CCQ score between baseline and 12 months between both groups. We used methods for standard sample size estimates for trials that randomised at the level of the individual[144] adjusting for clustering by inflating sample size estimates by the design effect given by 1+(n-1)where n is the average cluster size, and s the estimated intraclass correlation coefficient (ICC).[145] Sample size estimates are based on the mean difference in CCQ between intervention and control group. Using the minimal clinically important mean difference for the CCQ30, and the upper value of 0.05 from a range of ICC values identified in studies involving the older person in primary care[146], power calculations indicate that 40 clusters of practices with an average of 27 participants per cluster are required. To allow for subgroup analysis in MRC scores 1-2 versus 3-5, in total 1080 participants are need to be randomized to achieve a power of at least 80% with alpha levels of 0.05, including a participant loss to follow-up of 10% or a loss of 4 clusters at 12 months.

Randomization

Cluster randomization was at the level of the primary care team. The first author recruited the practices, and the selected participants were checked by the GP against formal inclusion and exclusion criteria before the intervention started. To enhance comparability between the intervention and control group, the clusters were matched and randomized by a researcher who was blinded to the identity of the practices. Matching was into pairs according to the following criteria: (i) percentage of patients from ethnic minorities, (ii) type of practice, (iii) practice location (urban/rural), (iv) age of GP, and (v) gender of the GP. Subsequently, the matched practices were randomized to the intervention group or the control group by using a computer-generated random number list.

Informed consent

Informed consent was provided by the GPs and the patients. The informed consent was acquired before the course took place and the practices started with their intervention.

Blinding

Because of the nature of the intervention, it is not possible to blind patients and primary care providers to practice group allocation. Therefore, blinded research nurses assess the outcomes. Patients are instructed not to report on their type of management to the outcome assessors.

Data analysis at baseline

Non-participation analysis at baseline

We recruited potential participants with an invitation letter including a postal CCQ questionnaire. Returned questionnaires were analysed to investigate if there were differences between participants and patients who fulfilled inclusion criteria, but refused to participate in the trial (non-participants). We compared differences on CCQ scores, sex and age using independent t-tests and chi-square tests.

Analysis plan

Analysis of effectiveness at 12 and 24 months

The final analysis of the trial will be carried out on an intention-to-treat basis. The freedom of the clusters to fill in the precise implementation of the intervention will probably relate to the (cost)-effectiveness of the intervention and, therefore, the clustering of patients in GP practices should be taken into consideration in the analysis.[147] Therefore, the results will be investigated with respect to the differences in intensity between and within clusters over time using multi-level analysis.

Pre-planned subgroup analyses

We will study the influence of age, sex, disease burden (MRC score 1-2 vs. 3-5), disease severity (GOLD stage), and socioeconomic status. The trial was specifically powered on the MRC 1-2 vs. 3-5 subgroup analyses; see 'Sample size calculation'.

Economic evaluation at 12 and 24 months

The economic evaluation will be performed according to the internationally agreed guidelines[148] and the national guidelines for pharmacy-economic research.[149] We will calculate the costs from a healthcare perspective and a broad societal perspective, in order to facilitate decision making. The healthcare perspective will include all costs covered by the healthcare sectors budget: development, implementation and healthcare utilization costs. The costs from societal perspective will include travel and productivity costs in addition to the costs from the healthcare perspective to capture (almost) all costs related to the intervention, irrespective of who actually bears them.

The healthcare utilization costs (excluding medication costs), travel costs and productivity costs of patients will be calculated using questionnaires at different time points (Table 3.2). These questionnaires will collect self-reported cost-related data by patients using a recall period of three months. Additionally, the type and amount of medication from the individual patients will be collected from the GP information systems. The unit costs per medication prescription will be based on the GIP Databank.45 Time and material resources associated with the training of the healthcare providers, the multidisciplinary team meetings in the GP practices, and the ICT support will be estimated based on course attendance, computer-documented minutes of ICT use, treatment plans, and professional self-report. Finally, the productivity costs will be estimated using the friction method, which implies that the costs of absenteeism will occur only for a fixed (friction) period ending at the moment that the employee is replaced.[51]

Cost-effectiveness (CEA) and cost-utility analyses (CUA)

The relation between the costs and the estimated health outcomes is expressed in cost-effectiveness ratios: (1) costs per QALY, (2) costs per exacerbation prevented, (3) costs per patient with a clinically relevant improvement of at least 0.4 units on the CCQ, (4) costs per patient with a clinically relevant (4 units) improvement on the SGRQ, and (5) costs per patient with a 1 point improvement on the MRC dyspnea scale. Adopting such a wide range of outcome measures in the economic evaluation is in line with recent guidelines of a joint ATS/ERS task force on outcome measurements in COPD that recommend taking a multi-outcome approach.[71] At the same time, comparison with the cost-effectiveness of other interventions for other diseases is made possible through the calculation of costs per QALY. Uncertainty around cost-effectiveness ratios will be dealt with in probabilistic sensitivity analysis in which costs and health outcomes will be bootstrapped and plotted on cost-effectiveness planes from which cost-effectiveness acceptability curves will be drawn.[150–152] In additional 'net monetary benefits'[153] will be calculated using different thresholds of the willingness to pay for a QALY and it will be investigated which patient, practice and team characteristics are related to the size of the net monetary benefits. The economic evaluation will compare differences in costs to differences in effects (CEA) and quality adjusted life-years (CUA). The analysis will have a 12 and 24-months time horizon. Sensitivity analyses will be performed on the perspective (societal versus healthcare) and the applied utility measure (Dutch EQ-5D).

BASELINE RESULTS

Primary care practices

The characteristics of the enrolled 54 general practices, which formed 40 clusters, are shown in Table 3.3. Numbers of included patients per participating cluster ranged from 11 to 79 patients. Most practices were single-handed (44%) or one or more partner practices (41%). Of all the practices, 50% were healthcare centers. The enrolled practices included a total of 76 participating GPs; the majority (61%) were males with a mean age of 50 (range 35-62) years and 16 (SD 8.2) years of practicing.

Table 3.3 Characteristics of included primary care practices in the RECODE study

GENERAL PRACTICES	
Number of GP practices	54
Number of clusters	40
Number of included patients per participating cluster, range	11-79
Type of practice,%	
Single-handed practice	44
One or more partner practice	41
Healthcare centre	15
Practice location,% urban	72
Patient practice population, n (range)	3418 (1750-16907)
Ethnic minorities,%	15
GENERAL PRACTITIONERS	
Number of participating GP's	76
Gender GP,% male	61
Age GP, years (range)	50 (35-62)
Years practicing, years (SD)	16 (8.2)

Current level of care of the practices

We assessed the current level of COPD care at baseline in all general practices to be able to report any difference in quality of care after 12 months. Results at baseline are shown in Table 3.4. Almost half of the RECODE patients (53%) have a registered smoking status; however, a standard spirometry test in the last year was less common, with only (12%) of the patients receiving spirometry.

Table 3.4 Description of current level of care of included GP practices: distribution of the performance indicators of the practices

MEASUREMENT	PROCESS INDICATOR	% (SD)
CATEGORY		
Smoking	% RECODE patients with registered smoking status	53 (27.9)
	% RECODE patients that are registered smokers	35 (19.3)
	%RECODE patients, which are registered smokers with stop-smoking advice in the last year	35 (34.3)
BMI	% RECODE patients of which the BMI is measured in the last year	42 (23.8)
Treatment & monitoring	% RECODE patients with inhalation technique controlled in the last year	13 (20.3)
	% RECODE patients with a spirometry test in the last year	12 (14.9)
	% RECODE patients with monitored functioning with a structured method (CCQ or MRC) in the last year	28 (27.4)
	% RECODE patients with controlled physical activity in the last year	30 (24.9)

Patient recruitment

Figure 3.2 shows the study flow chart until baseline. In total, 2886 patients were selected in 40 clusters of which 617 (21%) patients were excluded by their GP. Most of these excluded patients were registered as a COPD patient in the EMR; however, after evaluation they turned out to be mislabelled by their GP. After exclusion, 2269 patients were invited to participate, of which 48% participated (response 48%). Most patients indicated no reason for refusing (71%), while others expressed no interest (16%), did not consider themselves to be a COPD patient (6%), or reported not having troublesome COPD symptoms (6%). In total, we have been able to allocate 1086 COPD patients at baseline: 554 participants to the intervention group and 532 participants to the control group. Patients were included from September 2010 until September 2011.

Non-participation analysis

As we invited all eligible participants for this trial with an invitation letter with an attached CCQ questionnaire, we were able to determine any differences between participants of the trial and COPD patients eligible but declining randomization, in order to assess external validity (Table 3.5). Of all eligible patients who were invited to participate, 1549 questionnaires had analyzable data. We received a higher response rate (961 vs. 588) of returned CCQ questionnaires in the group of patients willing

to participate in the trial, compared to patients eligible but declining randomization. There was no difference in age between both groups. Significantly more men (54.7%) are participating in the RECODE trial compared to the proportion of men in patients who declined participation (46.9%). Furthermore, participants in the trial reported significantly more symptoms and disabilities on their functional and mental state, which was reflected in a mean total CCQ score of 1.8 (1.1), compared to 1.5 (1.1) in non-participants.

Figure 3.2 Flowchart of the recruitment to the baseline assessment of the RECODE study

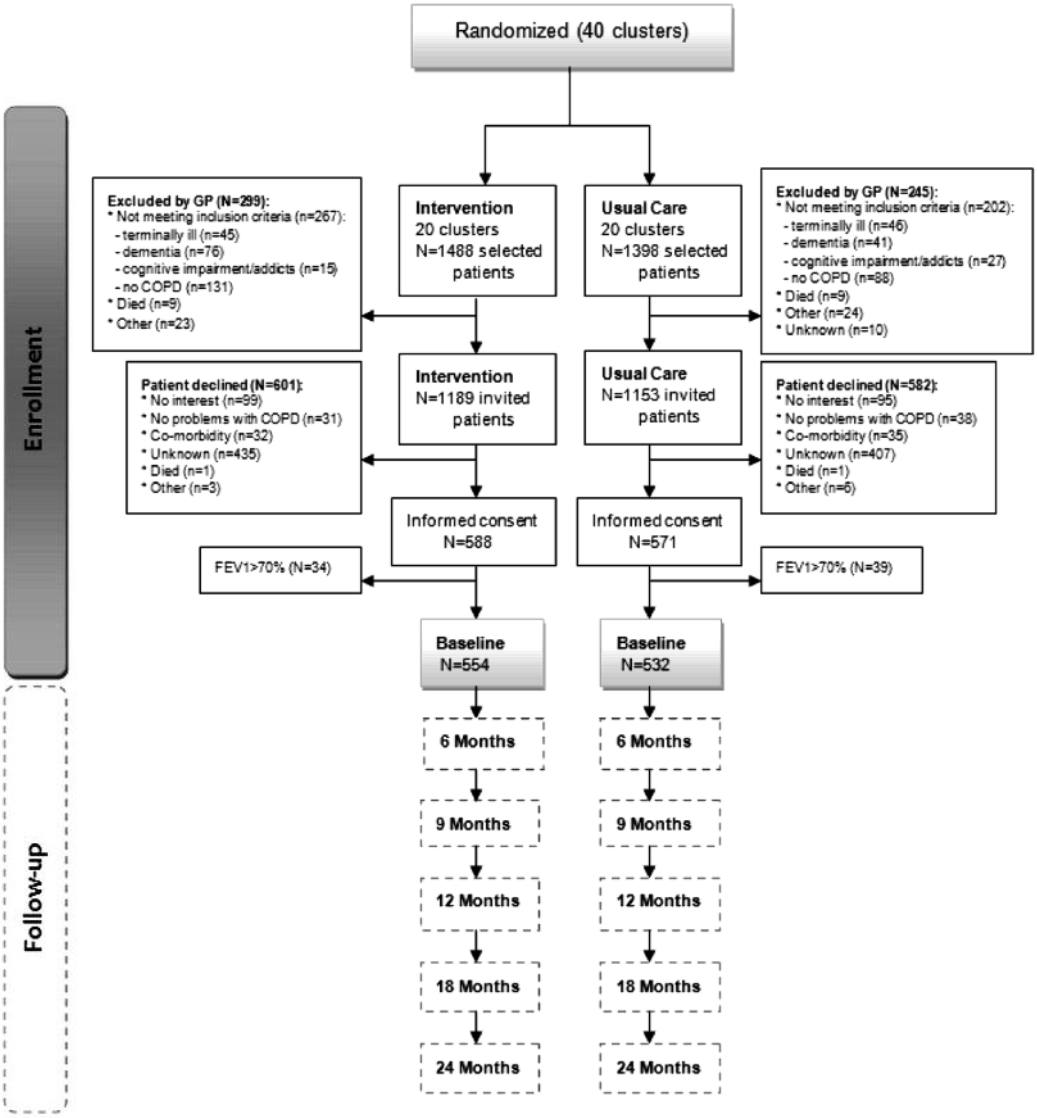


Table 3.5 Characteristics and comparison of participants and non-participants of the RECODE trial

	PARTICIPANT (N = 961)*	NON-PARTICIPANT (N = 588)	P-VALUE
Age, years (SD)	68.7 (11.0)	67.8 (11.5)	0.162
Males,%	54.7	46.9	0.003
CCQ			
Symptoms	2.4 (1.2)	1.9 (1.2)	<0.001
Functional state	1.8 (1.3)	1.5 (1.4)	<0.001
Mental state	0.9 (1.2)	0.7 (1.2)	<0.001
Total score	1.9 (1.1)	1.5 (1.1)	<0.001

Values are means (S.D.) unless stated otherwise. ** Of the 1086 RECODE patients, there were 961 CCQ questionnaires available at the time of initial invitation.

Baseline characteristics COPD patients

Table 3.6 presents the baseline demographic and clinical characteristics of the included COPD population. Enrolled subjects were mainly elderly (ex) smokers, and had moderate COPD which is reflected by a mean post-bronchodilator FEV1 of 68% predicted. We included COPD patients with substantial co-morbidities: 36.8% had a diagnosis of hypertension, 16.1% suffered from major cardiovascular disease, 14.7% had diabetes and 9.9% had a combined diagnosis of depression. Mean SGRQ total score was 35.6 (20.5) and mean CCQ total score was 1.5 (0.97). The proportion of patients with dyspnea on moderate exertion or worse (MRC score >2) comprised one third of the study population.

Table 3.6 Baseline demographic and clinical characteristics of the patients with COPD included in the RECODE study

	TOTAL (N = 1086)
Men,%	53.9
Age, y	68.3 (11.2)
Employment,%	28.3
Low education,%	40.3
Pulmonary function[1]	
Predicted FEV1**%	67.8
FER***%	57.7
GOLD-stage,%****	
I Mild	24.6

	TOTAL (N = 1086)
II Moderate	53.2
III Severe	19.4
IV Very severe	2.9
Smoking status,%	
Current	36.7
Former	53.2
Never	10.1
Co-morbidities	
Major cardiovascular disease,%	16.1
Hypertension,%	36.8
Diabetes,%	14.7
Depression,%	9.9
Charlson co-morbidity index	2.3 (1.3)
CCQ	
Symptoms	2.09 (1.21)
Functional state	1.40 (1.22)
Mental state	0.51 (0.98)
Total score	1.50 (0.97)
MRC	
score ≤2.%	66.6
score >2.%	33.4
MRC score (mean)	2.01 (1.28)
SGRQ	
Symptom	50.5 (20.9)
Activity	47.8 (29.5)
Impact	23.3 (19.6)
Total	35.6 (20.5)
EQ-5D	
Total score	0.74 (0.26)
EQ-VAS	67.0 (17.4)
SF-36	
Physical	38.3 (10.8)
Mental	48.6 (10.4)
IPAQ	
Total MET minutes	2925 (4683)
High physical activity,%	11.1
Moderate physical activity,%	0.6
Low physical activity,%	88.4
Self-management	
Taking initiatives	57.0 (17.9)
Investment behavior	60.4 (17.6)
Self-efficacy	65.3 (17.4)

**Values are means and corresponding standard deviations (SD) unless stated otherwise. **FEV1 predicted: Forced expiratory volume in 1 second, post-bronchodilator, predicted according to age and height. ***FER: forced expiratory ratio (FEV1 / FVC x 100%), FVC: forced vital capacity. ****Mild = FEV1 > 80%, Moderate = 50% ≤ FEV1 < 80%, Severe = 30% ≤ FEV1 <50%, Very severe = FEV1 < 30%*

1. Lungfunction was missing in 66 patients (34 control patients; 32 intervention patients).

DISCUSSION AND COMPARISON WITH OTHER STUDIES

Optimal COPD management continues to be an important area of research, as the worldwide prevalence is growing and costs will rise in coming decades. Furthermore, in contrast to asthma patients, medication has demonstrated to have limited effect in the management of COPD patients. IDM for chronic diseases has the potential to influence health status, while reducing total costs.6 However, the (cost) effectiveness of IDM in primary care COPD patients remains unknown, due to a paucity of randomized clinical trials in this field. This article presents the design and baseline results of the RECODE trial, which aims to assess the (cost) effectiveness of IDM for COPD patients in primary care.

We have chosen a cluster-randomized design to prevent cross-contamination of the IDM intervention within a practice. In order to enhance comparability between the intervention and control group at baseline, clusters were matched by stratification and randomized by a blinded researcher. We were able to allocate a broad sample of 1086 COPD patients (ranging from mild to very severe patients) with a response rate of participants of almost 50%. We can conclude from our non-participation analysis that we have recruited a sufficient proportion of patients with considerable complaints, and thus room for improvement. Furthermore, the included practices showed great diversity in the kind of practice, practice size and distribution of ethnic minorities, thereby contributing to high external validity.

To date, previous clinical trials of disease management or home-based rehabilitation trials in primary care have revealed encouraging results on quality of life.[154–158] Based on an earlier example of a published protocol[159], we compared several aspects of our current study to the previously conducted randomized trials which aimed to evaluate the effectiveness of such programs in primary care or in the home-based setting (Table 3.7).

Table 3.7 Characteristics of trials evaluating IDM programmes in primary care or home-based setting

	RECODE	Rea 2004	Boxall 2005	Fernandez 2009	Wetering 2010	Gottlieb 2011
Recruitment	P	P + S	P + S	S	S	P
Pilot study	+	-	-	-	-	-
Population	GOLD stage 1-4	GOLD stage 1-4	GOLD 4	GOLD 4	GOLD 2-3	GOLD 2
Intervention	Multidisciplinary team training, designing practice and patient relevant treatment plans including education, smoking cessation, physiotherapeutic reactivation, dietary intervention (24 mo)	Exacerbation action plan, structured follow-up by nurse, GP. Education about smoking cessation, medication (12 mo)	Home rehabilitation programma (12 wks), under supervision of physiotherapist. Educational sessions for patients and carers, including structured follow up by physiotherapists, nurses, occupational therapy	Home-rehabilitation programme (11 mo) under supervision of physiotherapist. Three education sessions	Intensive exercise programme (4mo), individualized education programme, smoking cessation, dietary intervention (if needed). 20mo maintenance phase, exercise at home (under supervision).	Intensive exercise and educational programme (7wks) led by multidisciplinary team. Smoking cessation counseling.
Included HCP	3-5	3	3	2	3	?
Randomization	Clustered	Clustered	Individual	Individual	Individual	Individual
Blinding outcome assessor	+	-	-	-	+	-
Stratification/matching	+	-	-	-	-	-
Powercalculation based on	MRC score >2	Hospital days	6MWD	Not mentioned	SGRQ	Not mentioned
Cost-effectiveness analysis	+	-	-	-	+	-
Included patients	1086	135	60	50	199	61
Follow-up (months)	24	12	3	12	24	18

Selection of patients

In respiratory medicine there is a lack of research on mild to moderate COPD patients, despite that over 80% of COPD patients suffer from this stage of disease and are often treated in primary care. Moreover, it has been shown that treatment decisions for asthma and COPD patients are usually based on studies including a very small and highly selected proportion of the real patient population; this indicates the need for more real-life studies targeted at the true population, and applying less exclusion criteria.[160] Former trials included a highly selected severely ill patient population[154,158] or recruited their patients in secondary care[155]; overall, this is not an uncommon phenomenon in primary care COPD trials.

Limited follow-up

Most studies presented data up to 12 months follow-up, while limited information is available on studies with long-term (18 or 24 months) follow-up. Gottlieb et al.[156] evaluated the effect of an intensive exercise and educational program in patients with moderate COPD during 18 months of follow-up. Although an effect was found on walking distance and quality of life, the effect on quality of life disappeared over 18 months. However, this result should be interpreted with caution, as the intensive rehabilitation program lasted only 7 weeks, which was followed by a maintenance phase including a monthly session focusing on ways of incorporating exercise in daily life. Furthermore, the authors acknowledged many dropouts before randomization, at randomization and during rehabilitation, potentially introducing bias and indicating substantial loss of power.[156] Another study evaluated the efficacy of a community-based COPD management program in less advanced (GOLD 2 and 3) COPD patients during 24 months follow-up. The SGRQ score initially improved in the intervention group compared to the control group. At 12 months, scores in the intervention group had returned to baseline, whereas in the usual care group it remained stable up to 12 months and worsened thereafter.[155]

Methodological aspects

Due to the nature of the intervention, blinding of participants and patients to the intervention is usually impossible. However, blinding of an outcome assessor can substantially diminish the risk of bias. All the above-mentioned studies, except for the trial of Wetering et al.[155], failed to introduce blinded outcome assessors or did not report this as such. In the study of Rea et al.[157], randomization was also clustered, comparable to our study; however, statistical analysis was at the level of the patient, thereby not taking the clustering coefficient in account. Furthermore,

the authors failed to allocate five practices to the correct treatment group.

Planned subgroups

Finally, this study differs from the other studies in that we based our sample size estimates on the a priori planned subgroup of patients with a MRC dyspnea score >2. We earlier reported that we found the greatest improvements on quality of life in these patients.[6] It is probably that lung function is still relatively well maintained at this stage, while patients experience considerable dyspnea and an impaired quality of life.[5] As a result of this pre-planned subgroup power analysis and to compensate for the intra-clustering, we allocated almost 1100 patients in the present trial according to protocol. As can be seen in Table 3.7, this number is much higher than that of earlier studies in this field.

CONCLUSION

It is acknowledged that not all patients who potentially benefit from an exercise training program, pulmonary rehabilitation, or smoking cessation intervention are actually receiving this type of support in daily practice. It is likely that costs will be lower when patients are detected and persuaded to change their lifestyle at an earlier stage, possibly reducing health decline and disease progression in the long term. To the best of our knowledge, this is the first and largest cluster randomized trial to evaluate the cost and clinical effectiveness of IDM in primary care COPD patients. The results of this study will provide insight into the clinical and cost-effectiveness of IDM in primary care COPD patients, also on the long term.

CHAPTER 4

Cost-effectiveness of integrated COPD care: the RECODE cluster randomized trial

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Accepted, BMJ open

ABSTRACT

Objectives: To investigate the cost-effectiveness of a Chronic Obstructive Pulmonary Disease (COPD) disease management (COPD-DM) program in primary care, called RECODE, compared to usual care.
Design: two-year, cluster-randomised controlled trial
Setting: 40 general practices in the western part of the Netherlands
Participants: 1086 patients with COPD according to GOLD (Global Initiative for COPD) criteria. Exclusion criteria were terminal illness, cognitive impairment, alcohol or drug misuse, and inability to fill in Dutch questionnaires. Practices were included if they were willing to create a multidisciplinary COPD team.
Interventions: A multidisciplinary team of caregivers was trained in motivational interviewing, setting-up individual care plans, exacerbation management, implementing clinical guidelines and redesigning the care process. In addition, clinical decision making was supported by feedback reports provided by an ICT program.
Main outcome measures: We investigated impact on health outcomes (quality-adjusted life years (QALYs), Clinical COPD Questionnaire, St. George's Respiratory Questionnaire, and exacerbations) and costs (healthcare and societal perspective).
Results: The intervention costs were €324 per patient. Excluding these costs, the intervention group had €584 (95% CI €86 to €1,046) higher healthcare costs than the usual care group and €645 (95% CI €28 to €1,190) higher costs from the societal perspective. Health outcomes were similar in both groups, except for 0.04 (95% CI -0.07 to -0.01) less QALYs in the intervention group.
Conclusions: This integrated care program for COPD patients that mainly included professional-directed interventions was not cost-effective in primary care.
Trial registration: Netherlands Trial Register NTR2268
Funding: Stichting Achmea Gezondheidszorg (SAG) and the Netherlands Organisation for Health Research and Development (Zon-MW).

INTRODUCTION

Disease management programs for Chronic Obstructive Pulmonary Disease (herein, COPD-DM) have been developed to change COPD care from acute, reactive and one-size-fits-all into integrated, pro-active and tailor-made. To stimulate the implementation of such programs in the Netherlands, a new payment policy (i.e. bundled payment) was recently implemented.[83] However, the wide implementation of these programs in the Netherlands, as is currently ongoing would benefit by a justification from a cost-effectiveness perspective.

Recent systematic literature reviews of COPD-DM programs showed favourable effects on both health outcomes and costs (mainly due to decreased hospitalization).[161,162] However, previous economic studies had poor methodological quality.[161,163] Most studies did not measure all relevant costs and health outcomes and did not perform incremental cost-effectiveness analyses.[161] For instance, there is little knowledge on the required investments in implementation of these programs. Furthermore, the generalizability of the outcomes of these studies was low, due to the inclusion of mainly severe COPD patients and the exclusion of patients with multi-morbidity.[62,160,161]

We aimed to conduct a comprehensive cost-effectiveness analysis (CEA) of a COPD-DM program in primary care compared to usual care in the Netherlands. This CEA was performed as part of a two-year cluster randomized controlled trial (RCT) evaluating the clinical effects of this RECODE program (acronym for **R**andomized clinical trial on **E**ffectiveness of integrated **CO**P**D** management in primary car**E**). [164,165]

In the clinical paper we concluded that, after 12 months, the RECODE program did not significantly improve the score on the Clinical COPD Questionnaire (CCQ) compared to usual care, despite an improved level of integrated care and a higher degree of self-reported physical activity.[164] Our current paper includes additional outcome measures not reported in the clinical paper and it reports 24-months results. This is important because it is often argued that it takes time before the effect of DM programs become clearly visible. The added value of a cost-effectiveness analysis is that we report the joint uncertainty in both effects and costs, allowing us to report the probability that the RECODE program would be cost-effective at various threshold values of the maximum acceptable costs per quality-adjusted life year (QALY) gained. Moreover, the publication of results in terms of cost-effectiveness is important to avoid selective reporting of positive studies. The published evidence is used to inform decision makers all across developed countries about whether and which COPD-DM programs to reimburse on a wider scale.

METHODS

This study was approved by the medical ethics committee, performed according to the study protocol[165], national[149] and international[148] guidelines for pharmaco-economic research, and reported according to the Consolidated Health Economic Evaluation Reporting Standard(CHEERS).[166]

Design and Intervention

RECODE is a 2-year cluster randomized trial in which 40 clusters of primary care teams were randomized to the COPD-DM program or usual care. The 20 teams of the intervention group were trained in essential components of effective COPD-DM: proper diagnosis, optimizing medication adherence, motivational interviewing, smoking cessation counselling, applying self-management plans including early recognition and treatment of exacerbations, physical (re)activation, and nutritional support. In addition, the teams learned the details of a web-based computer program for measuring and reporting process and outcome performance indicators, named ZORGDRAAD. This Information and Communications Technologies (ICT) application included a patient and provider portal that facilitated the communication within the multi-disciplinary teams as well as between care providers and patients. At the end of the 2-day course, each team developed a plan with steps to be taken in order to redesign the care process and integrate the COPD-DM program into their daily practice. After the course, the teams were invited to join refresher courses, received regular feedback reports on patients' outcomes and had access to ZORGDRAAD. The local healthcare insurer reimbursed physical reactivation for patients with a Medical Research Council (MRC) dyspnoea score >2, also if these patients had no supplementary insurance. All practices were flexible in determining and following their individual plans. Therefore, the mix and intensity of interventions for individual patients depended upon their health status, personal needs and preferences, as well as the actions taken by the team. Healthcare providers in the usual care group were asked to continue providing care as usually. Indicators of care as usual are reported before.[165]

Target population

The enrolment of primary care teams and their COPD patients took place between September 2010 and September 2011. Participating teams included at least one general practitioner (GP), one practice nurse and one physiotherapist. Patients had physician-diagnosed COPD according to GOLD guidelines.[15] Exclusion criteria were terminal illnesses, dementia, cognitive impairment, inability to complete questionnaires in Dutch, and hard drug or alcohol abuse. Other co-morbidity was not an exclusion

criterion. The GPs verified that the included patients fulfilled the inclusion and exclusion criteria. All participating GPs and COPD patients provided written informed consent before participation.

Outcomes

Costs were related to the following outcome measures:

1 QALYs based on the EuroQol-5D (EQ-5D) utility values using the Dutch value set[139,167];
2 proportion of patients with a minimal clinical important difference(MCID) (i.e. improvement ≥ 0.4) on the CCQ[30,138];
3 proportion of patients with a MCID (i.e. improvement ≥ 4) on the St. George's Respiratory Questionnaire(SGRQ)[119,168];
4 total number of COPD-exacerbations (moderate and severe). A moderate exacerbation was defined as a worsening of daily symptoms that led a patient's clinician to prescribe systemic corticosteroids and/or antibiotics, but did not require hospitalization. This information was extracted from the Electronic Medical Records (EMR). A severe exacerbation was defined as a worsening of symptoms that required a hospital admission. Hospital admissions were obtained from the resource use questionnaires and the EMR.

The EQ-5D, CCQ , SGRQ , and resource use questionnaire were administered at baseline, 6, 9, 12, 18, and 24 months.

Costs

Total two-year costs (not only related to COPD) were calculated from a healthcare perspective and a societal perspective. The healthcare perspective included all costs covered by the healthcare budget, i.e. medication prescriptions, contact with care providers (GP, medical specialist, nurse, physiotherapist, dietician, podiatrist, occupational therapist), home care, hospital admissions, emergency department visits, and pulmonary rehabilitation. The costs from the societal perspective additionally included travel costs and costs of productivity loss due to absence from paid work.

Patients reported the healthcare utilization (excluding medication), travel costs, days of absence from paid work due to illness (absenteeism) and lost productivity while being at work (presenteeism) in a resource use questionnaire with a recall period of three months.

The medication prescriptions were extracted from the EMRs of the GPs. Standard unit costs were obtained from the Dutch manual for costing research[149] and inflated to 2013 using the general consumer price index.[169] The costs of medications were obtained from the GIP-Databank

and included value added tax and pharmacist dispensing fees.[170] The productivity costs were estimated using the Friction Cost Approach, which assumes that productivity loss occurs as long as a sick employee is not replaced (the friction period).[51] We used a friction period of 115 days, i.e. the average duration of vacancies (87 days) increased with the expected number of weeks employers need before taking the decision to place a vacancy for temporary or permanent replacement of the worker (28 days).[171]

The intervention costs, defined as costs of training the teams, costs of the ICT support, and costs of the monitoring reports, were calculated based on course attendance (initial 2-day course and refresher courses), computer-documented ICT-use, and time involved in producing monitoring reports (for each practice, the estimated labour time was 2.5, 0.5, and 1 hour to produce the reports at baseline, 6 months and 12 months, respectively).

Statistical analysis

Data analysis was performed according to the intention-to-treat principle. Data from patients who discontinued the trial prematurely were included in the analysis up to the point of drop-out. Additionally, patients that dropped-out during the first year were asked to fill in a CCQ questionnaire at 12 months, if possible.

We used repeated measures models to assess differences between RECODE and usual care, correcting for time, age, gender, MRC dyspnoea score >2, baseline score and clustering of patients. The distribution and link function for each outcome was selected after comparing the goodness-of-fit of models with different specifications of the distribution and link functions. Models that had the lowest Akaike's Information Criterion were selected.

EQ-5D utilities were analysed using linear mixed models with a normal distribution and identity link. We calculated the number of QALY's for each patient as the area under the predicted utility curve, using linear interpolation between two utility measurements. Generalized linear mixed models with a binary distribution and logit link were used to analyse the proportion of patients with a MCID on the CCQ and SGRQ questionnaire. The differences in exacerbation rates were estimated using generalized linear mixed models with negative binomial distribution and log link. Costs were analysed with generalized linear mixed models using a log-normal distribution and identity link. The cost estimate for month 3 to 6 (based on the questionnaire administered in month 6) was linearly extrapolated to include month 0 to 3.[172] The same was done for the cost estimate of month 15 to 18 and 21 to 24.

Cost-effectiveness

Cost-effectiveness was reported in terms of costs per QALY. Additionally, the following incremental cost-effectiveness ratios (ICERs) were calculated: costs per additional patient with a MCID on the CCQ, costs per additional patient with a MCID on the SGRQ, and costs per exacerbation prevented. Taking a multi-outcome approach is in line with recent guidelines.[71]

Uncertainty around the ICERs was handled by bootstrapping the data 5,000 times. Bootstrapping means repeatedly drawing samples with replacement from the original dataset.[173] Each sample has the same size as the trial and for each sample the difference in costs and QALYs between RECODE and usual care and the ICER is calculated. The 2,5th and the 97,5th percentile of the 5,000 bootstrap replications form the 95% uncertainty interval of the differences in costs and QALYs. The 5,000 ICERs were plotted on cost-effectiveness planes.[174] In a cost-effectiveness plane, the horizontal axis displays the difference in effects and the vertical axis displays the difference in costs. The results of the bootstrap replications can fall into one of four quadrants: north-east quadrant (more cost and more effects); south-east quadrant (less cost and more effects); south-west quadrant (less cost and less effects); north-west quadrant (more cost and less effects) (Appendix 4.1). Finally, the probability that the RECODE program is cost-effective using different thresholds for the monetary value of a QALY was shown in cost-effectiveness acceptability curves.[175] This probability equals the proportion of bootstrap replications in which the ICER is lower than the threshold value.

Sensitivity and subgroup analyses

Two sensitivity analyses were performed: one with the inclusion of intervention costs and the other with a one year instead of a two year time horizon. Five subgroup analyses were performed to study the influence of age, sex, dyspnoea, lung function, and socioeconomic status. These were all pre-specified in the study protocol and the power calculation was based on the subgroup analyses by MRC dyspnoea score>2.[165]

RESULTS

Patients

The flowchart of patient inclusion has been presented elsewhere.[164] In total, we included 1086 COPD patients from 40 teams in the trial, 554 in the RECODE group and 532 in the usual care group. The baseline characteristics of the patients in the RECODE and usual care group are summarized in Table 4.1. The only statistically significant difference was a higher percentage of males in the usual care group (51 vs. 57%).

The proportion of patients who completed the trial was 76% in the RECODE group and 74% in the usual care group. Length of follow-up among the drop-outs was not significantly different between groups, with a mean (±sd) follow-up of 20.5 (±0.29) and 20.0 (±0.33) months, respectively. Patients who dropped out were significantly older and had a significantly worse baseline score on the CCQ , SGRQ , MRC-dyspnoea, and EQ-5D. Baseline characteristics between the drop-outs of the RECODE group and the usual care group were not significantly different.

Table 4.1 Baseline characteristics

	RECODE (N=554)	USUAL CARE (N=532)
Age (years), mean (SD)	68.2±11.3	68.4±11.1
Male sex (%)	50.5	57.3*
Employment (%)	27.7	28.8
Low education/ low Social Economic Status (%)	39.2	41.5
Marital status: Single (%)	37.0	38.3
FEV1% predicted , mean (SD)	67.7 (20.3)	67.9 (20.5)
Current smoker (%)	34.8	38.7
Former smoker (%)	53.8	52.6
Moderate exacerbation in the last year, mean (SD)	0.36 (0.83)	0.33 (0.78)
Severe exacerbation in the last three months, mean (SD)	0.02 (0.18)	0.02 (0.17)
Charlson comorbidity index	2.35 (1.26)	2.32 (1.27)
Major cardiovascular disease (%)	14.6	17.7
Hypertension (%)	35.4	38.3
Diabetes (%)	14.6	14.8
Depression (%)	9.8	10.1
MRC score, mean (SD)	2.06 (1.30)	1.95 (1.26)
MRC score > 2 (%)	35.1	31.6
CCQ score, mean (SD)	1.54 (0.98)	1.46 (0.96)
SGRQ total score, mean (SD)	36.7 (21.1)	34.5 (19.8)
EQ-5D score, mean (SD)	0.74 (0.25)	0.73 (0.28)*

Significant (p<0.05), *FEV1* forced expiratory volume in 1 second, *MRC* Medical Research Council, *CCQ* Clinical COPD Questionnaire, *SGRQ* St. George's Respiratory Questionnaire, *EQ-5D* EuroQoL-5D ,

Table 4.2 Intervention costs (in euros, 2013)

DM INTERVENTION	COST DESCRIPTION	% TEAMS WITH ANY USE OF	MEAN COST PER TEAM ± SD (€)	MEAN COST PER PATIENT ± SD (€)
RECODE Course	*Catering*	100	119 ± 56	4.78 ± 2.45
	Location	100	3 ± 4	0.15 ± 0.21
	Presenters	100	84 ± 37	50.9 ± 36.31
	*Other costs**	100	1,174 ± 587	3.63 ± 2.39
	Labour costs attendees	100	4,008 ± 1,683	163.72 ± 87.65
	Travel	100	48 ± 30	1.94 ± 1.24
Refresher course	*Catering*	70	29 ± 25	1.1 ± 0.97
	Location	70	-	-
	Presenters	70	146 ± 123	5.94 ± 6.63
	*Other costs**	70	-	-
	Labour costs attendees	70	273 ± 273	10.84 ± 11.69
	Travel	70	7 ± 6	0.25 ± 0.23
ICT system				
ZORGDRAAD	*Labour costs of ICT use*	50	42 ± 86	1.45 ± 2.65
	Labour costs of ICT support	100	1,354 ± 0	57.80 ± 24.07
Monitoring reports	*Labour costs of feedback report at baseline*	100	333 ± 141	13.56 ± 6.2
	Labour costs of feedback eport at 6 months	100	67 ± 28	2.71 ± 1.24
	Labour costs of feedback report at 12 months	100	133 ± 57	5.42 ± 2.48
Total	7,862 ± 2,543	324 ± 156*		

Other costs includes material and equipment used during the course

Costs

The intervention costs are presented in Table 4.2. The total intervention costs per patient ranged from €103 to €587 across clusters, with a mean (±sd) of €324 (±156) per patient. This variation is explained by the number of COPD patients per team, the use of the ICT system, the number of healthcare providers participating in the courses, and the different locations of the courses. The labour costs of the attendees of the RECODE courses were the main driver of the intervention costs (54%).

Complete 2-year medication data of 500 patients (90%) in the RECODE group and 478 (90%) in the usual care group were extracted from the EMRs. More than 85% of the participants used medication for obstructive airway diseases in the 2-year trial period (Table 4.3).

Of the 1086 patients 93% had complete health care utilization data at 6 months, 79% at 9 months, 88% at 12 months, 73% at 18 months, and 75% at 24 months. This was similar for both groups. The unit costs, observed mean use of resources, and associated costs, as reported by the patients are presented in Table 3. In both groups, important cost drivers were hospital admissions, home care, and productivity loss. Excluding intervention costs, the adjusted mean total 2-year costs (estimated from the generalized linear mixed model) were significant higher in the RECODE group than in the usual care group by €584 from the healthcare perspective and €645 from the societal perspective (Table 4.4).

Outcomes

Over a two year period, the number of QALYs was 0.04 (p=0.02) lower in the RECODE group than in the usual care group while there was no significant difference in percentage of patients with a MCID in CCQ, nor in any of the other outcomes (Table 4.4).

Cost-effectiveness

From a healthcare and societal perspective, the point-estimates of costs and effects pointed towards higher costs and lower effects of the RECODE program, resulting in negative ICERs for all outcome measures (QALYs, exacerbation avoided, additional patient with a MCID in the CCQ score, and additional patient with a MCID in the SGRQ score). The CE-planes of the different outcomes showed that the majority of the bootstrap replications (>98%) had higher costs. Furthermore, more than half of the bootstrap replications fell within the north-west quadrant of the plane indicating that RECODE was dominated by the usual care group, e.g. more costs and less effects.

Table 4.3 Unit costs, dataq sources, mean of use of resources and associated costs over the 2-years, as reported by the patients (unadjusted)

	Unit cost (€)	Source*	RECODE			usual care		
			Any use (%)	Mean use	Mean cost ± SD (€)	Any use (%)	Mean use	Mean cost ± SD (€)
Costs from healthcare perspective								
GP, (home) visits, phone contacts	15-46	a	91	16.23	476 ± 504	89	14.02	401 ± 450
Practice nurse, visits	23	b	74	5.51	131 ± 277	75	5.18	109 ± 166
Specialist, visits	78	a	78	10.05	784 ± 1,037	78	9.84	768 ± 973
Emergency department, visits	163	a	26	0.78	127 ± 284	23	0.79	129 ± 346
Physiotherapist, visits	39	a	53	25.82	1,007 ± 1,770	45	16.33	637 ± 1,260
Dietician, visits	29	a	21	1.45	42 ± 141	19	1.21	35 ± 148
Podiatrist, visits	32	b	43	3.78	121 ± 203	40	3.27	105 ± 167
Speech therapist, visits	36	a	3	0.12	4 ± 42	2	0.28	10 ± 158
Occupational therapy, visits	24	a	4	0.29	7 ± 76	3	0.32	8 ± 83
Rehabilitation centre, visits	78	a	12	3.86	459 ± 2,157	12	3.01	358 ± 1,731
Home care, hours of household help	26	a	22	34.42	895 ± 2,287	20	31.01	806 ± 2,171
Home care, hours of personal care	47	a	9	8.28	389 ± 1,995	8	9.49	446 ± 2,327
Home care, hours of nursing	70	a	6	2.11	148 ± 1,108	6	2.39	167 ± 1,064
Home care, other, hours	48	a	1	0.47	22 ± 262	2	0.65	31 ± 309
Hospital stay, days	493	a	25	4.65	2,293 ± 5,915	25	4.84	2,388 ± 7,522
Intensive care unit, days	2,356	a	5	0.49	1,161 ± 11,316	2	0.14	328 ± 2,658
Drugs for obstructive airway diseases	-	c	84	-	945 ± 814	84	-	934 ± 1,024
Other medication	-	c	91	-	1,367 ± 3,421	90	-	1,131 ± 2,506
Costs from societal perspective								
Travel expenses, public transport/car, KM	0.22	a	94	189.00	42 ± 56	92	174.43	38 ± 59
Productivity loss, absenteeism hours	31-43	a	11	47.74	1,698 ± 8,344	11	42.89	1,649 ± 8,448
Productivity loss, presenteeism hours	31-43		8	10.38	376 ± 2,304	9	10.92	374 ± 1,774

* Sources of unit costs used in the analysis: (a) Dutch guidelines for pharmacoeconomic research[149], (b) The Dutch Healthcare Authority NZA (c) GIP Databank [170]

Table 4.4 Results from the cost-utility and cost-effectiveness analysis from the base case (in euros, 2013)

	Costs				Effect			cost-effectiveness planes				
	RECODE		Usual Care	Difference (95% CI)	RECODE	Usual Care	Difference (95% CI)	ICER	NW C↑E↓	SW C↓E↓	NE C↑E↑	SE C↓E↑
Cost per QALY	HP	€ 5.119	€ 4.535	€ 584* (86 – 1,046)	1.40	1.44	-0.04* (-0.07 – -0.01)	-15,720	97.9	1.3	0.8	0.0
	SP	€ 5.750	€ 5.105	€ 645* (28 – 1,190)	1.40	1.44	-0.04* (-0.07 – -0.01)	-17,358	97.3	1.9	0.8	0.0
Cost per exacerbation avoided	HP	€ 5.119	€ 4.535	€ 584* (86 – 1,046)	0.78	0.65	-0.14 (-0.30 – 0.06)	-4,211	91.3	1.2	7.4	0.1
	SP	€ 5.750	€ 5.105	€ 645* (28 – 1,190)	0.78	0.65	-0.14 (-0.30 – 0.06)	-4,650	90.7	1.8	7.4	0.1
Cost per additional patient with a clinical relevant improvement in CCQ score	HP	€ 5.119	€ 4.535	€ 584* (86 – 1,046)	0.11	0.12	-0.02 (-0.06 – 0.02)	-35,772	75.2	1.0	23.5	0.3
	SP	€ 5.750	€ 5.105	€ 645* (28 – 1,190)	0.11	0.12	-0.02 (-0.06 – 0.02)	-39,498	74.8	1.4	23.3	0.5
Cost per additional patient with a clinical relevant improvement in SGRQ score	HP	€ 5.119	€ 4.535	€ 584* (86 – 1,046)	0.26	0.27	-0.01 (-0.07 – 0.04)	-46,508	66.5	0.9	32.3	0.4
	SP	€ 5.750	€ 5.105	€ 645* (28 – 1,190)	0.26	0.27	-0.01 (-0.07 – 0.04)	-51,353	66.1	1.3	32.0	0.6

* Significant (p<0.05), ** Significant (p<0.01), *QALY* quality-adjusted life years, *CCQ* Clinical COPD Questionnaire, *SGRQ* St. George's Respiratory Questionnaire, *HP* healthcare perspective, *SP* societal perspective, *CI* confidence interval, *ICER* incremental cost-effectiveness ratio, *NW* north-west (more cost and less effects), *SW* south-west (less cost and less effects), *NE* north-east (more cost and more effects) , *SE* south-east (more cost and less effects), *C* difference in costs, *E* difference in effects.

Sensitivity analyses

When including the intervention costs, the cost difference, which favoured usual care, further increased to a difference of €883 from the healthcare perspective and €1,005 from the societal perspective (Appendix 4.2).

Using a 12-month instead of a 24 month time horizon, the costs per patient were significantly higher in the RECODE group in comparison with the usual care group by €408 from the healthcare perspective and €370 from the societal perspective (Appendix 4.3). After 12 months, there was no significant difference in QALYs, or any of the other outcomes, except for the percentage of patients improving at least the MCID in CCQ_, which was 7% less in the RECODE group than in the usual care group. After 12 months, the costs per QALY ratio of RECODE compared to usual care was €38,471 from a healthcare perspective and €42,458 from a societal perspective. The probability that RECODE is cost-effective at a willingness-to-pay of €20,000 and €80,000 per QALY at 12 months was 8% and 79%, respectively (Appendix 4.4). From a societal perspective these probabilities were slightly higher, i.e. 15% and 81%.

Subgroup analyses

Only age showed a significant interaction with the effect of RECODE on costs (Appendix 4.5, 4.6). The difference in costs (healthcare and societal perspective) between RECODE and usual care was significantly lower in patients younger than 65 years, than in patients above 65 years. There was also a significant interaction between age and the effect of RECODE in terms of QALYs. In patients below 65 there was no significant difference in QALYs between RECODE and usual care, whereas in patients 65 or over there were fewer QALYs in RECODE than in usual care (Appendix 4). It is more likely that RECODE is cost-effective within the subgroup of patients <65 years.

DISCUSSION

This study compared the costs and health effects of a COPD-DM program in primary care (RECODE) with usual care in the Netherlands. Our results show that RECODE is not cost-effective from a healthcare as well as a societal perspective. The point-estimates of costs and effects pointed towards higher costs and no significant difference in effects, except for 0.04 less QALYs. The majority of bootstrap replications in the CE-planes showed that RECODE was dominated by usual care. The decrease in utility, especially in the second year, might be explained by the consistent pattern of no effect or a worse effect on the outcomes. The reduction in utility might also result from the increased awareness by patients of

their health problems as an effect of being enrolled in the RECODE program.

These unexpected findings cannot be related to weaknesses in the research design. The strength of our study lies in the inclusion of a large and representative group of COPD patients recruited in primary care. To avoid contamination, randomization was performed at cluster level. Since blinding of participants and clinicians was impossible, blinded research nurses collected the data, while patients were instructed not to report back on their type of intervention. Additional strengths of this study are the 2-year follow-up period, the broad range of health outcomes and costs categories included and the sophisticated analyses that took into account the hierarchical nature of the data. A limitation of our study is that we collected healthcare resource utilization at baseline, 6, 12, 18 and 24 months using a questionnaire with a 3-months recall period, necessitating the extrapolation of the 3-month data to 6 months to estimate the costs of month 3 to 6, 15 to 18 and 21 to 24. We chose to collect intermittent data for two reasons. The first was to avoid study drop-outs resulting from endless questionnaires or daily diaries over a long follow-up period. The second reason was that evidence from the literature suggests that intermittent data provides reliable estimates of total annual health expenditures.[172] A second limitation is that patients who dropped out were significantly older and had a significantly worse baseline score on the CCQ_, SGRQ_, MRC-dyspnoea, and EQ-5D, thus potentially jeopardizing the generalizability of the results. However, baseline characteristics of the drop-outs in the RECODE group and the drop-outs in the usual care group were not significantly different. Moreover, after correction for baseline scores no evidence of benefits of the intervention were found, indicating that dropout is unlikely to have biased the results.

There are several possible explanations for the finding that the RECODE intervention was not cost-effective. Firstly, it may be due to the relatively low intensity of our pragmatic intervention. The RECODE program did not require the teams to implement all elements of effective COPD-DM that they learned during the courses. Instead, each team made their own plan to redesign the care process and implement COPD-DM. Consequently, the mixture and intensity of interventions for individual patients was not only dependent upon health status, personal needs and preferences of the individual patients, but also on the specific focus that a team may have chosen, the level of implementation of the DM interventions and the context within which each team operates. As an example of an area that may not have been sufficiently addressed during the courses we should mention interventions to improve psychological health.[176] However, only 10% of the patients in the RECODE trial suffered

from a depression at baseline. Although this has probably influenced their motivation to change their health behaviour and may have increased unscheduled care,[176,177] it is unlikely to be a major explanation for the lack of effect. Obviously, further research is required to understand the conditions for a successful implementation and thus cost-effectiveness of a COPD-DM program.

Secondly, it is questionable whether the pragmatic provider-oriented interventions of the RECODE program (e.g. training and education, support in writing practice reform plans, ICT system Zorgdraad) were optimally translated into patient-oriented interventions. This is important because it has been shown that successful COPD-DM programs mainly include patient-oriented interventions.[161,162] Literature showed that exercise is an important success factor of a COPD-DM program[162] and education, exercise and relaxation are important factors for reducing the use of urgent and unscheduled healthcare among people with COPD.[178] In our study, physical exercise was not mandatory and only patients with MRC>2 received full reimbursement of physiotherapy.

Thirdly, there was limited room for improvement in comparison with previous studies due to the relatively high standard of COPD care in the Netherlands[12] and the low proportion of severe COPD patients in this study.[161,162] It could be that a program like RECODE would have led to more positive results in settings where the COPD care is less advanced. For instance, in 2005, when the standards of good COPD care in developed countries were less well developed, a Spanish study did find that a community-based integrated care program in frail COPD patients improved clinical outcomes including survival and decreased the emergency department visits.[11] Moreover, Bourbeau and collegues[117,179] demonstrated positive results of a COPD-DM program in patients recruited from 7 hospitals in Canada in 1999, while a similar program in 15 general practices in the Netherlands in 2006[12] found no long-term benefits and a study in the US in 2009 did even find negative results in patients recruited from 20 hospital-based outpatient clinics.[13] It might well be that as time passes and quality of COPD care improves, there is less room for improvement. However, even in the presence of incentivised quality improvement programs like the Quality and Outcome Framework in England, hospital admissions for COPD still occur more frequently among the least well served such as those in deprived areas.[180] So there is still room for improvement among certain sub-groups of COPD patients and it might be a question of targeting DM programs at those most likely to benefit.

Fourthly, changes in healthcare occurred during the study period that affected COPD care in the RECODE as well as the usual care group. Since

July 2010, a new bundled payment scheme for COPD patients has been introduced in the Netherlands to stimulate the integration of care.[63] In this scheme, healthcare insurers purchase integrated care from care groups by negotiating a fixed price per patient per year for all multidisciplinary COPD care required by a patient. As the bundle excludes secondary care and medications, it primarily stimulates the cooperation between different providers in the primary care setting. This increased attention for integrated chronic care and the ability to reimburse COPD interventions such as smoking cessation and nutritional counselling could have stimulated integrated care in the usual care group too.

Future research should determine the cost-effectiveness of more intensive COPD-DM programs in primary care using a long(er) time horizon. Hence, the gains from preventing patients with moderate COPD to progress to severe COPD are likely to be detected only in the long run.

In conclusion, this comprehensive economic evaluation of an integrated care program in primary care showed that the program increased costs but did not improve health outcomes. It even reduced QALYs. This is most likely due to the sub-optimal translation of the provider-oriented interventions of the RECODE program into patient-oriented interventions, the suboptimal implementation of the interventions, the relatively mild COPD population, and the national reforms in COPD care.

Appendix 4.1 Health economic terms

Incremental costs

= Difference in costs between the intervention and usual care group

= $Costs_{\text{intervention group}} - Costs_{\text{usual care group}}$

Incremental effects

= Difference in effects between the intervention and usual care group

= $Effect_{\text{intervention group}} - Effect_{\text{usual care group}}$

Incremental cost-effectiveness ratios (ICERs)

= ncremental costs / Incremental effects

= $(Costs_{\text{intervention group}} - Costs_{\text{usual care group}}) / (Effect_{\text{intervention group}} - Effect_{\text{usual care group}})$

Bootstrapping

Bootstrapping means repeatedly drawing samples with replacement from the original dataset.[173] That is to say the same record can occur more than once in a given bootstrap sample. Each sample has the same size as the trial and for each sample the difference in costs and QALYs between RECODE and usual care and the ICER is calculated. The 2,5th and the 97,5th percentile of the 5,000 bootstrap replications form the 95% uncertainty interval of the differences in costs and QALYs.

Cost-effectiveness plane

We plot the uncertainty around the difference in costs and effects in a cost-effectiveness plane (CE-plane). In a CE-plane, the horizontal axis displays the difference in effects and the vertical axis displays the difference in costs.[174] The results of the bootstrap replications fall into one of four quadrants:

- North-east quadrant: more cost and more effects;
- South-east quadrant: less cost and more effects (intervention is dominant);
- South-west quadrant: less cost and less effects;
- North-west quadrant: more cost and less effects (intervention is dominated).

In the most ideal situation, all the results of the bootstraps lay in lower-right corner of the plane, indicating lower costs and improved outcomes.

Cost-effectiveness acceptability curves

The cost-effectiveness acceptability curve shows the probability that the RECODE program is cost-effective using different thresholds for the willingness to pay for a quality adjusted life year.[175] This probability equals the proportion of bootstrap replications in which the ICER is lower than the threshold value.

References

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Appendix 4.2 Sensitivity analyses: impact on cost-utility and cost-effectiveness, with intervention costs

		Costs			Effect			CE-planes				
		RECODE	usual Care	Difference (95% CI)	RECODE	usual Care	Difference (95% CI)	ICER	NW	SW	NE	SE
With intervention costs												
Cost per QALY	HP	€ 5,528	€ 4,644	€ 883** (375 – 1,353)	1.40	1.44	-0.04* (-0.07 – -0.01)	-23,792	99.1	0.0	0.9	0.0
	SP	€ 6,211	€ 5,206	€ 1,005** (381 –1,570)	1.40	1.44	-0.04* (-0.07 – -0.01)	-27,053	99.0	0.2	0.9	0.0
Cost per exacerbation avoided	HP	€ 5,528	€ 4,644	€ 883** (375 – 1,353)	0.78	0.65	-0.14 (-0.30 – 0.06)	-6,373	92.5	0.0	7.5	0.0
	SP	€ 6,211	€ 5,206	€ 1,005** (381 –1,570)	0.78	0.65	-0.14 (-0.30 – 0.06)	-7,247	92.4	0.2	7.5	0.0
Cost per additional patient with a clinical relevant improvement in CCQ score	HP	€ 5,528	€ 4,644	€ 883** (375 – 1,353)	0.11	0.12	-0.02 (-0.06 – 0.02)	-54,139	76.2	0.0	23.8	0.0
	SP	€ 6,211	€ 5,206	€ 1,005** (381 –1,570)	0.11	0.12	-0.02 (-0.06 – 0.02)	-61,559	76.1	0.1	23.8	0.0
Cost per additional patient with a clinical relevant improvement in SGRQ score	HP	€ 5,528	€ 4,644	€ 883** (375 – 1,353)	0.26	0.27	-0.01 (-0.07 – 0.04)	-70,388	67.4	0.0	32.6	0.0
	SP	€ 6,211	€ 5,206	€ 1,005** (381 –1,570)	0.26	0.27	-0.01 (-0.07 – 0.04)	-80,035	67.3	0.1	32.6	0.1

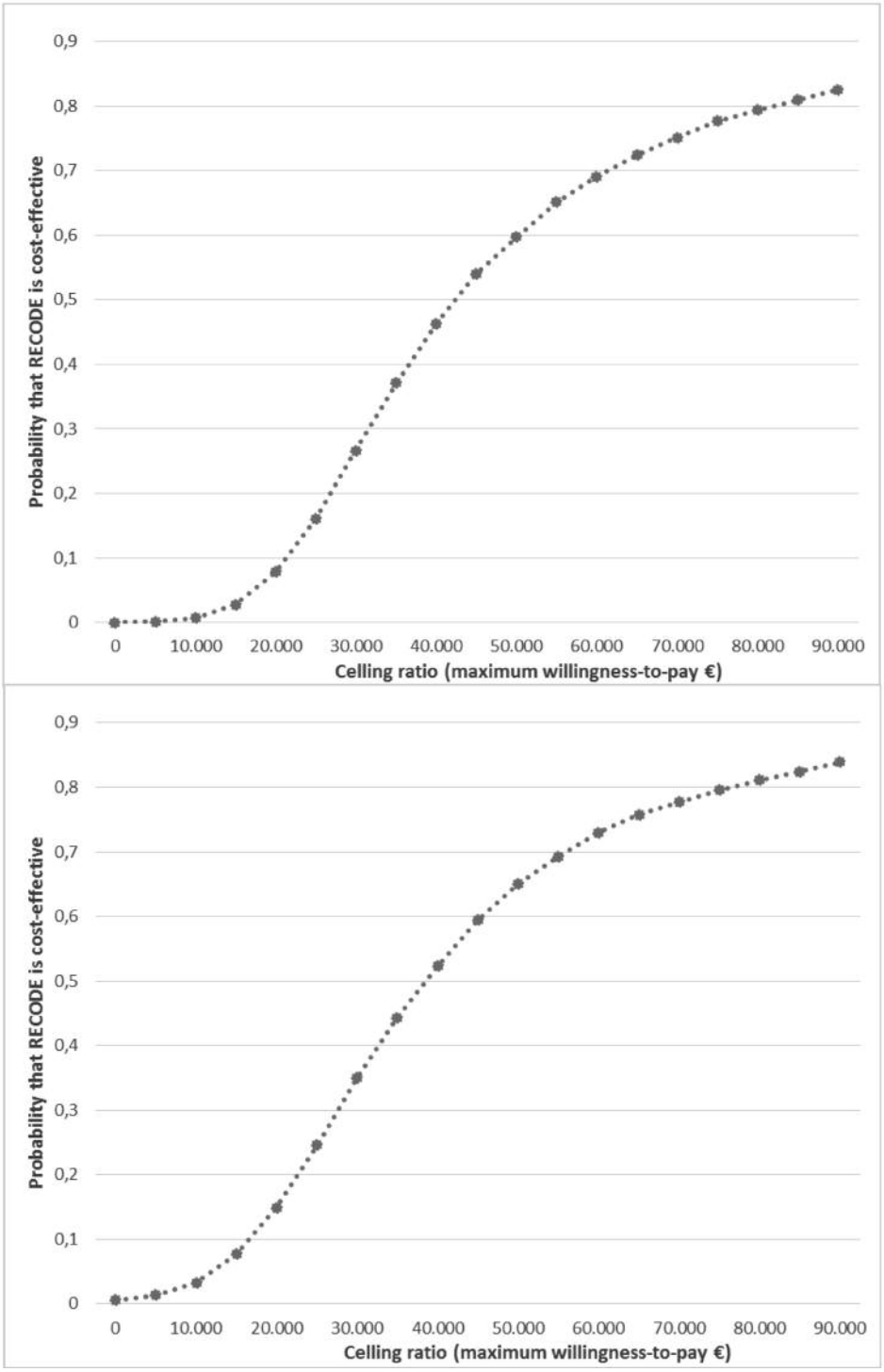
* Significant (p<0.05), ** Significant (p<0.01), *QALY* quality-adjusted life years, *CCQ* Clinical COPD Questionnaire, *SGRQ* St. George's Respiratory Questionnaire, *HP* healthcare perspective, *SP* societal perspective, *CI* confidence interval, *ICER* incremental cost-effectiveness ratio, *NW* north-west, *SW* south-west, *NE* north-east, *SE* south-east, *CE-planes* cost-effectiveness planes.

Appendix 4.3 Sensitivity analyses: impact on cost-utility and cost-effectiveness, 12 months' time horizon

		Costs			Effect			CE-planes				
		RECODE	usual Care	Difference (95% CI)	RECODE	usual Care	Difference (95% CI)	ICER	NW	SW	NE	SE
12 months' time horizon												
Cost per QALY	HP	€ 2,622	€ 2,214	€ 408** (193 – 607)	0.71	0.70	0.01 (-0.001 – 0.02)	42,458	3.6	0.0	96.4	0.0
	SP	€ 2,955	€ 2,585	€ 370* (90 – 206)	0.71	0.70	0.01 (-0.001 – 0.02)	38,471	3.6	0.0	95.8	0.6
Cost per exacerbation avoided	HP	€ 2,622	€ 2,214	€ 408** (193 – 607)	0.38	0.32	-0.06 (-0.14 – 0.05)	-7,401	87.3	0.0	12.7	0.0
	SP	€ 2,955	€ 2,585	€ 370* (90 – 206)	0.38	0.32	-0.06 (-0.14 – 0.05)	-6,706	86.8	0.5	12.7	0.0
Cost per additional patient with a clinical relevant improvement in CCQ score	HP	€ 2,622	€ 2,214	€ 408** (193 – 607)	0.19	0.26	-0.07** (-0.14 – -0.02)	-5,582	99.6	0.0	0.4	0.0
	SP	€ 2,955	€ 2,585	€ 370* (90 – 206)	0.19	0.26	-0.07** (-0.14 – -0.02)	-5,058	99.0	0.6	0.4	0.0
Cost per additional patient with a clinical relevant improvement in SGRQ score	HP	€ 2,622	€ 2,214	€ 408** (193 – 607)	0.36	0.37	-0.01 (-0.05 – 0.03)	-36,869	69.4	0.0	30.6	0.0
	SP	€ 2,955	€ 2,585	€ 370* (90 – 206)	0.36	0.37	-0.01 (-0.05 – 0.03)	-33,408	69.1	0.3	30.3	0.2

* Significant (p<0.05), ** Significant (p<0.01), *QALY* quality-adjusted life years, *CCQ* Clinical COPD Questionnaire, *SGRQ* St. George's Respiratory Questionnaire, *HP* healthcare perspective, *SP* societal perspective, *CI* confidence interval, *ICER* incremental cost-effectiveness ratio, *NW* north-west, *SW* south-west, *NE* north-east, *SE* south-east, *CE-planes* cost-effectiveness planes.

Appendix 4.4 Cost-effectiveness acceptability curves, healthcare (upper) and societal perspective (lower) with a 12 months' time horizon



Appendix 4.5 Subgroup analyses (age, gender, Medical Research Council (MRC) Dyspnoea scale, FEV_1, SES))

			Costs				Effect (QALY's)				CE-planes				
			RECODE	usual Care	Difference	P-value Inter-action	RECODE	usual Care	Difference	P-value Inter-action	ICER	NW	SW	NE	SE
Cost per QALY age subgroups															
HP	<65 years	N=411	€ 3,975	€ 3,801	€ 174 (-434 – 711)	0.03*	1.57	1.58	-0.02 (-0.06 – 0.03)	0.04*	**-9,820**	58.0	20.4	15.8	5.9
	≥65 years	N=675	€ 6,029	€ 5,028	€ 1,001* (248 – 1,701)		1.55	1.60	-0.05* (-0.10 – -0.01)		**-18,698**	98.8	0.5	0.7	0.0
SP	<65 years	N=411	€ 5,374	€ 5,158	€ 216 (-737 – 1,035)	0.03*	1.57	1.58	-0.02 (-0.06 – 0.03)	0.04*	**-12,171**	54.1	24.2	15.1	6.5
	≥65 years	N=675	€ 6,064	€ 5,079	€ 985* (224 – 1,679)		1.55	1.60	-0.05* (-0.10 – -0.01)		**-18,409**	98.7	0.6	0.7	0.0
Cost per QALY gender subgroups															
HP	Men	N=585	€ 4,725	€ 4,344	€ 381 (-250 – 963)	0.92	1.53	1.57	-0.04* (-0.08 – -0.01)	0.16	**-8,951**	88.4	10.5	1.1	0.1
	Women	N=501	€ 5,527	€ 4,756	€ 771 (-44 – 1,472)		1.35	1.37	-0.02 (-0.07 – 0.02)		**-35,680**	80.4	2.7	16.4	0.4
SP	Men	N=585	€ 5,226	€ 4,924	€ 302 (-502 – 1,000)	0.75	1.53	1.57	-0.04* (-0.08 – -0.01)	0.16	**-7,090**	78.2	20.7	0.9	0.2
	Women	N=501	€ 6,302	€ 5,331	€ 971* (106–1,748)		1.35	1.37	-0.02 (-0.07 – 0.02)		**-44,939**	81.8	1.4	16.7	0.2
Cost per QALY MRC subgroups															
HP	MRC≤2	N=725	€ 3,927	€ 3,500	€ 427 (-29– 821)	0.67	1.57	1.61	-0.04* (-0.07 – -0.003)	0.41	**-11,060**	99.5	2.9	1.5	0.1
	MRC>2	N=361	€ 8,721	€ 7,231	€ 1,489 (-164 – 2,881)		0.66	0.69	-0.04 (-0.10 – 0.03)		**-42,301**	81.2	2.8	15.5	0.5
SP	MRC≤2	N=725	€ 4,543	€ 4,101	€ 443 (-191 – 1,029)	0.52	1.57	1.61	-0.04* (-0.07 – -0.003)	0.41	**-11,464**	90.8	7.6	1.3	0.2
	MRC>2	N=361	€ 9,358	€ 7,744	€ 1,614 (-161 – 3,115)		0.66	0.69	-0.04 (-0.10 – 0.03)		**-45,846**	81.0	3.0	15.5	0.5

Continue on p. 96

Continuation **Appendix 4.5**

Cost per QALY lung function subgroups															
HP	FEV1≥50	N=674	€ 4,797	€ 4,025	€ 773** (198 – 1,287)	0.85	1.47	1.51	-0.04 (-0.07 – 0.003)	0.15	-21,762	96.0	0.5	3.5	0.0
	FEV1<50	N=193	€ 7,744	€ 7,415	€ 329 (-1,499 – 1,837)		1.39	1.34	-0.05 (-0.12 – 0.03)		-10,044	60.3	29.4	6.9	3.4
SP	FEV1≥50	N=674	€ 5,359	€ 4,537	€ 822* (159 – 1,420)	0.82	1.47	1.51	-0.04 (-0.07 – 0.003)	0.15	-23,155	95.5	1.0	3.5	0.0
	FEV1<50	N=193	€ 8,622	€ 8,170	€ 452 (-1,536 –2,139)		1.39	1.34	-0.05 (-0.12 – 0.03)		-7,310	63.3	26.5	7.2	3.1
Cost per QALY Social economic status (SES) subgroups															
HP	Low SES	N=399	€ 5,124	€ 4,562	€ 562 (-434 – 1,423)	0.46	1.04	1.09	-0.05 (-0.11 – 0.01)	0.15	-11,505	84.2	10.8	4.4	0.5
	Moderate/ high SES	N=590	€ 5,347	€ 4,598	€ 749 (74 – 1,362)		1.54	1.57	-0.03 (-0.07 – 0.01)		-24,627	91.9	1.5	6.5	0.1
SP	Low SES	N=399	€ 5,534	€ 4,859	€ 675 (-415 – 1,632)	0.49	1.04	1.09	-0.05 (-0.11 – 0.01)	0.15	-13,801	85.3	9.7	4.4	0.6
	Moderate/ high SES	N=590	€ 6,089	€ 5,372	€ 717 (-125 – 1,459)		1.54	1.57	-0.03 (-0.07 – 0.01)		-23,560	89.1	4.3	6.2	0.4

* Significant (p<0.05), ** Significant (p<0.01), QALY quality-adjusted life years, *MRC* Medical Research Council, *FEV1* forced expiratory volume in 1 second, *SES* Social Economic Status, HP healthcare perspective, *SP* societal perspective, *CI* confidence interval, *ICER* incremental cost-effectiveness ratio, *NW* north-west, *SW* south-west, *NE* north-east, *SE* south-east, *CE-planes* cost-effectiveness planes.

CHAPTER 5

Exploring the variation in implementation of a COPD disease management program and its impact on health outcomes: a post-hoc analysis of the RECODE cluster randomized trial

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Accepted, npj Primary Care Respiratory Medicine

ABSTRACT

Aim: This study aims to (1) examine the variation in implementation of a two-year COPD disease management program called RECODE, (2) analyse the facilitators and barriers to implementation and (3) investigate the influence of this variation on health outcomes.

Methods: Implementation variation among the 20 primary care teams was measured directly using a self-developed scale and indirectly through the level of care integration as measured with the Patient Assessment of Chronic Illness Care (PACIC), and the Assessment of Chronic Illness Care (ACIC). Interviews were held to obtain detailed information regarding the facilitators and barriers of implementation. Multilevel models were used to investigate the association between variation in implementation and change in outcomes.

Results: The teams implemented, on average, eight of the nineteen interventions and the specific package of interventions varied widely. Important barriers and facilitators of implementation were (in)sufficient motivation of healthcare provider and patient, the high starting level of COPD care, the small size of the COPD population per team, the mild COPD population, practicalities of the ICT system and hurdles in the reimbursement. Level of implementation as measured with our own scale and the ACIC was not associated with health outcomes. A higher level of implementation measured with the PACIC was positively associated with improved self-management capabilities, but this association was not found for other outcomes.

Conclusion: There was a wide variety in the implementation of RECODE, associated with barriers at individual, social, organisational, and societal level. There was little association between extent of implementation and health outcomes.

Trial registration: Netherlands Trial Register (NTR): NTR2268.

Keywords: disease management, implementation, COPD, heterogeneity

INTRODUCTION

Integrated Disease Management (DM) is a popular approach for improving quality and efficiency of care for chronic obstructive pulmonary disease (COPD) patients. However, the key elements of DM programs for COPD (herein, COPD-DM) are not yet fully understood.[75,78,82] The cost-effectiveness of these programs varies considerable[181], most likely depending on the duration, target population, and components of the intervention.[161,162] Moreover, wide variation exists, even in the implementation of a single program.[156,182] This variation can be due to adjustments for the local setting, or to differences in specific barriers and facilitators that influence implementation.[183,184] Therefore, it is important to understand the conditions needed for the successful implementation of a DM program.[185]

We aimed to (I) examine the variation in implementation of a single COPD-DM program (RECODE) between different primary care teams, (II) analyse the facilitators of and barriers to implementation and (III) investigate the association between the extent of implementation and health outcomes. This study was performed as a pre-specified part of the RECODE trial.[165]

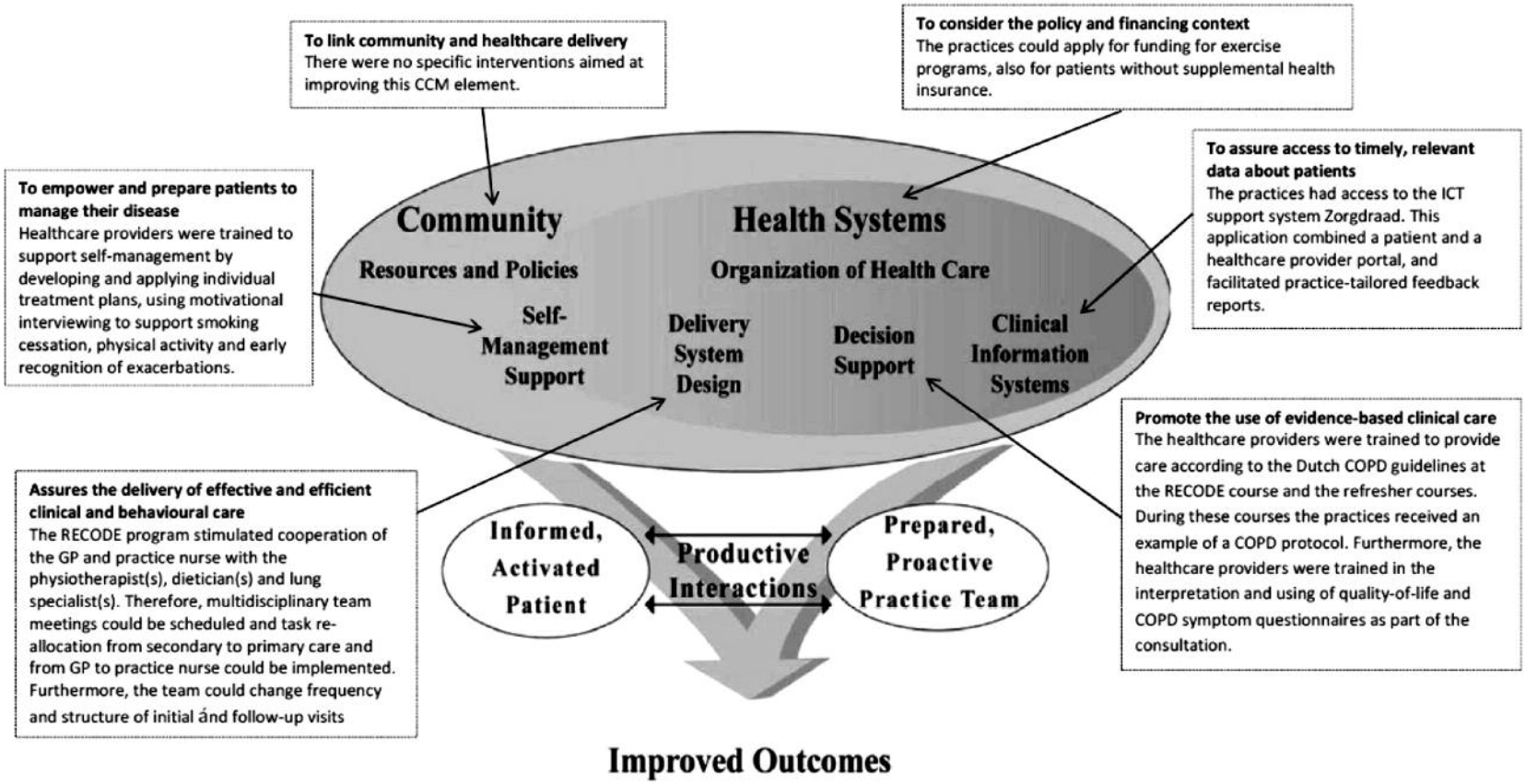
METHODS

Intervention

RECODE is a two-year cluster-RCT in which 40 primary care teams were randomised to DM or usual care.[165] The 20 intervention teams received a two-day training course in essential elements of effective COPD-DM. These elements are grouped by components of the Chronic Care Model (CCM), and described in Figure 5.1. The CCM is often used as conceptual framework for development and evaluation of DM programs.[76,78,79,161] The core of the CCM is the productive interaction between informed, activated patients and prepared, proactive teams of caregivers.[102] RECODE included interventions to improve five of the six interrelated CCM components. After the course, the teams were invited to join two refresher courses and had access to the ICT system 'Zorgdraad'. All teams were encouraged to write their own reform plan and tailor implementation strategies to their local circumstances. Therefore, the package of interventions that patients received was not only dependent upon their health status, personal needs, and preferences, but also on local adaptation and level of implementation of interventions.

The ICT system 'Zorgdraad' included a patient portal and a healthcare provider portal, but was not an e-consultation system. The patient portal contained educational material, had a section containing personal treatment goals and room to write down personal notes. The provider portal

Figure 5.1 The RECODE interventions grouped by the components of the Chronic Care Model from Wagner and colleagues 2001



had room for a protocol to guide frequency and content of COPD monitoring, entering quality of life scores and results from follow-up and examinations. Information from Zorgdraad was used to generate practice-tailored feedback reports on patients' health outcomes at baseline, six and twelve months. These reports were generated by the researchers and sent to the practices to support prioritizing the healthcare needs. It was intended that practice nurses would give the COPD patients instructions and information through the patient-portal.

Participants

The 20 intervention teams included at least one general practitioner (GP), one practice nurse, and one physiotherapist specialised in COPD care. Thirteen teams also included a dietician. The teams enrolled 554 COPD patients, according to Global Initiative for COPD (GOLD) guidelines[15] and because few exclusion criteria were applied, they represent the primary care COPD population in the Netherlands.[165]

Setting

In the Netherlands, GPs act as gatekeepers to hospital care; patients need a referral from the GP to visit a specialist in a hospital clinic.[186] Hence, the vast majority of COPD patients is treated by the GP. The Ministry of Health activity has been stimulating the implementation of integrated care programs for chronic diseases such as COPD for quite some time. This was reinforced by the introduction of a bundled payment system in 2010.[83] This has strengthened the collaboration between different primary care professionals involved in COPD care. Primary care practice nurses play a key role in providing integrated care. A practice nurse is a new profession that was introduced in the early 2000s and several tasks formerly performed by GPs were shifted towards this nurse.[186] The majority (80%) of the practice nurses have a general background in nursing and received additional training in one of more particular chronic diseases. They are predominantly involved in the care for chronically ill patients. For COPD patients this includes for example periodic monitoring, spirometry testing, inhalation instructions, smoking cessation counselling, coaching patients to become more physically active, and teaching patients to recognize exacerbations early.[187] At present, 80% of the Dutch practices, which have an average practise size of 2,350 patients, has at least one practice nurse who takes care of chronically ill patients for at least two days a week.

Implementation

The level of implementation was measured directly with a self-developed scale. The scale measured the implementation of 19 interventions in five CCM components that were included in the RECODE program (Appendix 5.1). Three researchers independently assessed whether an intervention was actually implemented (score=1) or not (score=0) and disagreements were discussed in a consensus meeting. The sum of these 19 scores comprised the total score on the self-developed scale. The information that the researchers used to score the scale was obtained from a questionnaire administered to the teams after one year and a semi-structured telephone interview with the teams after two years. Questions were asked about COPD care before RECODE, changes in COPD care as a result of RECODE and barriers to and facilitators of implementation. The interviews were recorded and transcribed verbatim. Finally, information was recorded on attendance of professionals at the training and refresher courses, ICT use, and use of additional reimbursement for physiotherapy.

The level of implementation was also measured indirectly through the assessment of the level of integrated care that was achieved. The latter was measured from the patient's perspective with the Patient Assessment Chronic Illness Care (PACIC) Questionnaire[188] at baseline,6,9,12,18, and 24 months (ranging from 1 (lowest level) to 5 (highest level)) and the healthcare provider's perspective, using the Assessment of Chronic Illness Care (ACIC) (ranging from 0 to 11, with 11 representing optimal care) at baseline and twelve months.[143]

Barriers and facilitators

Reported barriers and facilitators of implementation were categorised as individual, social, organisational, or broader societal factors.[189] Individual factors were related to caregivers and consisted of cognitive, motivational, and behavioural factors, as well as personal characteristics including health status. Social factors were related to professional teams/networks. Organisational factors included the organisational structure, culture, and work processes, as well as the availability of necessary resources. Societal factors related to the healthcare system and societal and political developments.

Starting level

We distinguished three starting levels: (1) ad-hoc reactive COPD care, (2) structural diagnosis of COPD patients, and (3) structural diagnosis ánd proactive follow-up of COPD patients. Teams with 'ad-hoc reactive COPD care' had (virtually) no DM. For these teams, RECODE marked the start of structured COPD care. Teams with 'structural diagnosis of COPD pa-

tients' had begun to structure their COPD care, performed spirometry, and had an overview of the COPD population in their practice. Teams with 'structural diagnosis ánd proactive follow-up of COPD patients' additionally had an established control-visit/follow-up structure, and applied strategies to support self-management.

Health outcomes

We measured health-related quality of life on the Clinical COPD Questionnaire (CCQ),[30] St. George Respiratory Questionnaire (SGRQ),[168] and the EuroQoL-5 dimension questionnaire (EQ-5D).[139,190] We measured dyspnoea by the Medical Research Council (MRC) dyspnoea score with a scale from 1 to 5,[191] physical activity by the International Physical Activity Questionnaire,[141] and self-management abilities by the components 'taking initiatives', 'investment behaviour', and 'level of self-efficacy' from the Self-Management Ability Scale-30 (SMAS-30).[140] The questionnaires were administered at baseline and 6,9,12,18, and 24 months.

Statistical analysis

Descriptive statistics of patients' and teams' characteristics were calculated. We used two-tailed, paired t-tests to investigate improvements in the level of integrated care as measured by the PACIC and the ACIC.

During the RECODE study, there is a variation in changed outcomes in the intervention group.[164] In this study we investigated the association between variation in implementation as measured with our own developed scale and ACIC and change in health outcomes within the same time period using two-level (patients nested in teams) linear mixed-effect models, correcting for starting score of different health outcomes and starting level of COPD care. To investigate the impact of the level of implementation as measured with the PACIC on change in health outcomes within the same time period, we used three-level (longitudinal measurements nested in patients nested in primary care teams) linear mixed-effect models, correcting for time, starting score of different health outcomes, and starting level of COPD care. We used six time points (baseline, 6, 9, 12, 18 and 24 months) to estimate the impact of implementation as measured with the PACIC. These models were specified for eight dependent variables: change in CCQ , SGRQ , EQ-5D, MRC, MET minutes, taking initiatives, investment behaviour, and self-efficacy.

RESULTS

Table 5.1 summarises the characteristics of the teams and their COPD patients. Each team enrolled 11–55 patients and 53 percent of the teams were delivering ad-hoc reactive care.

The telephone interviews were held with five GPs and 17 practice nurses from 17 of the 20 (85%) teams. These interviews varied in length between 20 and 45 minutes. Three (15%) teams could not be interviewed because the participating caregiver(s) had left or changed practice or because the caregiver(s) lacked time. The response rate of the questionnaires can be found in Appendix 5.2.

Table 5.1 Sample characteristics

CHARACTERISTICS OF THE PRIMARY CARE TEAMS (N=20)	
Practice location, urban, n (%)	14 (70)
Practice type, Single-handed practice, n (%)	8 (40)
Practice type, One or more partner practice, n (%)	9 (45)
Practice type, Healthcare centre, n (%)	3 (15)
Patient practice population, n (range)	3900 (1900-8100)
Participating COPD patients, (range)	28 (11-55)
Ethnic minorities, %	16 (1-60)
Years practicing GP, y	13 (3-25)
Starting level*,	
- ad-hoc reactive COPD care, n (%)	9 (53)
- structural diagnosis of COPD patients, n (%)	4 (24)
- structural diagnosis ánd proactive follow-up of COPD patients, n (%)	4 (24)
PATIENT CHARACTERISTICS (N=554)	
Men, %	50.5
Age (mean, SD)	68.2 (11.3)
GOLD stage I, %	25.3
GOLD stage II, %	52.6
GOLD stage III, %	19.0
GOLD stage IV, %	3.1
CCQ (mean, SD)	1.54 (0.98)
SGRQ (mean, SD)	36.7 (21.1)
EQ-5D (mean, SD)	0.74 (0.25)
MRC (mean, SD)	2.06 (1.30)
MET minutes (mean, SD)	3101 (4652)
SMAS, taking initiatives (mean, SD)	56.8 (18.1)
SMAS, investment behaviour (mean, SD)	61.4 (17.0)
SMAS, self-efficacy (mean, SD)	66.0 (17.2)*

tarting level was missing in 3 teams; *CCQ* Clinical COPD Questionnaire, *SGRQ* St. George's Respiratory Questionnaire,*EQ-5D* EuroQoL-5D, *MRC* Medical Research Council, *MET* metabolic equivalent time, *SMAS* Self-Management Ability Scale.

Implementation

The teams implemented, on average, 8 of the 19 interventions (range: 2–14, Table 5.2). The most frequently applied interventions were cooperation with physiotherapist(s) (88%), exacerbation management (76%), and active identification and monitoring of high-risk COPD patients (71%). Only a few teams improved cooperation with lung specialist(s) (18%), substituted care from secondary to primary care (24%), actively applied motivational interviewing to improve self-management (18%), and used additional funding for physiotherapy (12%). In the second study year, none of the teams used Zorgdraad. Teams with a lower starting level implemented, on average, more interventions than teams with a higher starting level.

The total PACIC score, did not significantly change over the study-period (Table 5.3). However, the PACIC component 'decision support' significantly decreased. Even though the total ACIC score did not significantly change, the ACIC components 'organization of healthcare system', 'community linkages', and 'self-management' significantly improved over the first year.

Table 5.2 Implementation of 19 interventions of integrated COPD care over 2 year follow-up period per primary care team

Interventions / Teams	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV	XV	XVI	XVII	Total
Delivery system design																		
Improved cooperation with physiotherapist(s)	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	**15**
Improved cooperation with dietician(s)	0	0	0	0	1	1	0	1	1	1	1	0	1	1	1	1	0	**10**
Improved cooperation with lung specialist(s)	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	1	0	**3**
More multidisciplinary PCT meetings	0	0	1	0	0	0	0	0	0	1	0	0	0	1	0	1	1	**5**
Task re-allocation from GP to practice nurse or specialized nurse	0	1	0	1	0	0	0	1	0	0	0	1	0	0	1	1	1	**7**
Substitution of care from secondary to primary care	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	1	1	**4**
Change in follow-up and visit structure	0	0	0	0	1	0	0	1	0	0	1	1	1	1	1	1	1	**9**
Decision support																		
Attendance of four disciplines at the initial RECODE course	0	0	1	0	0	0	1	1	0	1	1	1	0	1	0	1	1	**9**
Attendance of two or more disciplines at the RECODE refresher day(s)	1	0	0	0	0	1	0	0	1	0	0	1	0	1	1	1	1	**8**
Implementation / amending COPD protocol	0	0	0	0	0	0	0	0	0	0	1	0	1	1	1	1	1	**6**
More use of results from quality-of-life and COPD symptom questionnaires as part of consultation	0	1	0	0	1	1	0	0	1	1	1	1	1	0	1	1	1	**11**
Self-management strategies																		
More individual treatment plan are developed	0	0	0	0	0	0	1	0	1	1	1	1	1	1	1	0	1	**9**
Change in smoking cessation support	0	1	0	0	0	0	0	0	1	0	0	0	1	1	0	0	0	**4**
Early recognition of exacerbations	0	0	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	**13**
Change in motivational interviewing	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	**3**
Clinical information system																		
Initial use of the ICT support system Zorgdraad	0	0	0	0	0	1	1	0	1	1	0	1	0	1	0	1	1	**8**
Sustained use of the ICT support system Zorgdraad	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**0**
Change in active identification and monitoring of high risk COPD patients inside the practice e.g. using feedback reports	1	0	0	1	1	1	0	1	0	1	1	1	1	1	1	0	1	**12**
Healthcare system																		
Additional funding for physiotherapy	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	**2**
Total implementation score	**2**	**4**	**4**	**4**	**6**	**6**	**7**	**7**	**8**	**9**	**9**	**10**	**11**	**12**	**12**	**13**	**14**	
Starting level	**3**	**1**	**3**	**1**	**3**	**1**	**2**	**2**	**2**	**3**	**1**	**1**	**2**	**1**	**1**	**1**	**1**	

Table 5.3 Level of integrated care experienced by the patients (PACIC) and healthcare provider (ACIC)

	Baseline		12 Months		24 Months		Difference over 1 year		Difference over 2 year	
	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
PACIC (N=436 (baseline), N=457 (12 months), N=353 (24 months))										
Patient activation	2,31	1,26	2,29	1,14	2,33	1,16	-0,03	1,34	-0,08	1,34
Decision support	2,91	1,15	2,73	1,13	2,75	1,11	-0.19**	1,17	-0.25**	1,14
Goal setting	2,12	1,01	2,16	0,98	2,17	0,97	0,05	1,05	-0,05	1,03
Problem solving	2,22	1,15	2,26	1,13	2,27	1,15	0,04	1,18	-0,06	1,17
Follow-up	1,83	0,9	1,93	0,93	1,99	0,96	0.12*	0,98	0,08	0,96
Total PACIC score	2,28	0,95	2,26	0,94	2,31	0,96	-0,05	0,95	-0,05	0,95
ACIC (N=20 (baseline), N=13 (12 months))										
Organization of Healthcare System	5,49	2,57	6,63	1,67	-	-	1.32*	2,07	-	-
Community Linkages	4,94	2,25	5,89	2,07	-	-	1.23*	1,53	-	-
Self-management	5,09	1,65	6,37	1,55	-	-	1.55*	1,87	-	-
Decision support	6,12	1,81	6,59	0,93	-	-	0,47	1,7	-	-
Delivery System design	6,24	1,96	6,32	1,54	-	-	0,32	2,06	-	-
Clinical information system	5,31	2,18	5,68	1,19	-	-	-0,04	1,98	-	-
Integration score	4,61	1,79	4,97	1,38	-	-	0,45	2,18	-	-
Total ACIC score	5,41	1,73	6,07	1,10	-	-	0,75	1,44	-	-

*P<0.05 **P<0.01, *PACIC* Patient Assessment Chronic Illness Care, *ACIC* Assessment Chronic Illness Care

BARRIERS AND FACILITATORS

Table 5.4 summarises the barriers and facilitators to implementation as they were perceived by the teams grouped into individual, social, organisational and broader societal factors. These groups were not mutually exclusive.

Table 5.4 The encountered barriers and facilitators of the multidisciplinary teams to their implementation of the RECODE program

FACILITATORS	BARRIERS
INDIVIDUAL FACTORS	
> Improved knowledge of healthcare providers > Motivated healthcare providers to change COPD care	> Unmotivated patients to change lifestyle due to underestimation of COPD symptoms > Unmotivated healthcare providers to use 'Zorgdraad' due to unclear instructions, the inconvenient system and a lack of time to determine how 'Zorgdraad' worked.
SOCIAL FACTORS	
> The implementation experiences of the teams motivated and inspired other teams	> Variability in adoption of 'Zorgdraad' between team members jeopardized the potential contribution of the ICT system to their purposes.
ORGANISATIONAL FACTORS	
> Low starting level of integrated care result in room for improvements > The practice-tailored feedback reports on patients' health outcomes develop insight into own routines and patients' needs	> Lack of adherence to the agreements between primary and secondary care > Small proportion of COPD patients who are in need for multi-disciplinary treatment > Staff turnover who followed the RECODE course(s) Problems with transferring information from ZORGDRAAD onto the different clinical information system the practices used
BROADER SOCIETAL FACTORS	
> Better guidance and/or financial arrangements arranged by the care group to improve COPD care	> Lack of reimbursement of exercise programs and nutritional support > Reimbursement of smoking cessation counselling and medication conditional on certain factors; when provided by healthcare providers who are registered as smoking cessation counsellors

Individual factors

Caregivers were positive about the RECODE course, stating that it was informative, increased attention to COPD, and inspired and motivated them to improve COPD care. For instance, thirteen teams reported a greater awareness of early recognition of exacerbations and many teams implemented symptom-reporting policies to increase early treatment of exacerbations. Teams also fine-tuned self-management which were already (partly) integrated. For instance, most teams were familiar with motivational interviewing and individual treatment plans but not every plan was put in writing or was made in consultation with the patient.

A barrier of implementation was the lack of motivation of patients. Several teams reported difficulties in persuading COPD patients to adopt healthier behaviour because they did not feel ill or did not experience (many) problems. Furthermore, due to the lack of patients' motivation, familiarity with computers and obligation to use web-based applications, few patients used Zorgdraad. The lack of motivation or time to determine how Zorgdraad worked was also an important barrier for caregivers to use Zorgdraad.

Social factors

During the refresher courses, the teams discussed their implementation experiences with other teams. That way they motivated, inspired and learned from each other. These presentations were generally appreciated, although some were dissatisfied that presenters had begun implementation rather late, as a result of which they had little experience to share.

The professional network in which the teams operated was also a barrier of implementation. For instance, inconsistent use of Zorgdraad among team members jeopardized the potential contribution of Zorgdraad to their purposes.

Organisational factors

Teams with a lower starting level had more room for improvements. For example, only teams with no structured COPD care developed new protocols. Furthermore, four teams changed smoking cessation support because most teams reported that this was already integrated in their COPD care. Moreover, four teams did not re-allocate tasks from the GP to the practice nurse because they reported that most of the COPD care had already been re-allocated to the practice nurse.

The implementation was also facilitated by the feedback reports on the health outcomes of their patients that each practice received. Several teams indicated a better overview and greater ability to manage progression of their COPD patients. In this way the reports helped to actively track high-risk COPD patients.

Four teams reported changes in referring patients to primary/secondary care. Three teams explicitly discussed referral criterion while in one team the lung specialist noticed changes in primary care and referred more patients back without explicit deliberation. A barrier for task re-allocation from secondary to primary care was that not every lung specialist adhered to the new agreements.

The main barriers for improving cooperation with the dietician were the low proportion of patients who were eligible to be referred for nutritional support. The low number of patients and staff turnover was also reported as reasons for not using Zorgdraad and organizing periodically scheduled multidisciplinary meetings. Additionally, problems with transferring information to the team's information system was an important barrier of Zorgdraad.

Broader societal factors

A bundled payment scheme for COPD patients was introduced in the Netherlands, almost simultaneously with the start of RECODE.[83] Since this reform, health insurers purchase integrated multidisciplinary COPD care from care groups. As a result the focus on COPD care increased, financial coverage improved, and/or secondary caregivers became more involved. This facilitated the implementation of RECODE. However, three teams reported that they abandoned or temporarily stopped with RECODE because they had to concentrate on preparing the integrated care program as was purchased by the insurer and the formal installation of a care group. A care group is a legal entity, usually owned by GPs, which subcontracts individual professionals to provide care.

The lack of full reimbursement of physiotherapy and smoking cessation support was an important barrier for patient participation in these RECODE components. The lack of reimbursement of physiotherapy was partly solved by the RECODE research team, which arranged supplementary funding by healthcare insurers for COPD-specific exercise training programs for patients with a MRC Dyspnea score>2, including those without supplementary health insurance. The reason for the limited use (12%) of the funding remains unclear. One respondent stated that the funding was not used because attention to RECODE declined, and many patients did not qualify for the reimbursement.

ASSOCIATION BETWEEN LEVEL OF IMPLEMENTATION AND HEALTH OUTCOMES

Table 5 shows the association between the level of implementation of RECODE (as measured either by our own implementation scale, by the change in PACIC and the change in ACIC) and the change in health out-

comes within the same time period. A higher level of integrated care as measured by the self-developed scale was not associated with better health outcomes (Table 5.5). The indirect assessment of implementation, measured as the change in the level of integrated care from the patient's perspective (PACIC), was associated with a significantly higher 'SMAS, taking initiatives' score and a significantly higher 'SMAS, investment behaviour' score. For example, one unit improvement in PACIC score between baseline and 24 months was associated with a 1.2 unit improvement in 'SMAS taking initiative score' between baseline and 24 months. This association was not found in other health outcomes. Over the one-year study period, the total score on changed level of integrated care from the healthcare provider's perspective (ACIC), was not associated with better health outcomes. Within the subgroup of patients with a clinically relevant improvement on the CCQ or SGRQ , a higher level of integrated care (self-developed scale, PACIC or ACIC) was not associated with better health outcomes.

Table 5.5 Multilevel models: influence of implementation on change in outcomes

	SELF-DEVELOPED		**SCALE†**		**Δ PACIC‡**	**Δ ACIC†**
	ß	N	β	N	β	N
Δ CCQ	0,001	327	-0,021	1629	0,004	297
Δ SGRQ	-0,138	308	-0,119	1624	0,492	284
Δ EQ-5D	0,004	330	-0,001	1701	-0,016	280
Δ MRC	0,074	345	-0,037	1733	-0,02	287
Δ MET minutes	94	310	173	1710	390	250
Δ SMAS, Taking initiatives	0,01	309	1,211**	1719	1,004	251
Δ SMAS, Investment behaviour	-0,228	310	1,349**	1712	0,781	252
Δ SMAS, Self-efficacy	-0,013	308	0,592	1708	0,443	252

* Significant (p<0.05), ** Significant (p<0.01), † Two-level models (patients nested in teams), correcting for starting score of different health outcomes and starting level of COPD care, ‡ Three-level models (measurement occasions nested in patients nested in teams), correcting for time, starting score of different health outcomes, and level of COPD care,
PACIC Patient Assessment Chronic Illness Care, *ACIC* Assessment Chronic Illness Care, *CCQ* Clinical COPD Questionnaire, *SGRQ* St. George's Respiratory Questionnaire, *EQ-5D* EuroQoL-5D, *MRC* Medical Research Council, *MET* metabolic equivalent time, *SMAS* Self-Management Ability Scale.

DISCUSSION

Main findings

This study showed that a pragmatic (non-experimental) implementation of a COPD-DM program resulted in a low level and a wide variety of implementation across different teams. Important barriers of implementation were insufficient motivation of patients, high starting level of COPD care, small size of the COPD population per team, mild COPD population, practicalities of the ICT system and hurdles in the reimbursement. Level of implementation as measured with our own scale and the ACIC was not associated with health outcomes. A higher level of implementation measured with the PACIC was positively associated with improved self-management capabilities, but this association was not found for other outcomes.

Strengths and limitations

This study has several strengths. First, a broad range of outcome measures and implementation measurements including different perspectives were used. Second, independent scoring of the self-developed scale ensured the objectivity of the results. Third, the interviewer was not involved in the core research team, which reduced pressure to give desirable answers. This study also has several weaknesses. It was not possible to compare the implemented interventions of the intervention teams with the control teams because, to prevent an additional intervention effect, we did not evaluate changes in COPD care in the control group. Therefore, it was not always possible to determine whether changes were caused by RECODE or other factors, such as parallel projects. Second, most interviews were held with only one representative of the team. However, we interviewed practice nurses or GPs, who were the project leaders and provided the best overview of COPD care in their team. Third, the response rate on the ACIC questionnaire at 12 months was low (65%). However, the ACIC score at baseline did not differ much between the responders and the non-responders.

Relation to previously published work

In line with previous pragmatic studies,[192,193] the teams implemented various interventions, but none implemented all interventions. Indeed, on average, less than half (42%) of the interventions were implemented despite the fact that the individual interventions has been shown to improve health outcomes.[4,76,78,161] These findings further support the idea of Pinnock e.a.[194] who suggest that after proven efficacy, the translation of interventions into a practical service should be evaluated in an implementation study. This translation seems to result in lower but more realistic outcomes of the interventions[195,196]

RECODE was facilitated by informed and motivated caregivers, which corroborates an earlier study.[184] Despite this, the caregivers were not able to implement all interventions. In addition, they become demotivated because Zorgdraad was not adequately functioning on time.

COPD patients were not always motivated to change; as COPD patients perceive their suboptimal health status as 'normal', COPD had become a way of life.[197] Excluding unmotivated patients may improve the (cost-)effectiveness of COPD-DM programs. Specific interventions to change the motivational status of patients are therefore required.

A barrier for implementation was the low potential for improvement due to the high starting level of COPD care and the mild COPD population. The absence of improvements due to already high levels of COPD care was pointed out in earlier primary care trials.[12,198]

The perceived usefulness of Zorgdraad was low. The teams that did use Zorgdraad experienced problems with practicalities and variability in adoption of the system between team members. Furthermore, teams reported unclear instructions and a lack of time or motivation to determine how Zorgdraad worked. A large review corroborates that usefulness, compatibility with work and time were important barriers for implementation of an ICT system.[199]

The last important barrier of implementation was the hurdles in reimbursement. As teams reported the formation of care groups as facilitator, the ongoing wide implementation of the bundled payment system in the Netherlands might be a step in the good direction of solving the reimbursement issues. In this system healthcare insurers purchase integrated multidisciplinary COPD care from care groups.[63] However, in practice the financed package varies widely and therefore, not all multidisciplinary care required by a COPD patient is included.[200]

In accordance with our results, previous studies have demonstrated that an improved PACIC score, improved self-management.[192,201] Despite this, our self-developed scale or ACIC score was not associated with better health outcomes. Therefore, implementation of only a few interventions by some teams does not, however, guarantee improvements in patients' outcomes in comparison with other teams.

Implications

This study showed that a pragmatic COPD-DM program that primarily targets caregivers seems to result in only modest improvements in care. We learned that focus should be more on patient-oriented interventions. Hence, multiple COPD-DM programs have shown that patient-oriented interventions or a combination of patient-oriented, provider-oriented, and organisational interventions lead to significant improvements in

health outcomes.[192,202] Furthermore, the interventions should be tailored to patients' needs, skills and preferences which will imply that, on average, a COPD-DM program for milder COPD patients will include less or less intensive interventions than a COPD-DM program for more severe patients.

The room for improvement and the proportion of motivated patients is higher among a selection of COPD patients with a high disease burden. However, focussing on more severe COPD reduces the number of patients who participate in the program. Consequently, the motivation of professionals to invest time in optimizing the program and negotiating with health insurers on reimbursement of the program, may decrease. It is a challenge for further programs to find the right balance between sufficient room for improvement and economies of scale. In finding this balance, we should account for the fact that long-term gains can be increased if we can prevent moderate COPD patients to progress to severe COPD.

CONCLUSIONS

This study adds valuable input to the discussion on development and implementation of COPD-DM programs. We observed a low level and wide variability of implementation across different primary care teams. Barriers and facilitators of the implementation were related to factors at individual, social, organisational, and broader societal level. There was little association between level of implementation and improved health outcomes.

Appendix 5.1 Detailed description of the different interventions and results of the RECODE program

INTERVENTION	EXPLANATION OF RESULT
DELIVERY SYSTEM DESIGN	
Improved cooperation with physiotherapist(s)	The practice nurse, GP and physiotherapist(s) have agreed on the indications of referral, communication regarding patients, coordination of the treatment of COPD patients.
Improved cooperation with dietician(s)	The practice nurse, GP and dietician(s) have agreed on the indications of referral, communication regarding patients and coordination of the treatment of COPD patients.
Improved cooperation with lung specialist(s)	The practice nurse, GP and lung specialist(s) have agreed on the indications of referral, communication regarding patients and coordination of the treatment of COPD patients.
More multidisciplinary team meetings	Scheduled meetings regarding individual COPD patients, exchanging medical knowledge, and/or organisation of care with at least the GP, practice nurse and physiotherapist are organized
Task re-allocation from GP to practice nurse or specialized nurse	The practice nurse has taken over tasks that were tasks of the GP before the start of the RECODE study.
Substitution of care from secondary to primary care	Primary healthcare providers have taken over tasks that were tasks of secondary healthcare providers before the start of the RECODE study.
Change in follow-up and visit structure	Patients visit the practice nurse or GP according to a structural follow-up plan.
DECISION SUPPORT	
Attendance of four disciplines at the initial RECODE course	Four different disciplines of healthcare providers (GP, practice nurse, physiotherapist, dietician) of the team attended the RECODE course.
Attendance of two or more disciplines at the RECODE refresher day(s)	Two or more healthcare providers from different disciplines attended the reunion.
Implementation / amending COPD protocol	The original COPD protocol is adapted or a new COPD protocol is developed and implemented.
More use of results from quality-of-life and COPD symptom questionnaires as part of consultation	The practice nurse started to use quality of life questionnaires (e.g. Clinical COPD Questionnaire (CCQ) or MRC) in consults with patients
SELF-MANAGEMENT STRATEGIES	
More Individual treatment plan are developed	Patients and practice nurses or GPs begun to jointly formulate personal goals and these goals are recorded in the patient's file.
Change in smoking cessation support	The practice nurse or GP pays different/more attention to smoking cessation than before the start of the RECODE study.

Early recognition of exacerbations	The practice nurse or GP pays more attention to teaching patients the early recognition of and the way to respond to exacerbations than before the start of the RECODE study.
Change in motivational interviewing	The practice nurse or GP started to use the motivational interviewing technique (more often) to understand and make use of patients' personal goals in physical reactivation and lifestyle changes.
CLINICAL INFORMATION SYSTEM	
Initial use of the ICT support system Zorgdraad	The healthcare provider(s) actively tried to use Zorgdraad by logging in on Zorgdraad and receiving individual instructions from an ICT implementation expert.
Sustained use of the ICT support system Zorgdraad	Using Zorgdraad after 12 months
Change in active identification and monitoring of high risk COPD patients inside the practice e.g. using feedback reports	Active identification and monitoring of high risk patients inside the practice (on basis of the feedback reports).
HEALTHCARE SYSTEM	
Additional funding for physiotherapy	The practice used the supplementary funding provided by the local healthcare insurer for a COPD-specific exercise training program for RECODE patients with MRC scores >2.

Appendix 5.2 Response rate

Health outcomes	N (%) at baseline	N (%) at 12 months	N (%) at 24 months
PATIENT			
PACIC	436 (79)	457 (82)	353 (64)
CCQ	553 (100)	515 (93)	394 (71)
SGRQ	550 (99)	496 (90)	372 (67)
EQ-5D	546 (99)	498 (90)	408 (74)
MRC	553 (100)	499 (90)	418 (75)
MET minutes	515 (93)	472 (85)	395 (71)
SMAS, Taking initiatives	518 (94)	476 (86)	391 (71)
SMAS, Investment behaviour		517 (93)	475 (86) 391 (71)
SMAS, Self-efficacy	516 (93)	473 (85)	391 (71)
HEALTHCARE PROVIDER			
12-month questionnaire	-	13 (65)	-
ACIC	20 (100)	13 (65)	-

PACIC Patient Assessment Chronic Illness Care, *CCQ* Clinical COPD Questionnaire, *SGRQ* St. George's Respiratory Questionnaire, *EQ-5D* EuroQoL-5D, *MRC* Medical Research Council, *MET* metabolic equivalent time, *SMAS* Self-Management Ability Scale, *ACIC* Assessment Chronic Illness Care

CHAPTER 6

Does registration of performance indicators improve health outcomes in COPD?: a post-hoc analysis of the RECODE cluster randomised trial.

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ABSTRACT

Background: Performance-based financial incentives for healthcare providers have been introduced to facilitate the implementation of integrated care programs. The aim of these programs is to enhance patients' health by improving quality of care. Performance indicators are used to measure quality of care and reward healthcare providers. However, the real benefit to patients remains largely uncertain.

Aim: To investigate (I) if implementation of an integrated care program improves performance indicators and subsequently (II) if improved performance indicators lead to improved health outcomes.

Methods: This is a sub-study of the Dutch RECODE cluster-randomised controlled trial, the largest clinical trial of an integrated care program for Chronic Obstructive Pulmonary Disease (COPD) patients in primary care to date. From 38 Dutch GPs, we collected three-year prospective data on performance indicators and health outcomes (smoking status, physical activity, health-related quality-of-life (HRQoL)) of 913 COPD patients. Multi-level repeated measures models were used to analyse the data.

Results: COPD performance indicators improved over time and these improvements were higher in the integrated care group, indicating improved quality of care. Four indicators (registered BMI, physical activity, functional status, and spirometry test) were associated with an immediate improvement (in the same year) in disease-specific HRQoL. The latter indicator and the indicator 'inhalation technique checked' had a delayed impact on HRQol (improvement in the next year). The indicators related to smoking did not affect health outcomes.

Conclusions: The RECODE program did improve COPD performance indicators of the quality of care and some of these indicators were predictive of improved HRQoL.

INTRODUCTION

Many countries have introduced performance-based payments schemes to facilitate the implementation of integrated care programs.[63] These schemes generally provide incentives to healthcare providers to improve performance indicators that measure processes of care and intermediate health outcomes.[203] In the United States (US), the private healthcare insurer Blue Cross Blue Shield of Massachusetts implemented a case-mix adjusted global payment system with two-sided financial risk sharing called the Alternative Quality Contract (AQC), which pays providers a bonus for quality since 2009.[204] In England, healthcare providers receive financial rewards up to 30% of their salary for achieving indicator thresholds set out in the Quality and Outcome Framework (QOF) since 2004.[205,206] In the Netherlands, the Dutch College of General Practitioners (NHG) developed lists of performance indicators for various diseases.[207] These lists are increasingly used in contract negotiations between insurers and providers of integrated care programs. Moreover, since 2015 there is a new payment scheme introduced for general practices in the Netherlands with includes financial incentives to reward quality and innovations (which will cover approximately 5-10% of the total practice costs).[208]

The justification for incentivizing healthcare providers to improve processes is the assumption that improved quality of care leads to improved health outcomes. A key assumption in the causal pathway is that improvements in performance indicators alter the decision-making process of the healthcare providers, especially regarding treatment decisions.[64–66] Audit, feedback and public reporting of performance indicators, linked with financial incentives are mechanisms to stimulate these changes. Review studies have shown that performance indicators may be effective in improving quality of care. However, the real benefit to patients remains largely uncertain.[67–69]

The aim of this study is twofold. The first is to investigate if a Dutch integrated care program improves performance indicators. The second is to investigate the impact of performance indicators on health outcomes. These questions were addressed within the context of the RECODE study, the largest clinical trial of an integrated care program for Chronic Obstructive Pulmonary Disease (COPD) patients in primary care to date.[164,165] As part of this study we collected three-year prospective data on performance indicators (one year before the start of RECODE and two-years during the RECODE study period) and periodically assessed patients' reported outcomes.

METHODS

Setting

RECODE was a two-year cluster randomised trial including 20 primary care teams who were randomised to the intervention group that implemented an integrated care program and 20 teams who were randomised to the usual care group. From these 40 teams we recruited 1,086 patients with physician-diagnosed COPD according to GOLD guidelines.[15] Exclusion criteria were terminal illnesses, dementia, cognitive impairment, inability to complete questionnaires in Dutch, and hard drug or alcohol abuse. Other co-morbidity was not an exclusion criterion. The COPD patients in the RECODE trial were found to be representative of the COPD population treated in primary care in the Netherlands. All participants provided written informed consent before participation and the study was approved by the medical ethics committee of the Leiden University Medical Centre. Practices and patients were recruited between 2010 and 2011. Design and full clinical results of this study have been reported elsewhere.[164,165]

Performance indicators

From the NHG list of COPD performance indicators[207], we were able to extract the following indicators from the electronic medical record systems (EMRs) of the general practitioners (GPs): if smoking status was registered, if patient was a registered smoker, if a registered smoker had a smoking-cessation advice in the last year, if BMI was registered in the last year, if physical activity was registered in the last year, if the inhalation technique was checked in the last year, if a spirometry test was done in the last year, if functional status was monitored with a structured method such as the Clinical COPD Questionnaire (CCQ)[30], Medical Research Council (MRC) dyspnoea questionnaire[191] or Respiratory Illness Questionnaire-MOnitoring (RIQ-MON)[209] in the last year. For each patient, we extracted whether the performance indicator was positive (score=1=yes) or negative (score=0=no). Note that only the indicator 'is patient a smoker' is an outcome indicator; all other indicators are process indicators.

Health outcomes

Health-related quality of life (HRQoL) was measured using the three-level EuroQol-5D (EQ-5D)[190], Saint George Respiratory Questionnaire (SGRQ)[119] and Clinical COPD Questionnaire (CCQ).[30] The EQ-5D is a generic HRQoL instrument and the SGRQ and CCQ are COPD-specific instruments. The level of physical activity was calculated from the International Physical Activity Questionnaire (IPAQ) by multiplying the

frequency and duration of walking, moderate-intensity activities, and vigorous-intensity activities in terms of the energy requirements, to yield a score in metabolic equivalent time (MET) minutes.[141] These questionnaires were administered as part of the RCT and in the current study we used the measurements at baseline, 12 and 24 months. Smoking status (smoker or no smoker) was extracted from the EMR of the GPs, as mentioned above.

Intervention

The 20 teams of the intervention group started with a two-day multidisciplinary course in essential components of integrated COPD care according to the national and international guidelines: adequate diagnosis and treatment, motivational interviewing, smoking cessation counselling, applying self-management plans including early recognition and treatment of exacerbations, physical (re)activation, and nutritional support. In addition, the teams learned the details of a web-based computer program for measuring and reporting process and outcome data, named ZORGDRAAD. This ICT program included a patient and provider portal that facilitated the communication within the multi-disciplinary teams as well as between caregivers and patients. At the end of the course, each team developed a plan with steps to be taken in order to redesign the COPD care. To ensure implementation of these plans, the teams were invited to join refresher courses, received regular feedback reports on patients' outcomes, had access to the ICT system ZORGDRAAD and the local healthcare insurer solved the problem that not all patients had insurance for physiotherapy by offering reimbursement of physical reactivation by a physiotherapist. Healthcare providers in the control group were asked to continue practicing care as usual.[165]

Statistical analysis

To assess differences in performance indicators between RECODE and usual care (aim 1) we used three-level (longitudinal measures nested in patients nested in primary care teams) logistic mixed-effects regression models, including an intervention dummy and time (year 0, year 1, year 2). To assess the impact of performance indicators on changes in health outcomes (smoking status, physical activity, HRQoL) during the same year (aim 2), we used three-level linear mixed-effects regression models, including an intervention dummy and starting score of different health outcomes as measured at the beginning of a year. Because there may be a delay between indicator registration and improvement in health outcomes, we also assessed the additional impact of performance indicators and change in health outcomes in the next year, including an interven-

tion dummy, the starting score of different health outcomes and the performance indicators in the same year.

RESULTS

In this sub-study of the RECODE trial, we included 38 of the 40 practices (95%) and 913 of the 1,086 patients (84%) (475 in the RECODE group and 438 in the usual care group). The remaining practices and patients were excluded because data could not be extracted from the EMRs. In Table 6.1 the baseline characteristics of the patients are presented. They were comparable to the characteristics of the entire RECODE population.[165]

Figure 6.1 shows that most performance indicators improved over time. The percentage of patients in which all process indicators were registered was 2.7%, 2.5%, and 4.6% in year 0, 1 and 2, respectively. Interestingly, while the performance on the indicator 'smoking status registered' improved over time, the performance on the indicator 'registered smoker with smoking-cessation advice' decreased over time.

Table 6.2 shows that providing integrated care had a positive effect on the likelihood to register (i) all process indicators, (ii) smoking status, (iii) BMI, (iv) physical activity, (v) inhalation technique, and (vi) spirometry test in the second year but not in the first year. The odds of having functional status monitored with a structured method altered from being significantly higher in the integrated care group in the first year to being significantly lower in the second year.

Table 6.3 shows the impact of the performance indicators on change in health outcomes. Four performance indicators were significantly associated with an improvement in SGRQ during the same year, i.e. BMI registered, physical activity registered, spirometry test done and functional status monitored with a structured method. The latter two were also significantly associated with an improvement in CCQ during the same year. The improvements in CCQ score or SGRQ score do not exceed the minimal clinically important difference of 0.4 points[138] and 4 points[119], respectively. The association between performance indicators and health outcomes was not significantly different between the usual care group and the integrated care group (i.e. interaction terms between performance indicators and treatment group were not statistically significant; data not shown).

The indicators related to smoking did not affect health outcomes and the indicator 'physical activity registered in the last year' did not improve physical activity (Table 6.3).

When assuming a 1-year delay between registration of performance indicators and impact on health outcomes, the association between improved registration and improved disease-specific HRQoL largely disap-

peared. Moreover, the impact of the indicator 'functional status monitored with a structured method' on changes in CCQ score decreased significantly in the next year. However, two indicators, i.e. having inhalation technique checked and spirometry test done, were associated with improvement in generic HRQoL as measured by the EQ-5D.

Table 6.1 Baseline characteristics

	Subset of RECODE population Intervention group (N=475)	Subset of RECODE population Usual care group (N=438)	Subset of RECODE population (N=913)	Total RECODE population (N=1,086)
CHARACTERISTIC	Mean (SD)	Mean (SD)	**Mean (SD)**	Mean (SD)
Age (years)	67.8 (11.0)	68.0 (11.0)	**67.9 (11.0)**	68.3 (11.2)
Gender (Male), %	51.0	56.0	**53.0**	53.9
Employment, %	27.8	29.1	**28.4**	28.3
Low education, %	38.7	40.7	**39.7**	40.3
Mean (SD) FEV_1 % predicted	68.2	67.7	**67.9**	67.8
Current smoker, %	35.9	38.0	**36.9**	36.7
Major cardiovascular disease, %	14.1	15.7	**14.9**	16.1
Hypertension, %	35.2	38.3	**36.7**	36.8
Diabetes, %	13.7	14.3	**14.0**	14.7
Depression, %	9.0	9.6	**9.3**	9.9
CCQ score:	1.5 (0.97)	1.4 (0.93)	**1.5 (0.95)**	1.5 (0.97)
SGRQ score:	35.8 (21.0)	33.2 (19.4)	**34.6 (20.3)**	35.6 (20.5)
EQ-5D score	0.75 (0.25)	0.73 (0.28)	**0.74 (0.26)**	0.74 (0.26)
IPAQ, total MET minutes	3,277 (4,753)	3,139 (4,983)	**3,210 (4,864)**	2,925 (4,683)

Values are numbers (percentages) unless stated otherwise, *FEV_1* forced expiratory volume in 1 second, *CCQ* Clinical COPD Questionnaire, *SGRQ* St George's Respiratory Questionnaire, *EQ-5D* EuroQol-5D, *IPAQ* International Physical Activity Questionnaire, *MET* metabolic equivalent time

Figure 6.1 Performance indicators over time (both treatment groups combined)

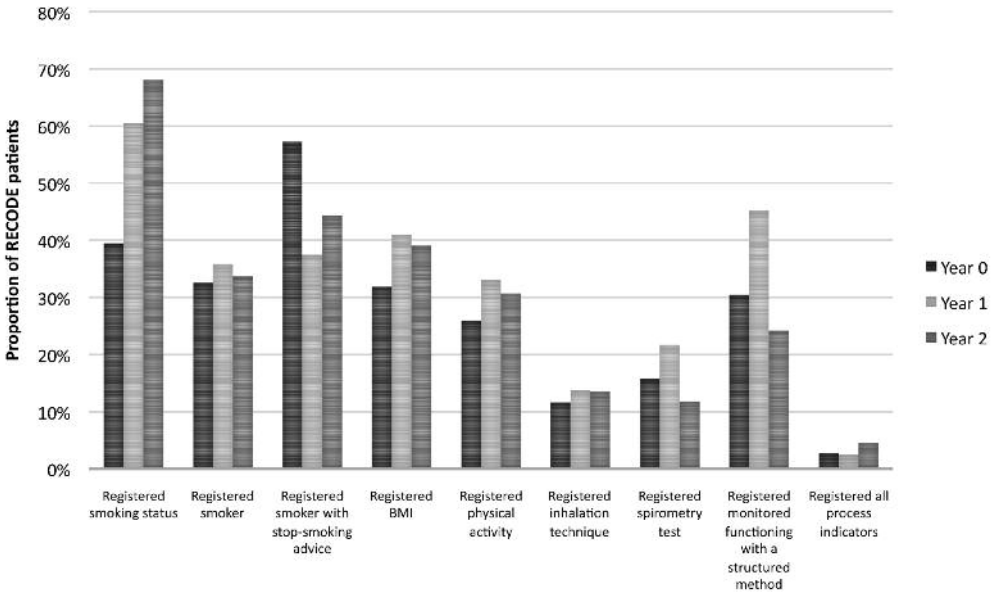

Table 6.2 Performance indicators in the RECODE and usual care group over time

Odds Ratio	Registered smoking status	Registered smoker	Registered smoker with smoking-cessation advice	Registered BMI	Registered physical activity	Registered inhalation technique	Registered spirometry test	Registered monitored functioning with a structured method	Registered all process indicators
Year 1	46.2**	0.72	0.35**	1.46*	1.48*	1.25	1.75*	1.45*	0.93
Year 2	270.6**	0.39	0.36**	1.00	0.61*	0.73	0.57*	0.88	0.73
Intervention*Year1	2.68	1.69	0.93	1.36	1.26	1.03	0.99	3.39**	.92
Intervention*Year2	5.54*	1.79	1.56	2.08**	5.62**	3.31**	1.99*	0.46**	3.93*
Intercept	0.07**	2.0e-5**	1.68	0.34**	0.18**	0.04**	0.08**	0.20**	.003
Number of observations	2,434	1,351	462	2,434	2,434	2,434	2,434	2,434	2,434

* Statistically significant difference (P<0.05), ** Statistically significant difference (P<0.01)

Table 6.2 Impact of performance indicators on change in health outcomes

	Changes in the same year as the indicator was registered			*Changes in the next year as the indicator was registered*		
Physical activity and smoking	**Δ MET minutes**	**Smoker**		**Δ MET minutes**	**Smoker**	
A patient with registered smoking status		N.A.			-1.419	
A patient of which the physical activity is checked in the last year	0.37			61.1		
Health-related quality of life	**Δ CCQ**	**Δ SGRQ**	**Δ EQ-5D**	**Δ CCQ**	**Δ SGRQ**	**Δ EQ-5D**
A patient with registered smoking status	-.062	-1.196	.016	.105	1,287	.017
A registered smoker	-.050	-.485	-.003	-0.134	1.39	-0.021
A registered smoker with smoking-cessation advice in the last year	.089	-.050	.021	-0.16	-0.111	-0.057
A patients with BMI registered in the last year	-.057	-1.564*	.012	0.026	0.744	0.012
A patient with physical activity is registered in the last year	-.043	-1.549*	.003	-0.01	0.033	0.018
A patient with inhalation technique checked in the last year	-.053	-1.414	.009	-0.099	-0.971	.047**
A patient with a spirometry test in the last year	-.129**	-3.198**	.010	-0.023	-0.429	.042**
A patient with functional status monitored with a structured method in the last year	-.113**	-1.966**	.019	0,092*	1.358	0.004
All process indicators registered	.069	-2.397	.041	-0.073	0.27	-0.007

* Statistically significant difference (P<0.05), ** Statistically significant difference (P<0.01), *MET* metabolic equivalent time, *CCQ* Clinical COPD Questionnaire, *SGRQ* St George's Respiratory Questionnaire; *EQ-5D* EuroQol-5D, Models are adjusted for starting score of different health outcome, intervention and longitudinal measurements nested in patients nested in primary care teams (and for the impact of the indicators on health outcomes in the same year)

DISCUSSION

This study showed that six of the eight COPD performance indicators improved more in the integrated care group as compared to the usual care group, mostly in year 2 of the trial. This indicates an improvement in the quality of care, which is in line with the improvements that were seen in the domain of the Patient Assessment of Chronic Illness Care (PACIC) questionnaire that measures follow-up of patients and coordination of care.[164] An exception was the indicator 'functional status monitored with a structured method'. In the first year, the integrated care group scored significantly better than the usual care group on this indicator, whereas the opposite was found in the second year. This might be related to the fact that GP practices in the integrated care group got feedback on the CCQ scores (i.e. one of the structure methods to monitor functional status) of their COPD patients after 0, 6 and 12 months as part of the intervention in the clinical trial. These CCQ scores were copied into the EMR. As a result, the GPs might have felt it was less important to register this performance indicator because they got the results anyway.

Four indicators (BMI registered, physical activity registered, spirometry test done, and functional status monitored with a structured method) were associated with an immediate significant improvement in disease-specific HRQoL. Moreover, two indicators (inhalation technique checked and spirometry test done) had a delayed impact on generic HRQol (improvement in the year after the indicator was registered). The observation that a spirometry test had both an immediate and a delayed positive impact on HRQoL indicates that the effect of spirometry lasts (at least) two years. These findings support the recently updated Dutch Care Standard for COPD which recommends to perform spirometry every two year for stable COPD patients instead of every year.[24] It was further interesting to observe that the indicators related to smoking did not affect health outcomes. Moreover, smoking registration did not affect the smoking status in the next year. These results are related to the improved likelihood to have a registered smoking status while the likelihood to get smoking-cessation advice decreased over time. It is important to notice that the effect of smoking indicators could have been influenced by changes in the reimbursement policy for smoking cessation support during the RECODE study (i.e. full reimbursement of pharmacological support and counselling in 2011, no reimbursement of pharmacological support in 2012 and conditional reimbursement (only when pharmacological support is combined with counselling) in 2013).[210–212]

The RECODE trial provides a unique opportunity to conduct this study due to the long term follow-up, the broad range of HRQoL meas-

ures and the inclusion of a sizeable real-world, heterogeneous study population. This study is limited by the fact that differences in performance might not only be due to true differences in care delivered but also due to registration problems.[213] For instance, it is possible that some indicators were registered at a different place in the EMR than where it should be. However, these problems were the same in both treatment groups.

The achievements on the performance indicators in our study (12%-68%) was lower than in the InEen study, a study among 70 care groups in the Netherlands, that measured achievements ≥60% on the same indicators.[214] However, the InEen study was at risk of selection bias because they only include GP practices that were part of a care group (e.g. a formal organization of primary care providers which negotiates with health insurers about the price and the quality of a package of care to treat patients with COPD; the care group subcontracts the individual care providers). There is evidence that practices who joined care groups increased the quality of their registration due to reduced registration problems over time.[214]

This is the first study which investigated the impact of an integrated care program for COPD patients on performance indicators. Earlier studies demonstrated that integrated care improves the PACIC score for patients with COPD[215,216] and performance indicators for patients with cognitive[217] or physical disabilities[218], diabetes[219,220], and heart failure.[221] To the best of our knowledge, none of the previous studies investigated the impact of performance indicators on HRQoL. Most studies used other outcome measures. One study found that performance indicators predict only small differences in mortality across 3,657 hospitals in the US.[222] Another study found no association between clinical performance and emergency admissions and mortality for COPD across general practices in two English primary care trusts.[223] Moreover, recent studies report positive associations between financial rewards for performances and patients' outcomes. For instance, Song and colleagues[224] found that global budget contracts with quality incentives had resulted in lower spending growth and generally greater quality improvements after four years. Furthermore, Harrison and colleagues[203] demonstrated that UK's QOF pay-for-performance scheme was associated with a decrease in emergency admissions for incentivized conditions compared to conditions that were not incentivized under the scheme.

This study showed that the RECODE integrated care program did improve the quality of COPD care in the Netherlands. Some performance indicators (BMI registered, physical activity registered, spirometry test done, functional status monitored with a structured method and inhalation technique checked) were predictive of improved HRQoL, whereas

the others were not. To improve the impact of registering performance indicators and to accommodate performance-based payment of integrated care, further research should determine which indicators are most relevant for which target group. It is plausible that some indicators are only necessary, feasible and effective for a subset of patients with considerable disease burden who are sufficiently motivated to change.[205] Additionally, ICT systems of the healthcare providers should better facilitate the extraction and reporting of performance indicators and reduce the burden of registration, especially since the workload in primary care has increased substantially.

CHAPTER 7

Investigating the longitudinal association between medication adherence and health-related quality of life in COPD: methodological challenges

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Submitted

ABSTRACT

Background: The association between non-adherence to medication and health-related quality-of-life (HRQoL) in COPD remains poorly understood. Researchers are facing methodological challenges and different ways to tackle these challenges have probably contributed to the conflicting results with respect to the direction of the association.

Aim: To investigate the association between medication adherence and HRQoL, thereby illustrating the methodological challenges that need to be addressed.

Methods: We used longitudinal patient-level data from a cluster-randomized controlled trial (i.e. RECODE). We had three-year data on type and dose of COPD maintenance medication prescribed and HRQoL (CCQ , SGRQ , EQ-5D) of 511 COPD patients. A linear mixed model was used to assess the association between adherence and HRQoL using a fixed cut-off of 80% of the proportion of days covered (PDC) to define adherence. Subsequently, we investigate the impact of (i) disease severity; (ii) lifestyle; and (iii) reversed causality. We performed sensitivity analyses to investigate the impact of changing the definition of adherence.

Results: In unadjusted analyses, and analyses adjusting for demographic characteristics only, SGRQ score was worse in the adherent compared to the non-adherent group. This association disappeared when correcting for disease severity and/or lifestyle. A better SGRQ score was predictive of decreased adherence in the following year. However, accounting for the previous HRQoL did not result in positive associations between adherence and HRQoL. When defining four categories of adherence, patients with a PDC between 80-99% had a significantly worse SGRQ score compared to patients with a PDC <60%, even after correction for lifestyle. There was no significant association between adherence and CCQ or EQ-5D.

Conclusion: This study showed persistent methodological challenges in the investigation of the effect of medication adherence on HRQoL in COPD. A positive association of adherence and HRQoL was not found, even after adjusting for lifestyle, disease severity, and previous HRQoL.

INTRODUCTION

Despite positive results of COPD medication found in randomized controlled clinical trials, adherence to Chronic Obstructive Pulmonary Disease (COPD) medication is low in routine daily practice.[84–86] Two recent reviews evaluated the consequences of non-adherence for health-related quality of life (HRQoL) in patients with COPD.[225,226] They found that at least 50% of the studies reported no or negative associations between medication adherence and HRQoL and they concluded that the association between non-adherence and HRQoL remains poorly understood. Researchers are facing several methodological challenges such as the possibility of confounding by disease severity and healthy lifestyle. Different ways to overcome these challenges have probably contributed to the conflicting results that were reported with respect to the direction of the association (positive or negative).[225,226] A more systematic analytical approach might contribute to a better understanding of the causal pathway of the association between adherence and HRQoL.

We used longitudinal patient-level data from the RECODE study, the largest 2-year cluster randomized trial in 40 primary care groups (N=1,086) comparing a COPD disease management program with usual care, to investigate the association between medication adherence and HRQoL. [164,165] As part of this trial, data on medication prescribed during the 2-year trial period as well as the year prior to the trial were extracted from the general practitioners' (GP) electronic medical records (EMR). During the same 2-year period, patients' HRQoL was periodically assessed as part of the trial. Hence, the RECODE-dataset provides a unique opportunity to investigate the association between medication adherence and HRQoL, while systematically investigating the role of disease severity and healthy lifestyle in this association. The dataset also allowed us to study reversed causality, i.e. whether adherence in a particular year was influenced by HRQoL in the year before.

METHODS

Study population

The RECODE trial recruited patients with physician-diagnosed COPD according to GOLD guidelines. Exclusion criteria were terminal illnesses, dementia, cognitive impairment, inability to complete questionnaires in Dutch, and hard drug or alcohol abuse. Other co-morbidity was not an exclusion criterion. The COPD patients in the RECODE trial were found to be representative of the COPD population treated in primary care in the Netherlands.[165] For the current study, we included all RECODE patients from 23 of the 40 RECODE primary care groups with at least two prescriptions for COPD maintenance medication in one year and com-

plete HRQoL records in that same year. Patients from the intervention group as well as the control group were included. The remaining practices and patients were excluded because data on type of medication and dosage prescribed could not be extracted from the EMRs.

Drug adherence

The COPD maintenance medication included long-acting ß2-agonists (LABA), long-acting muscarinic antagonists (LAMA), inhaled corticosteroids (ICS), or fixed-dose LABA/ICS combinations. Medication prescriptions and prescribed daily doses were extracted from the EMR of the GPs. For each year, adherence was calculated as the proportion of days covered (PDC), a method used in various previous adherence studies in COPD.[91,227,228] For prescriptions extending beyond the end of the analysis period, the days covered were truncated at the end of the period. The average PDC was used if patients used medications from different maintenance medication categories (LABA, LAMA, ICS, LABA/ICS combinations). Patients were classified as adherent if their (average) PDC equalled or exceeded 80%. This threshold is frequently used in adherence studies, also in COPD.[227,229–232] In sensitivity analyses, we investigate the impact of changing the definition of adherence by using (i) a categorical variable with four categories of PDC, i.e <60%, 60-79%, 80-99%, >99%, (ii) PDC as a continuous variable, and (iii) the minimum (or maximum) PDC if patients used medications from different maintenance medication categories (LABA, LAMA, ICS, LABA/ICS combinations).

Health Related Quality of Life

HRQoL was measured using the Clinical COPD Questionnaire (CCQ)[30,138], the Saint George's Respiratory Questionnaire (SGRQ)[119,168] and the 3-level EuroQoL-5Dimensions (EQ-5D)[190] at baseline, after 1 year and after 2 years. The first two questionnaires (CCQ and SGRQ) are COPD-specific instruments and the EQ-5D is a generic HRQoL instrument used to calculate utilities. Note that a higher score on SGRQ and CCQ indicates a worse HRQoL, whereas a higher score on EQ-5D indicates a better HRQoL.

Statistical analysis

We investigated the association between adherence during one year with HRQoL at the end of this year, i.e. the association between adherence during the pre-trial year and HRQoL at baseline, adherence during the first trial-year and HRQoL at 12 months, and adherence over the second trial-year and HRQoL at 24 months. We used linear mixed models to assess this association using a fixed cut-off of 80% to define adherent (≥80%)

and non-adherent patients (<80%). We investigated the interaction between trial-arm and medication adherence to see if both groups in the trial could be combined.

Base-case analyses

We started with a linear mixed model with a random intercept and no confounders, thereafter, we included age, gender and level of education (0 high education; 1 low education [defined as no or only primary education]), but no other confounders. Subsequently, this simple, though often used analysis, was expanded. First, by controlling for disease severity, second, by controlling for healthy lifestyle and third, by investigating potential reversed causality. These three analyses represent the challenges that researchers are facing when adequately assessing the association between medication adherence and HRQoL [226]. A more detailed description of these challenges is given below.

Challenge 1: Adequately correcting for disease severity

It is likely that more severely ill patients have a higher need for medication and as a result they may be more adherent. Hence, a correction for differences in disease severity between adherent and non-adherent patients is necessary. Therefore, we estimated a linear mixed model with a random intercept and correction for four indicators of disease severity, i.e. the forced expiratory volume in 1 second as percentage of the predicted value (FEV_1%pred) at baseline, the total exacerbation rate (moderate or severe) in the 12 months prior to the adherence measurement, the Medical Research Council (MRC) dyspnoea scale[28] at the start of the adherence measurement and the Charlson comorbidity index at baseline.[233] A moderate exacerbation was defined as a worsening of COPD symptoms that led a patient's clinician to prescribe systemic corticosteroids and/or antibiotics, but did not require hospitalization. This information was extracted from the EMR. A severe exacerbation was defined as a worsening of COPD symptoms that required a hospital admission. Hospital admissions were obtained from the resource use questionnaires completed by the patients and confirmed by the EMR. The resource use questionnaire was administered as part of the RCT at baseline, 6, 9, 12, 18 and 24 months.

Challenge 2: Addressing a potential healthy-adherer effect

Some studies suggested that therapy adherence is an indicator of overall healthy lifestyle. It is argued that those who take good care of their health in general, by adopting a healthy lifestyle, are more likely to be adherent to medication. Hence, a positive association between adherence and

HRQoL could be caused by a healthy lifestyle in general. This is referred to as the "healthy-adherer effect" [227,234]. Therefore, we estimated a linear mixed model with a random intercept and including three variables that are indicators of a healthy lifestyle in general measured at the same time as the HRQoL. These variables were smoking status (smoker or no smoker), level of physical activity and self-efficacy. We calculated the level of physical activity from the International Physical Activity Questionnaire (IPAQ) by multiplying the frequency (in days) and duration (in minutes) of walking, moderate-intensity activities, and vigorous-intensity activities in terms of the energy requirements, to yield a score in metabolic equivalent time (MET) minutes.[141] We measured the level of self-efficacy from the Self-Management Ability Scale-30 (SMAS-30).[140] The IPAQ , SMAS-30 and smoking status questions were administered at the same time as the HRQoL measurement (i.e. baseline, 12 and 24 months). We hypothesized that a higher score on IPAQ or SMAS-30 and non-smoking status would indicate a healthier lifestyle. In this way, we aimed to 'correct' for a possible healthy-adherer effect.

Challenge 3: Investigating potential reversed causality

In the previous analyses, we assessed the effect of adherence during a particular year on HRQoL at the end of that same year. However, reversed causality may be present, meaning that HRQoL measured at the beginning of a year may influence adherence to medication during that year. A better HRQoL may improve adherence ("I am feeling good so I need to keep taking my medication"), but it may also lead to a reduction in adherence ("because I am feeling good I need less medication"). To unravel this association, we studied whether an improvement greater than or equal to the minimal clinically important difference (MCID) in HRQoL (≥4 points on the SGRQ[119]; ≥0.4 points on the CCQ[138]) during the first trial-year changed the PDC in the second trial-year using a t-test. In addition, we account for the previous HRQoL in a linear model with an unstructured covariance matrix for repeated measures.

RESULTS

Dataset characteristics

The 23 primary care groups that had complete EMR regarding type and dosage of medication prescribed, enrolled 658 patients into the RECODE trial (61% of all patients in the trial). From these 658 patients, we excluded 147 patients (22%) because they did not have at least two prescriptions for COPD maintenance medication in one year and complete HRQoL records in that same year. In total, 511 COPD patients have been included in this study. The patient characteristics were very similar to those in the

total RECODE study population (Appendix 7.1). For each year, we calculated the PDC for the 511 participants. We were able to combine the observations of the intervention and control group into the same analysis, because the RECODE intervention did not specifically target adherence and adherence to COPD medication and (change in) HRQoL in these two groups were comparable (data not shown).

Table 7.1 presents the patient characteristics of the dataset split into adherent and non-adherent patients. The proportions of patients who were adherent were 63%, 57% and 58% in year 0, 1 and 2, respectively. The proportion of low educated patients was significantly higher in the non-adherent group (49%) compared to the adherent group (38%) in year 0. Furthermore, the adherent group had worse average MRC and SGRQ scores compared to the non-adherent group in year two.

Base-case analyses

The results of the base-case analyses are shown in Table 7.2. In the unadjusted analyses the adherent group had worse quality of life than the non-adherent group. In the case of the SGRQ, this difference was statististically significant (P=0.034) and close to clinical-relevance threshold of 4.[119] This difference diminished after adjusting for the sociodemographic variables age, sex, and education (P=0.098).

Correcting for disease severity

When indicators of disease severity (FEV_1%pred, prior exacerbations, MRC dyspnoea score, Charlson comorbidity index) were added, the associations between adherence and HRQoL decreased, regardless of how we measured HRQoL (Table 7.2).

Correcting for healthy lifestyle

When further adding indicators of a healthy lifestyle in general (level of physical activity, self-efficacy and smoking status), we did not find a relationship between adherence and HRQoL either (Table 7.2).

Reversed causality

The PDC of patients with an improvement greater than or equal to the MCID in SGRQ score (i.e. ≥4 points)[119] over the first trial-year decreased on average with 2.6% during the second trial-year year, whereas the PDC of patients without such an improvement increased with 2%, leading to a significant difference in change in PDC of 4.6% between these two groups (Table 7.3). This indicates that improved HRQoL may reduce future adherence. This association was found for the SGRQ but not for the CCQ, nor did we find an association between a clinically relevant dete-

rioration in HRQoL and an improved adherence in the next year (Table 7.3). However, accounting for the previous HRQoL (using a linear model with unstructured covariance matrix for repeated measures), still did not result in the expected positive associations between adherence and HRQoL, regardless of how we measured HRQoL (Appendix 7.2).

Table 7.1 Patients' characteristics of adherent and non-adherent COPD patients

	YEAR 0		YEAR 1		YEAR 2	
Characteristic	Non-adherent (PDC<80%) N=171	Adherent (≥80%) N=294	Non-adherent (PDC<80%) N=213	Adherent (≥80%) N=278	Non-adherent (PDC<80%) N=197	Adherent (≥80%) N=272
Age (years) (SD)	67 (11)	68 (11)	68 (11)	68 (10)	67 (11)	68 (10)
Male (%)	45.0	45.9	50.2	50.4	54.8	49.6
Low education (%)	48.7	37.5*	39.0	42.7	39.8	42.7
FEV_1%pred (SD)	67.8 (20.0)	65.1 (20.1)	67.0 (18.1)	65.2 (21.0)	67.7 (17.8)	64.4 (20.3)
Exacerbations (SD)	.42 (.87)	.50 (.99)	.50 (1.04)	.68 (1.19)	1.04 (1.95)	1.42 (2.18)
MRC dyspnoea (SD)	2.1 (1.3)	2.0 (1.3)	2.1 (1.3)	2.3 (1.3)	2.2 (1.3)	2.5 (1.4)*
Charlson comorbidity index (SD)	2.4 (1.2)	2.3 (1.2)	2.3 (1.3)	2.3 (1.1)	2.3 (1.3)	2.3 (1.2)
Total MET minutes (SD)	3114 (4940)	2539 (4921)	3168 (4807)	2716 (4471)	3325 (4462)	2682 (4253)
Self-efficacy (SD)	64.8 (17.7)	65.5 (17.2)	64.2 (16.9)	62.9 (16.8)	66.0 (18.5)	64.2 (16.3)
Smoker (%)	39.6	33.4	30.9	30.2	49.0	43.8
CCQ (SD)	1.54(1.03)	1.41 (.89)	1.49 (.96)	1.53 (.96)	1.72 (.95)	1.88 (1.02)
SGRQ (SD)	35.7 (21.0)	34.6 (19.9)	34.5 (20.9)	35.6 (20.2)	33.7 (21.5)	39.7 (23.5)*
EQ-5D utility (SD)	.74 (.26)	.74 (.27)	.72 (.26)	.72 (.27)	.78 (.25)	.80 (.21)

*Significant (P<0.05), *SD* Standard Deviation, *PDC* Proportion of Days Covered, *FEV_1%pred* predicted percentage of Forced Expiratory Volume in 1 second, *MRC* Medical Research Council, *MET* Metabolic Equivalent Time, *CCQ* Clinical COPD Questionnaire, *SGRQ* Saint George's Respiratory Questionnaire, *EQ-5D* EuroQoL 5-Dimensions

Table 7.2 Linear mixed models with and without correcting for demographics, disease severity and healthy-lifestyle variables

CCQ		*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*
	Intercept	1.46	<.01	1.30	<.01	1.18	<.01	2.72	<.01	1.88	<.01
	Adherence	**.09**	**.17**	**.07**	**.31**	**.01**	**.84**	**.12**	**.14**	**.07**	**.28**
	Time	.30	<.01	.30	<.01	.21	<.01	.32	<.01	.21	<.01
Demographics	Age			.0001	.97	-.01	.02	-.005	.26	-.01	.06
	Men			-.03	.72	.08	.15	-.04	.61	.08	.24
	Low education			.45	<.01	.22	<.01	.36	<.01	.16	.02
Disease severity	FEV_1% pred					-.005	<.01			-.005	.01
	Exacerbations					.15	<.01			.14	<.01
	MRC dyspnoea					.38	<.01			.37	<.01
	Charlson comorbidity index					.06	.01			.01	.69
Healthy lifestyle	MET minutes							-2.1e-5	.04	7.5e-6	.38
	Self-efficacy							-.02	<.01	-.01	<.01
	Smoker							.14	.096	.14	.06
	Observations (N)	825		754		726		542		524	
SGRQ		*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*
	Intercept	33.3	<.01	24.6	<.01	21.9	<.01	58.9	<.01	40.4	<.01
	Adherence	**3.27**	**.03**	**2.58**	**.098**	**.51**	**.67**	**2.29**	**.18**	**1.01**	**.44**
	Time	2.02	.19	2.35	.13	.55	.64	2.94	.11	.36	.80
Demographics	Age			.09	.25	-.08	.21	-.03	.73	-.06	.38
	Men			-1.90	.23	1.00	.41	-3.39	.05	-.32	.82
	Low education			10.1	<.01	4.62	<.01	9.28	<.01	4.47	<.01
Disease severity	FEV_1% pred					-.11	<.01			-.15	<.01
	Exacerbations					3.47	<.01			3.71	<.01
	MRC dyspnoea					9.14	<.01			8.36	<.01
	Charlson comorbidity index					1.37	<.01			.77	.18
Healthy lifestyle	MET minutes							-.001	.02	1.9e-4	.25
	Self-efficacy							-.37	<.01	-.22	<.01
	Smoker							-.52	.78	-.52	.72
	Observations (N)	794		729		704		542		523	
EQ-5D		*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*
	Intercept	.72	<.01	.65	<.01	.80	<.01	.35	<.01	.63	<.01
	Adherence	**.01**	**.77**	**.01**	**.62**	**.02**	**.27**	**.004**	**.85**	**.01**	**.63**
	Time	.07	<.01	.06	<.01	.07	<.01	.06	<.01	.07	<.01
Demographics	Age			.001	.22	.002	.01	.001	.29	.001	.18
	Men			.06	<.01	.04	.03	.07	<.01	-.04	.02
	Low education			-.09	<.01	-.05	<.01	-.08	<.01	-.05	.02
Disease severity	FEV_1% pred					-.0002	.62			-.001	.32
	Exacerbations					-.02	<.01			-.02	.02
	MRC dyspnoea					-.05	<.01			-.04	<.01
	Charlson comorbidity index					-.04	<.01			-.03	<.01
Healthy lifestyle	MET minutes							-7.0e-7	.77	-4.6e-6	.05
	Self-efficacy							.005	<.01	.004	<.01
	Smoker							-.02	.37	-.03	.17
	Observations (N)	827		760		733		555		535	

CCQ Clinical COPD Questionnaire, *SGRQ* Saint George's Respiratory Questionnaire, *EQ-5D* EuroQoL 5-Dimensions, *FEV_1% pred* predicted percentage of Forced Expiratory Volume in 1 second, *MRC* Medical Research Council, *IPAQ* International Physical Activity Questionnaire, *MET* Metabolic Equivalent Time

Table 7.3 Clinically important difference in HRQoL in the first trial-year and changed adherence in the second trial-year

		MCID at year 1	ΔPDC (PDC year 2-PDC year 1)	Mean Difference	P-value	Observations (N)
Improvement	CCQ	no	0.1%	-2.4%	.326	437
		yes	2.5%			
	SGRQ	no	2.0%	4.6%	.038	422
		yes	-2.6%			
Deterioration	CCQ	no	1.3%	2.0%	.373	437
		yes	-0.7%			
	SGRQ	no	0.8%	1.5%	.502	422
		yes	-0.7%			

HRQoL health-related quality of life, *MCID* Minimal Clinically Important Difference, *CCQ* Clinical COPD Questionnaire, *SGRQ* Saint George's Respiratory Questionnaire, *PDC* Proportion of Days Covered, Unpaired t test, no MCID vs MCID.

Sensitivity analyses

The results of the sensitivity analyses to investigate the impact of changing the definition of adherence are presented in Appendix 7.3 to 7.6. Appendix 7.2 shows the results of the sensitivity analyses in which we used four categories of PDC (i.e. <60%, 60-79%, 80-99%, >99%). Patients with a PDC of 80-99% had a significantly higher SGRQ score than patients with a PDC <60%, indicating a worse HRQoL. This difference of 4.47 exceeds the MCID of 4 points on the SGRQ.[119] Also after correction for demographics and healthy lifestyle variables, patients with a PDC of 80-99% had a significantly higher SGRQ score than patients with a PDC <60%. After controlling for disease severity, patients with a PDC of 80-99% had no longer a significantly higher SGRQ score. Using PDC as a continuous variable, we did not find an association between adherence and HRQoL, independent of whether we corrected for demographics, healthy lifestyle and disease severity (Appendix 7.3). Neither did we find an association with adherence using the minimum PDC if patients used medication from different maintenance medication categories (Appendix 7.4). However, when using the maximum PDC if patients used medication from different maintenance medication categories, adherent patients had a significantly higher SGRQ and CCQ score than non-adherent patients, even after correcting for demographics. These differences in the SGRQ score (5.75 and 4.81) exceed the MCID of 4 points[119] but the differences in the CCQ score (0.17 and 0.15) did not exceed the MCID of 0.4 points.[138]

DISCUSSION

This study investigated the dynamic relationship between adherence to COPD medication and HRQoL. In unadjusted analyses, we found that adherent patients had a worse SGRQ score. This association disappeared when we corrected for healthy lifestyle and, especially, disease severity. This demonstrates the importance of this correction. However, after this correction we did not find that better adherence led to better HRQoL. We found some indications of reversed causality because an improvement in SGRQ score during the first year was associated with a reduction in adherence during the second year, whereas no improvement in SGRQ was associated with an increase in adherence.

The first challenge sought to determine the impact of correcting for disease severity. Our hypothesis was that more severely ill patients have a higher need for medication and as a result they are more likely to be adherent, thus making a correction for disease severity necessary when studying the association between adherence and HRQoL. Turner and colleagues[89] found that FEV1%pred and shortness of breath were worse in the adherent group compared to the non-adherent group, while the FEV1%pred did not significantly differ between these groups in two other studies.[88,92] Furthermore, Ingebrigtsen and colleagues[235] concluded that although disease severity was associated with increased adherence, the use of and adherence to medication was low, even in severe and very severe COPD. Adherence in COPD seems also to be influenced by comorbidities such as depression.[236,237] We only found in the second year, that the adherent patients did have a worse MRC and SGRQ score than the non-adherent patients. Nevertheless, correction for disease severity removed the association between better adherence and worse SGRQ score. Therefore, it is of absolute importance to accurately account for disease severity.

In the second challenge, we determined the impact of a potential healthy-adherer effect. Our hypothesis was that those who take good care of their health in general (healthy lifestyle) are more likely to be adherent to medication, thus making it important to correct for differences in lifestyle. We did not find any statistically significant differences in smoking status, physical activity and self-efficacy between the adherent and non-adherent group. This was in accordance with, Turner and colleagues[89], who also found that the exercise level between the adherent and non-adherent group did not differ. In contrast, other studies did seem to be consistent with the "healthy-adherer" impact: the proportion of smokers[88,89,236] and drinkers[89] was lower among the adherer group and COPD patients with higher self-efficacy scores[236] were more likely to be classified as adherent.

The impact of correcting for indicators of a healthy lifestyle in our study depended on the definition of adherence. When we defined adherence as a PDC ≥ 80%, correction for lifestyle reduced the association between a better adherence and a worse SGRQ score and left it statistically non-significant. Still, the reduction of the association was markedly smaller than when we adjusted for disease severity. When we used categories for PDC-levels, patients with good adherence (PDC 80%-99%) still had a relatively bad average SGRQ score. We found similar results if we used the maximum PDC, i.e. good adherence was associated with worse CCQ and SGRQ scores even after correcting for healthy lifestyle variables.

In the third challenge, we investigated the presence of potential reversed causality. In line with Agh and colleagues[226], a better SGRQ score was predictive of decreased adherence to COPD medications during that year. However, accounting for previous HRQoL did not result in positive associations between adherence and HRQoL, regardless of how we measured HRQoL. It is plausible that more frequent measurements of HRQoL and clinical variables, combined with adherence calculations over shorter intervals, would lead to better estimates of the causal effect of adherence on HRQoL. Hence, it is likely that HRQoL at the end of each year was mainly affected by adherence in the weeks or months immediately prior to the measurement, and not as much by adherence over the full year. Similarly, adherence could have been influenced by current disease symptoms, more than by HRQoL in a more distant past.

We did not find a linear relationship between the degree of medication adherence and HRQoL. Patients with a PDC of 80-99% had a substantially and significantly worse SGRQ score than patients with a PDC below 60%, but patients with a PDC of ≥100% did not. None of the previous adherence studies in COPD performed analyses using various cut-off values to define adherence and only two studies[88,92] explained the reason for their cut-off value chosen.

It was interesting that we have not found any association between adherence and the generic HRQoL instrument EQ-5D whereas we did find an association between adherence and the disease-specific HRQoL instruments (SGRQ and CCQ). These findings might be due to the fact that disease-specific questionnaires seem to be more sensitive in finding differences in symptoms that are not usually picked up by the generic instruments.[238–240] We therefore advise researchers to use disease-specific instruments when assessing the relationship between adherence and HRQoL.

Most previous studies on the association between adherence and health outcomes relied on proxies for disease severity because other indicators of disease severity (e.g. lung function) were lacking.[228,241] Using

the RECODE study, we were able to use various indicators of disease severity. Moreover, we were able to investigate the association between adherence and both generic and disease-specific HRQoL. Furthermore, due to (i) the inclusion of RECODE patients from the intervention group as well as the control group and (ii) the repeated measurements of the patients, we included over 800 observations in our analyses.

This study has some limitations. One is that the adherence data of the present study were based on EMR. These data do not indicate whether a patient has actually filled the prescription and has subsequently taken the medication (appropriately). Hence, it is likely that adherence has been overestimated, but this measurement is generally more accurate than estimations from physicians and self-reports by patients.[231] Second, patients registered in primary care groups that had incomplete EMR with respect to medication could not be included in this study. However, this is likely to be an ICT problem and not an indication of a systematic difference between practices. Indeed, the baseline characteristics of the subset of RECODE patients in the current study were comparable to characteristics of the full RECODE dataset.

To conclude, we were unable to find a positive association between COPD medication adherence and HRQoL. Even after adjusting for potential confounders such as demographics, disease severity and healthy lifestyle variables, we did not find a positive relationship. Our analyses demonstrated that the lack of correction for disease severity and healthy lifestyle variables may even result in a reversed association; patients with good COPD medication adherence had a worse HRQoL compared to patients with poor COPD medication adherence. Further studies should improve the adjustment for disease severity and previous HRQoL, perhaps by using shorter intervals.

APPENDIX

Appendix 7.1 Baseline characteristics compared to total RECODE population

CHARACTERISTIC	SUBSET OF RECODE POPULATION (N=511)	TOTAL RECODE POPULATION (N=1.086)
Age (years) (SD)	68.0 (10.7)	68.3 (11.2)
Male (%)	51.0	53.9
Low education (%)	41.5	40.3
FEV_1 %pred	66.1	67.8
Charlson comorbidity index (SD)	2.3 (1.2)	2.3 (1.3)
MET minutes (SD)	2.781 (4.308)	2.925 (4.683)
Self-efficacy (SD)	65.1 (17.6)	65.3 (17.4)
Current smoker (%)	37.3	36.7
CCQ (SD)	1.47 (0.94)	1.50 (0.97)
SGRQ (SD)	35.0 (20.3)	35.6 (20.5)
EQ-5D utility (SD)	0.74 (0.27)	0.74 (0.26)

SD Standard Deviation, *FEV_1%pred* predicted percentage of Forced Expiratory Volume in 1 second, *MET* Metabolic Equivalent Time, *CCQ* Clinical COPD Questionnaire, *SGRQ* Saint George's Respiratory Questionnaire, *EQ-5D* EuroQoL 5-Dimensions

Appendix 7.2 Linear mixed models accounting for the previous HRQoL

CCQ		*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*
	Intercept	1.50	<.01	1.34	<.01	1.18	<.01	2.69	<.01	2.11	<.01
	Adherence	**.02**	**.77**	**-.003**	**.96**	**.01**	**.92**	**.03**	**.64**	**.07**	**.29**
	Time	.34	<.01	.34	<.01	.26	<.01	.35	<.01	.25	<.01
Demographics	Age			.0001	.98	-.004	.19	-.005	.32	-.01	.09
	Men			-.04	.62	.05	.50	-.04	.71	.07	.33
	Low education			.48	<.01	.29	<.01	.36	<.01	.21	<.01
Disease severity	FEV_1% pred					-.01	<.01			-.005	<.01
	Exacerbations					.09	<.01			.11	<.01
	MRC dyspnoea					.29	<.01			.31	<.01
	Charlson comorbidity index					.08	<.01			.03	.36
Healthy lifestyle	MET minutes							-2.0e-5	.02	2.7e-6	.75
	Self-efficacy							-.02	<.01	-.01	<.01
	Smoker							.18	.04	.14	.06
	Observations (N)	825		754		726		542		524	
SGRQ		*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*
	Intercept	35.3	<.01	28.0	<.01	30.4	<.01	49.9	<.01	42.9	<.01
	Adherence	**-.27**	**.82**	**-.27**	**.82**	**.30**	**.80**	**.85**	**.58**	**1.26**	**.36**
	Time	3.75	<.01	3.67	<.01	2.22	<.01	2.97	<.01	.89	.46
Demographics	Age			.07	.17	-.02	.83	.01	.88	-.05	.51
	Men			-2.72	<.01	-.73	.64	-3.07	.11	-.53	.72
	Low education			10.1	<.01	6.61	<.01	9.18	<.01	5.28	<.01
Disease severity	FEV_1% pred					-.21	<.01			-.17	<.01
	Exacerbations					1.73	<.01			2.93	<.01
	MRC dyspnoea					5.28	<.01			7.13	<.01
	Charlson comorbidity index					2.33	<.01			1.09	.08
Healthy lifestyle	MET minutes							-.0002	.18	1.8e-4	.28
	Self-efficacy							-.29	<.01	-.23	<.01
	Smoker							1.19	.53	.09	.96
	Observations (N)	794		729		704		542		523	
EQ-5D		*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*
	Intercept	.72	<.01	.68	<.01	.77	<.01	.33	<.01	.56	<.01
	Adherence	**.002**	**.89**	**.004**	**.80**	**.01**	**.53**	**.006**	**.78**	**.01**	**.71**
	Time	.07	<.01	.06	<.01	.07	<.01	.05	<.01	.06	<.01
Demographics	Age			.001	.47	.002	.10	.001	.21	.002	.13
	Men			.06	<.01	.04	.05	.07	<.01	.05	.02
	Low education			-.09	<.01	-.06	<.01	-.08	<.01	-.05	.02
Disease severity	FEV_1% pred					.0002	.67			-.0003	.59
	Exacerbations					-.02	.03			-.02	.03
	MRC dyspnoea					-.03	<.01			-.03	<.01
	Charlson comorbidity index					-.04	<.01			-.03	<.01
Healthy lifestyle	MET minutes							2.9e-7	.90	-3.3e-6	.16
	Self-efficacy							.005	<.01	.004	<.01
	Smoker							-.01	.54	-.02	.32
	Observations (N)	827		760		733		555		535	

CCQ Clinical COPD Questionnaire, *SGRQ* Saint George's Respiratory Questionnaire, *EQ-5D* EuroQoL 5-Dimensions, *FEV_1% pred* predicted percentage of Forced Expiratory Volume in 1 second, *MRC* Medical Research Council, *IPAQ* International Physical Activity Questionnaire, *MET* Metabolic Equivalent Time

Appendix 7.3 Linear mixed models using four categories of PDC

CCQ		*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*
	Intercept	1.46	<.01	1.38	<.01	1.17	<.01	2.72	<.01	1.85	<.01
	Adherence (PDC <60%)	**ref.**		**ref.**		**ref.**		**ref.**		**ref.**	
	Adherence (PDC 60-79%)	**-.01**	**.93**	**-.03**	**.75**	**.01**	**.95**	**.01**	**.90**	**.06**	**.53**
	Adherence (PDC 80-99%)	**.11**	**.21**	**.09**	**.33**	**.05**	**.49**	**.19**	**.07**	**.14**	**.09**
	Adherence (PDC >99%)	**.06**	**.58**	**.004**	**.97**	**-.05**	**.57**	**.02**	**.85**	**.03**	**.78**
	Time	.30	<.01	1.32	<.01	.22	<.01	.33	<.01	.21	<.01
Demographics	Age			.0001	.99	-.01	.02	-.005	.25	-.01	.05
	Men			-.03	.72	.08	.15	-.04	.60	.08	.23
	Low education			.45	<.01	.22	<.01	.35	<.01	.16	.03
Disease severity	FEV_1% pred					-.005	<.01			-.004	.02
	Exacerbations					.15	<.01			.14	<.01
	MRC dyspnoea					.38	<.01			.37	<.01
	Charlson comorbidity index					.06	.01			.01	.64
Healthy lifestyle	MET minutes							-2.1e-5	.04	8.0e-6	.35
	Self-efficacy							-.02	<.01	-.01	<.01
	Smoker							.14	.09	.13	.06
	Observations (N)	825		754		542		542		524	
SGRQ		*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*
	Intercept	32.9	<.01	25.0	<.01	21.7	<.01	59.1	<.01	40.2	<.01
	Adherence (PDC <60%)	**ref.**		**ref.**		**ref.**		**ref.**		**ref.**	
	Adherence (PDC 60-79%)	**0.74**	**.75**	**-.24**	**.92**	**.07**	**.97**	**-.60**	**.81**	**.08**	**.97**
	Adherence (PDC 80-99%)	**5.15**	**.01**	**4.30**	**.03**	**2.24**	**.15**	**4.21**	**.05**	**2.79**	**.10**
	Adherence (PDC >99%)	**0.93**	**.68**	**-.55**	**.81**	**-2.22**	**.20**	**-1.46**	**.55**	**-1.78**	**.35**
	Time	2.06	.18	2.39	.12	.63	.59	3.20	.08	.67	<.01
Demographics	Age			.09	.27	-.08	.18	-.03	.72	-.06	.35
	Men			-1.93	.22	.99	.41	-3.46	.04	.34	.80
	Low education			10.0	<.01	4.51	<.01	9.05	<.01	4.29	<.01
Disease severity	FEV_1% pred					-.11	<.01			-.15	<.01
	Exacerbations					3.46	<.01			3.67	<.01
	MRC dyspnoea					9.14	<.01			8.34	<.01
	Charlson comorbidity index					1.45	<.01			.89	.12
Healthy lifestyle	MET minutes							-.0004	.02	.0002	.23
	Self-efficacy							-.37	<.01	-.23	<.01
	Smoker							-.40	.83	-.42	.77
	Observations (N)	794		729		704		542		925	
EQ-5D		*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*
	Intercept	.72	<.01	.65	<.01	.79	<.01	.36	<.01	.64	<.01
	Adherence (PDC <60%)	**ref.**		**ref.**		**ref.**		**ref.**		**ref.**	
	Adherence (PDC 60-79%)	**-.004**	**.87**	**.01**	**.78**	**.02**	**.48**	**-.04**	**.23**	**-.03**	**.32**
	Adherence (PDC 80-99%)	**.008**	**.73**	**.01**	**.63**	**.02**	**.31**	**-.02**	**.45**	**-.01**	**.57**
	Adherence (PDC >99%)	**-.004**	**.86**	**.01**	**.60**	**.03**	**.18**	**.001**	**.98**	**.01**	**.61**
	Time	.07	<.01	.06	<.01	.07	<.01	.06	<.01	.07	<.01
Demographics	Age			.001	.22	.002	.01	.001	.29	.001	.16
	Men			.06	<.01	.04	.03	.07	<.01	.04	.02
	Low education			-.09	<.01	-.05	<.01	-.08	<.01	-.04	.02
Disease severity	FEV_1% pred					-.0002	.62			-.001	.27
	Exacerbations					-.02	<.01			-.02	.02
	MRC dyspnoea					-.05	<.01			-.04	<.01
	Charlson comorbidity index					-.04	<.01			-.03	<.01
Healthy lifestyle	MET minutes							-8.5e-7	.72	-4.7e-6	.04
	Self-efficacy							.005	<.01	.004	<.01
	Smoker							-.02	.37	-.03	.17
	Observations (N)	827		760		733		555		535	

CCQ Clinical COPD Questionnaire, *SGRQ* Saint George's Respiratory Questionnaire, *EQ-5D* EuroQoL 5-Dimensions, *FEV_1% pred* predicted percentage of Forced Expiratory Volume in 1 second, *MRC* Medical Research Council, *IPAQ* International Physical Activity Questionnaire, *MET* Metabolic Equivalent Time

Appendix 7.4 Linear mixed models using PDC as a continuous variable

CCQ		*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*
	Intercept	1.40	<.01	1.28	<.01	1.20	<.01	2.68	<.01	1.84	<.01
	Adherence (continuous)	**.14**	**.29**	**.07**	**.62**	**-.03**	**.80**	**.17**	**.30**	**.12**	**.34**
	Time	.29	<.01	.30	<.01	.21	<.01	.32	<.01	.20	<.01
Demographics	Age			.0003	.94	-.01	.03	-.005	.24	-.01	.06
	Men			-.03	.69	.08	.16	-.04	.59	.08	.24
	Low education			.45	<.01	.22	<.01	.36	<.01	.16	.02
Disease severity	FEV_1% pred					-.005	<.01			-.004	.02
	Exacerbations					.15	<.01			.14	<.01
	MRC dyspnoea					.38	<.01			.37	<.01
	Charlson comorbidity index					.06	.01			.01	.73
Healthy lifestyle	MET minutes							-2.1e-5	.04	7.5e-6	.37
	Self-efficacy							-.02	<.01	-.01	<.01
	Smoker							.14	.11	.13	.07
	Observations (N)	825		754		726		542		524	
SGRQ		*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*
	Intercept	31.4	<.01	23.7	<.01	22.5	<.01	59.0	<.01	40.8	<.01
	Adherence (continuous)	**4.96**	**.11**	**2.86**	**.37**	**-.58**	**.81**	**1.86**	**.58**	**.34**	**.90**
	Time	1.94	.21	2.34	.13	.57	.63	2.93	.11	.35	.81
Demographics	Age			.09	.24	-.07	.22	-.03	.71	-.06	.38
	Men			-1.98	.21	.97	.42	-3.48	.04	-.37	.79
	Low education			10.1	<.01	4.64	<.01	9.32	<.01	4.50	<.01
Disease severity	FEV_1% pred					-.11	<.01			-.15	<.01
	Exacerbations					3.48	<.01			3.71	<.01
	MRC dyspnoea					9.15	<.01			8.37	<.01
	Charlson comorbidity index					1.37	<.01			.76	.19
Healthy lifestyle	MET minutes							-.001	.01	.0002	.26
	Self-efficacy							-.37	<.01	-.22	<.01
	Smoker							-.62	.74	-.55	.70
	Observations (N)	794		729		704		542		523	
EQ-5D		*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*
	Intercept	.70	<.01	.63	<.01	.77	<.01	.35	<.01	.62	<.01
	Adherence (continuous)	**.03**	**.44**	**.04**	**.22**	**.06**	**.06**	**.01**	**.83**	**.02**	**.64**
	Time	.07	<.01	.06	<.01	.07	<.01	.06	<.01	.07	<.01
Demographics	Age			.001	.25	.002	.02	.001	.30	.001	.19
	Men			.06	<.01	.04	.03	.07	<.01	.04	.02
	Low education			-.09	<.01	-.05	<.01	-.08	<.01	-.05	.02
Disease severity	FEV_1% pred					-.0002	.68			-.001	.33
	Exacerbations					-.02	<.01			-.02	.02
	MRC dyspnoea					-.05	<.01			-.04	<.01
	Charlson comorbidity index					-.04	<.01			-.03	<.01
Healthy lifestyle	MET minutes							-6.8e-7	.78	-4.6e-6	.05
	Self-efficacy							.005	<.01	.004	<.01
	Smoker							-.02	.37	-.03	.17
	Observations (N)	827		760		733		555		535	

CCQ Clinical COPD Questionnaire, *SGRQ* Saint George's Respiratory Questionnaire, *EQ-5D* EuroQoL 5-Dimensions, *FEV_1% pred* predicted percentage of Forced Expiratory Volume in 1 second, *MRC* Medical Research Council, *IPAQ* International Physical Activity Questionnaire, *MET* Metabolic Equivalent Time

Appendix 7.5 Linear mixed models using the minimum PDC if patients used medications from different maintenance medication categories

CCQ		*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*
	Intercept	1.48	<.01	1.23	<.01	1.10	<.01	2.72	<.01	1.85	<.01
	Adherence (minimum)	**.06**	**.41**	**.03**	**.70**	**.01**	**.89**	**.04**	**.61**	**.04**	**.50**
	Time	.20	<.01	.30	<.01	.22	<.01	.32	<.01	.21	<.01
Demographics	Age			.001	.65	-.01	.07	-.004	.35	-.01	.10
	Men			-.04	.53	.07	.23	-.05	.50	.07	.29
	Low education			.45	<.01	.22	<.01	.36	<.01	.16	.02
Disease severity	FEV_1% pred					-.01	<.01			-.005	.01
	Exacerbations					.15	<.01			.14	<.01
	MRC dyspnoea					.37	<.01			.36	<.01
	Charlson comorbidity index					.06	<.01			.01	.63
Healthy lifestyle	MET minutes							-2.3e-5	.02	6.0e-6	.48
	Self-efficacy							-.02	<.01	-.01	<.01
	Smoker							.14	.11	.13	.06
	Observations (N)		817		748		720		537		519
SGRQ		*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*
	Intercept	33.9	<.01	23.3	<.01	20.6	<.01	58.6	<.01	39.6	<.01
	Adherence (minimum)	**2.22**	**.15**	**1.46**	**.35**	**.16**	**.90**	**2.90**	**.69**	**.44**	**.74**
	Time	2.10	.18	2.41	.12	.65	.59	2.90	.11	.37	.80
Demographics	Age			.12	.13	-.05	.40	-.02	.86	-.05	.50
	Men			-2.30	.15	.72	.55	-3.67	.03	-.47	.73
	Low education			10.2	<.01	4.69	<.01	9.32	<.01	4.48	<.01
Disease severity	FEV_1% pred					-.12	<.01			-.15	<.01
	Exacerbations					3.51	<.01			3.76	<.01
	MRC dyspnoea					9.09	<.01			8.34	<.01
	Charlson comorbidity index					1.40	<.01			.80	.17
Healthy lifestyle	MET minutes							-.001	.01	.0002	.31
	Self-efficacy							-.36	<.01	-.22	<.01
	Smoker							-.57	.76	-.48	.74
	Observations (N)		786		723		698		537		518
EQ-5D		*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*
	Intercept	.71	<.01	.68	<.01	.82	<.01	.37	<.01	.65	<.01
	Adherence (minimum)	**.01**	**.66**	**.01**	**.44**	**.02**	**.21**	**.01**	**.78**	**.01**	**.62**
	Time	.07	<.01	.06	<.01	.07	<.01	.06	<.01	.07	<.01
Demographics	Age			.001	.45	.002	.05	.001	.38	.001	.26
	Men			.07	<.01	.04	<.01	.07	<.01	.05	.01
	Low education			-.09	<.01	-.05	<.01	-.08	<.01	-.05	.01
Disease severity	FEV_1% pred					-.0001	.74			-.0005	.35
	Exacerbations					-.02	<.01			-.02	.02
	MRC dyspnoea					-.05	<.01			-.04	<.01
	Charlson comorbidity index					-.04	<.01			-.03	<.01
Healthy lifestyle	MET minutes							-4.6e-8	.99	-3.9e-6	.10
	Self-efficacy							.005	<.01	.004	<.01
	Smoker							-.02	.31	-.03	.13
	Observations (N)		819		754		727		550		530

CCQ Clinical COPD Questionnaire, *SGRQ* Saint George's Respiratory Questionnaire, *EQ-5D* EuroQoL 5-Dimensions, *FEV_1% pred* predicted percentage of Forced Expiratory Volume in 1 second, *MRC* Medical Research Council, *IPAQ* International Physical Activity Questionnaire, *MET* Metabolic Equivalent Time

Appendix 7.6 Linear mixed models using the maximum PDC if patients used medications from different maintenance medication categories

CCQ		*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*
	Intercept	1.39	<.01	1.21	<.01	1.11	<.01	2.66	<.01	1.81	<.01
	Adherence (maximum)	**.17**	**.02**	**.15**	**.05**	**.04**	**.52**	**.17**	**.05**	**.12**	**.09**
	Time	.30	<.01	.30	<.01	.21	<.01	.32	<.01	.20	<.01
Demographics	Age			.001	.87	-.01	.05	-.005	.26	-.01	.06
	Men			-.03	.65	.08	.19	-.04	.64	.08	.22
	Low education			.45	<.01	.22	<.01	.35	<.01	.16	.02
Disease severity	FEV_1% pred					-.01	<.01			-.004	.02
	Exacerbations					.15	<.01			.14	<.01
	MRC dyspnoea					.37	<.01			.37	<.01
	Charlson comorbidity index					.06	.01			.01	.75
Healthy lifestyle	MET minutes							-2.2e-5	.03	6.3e-6	.47
	Self-efficacy							-.02	<.01	-.01	<.01
	Smoker							.14	.09	.14	.06
	Observations (N)		818		749		721		542		520
SGRQ		*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*
	Intercept	31.1	<.01	22.3	<.01	22.2	<.01	57.2	<.01	38.7	<.01
	Adherence (maximum)	**5.75**	**<.01**	**4.81**	**<.01**	**1.43**	**.27**	**3.34**	**.06**	**1.87**	**.19**
	Time	2.19	.15	2.41	.12	.62	.60	2.89	.11	.38	.79
Demographics	Age			.10	.22	-.06	.32	-.03	.76	-.06	.42
	Men			-2.13	.17	.80	.51	-3.43	.05	-.34	.81
	Low education			9.99	<.01	4.70	<.01	9.14	<.01	4.41	<.01
Disease severity	FEV_1% pred					-.11	<.01			-.15	<.01
	Exacerbations					3.51	<.01			3.76	<.01
	MRC dyspnoea					9.09	<.01			8.37	<.01
	Charlson comorbidity index					1.36	<.01			.73	.20
Healthy lifestyle	MET minutes							-.001	.01	.0002	.30
	Self-efficacy							-.36	<.01	-.22	<.01
	Smoker							-.48	.79	-.45	.76
	Observations (N)		820		724		699		538		519
EQ-5D		*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*
	Intercept	.72	<.01	.69	<.01	.82	<.01	.39	<.01	.66	<.01
	Adherence (maximum)	**-.01**	**.65**	**-.004**	**.82**	**.02**	**.34**	**-.01**	**.63**	**.001**	**.96**
	Time	.07	<.01	.06	<.01	.07	<.01	.06	<.01	.07	<.01
Demographics	Age			.001	.43	.002	.05	.001	.40	.001	.28
	Men			.07	<.01	.04	<.01	.07	<.01	.05	.01
	Low education			-.09	<.01	-.05	<.01	-.08	<.01	-.05	.01
Disease severity	FEV_1% pred					-.0001	.81			-.0005	.36
	Exacerbations					-.02	<.01			-.02	.02
	MRC dyspnoea					-.05	<.01			-.04	<.01
	Charlson comorbidity index					-.04	<.01			-.03	<.01
Healthy lifestyle	MET minutes							-5.3e-8	.98	-4.0e-6	.09
	Self-efficacy							.005	<.01	.004	<.01
	Smoker							-.02	.33	-.03	.14
	Observations (N)		820		755		728		551		531

CCQ Clinical COPD Questionnaire, *SGRQ* Saint George's Respiratory Questionnaire, *EQ-5D* EuroQoL 5-Dimensions, *FEV_1% pred* predicted percentage of Forced Expiratory Volume in 1 second, *MRC* Medical Research Council, *IPAQ* International Physical Activity Questionnaire, *MET* Metabolic Equivalent Time

CHAPTER 8

Are GOLD ABCD groups better associated with health status and costs than GOLD 1234 grades?

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Prim Care Respir J 2014; 23(1): 30-37

ABSTRACT

Aim: To investigate the association of the GOLD ABCD groups classification with costs and health-related quality-of-life (HRQoL) and compare this with the GOLD 1234 grades classification that was primarily based on lung function only.

Methods: In a cross-sectional study, we selected patients diagnosed with COPD from electronic medical records of general practices. Multi-level analysis was used with costs (medication, primary care, healthcare, societal), disease specific (CCQ and SGRQ) and generic (SF-36 and EQ-5D) HRQoL as independent variables. Either the new or the old GOLD stages were included in the analysis together with several covariates (age, gender, living situation, co-morbidity, self-efficacy, smoking, education, employment).

Findings: 611 patients from 28 general practices were categorized in GOLD-A (333), GOLD-B (110), GOLD-C (80) and GOLD-D (88). Groups GOLD-B and GOLD-D had the highest prevalence of co-morbidities, and the lowest level of physical activity, self-efficacy and employment. The models with GOLD ABCD groups were stronger related to and explained more variance in costs, disease-specific and generic HRQoL than the models with GOLD 1234 grades. Mean CCQ score worsened significantly with 1.04 (GOLD-B), 0.4 (GOLD-C) and 1.21 (GOLD-D) compared to GOLD-A. Healthcare costs per patient were significantly higher in GOLD-B (72%), GOLD-C (74%) and GOLD-D (131%) as compared with GOLD-A patients.

Conclusion: The GOLD ABCD groups classification was more associated with costs and HRQoL than the GOLD 1234 grades classification. Furthermore, people with GOLD-C had a better HRQoL than people with GOLD-B, but their costs did not differ.

INTRODUCTION

Assessment, monitoring, and treatment of chronic obstructive pulmonary disease (COPD) have long been driven by the level of airflow limitation. However, emphasis has recently shifted towards better understanding of the heterogeneity among patients with COPD. This led to the revision of the strategy document of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) in 2011.[1] In the 2011 GOLD strategy COPD is not only classified with the spirometric 1234 grades, but also with the ABCD groups.[1] According to the ABCD groups, the assessment of COPD is based on symptoms and the risk of experiencing an exacerbation in addition to lung function.[1,15] Low or high symptom burden can be determined using the Modified British Medical Research Council (mMRC) dyspnoea scale[28] (mMRC<2 vs. mMRC≥2) or the COPD Assessment Test (CAT) (CAT<10 vs. CAT≥10).[29] A low or a high risk is based on the history of exacerbations (<2 or ≥2 exacerbations in the previous 12 months) or the forced expiratory volume in 1 second (FEV_1) as percentage of the predicted value (≥50% or <50%), whichever results in a higher risk. Based on this information the patient is placed into one of the four groups ABCD. Ultimately, the GOLD classification should estimate current health status, predict future health outcomes, and guide therapy.[1]

Several studies have investigated the association between the GOLD ABCD groups and health outcomes.[4-7] Lange et al.[4] investigated the ability of the GOLD ABCD groups to predict the risk of exacerbations and mortality in two Danish general populations combined. However, the FEV_1% predicted was based on pre-bronchodilator values, which can overestimate the prevalence of severe COPD. Han et al.[5] evaluated the influence of symptom instrument choice on patient category assignment and prospective exacerbation risk by GOLD group in the COPDGene cohort with patients recruited in hospitals. Soriano et al.[6] compared the distribution and the prognostic validity of the GOLD ABCD groups to the GOLD 1234 grades as predictors for mortality in eleven small Spanish cohorts that were combined. Agusti et al.[7] used the ECLIPSE data to investigate the ability of the GOLD ABCD groups to predict mortality, exacerbations, and hospitalizations. Furthermore, two studies compared the ability of the GOLD 1234 grades and GOLD ABCD groups to predict mortality[8,9] and hospitalizations.[8] However, none of these studies have used such a wide variation of different disease-specific and generic health-related quality of life (HRQoL) measurements as we did in our study. Moreover, none has investigated the association with costs. The latter is important information for decision-analytic models that estimate the cost-effectiveness of COPD treatments in different subgroups.

The aim of our study was to investigate the association of the GOLD ABCD groups classification with a wide range of HRQoL outcomes and cost categories. We compared this with the GOLD 1234 grades classification that was based on lung function only. This study was performed in patients with COPD recruited in primary care, where the vast majority of patients with COPD are treated.

METHODS

Setting

We selected patients diagnosed with COPD from electronic medical records of general practices (EMR-GP) in the Western part of the Netherlands between September 2010 and September 2011. Participants had post-bronchodilator FEV_1/Forced Vital Capacity ratio of <0.7. Patients with terminal illnesses, dementia, cognitive impairment, hard drug abuse, alcohol abuse, or patients who were unable to fill out Dutch questionnaires were excluded. The general practitioners verified that the included patients fulfilled the inclusion and exclusion criteria. All participants provided written informed consent before participation. The study was approved by the Medical Ethics Committee of the Leiden University Centre.

Data

Participants completed the following questionnaires with the support of research nurses: Clinical COPD Questionnaire (CCQ)[10]; St. George Respiratory Questionnaire (SGRQ)[11]; MRC Dyspnoea Scale[2]; Short Form-36 (SF-36)[12]; EuroQoL-5 dimensions (EQ-5D), including both the descriptive part and the Visual Analogue Scale (EQ-5D-VAS)[13]; and a questionnaire asking about healthcare utilization, travel expenses, and absence from paid work in the three months prior to questionnaire completion. Medication prescription was extracted from the EMR-GP. EQ-5D utilities were estimated using the Dutch value set.[14] We collected patient characteristics such as age, gender, co-morbidity, education level, marital status, employment status, self-efficacy, and smoking status. Further details are given in Table 8.1.

Participants were classified according to both 1234 grades and ABCD group.[1] Low symptom burden was defined as mMRC<2 and high symptom burden as mMRC≥2. Spirometry data were obtained from the EMR-GP. If spirometry data were unavailable, a respiratory nurse contacted the individual participants for a spirometry test. The number of exacerbations in the previous 12 months was determined according to International Classification of Primary Care (ICPC) registrations in the EMR-GP. Exacerbations were defined as prescriptions for: (1) prednisone with or

without antibiotic, unless the ICPC explicitly indicated a reason other than COPD exacerbation; or (2) antibiotics alone with an ICPC description of a COPD exacerbation. A gap of at least 21 days between prednisone prescriptions was used to distinguish subsequent exacerbations and define different events.

Patient subgroups were created within GOLD-C and GOLD-D, i.e. those at high risk due to low lung function (GOLD-C_1&D_1), history of frequent exacerbations (GOLD-C_2&D_2), or both (GOLD-C_3&D_3).

Table 8.1 The input and outcome variables used in the analysis

Input variable		
GOLD	*1234 grades*	GOLD-1, GOLD-2, GOLD-3, GOLD-4. Reference group is GOLD-1
	ABCD groups	GOLD-A, GOLD-B, GOLD-C, GOLD-D. Reference group is GOLD-A
Patient characteristic	*Co-morbidity*	Charlson co-morbidity index [233]
	Age	Age of the participants in years at the time of the interview
	Gender	0 female; 1 male
	Low Education	0 high education; 1 low education (defined as no or only primary education)
	Single	0 not single (married/ living together); 1 single (never married, divorced, widow(er))
	Employment	0 not employed; 1 employed
	Self-efficacy	Component of the Self-Management Ability Scale from 0 (worst) to 100 (best)
	Smoking	never smoker; former smoker and smoker. Reference group is never smoker
Outcome variable		
Disease specific HRQoL	*CCQ*	0 (best) to 6 (worst). With 3 sub scores: Symptoms, Functional state and Mental state. The minimum clinically important difference is -0.4 points [30,138]
	SGRQ	Scale from 0 (best) to 100 (worst). With 3 sub scores: symptom, activity, and impact. The minimum clinically important difference is 4 points [119]
Generic HRQoL	*EQ-5D-VAS*	Scale from 0 (worst imaginable health state) to 100 (best imaginable health state) [242]
	SF-36 physical	Scale from 0 (worst) to 100 (best) [73,243]
	SF-36 mental	Scale from 0 (worst) to 100 (best) [73,243]
Cost	*Medication*	Average medication costs in 3 months (including non-COPD medication)
	Primary care	Costs of GP, dietician, physiotherapist, podiatrist, occupational therapist, home care
	Healthcare costs	Costs of medication, primary care, hospital days, intensive care days, specialist visits, ED visits and pulmonary rehabilitation
	Costs from societal perspective	Healthcare, travel and productivity costs

*HRQoL= health related quality of life, CCQ= Clinical COPD Questionnaire, SGRQ= St George Respiratory Questionnaire, EQ-5D-VAS= EuroQoL 5 dimensions-visual analogue scale

We defined 4 different categories of costs (medication costs, costs in the primary care sector, total healthcare costs, and total costs from a societal perspective). Medication costs included COPD- and non-COPD-related prescriptions. Primary care costs included costs of consulting with a GP, nurse, dietician, physiotherapist, podiatrist, or occupational therapist, and costs of home care provided by home care organisations. Total healthcare costs included medication costs, costs of primary care plus hospital admissions, consultations with medical specialists, emergency department visits, and pulmonary rehabilitation costs. In addition to the total healthcare costs, the costs from a societal perspective included travel costs of patients to healthcare providers and costs of productivity losses.

Standard unit costs were obtained from the Dutch manual for costing research[15] inflated to 2012 values using the general consumer price index.[16] The costs of medications were obtained from the GIP-Databank, including taxes and pharmacist dispensing fees.[17] The productivity costs were estimated using the Friction Cost Approach, which assumes that productivity loss only occurs during the time it takes to replace a sick employee (the friction period).[18] We used a friction period of 115 days.[15]

Statistical analyses

Descriptive statistics of patient characteristics, clinical measures, HRQoL, and costs were provided. Continuous variables were summarized by mean and standard deviation, categorical variables were summarized by frequencies. We used ANOVAs for normally-distributed variables, Kruskal-Wallis tests for non-normally distributed continuous variables, and Pearson's chi-square tests for categorical variables to test for differences between the four 1234 grades and ABCD groups. *P*-values <0.05 were considered statistically significant.

We modelled disease-specific and generic HRQoL as functions of the 1234 grades and the ABCD groups controlling for patient characteristics using linear mixed-effects models. We accounted for the hierarchical nature of the data in these multi-level models with level 1 patient and level 2 general practices. This model was specified for 6 different outcome variables: CCQ_, SGRQ_, EQ-5D, EQ-5D-VAS, SF-36 mental component, and SF-36 physical component. The inclusion of a covariate was based on the likelihood ratio test that is suitable to compare the goodness-of-fit of nested models.[19] The following covariates were considered for inclusion: Charlson co-morbidity index, age, gender, low education, employment status, self-efficacy, and smoking status.

We also modelled costs as a function of the 1234 grades and the ABCD groups. We used a generalized linear mixed model suitable for analysing

the right-skewed cost data. The distribution and link function were selected after comparing the goodness-of-fit of models with different specifications of the distribution and link functions. Models that had the lowest Akaike's information criterion (AIC) and the Bayesian information criterion (BIC) were selected. Four cost categories were used as outcome variables: healthcare costs, medication costs, primary care costs, and total costs from a societal perspective.

In all models, we used an unstructured covariance matrix since that does not impose a particular pattern on the covariance. To correct for incorrect specifications of the covariance matrix we used sandwich estimators. The AIC compared the goodness-of-fit of the model that included the ABCD groups with the model that included the 1234 grades. Furthermore, the models were compared with respect to the proportion of explained variance measured at the patient level ().[20] Finally, we tested whether the four ABCD groups statistically differ from each other in the 4 cost and 6 HRQoL models.

RESULTS

Descriptive statistics

Figure 8.1 shows the study flow-chart. From the 2006 potential participants 575 (29%) participants were excluded by their GP. Most of these (59%) were misdiagnosed by their GP. From the remaining 1431 potential participants 57% refused to participate in the study. Most of these indicated no reason for refusing (73%), while others expressed no interest (16%), or reported not having troublesome COPD symptoms (5%). In total, we included 611 participants diagnosed with COPD from 28 general practices. Fifty-five percent were classified in GOLD-A, followed by 18% in GOLD-B, 13% in GOLD-C, and 14% in GOLD-D (Table 8.2). Patients with low exacerbation risks (GOLD-A and GOLD-B) were mainly former GOLD-2 patients (70%). Groups of patients with high exacerbation risks (GOLD-C and GOLD-D) included patients from all former GOLD classes, but were mainly from GOLD-3 (65%). Table 8.2 shows that the major criterion for classifying patients as high-risk was low lung function.

The sample characteristics, according to GOLD group, are presented in Table 8.3. Patients with GOLD-B were older, more often single, and had a lower level of education than patients in other groups. GOLD-C had the highest percentage of current smokers (45%). GOLD-B and GOLD-D had the greatest prevalence of cardiac morbidities, diabetes, and depression in addition to the lowest employment levels, self-efficacy scores, and levels of physical activity.

Patients with GOLD-A had the least impaired disease-specific and generic HRQoL, followed by patients with GOLD-C, GOLD-B, and GOLD-

Figure 8.1 Flow-chart showing inclusion of patients in the study

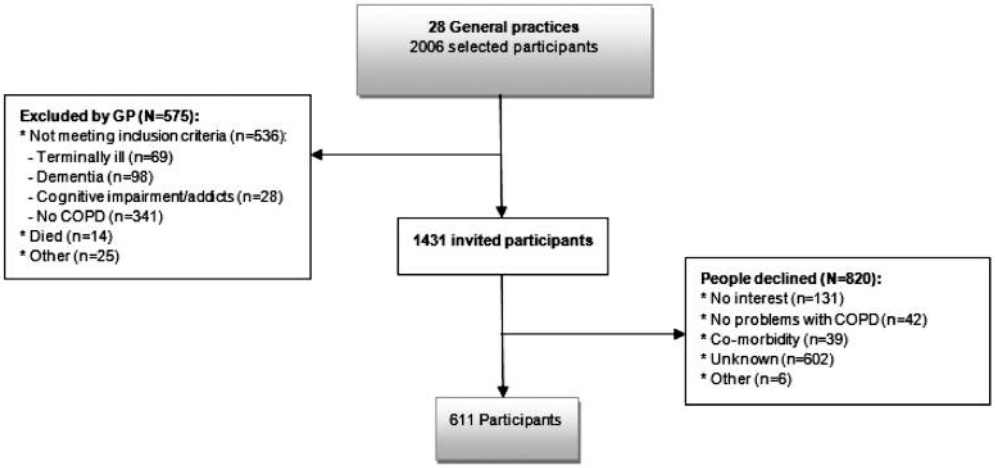


Table 8.2 Patient sample distributed according to the GOLD 1234 grades and ABCD groups classification

	GOLD-1	GOLD-2	GOLD-3	GOLD-4	TOTAL
GOLD-A	105	228	0	0	333 (55%)
GOLD-B	30	80	0	0	110 (18%)
GOLD-C	10	14	51	5	80 (13%)
GOLD-$C_{1\ (lung\ function)}$	0	0	38	5	43
GOLD-$C_{2\ (exacerbation)}$	10	14	0	0	24
GOLD-$C_{3\ (lung\ function + exacerbation)}$	0	0	13	0	13
GOLD-D	4	13	59	12	88 (14%)
GOLD-$D_{1\ (lung\ function)}$	0	0	49	8	57
GOLD-$D_{2\ (exacerbation)}$	4	13	0	0	17
GOLD-$D_{3\ (lung\ function + exacerbation)}$	0	0	10	4	14
TOTAL	**149 (24%)**	**335 (55%)**	**110 (18%)**	**17 (3%)**	**611 (100%)**

D, for all HRQoL measures. Patients with GOLD-A had the lowest costs while patients with GOLD-D had the highest.

Table 8.3 Sample characteristics according to GOLDABCD groups classification

		GOLD-A (N=333)	GOLD-B (N=110)	GOLD-C (N=80)	GOLD-D (N=88)	Average (N=611)	P-value
Disease	*FEV_1*	73.2 (14.6)	72.1 (16.4)	50.3 (19.9)	43.6 (16.4)	65.7 (19.8)	
	FER	58.8 (8.3)	58.2 (9.1)	47.1 (12.8)	44.2 (13.3)	55.1 (11.6)	
	Exacerbation rate	0.14 (0.34)	0.25 (0.43)	1.51 (1.71)	1.56 (2.02)	0.54 (1.20)	
	MRC dyspnoea	1.26 (0.67)	3.45 (0.67)	1.40 (0.54)	3.64 (0.68)	2.01 (1.24)	
	Charlson Index	2.14 (1.11)	2.61 (1.34)	2.08 (1.11)	2.52 (1.35)	2.27 (1.21)	0.002
	Severe cardiac problems, %	10%	25%	18%	18%	15%	0.002
	Diabetes, %	12%	19%	12%	21%	15%	0.091
	Depression, %	7%	14%	12%	14%	10%	0.067
Patient	*Age*	67 (11)	72 (11)	69 (10)	69 (10)	68 (11)	0.001
	Men, %	58%	48%	60%	55%	56%	0.279
	Low education, %	34%	56%	51%	49%	43%	<0.001
	Single, %	33%	51%	33%	36%	37%	0.018
	Employment, %	36%	15%	29%	13%	28%	<0.001
	Self-efficacy	68.5 (16.4)	61.1 (17.1)	69.8 (16.0)	57.8 (17.3)	65.7 (17.1)	<0.001
Health behaviour	*Smoker, %*	35%	34%	45%	27%	35%	0.166
	Former smoker, %	56%	53%	50%	66%	56%	
	Non-smokers, %	8%	13%	5%	7%	8%	
	MET-min	3876 (5331)	1211 (1717)	3112 (4906)	1304 (2564)	2923 (4630)	<0.001
	High/moderate physical activity, %	15%	4%	14%	3%	11%	0.001
	Low physical activity, %	85%	96%	86%	97%	89%	
HRQoL	*CCQ*	1.04 (0.70)	2.20 (0.99)	1.41 (0.73)	2.42 (0.91)	1.50 (0.98)	<0.001
	SGRQ	25.5 (14.6)	51.8 (17.4)	33.9 (16.6)	56.3 (16.8)	35.8 (20.3)	<0.001
	EQ-5D	0.81 (0.22)	0.62 (0.30)	0.76 (0.24)	0.64 (0.28)	0.74 (0.26)	<0.001
	EQ-5D-VAS	73.6 (14.0)	58.1 (17.0)	68.3 (14.4)	54.9 (17.7)	67.4 (17.0)	<0.001
	SF36 Physical	42.7 (9.4)	32.6 (10.0)	40.0 (8.9)	28.9 (8.6)	38.5 (10.8)	<0.001
	SF36 Mental	50.8 (9.2)	45.9 (10.6)	48.9 (10.4)	45.3 (11.1)	48.9 (10.1)	<0.001
Cost	*Medication*	219 (209)	336 (365)	427 (691)	361 (253)	288 (353)	<0.001
	Primary care	173 (232)	289 (299)	213 (298)	425 (457)	236 (307)	<0.001
	Healthcare costs	653 (1375)	1124 (1737)	1143 (1497)	1877 (2778)	978 (1772)	<0.001
	Costs from societal perspective	917 (1857)	1164 (1749)	1640 (3022)	2195 (4674)	1240 (2633)	<0.001

*Values are means (S.D.) unless stated otherwise, *FEV_1* Forced expiratory volume in 1 second, *FER* Forced expiratory ratio, *MRC* Medical Research Council Dyspnoea scale, *MET-min* Metabolic equivalent time, *HRQoL*=health related quality-of-life, *CCQ* Clinical COPD Questionnaire, *SGRQ* St George Respiratory Questionnaire, *EQ-5D-VAS* visual analogue scale, *SF36* Short Form 36

Association between GOLD classifications and HRQoL

Table 8.4 shows the results of the multi-level models for HRQoL. The AIC of the models with the GOLD ABCD groups classification were lower than those with the GOLD 1234 grades classification, indicating a better model fit. Furthermore, these models explained more variance between patients compared to models with the GOLD 1234 grades classification, as indicated by a higher R-square.

Patients with GOLD-B, GOLD-C, and GOLD-D had significantly worse HRQoL than those in GOLD-A across all questionnaires after controlling for patient characteristics. For example, the mean CCQ score of patients with GOLD-D was 1.21 worse than the mean CCQ score of patients with GOLD-A. Appendix 8.1 shows the pairwise differences from the HRQoL models, first with GOLD-A as reference category, than GOLD-B etc. The HRQoL was significantly different between GOLD-B and GOLD-C, and between GOLD-C and GOLD-D, except for the SF-36 mental component. The HRQoL difference between patients with GOLD-B and GOLD-D was only significant for the SF-36 physical component. The GOLD group order, by increasingly impaired HRQoL was GOLD-A, GOLD-C, GOLD-B, and GOLD-D.

The GOLD 1234 grades classification showed greater impairment of HRQoL as GOLD grade increased, but differences were not statistically significant between GOLD-1 and GOLD-2 in SF-36 physical component, GOLD-1, GOLD-2, and GOLD-3 in SF-36 mental component, and GOLD-1, GOLD-2, GOLD-3, and GOLD-4 in EQ-5D score.

Association between GOLD classifications and costs

Cost models with a lognormal distribution and identity link function showed the best fit (Appendix 8.2). The estimated b-coefficients from our cost models were transformed in the exponential form which allows us to interpret them as the percentage of change in costs. Table 5 shows the results of these generalized linear mixed cost models. The AIC of cost models with the GOLD ABCD groups were slightly lower, indicating a better model fit, and they explained more variance than those with the GOLD 1234 grades. This suggests models using the GOLD ABCD groups classification performed better.

Patients with GOLD-B, GOLD-C, and GOLD-D had significantly higher costs than patients with GOLD-A, except for primary care costs. Total healthcare costs were significantly higher for patients with GOLD-B (72%), GOLD-C (74%), and GOLD-D (131%) than GOLD-A. Costs of patients with GOLD-B were similar to those with GOLD-C, but significantly lower than those with GOLD-D (Appendix 8.3). Overall the rank ordering of GOLD group by increasing costs was GOLD-A, GOLD-B, GOLD-C, and GOLD-D.

The GOLD 1234 grades classification also showed that healthcare costs increased with increasing GOLD grade, (9% higher in GOLD-2, 71% higher in GOLD-3, and 193% higher in GOLD-4 compared to GOLD-1).

Table 8.4 The health related quality-of-life models

	Outcome variable	CCQ		SGRQ		EQ-5D		EQ-5D-VAS		SF-36 physical		SF-36 mental	
Input variable		**ABCD groups**	**1234 grades**	**ABCD groups**	**1234 grades**	**ABCD groups**	**1234 grades**	**ABCD groups**	**1234 grades**	**ABCD groups**	**1234 grades**	**ABCD groups**	**1234 grades**
	Intercept	2.54**	2.52**	37.53**	41.15**	0.43**	0.45**	44.23**	44.53**	41.55**	38.61**	20.42**	22.20**
GOLD	GOLD-B	1.04**		23.08**		-0.18**		-13.52**		-8.83**		-2.99*	
	GOLD-C	0.36**		8.38**		-0.07**		-5.53**		-2.62*		-2.33*	
	GOLD-D	1.21**		27.67**		-0.13**		-15.17**		-11.90**		-2.93*	
	GOLD-2		0.30**		7.72**		0.00		-4.31**		-2.16		-0.86
	GOLD-3		0.68**		15.52**		-0.02		-7.74**		-6.02**		-1.95
	GOLD-4		1.06**		29.65**		-0.14		-15.14**		-9.91**		-7.85**
Patient	Charlson Index	0.13**	0.18**	2.15**	3.48**	-0.04**	-0.05**	-1.25*	-2.02**	-1.82**	-2.28**	-0.63	-0.70
	Age	-0.02**	-0.01*			0.00**	0.00*	0.17*	0.11			0.23**	0.20**
	Low education	0.16**	0.25**	3.17**	5.32**	0.00	-0.02	-0.69	-1.98	-0.29	-1.12	-0.94	-1.33
	Single	0.15	0.24**	1.14	4.10**	-0.03	-0.04					-2.15**	-2.45**
	Employment	-0.17*	-0.29*	-0.27	-3.56			1.16	2.94*	0.83	2.29*		
	Self-efficacy	-0.01**	-0.02**	-0.25**	-0.35**	0.00**	0.00**	0.29**	0.35**	0.07**	0.11**	0.25**	0.26**
	Smoker											-0.66	-0.41
	Former smoker											0.31	0.73
R_1^2, %		47.5	31.2	51.1	32.4	22.4	16.4	31.5	22.2	32.1	19.7	30.5	29.6
AIC		1176.6	1321.9	4341.6	4518.6	-38.2	1.4	4392.2	4457.2	3810.8	3901.0	3797.7	3797.9

* Significant ($p<0.05$), ** Significant ($p<0.01$), *CCQ* Clinical COPD Questionnaire, *SGRQ* St George Respiratory Questionnaire, *EQ-5D-VAS* visual analogue scale, *SF36* Short Form 36, *AIC* Akaike's information criterion, the variable gender did not had an added value for the models, thus gender is not presented in this table

Table 8.5 Cost models

Input variable	Outcome variable	Healthcare costs		Medication costs		Primary care Costs		Costs from societal perspective	
		ABCD groups Exp(β)	1234 grades Exp(β)	ABCD groups Exp(β)	1234 grades Exp(β)	ABCD groups Exp(β)	1234 grades Exp(β)	ABCD groups Exp(β)	1234 grades Exp(β)
	Intercept	296.52**	312.09**	70.90**	71.07**	87.90**	94.78**	351.50**	414.30**
GOLD	GOLD-B	1.72**		1.28*		1.53**		1.53**	
	GOLD-C	1.74**		1.64**		1.20		1.70**	
	GOLD-D	2.31**		1.64**		2.37**		2.11**	
	GOLD-2		1.09		1.05		1.03		1.10
	GOLD-3		1.71**		1.50**		1.54**		1.62**
	GOLD-4		2.93**		2.01**		2.56*		3.20**
Patient	Charlson Index	1.16**	1.18**	1.16**	1.17**	1.13**	1.16**	1.12**	1.14**
	Age	1.00	1.00	1.01*	1.01**				
	Men	0.87	0.82					0.84	0.82*
	Low education	1.21*	1.29**					1.13	1.19
	Employment	0.95	0.89	1.04	1.02	0.86	0.71*		
	Self-efficacy	1.00	1.00	1.00	1.00			1.00	1.00
	Smoker	0.84	0.80					0.97	0.93
	Former smoker	1.24	1.18					1.37*	1.32
R_1^2, %		25.8	22.1	12.1	9.8	10.6	7.4	13.3	10.9
AIC		1475.8	1500.1	1405.6	1415.5	1538.3	1556.9	1608.9	1622.6

* Significant (p<0.05), ** Significant (p<0.01), *AIC* Akaike's information criterion

DISCUSSION

Main Findings

We found that the GOLD ABCD groups classification was stronger related to HRQoL (disease-specific and generic) and costs than the GOLD 1234 grades classification. Multi-level analysis of HRQoL and costs using (generalized) linear mixed models incorporating the GOLD ABCD groups classification consistently explained a higher proportion of the variance between patients and had better goodness-of-fit than models incorporating the GOLD 1234 grades classification.

The rank order of GOLD ABCD groups from best to worst HRQoL found in this primary care population was: GOLD-A, GOLD-C, GOLD-B, GOLD-D. HRQoL was better in patients with GOLD-C than GOLD-B, despite higher exacerbation rates and lower lung function. This can be attributed to the higher level of symptoms in GOLD-B since the results were corrected for a higher score on the Charlson co-morbidity index, lower physical activity level, lower self-efficacy scores, lower educational level, lower employment rate, and higher proportion of single patients with GOLD-B compared to GOLD-C. Moreover, we found that the GOLD 1234 grades classification could not distinguish between GOLD-1 and GOLD-2 with respect to generic HRQoL. Reclassifying patients with GOLD-1 and GOLD-2 into high (GOLD-B) and low symptom burden (GOLD-A) (table 2) led to clearer differences in disease-specific and generic HRQoL. Similarly, the separation of patients withGOLD-3 and GOLD-4 into GOLD-C and GOLD-D, led to clearer distinctions in HRQoL. Patients with lower risk levels had a significantly better HRQoL than patients with a higher risk level and adding symptom burden to lung function has improved the discriminative capabilities of the GOLD classification.

The rank order of GOLD groups by increased costs was: GOLD-A, GOLD-B, GOLD-C, GOLD-D. The GOLD 1234 grades classification could not distinguish between GOLD-1 and GOLD-2 but the GOLD ABCD groups classification did show that costs in GOLD-B, GOLD-C, and GOLD-D differed from costs in GOLD-A. Despite the fact that the model with the GOLD groups explained somewhat more variation in costs, none of the cost categories showed a statistically significant difference between GOLD-B and GOLD-C. Apparently, the higher level of symptoms in GOLD-B did not lead to more health-care use.

Strengths and limitations of this study

Apart from the wide range of HRQoL measures and costs that was used, the strength of our study lies in the large number of patients with COPD from many general practices. The sample covers the entire range of

COPD severity and is representative of the Dutch COPD population because we applied few inclusion and exclusion criteria. Although we have recruited patients in primary care, the sample also included patients seen by pulmonary physicians in hospitals. That is because the patients referred to secondary care are still included in the GP's records. Our severity distribution (24% GOLD-1, 55% GOLD-2, 18% GOLD-3, 3% GOLD-4) was comparable to the severity distribution that was previously reported in primary care (27% GOLD-1, 55% GOLD-2, 15% GOLD-3, and 2% GOLD-4).[21] Moreover, like other primary care studies[22,23], approximately one-third of our study population had a high symptom burden (mMRC≥2).

This study has some limitations. One is that healthcare utilization was self-reported, except for prescriptions. This may have led to an underestimation of costs. If that occurred to an equal extent in all four GOLD classes, differences between the four classes are not biased.[24] Another limitation is that the exacerbation history was retrospectively obtained from prednisone and antibiotic prescriptions in combination with ICPC codes recorded in the EMR-GP. This way, mild exacerbations cannot be included. Although these mild exacerbations are unlikely to affect costs they may affect HRQoL. A third limitation was that, despite its size (>600 patients) our sample size was still insufficient to allow subgroup analysis within GOLD-C and GOLD-D. That is because most patients had either GOLD-A or GOLD-B. GOLD-C and GOLD-D contain a mixture of patients with a high risk due to a low lung function, a history of frequent exacerbations, or both (Table 2). The latter patients are likely to have a worse HRQoL and higher healthcare costs. However, we were unable to confirm this.

Interpretation of findings in relation to previously published work

Since the GOLD strategy revision in 2011, several studies investigated the distribution and characteristics of the GOLD ABCD groups and their association with outcomes.[4-9] Lange et al.[4] and Leivseth et al.[9] recruited patients in the general population, while Han et al.[5], Soriano et al.[6], Augusti et al.[7], and Johannessen et al.[8] recruited patients mostly in hospital settings. We recruited patients from primary care, which is most likely the reason why we found more GOLD-C patients and less GOLD-D patients than in the latter four studies.[5-8] Despite the difference in recruitment setting, our finding that comorbidities were particularly prevalent in the two 'high symptom' groups (GOLD-B and GOLD-D) is in line with previous studies.[7-8] Furthermore, like previous reports[4-5], we found that patients were often categorized at high risk of exacerbation because of lung function rather than exacerbation history. Only 30% of GOLD-C patients

and 19% of GOLD-D patients were assigned to high risk groups because of their exacerbation history. Also consistent with earlier studies[5,22], was our finding that HRQoL for GOLD-C patients was better than GOLD-B patients. Three studies found that 3-year survival was similar for GOLD-B and GOLD-C patients[4,6,7], but results seem to change on the long term, because one study found that patients in GOLD-B had a better survival then those in GOLD-C after 10 years follow up.[6] Two studies concluded that the GOLD ABCD groups classification did not differ significantly from the GOLD 1234 grades classification in terms of predicting mortality[6,8] and hospitalizations.[8] Moreover, in one study[9] the GOLD 1234 grades predicted mortality better than the GOLD ABCD groups.

Debates on the GOLD ABCD groups classification are ongoing. For example, it has been suggested that 1 severe exacerbation requiring hospitalization should qualify a patient as having a high-risk.[26,27] In our sample there were only three hospitalizations for COPD exacerbations among the low-risk group in the past three months. One occurred in GOLD-A and two in GOLD-B. Moving these patients to the high risk groups would not have changed our results.

Implications for future research, policy, and practice

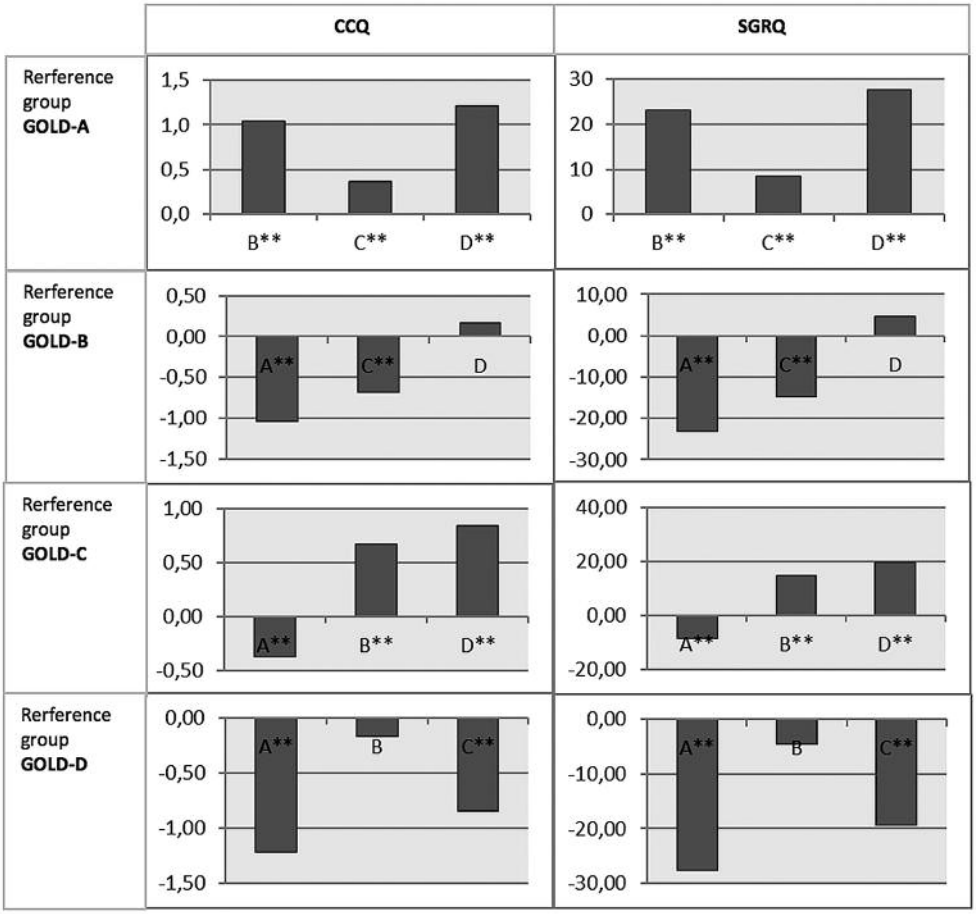
Whether the GOLD ABCD groups classification will lead to major changes in daily practice is questionable. The GOLD ABCD groups classification certainly raises awareness among physicians that assessment of COPD severity should include multiple components other than lung function. It stimulates patient-centred outcome thinking. It is a step towards personalized medicine, although that would also require an integrated assessment of for example risk factors, biomarkers, exercise capacity, nutritional status, multi-morbidities, personal goals, illness perceptions, and coping behaviour as is currently advocated by the Dutch Care Standard for COPD.[28]The GOLD ABCD groups classification may have consequences for decision-analytic models that aim to assess the cost-effectiveness of COPD treatments. Currently, most of these models are state-transition models in which the states are defined by FEV1% predicted and exacerbations. However, these models are also moving towards the simulation of individual patients with different characteristics. Adopting the GOLD ABCD groups classification may be a step towards this, although it still needs to be demonstrated that the cost-effectiveness of treatments indeed varies between the GOLD ABCD groups.

CONCLUSIONS

Onderkant formulier

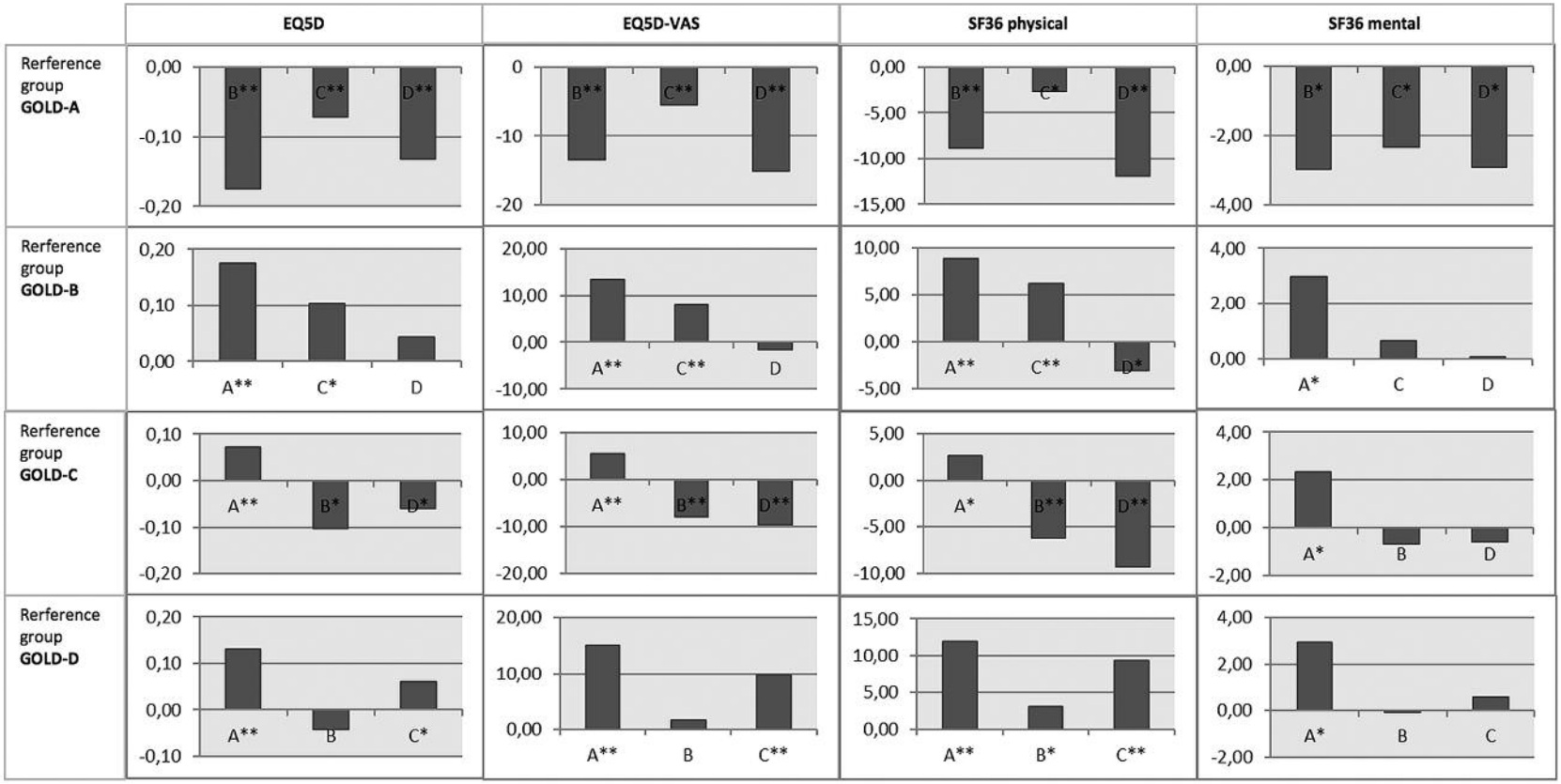
The GOLD ABCD groups classification stimulates a multi-dimensional assessment of COPD severity that appears to be more strongly related to HRQoL (disease-specific and generic) and costs than the GOLD 1234 grades classification that was mainly based on lung function. Reclassifying the former GOLD-1 and GOLD-2 patients into the GOLD ABCD groups classification clearly led to a greater difference in HRQoL (disease-specific and generic) and costs between groups. Similarly, separating former GOLD-3 and GOLD-4 patients into GOLD-C and GOLD-D, led to a clearer difference in HRQoL. Furthermore, a patient with GOLD-C had a better HRQoL than a patient with GOLD-B, but their costs did not differ.

Appendix 8.1a Differences in GOLD grade estimated by the disease-specific HRQoL models as shown in table 8.4 with the different GOLD grades as reference category



* Significant (p<0.05), ** Significant (p<0.01), *CCQ* Clinical COPD Questionnaire, *SGRQ* St George Respiratory Questionnaire

Appendix 8.1b Differences in GOLD grade estimated by the generic HRQoL models as shown in table 8.4 with the different GOLD grades as reference category



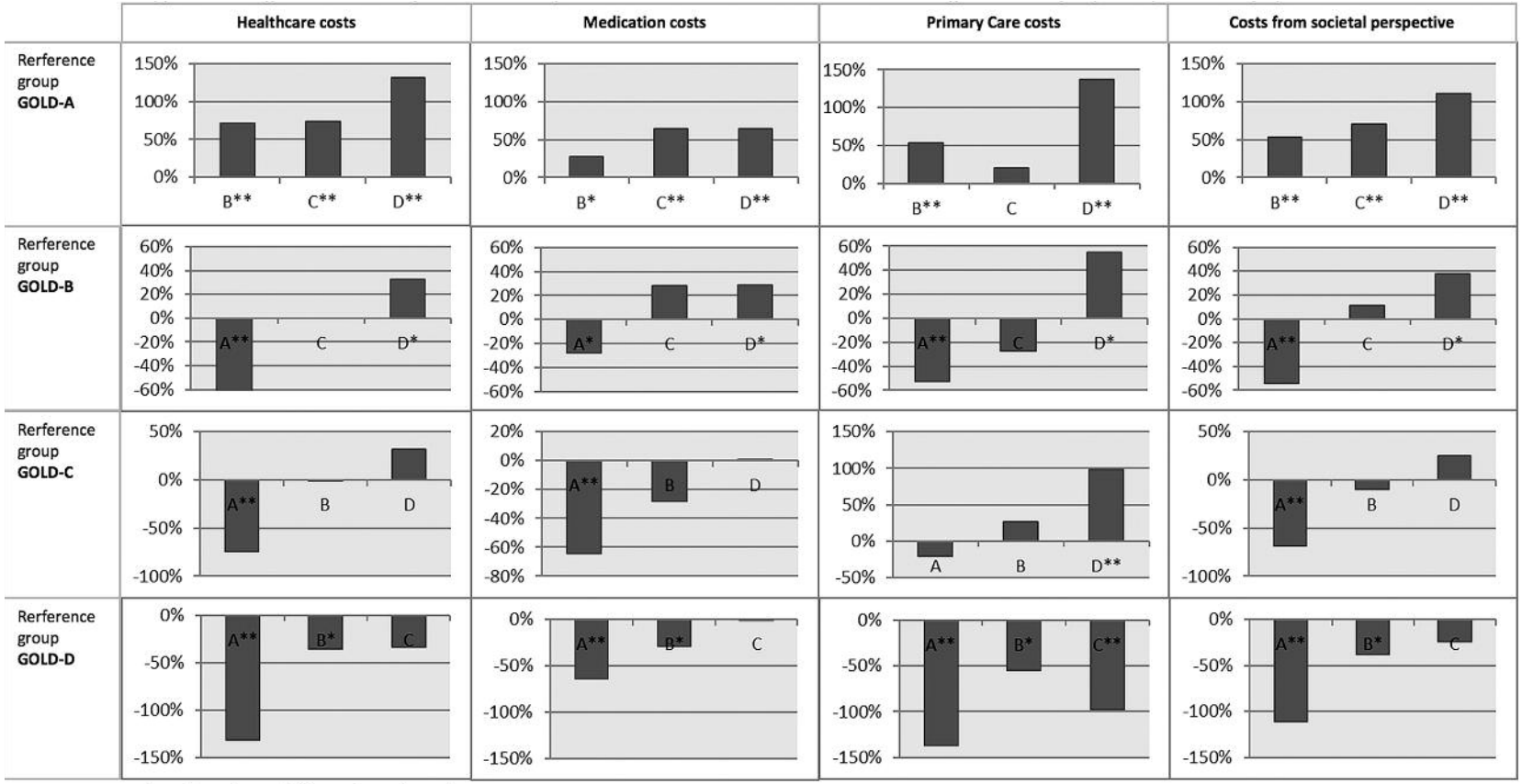
* Significant (p<0.05), ** Significant (p<0.01), *EQ-5D-VAS* visual analogue scale, *SF36* Short Form 36

Appendix 8.2 Distribution and link function

Outcome	Link function	Goodness-of-fit test	Distribution Gaussian	Gamma	Lognormal	Exponent
Healthcare costs	Identity	AIC	9375		**1461**	
		BIC	9395		**1481**	
	Log	AIC		8193		8200
		BIC		8213		8218
Medication costs	Identity	AIC	7182		**1300**	
		BIC	7201		**1320**	
	Log	AIC		6736		6906
		BIC		6756		6925
Primary care costs	Identity	AIC	7522		**1469**	
		BIC	7542		**1489**	
	Log	AIC		6335		6763
		BIC		6355		6781
Costs from societal perspective	Identity	AIC	9781		**1557**	
		BIC	9811		**1577**	
	Log	AIC		8431		8430
		BIC		8451		8448

AIC Akaike's information criterion, *BIC* Bayesian information criterion.

Appendix 8.3 Differences in GOLD grade estimated by the cost models as shown in Table 8.5 with the different GOLD groups as reference category



* Significant (p<0.05), ** Significant (p<0.01)

CHAPTER 9

Mapping the Clinical COPD Questionnaire onto generic preference-based EQ-5D utility values.

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Value Health 2015; 18(2): 299-307

ABSTRACT

Objectives: This study aims to develop a model to predict mean EQ-5D utilities from Clinical COPD Questionnaire (CCQ) scores.

Methods: To include a broad range of patients with different severity levels of COPD, we used the data from three trials (RECODE and GO-AHEAD, MARCH trial) including 5751 observations. Data was randomly split into an estimation and a validation sample. The conceptual similarity between the CCQ and EQ-5D was assessed using correlation matrix and principal component analysis (PCA). Different types of models were created with increasing complexity. We selected the final model based on the Mean Absolute Error and Root Mean Square Error of the internal and external validity. We also developed models for different value sets of the EQ-5D.

Results: The PCA showed that the CCQ domains functional state and mental state gave detailed information on four dimensions of the EQ-5D (mobility, self-care, usual activities, depression/anxiety). The EQ-5D dimension pain/discomfort formed a separate construct on which no CCQ item loaded. Our recommended model was able to predict the mean EQ-5D utility in the internal validation sample well. The ability to predict the mean in a different population was less good. The model underestimated EQ-5D utilities in milder health states and overestimated them in more severe health states. The predictive ability of the mapping models was similar across different EQ-5D value sets.

Conclusions: The mean EQ-5D utilities can be predicted from CCQ scores. However, the mapping algorithm is not ideal because of conceptual differences between the CCQ and EQ-5D questionnaire.

INTRODUCTION

Studies assessing the effectiveness of new chronic obstructive pulmonary disease (COPD) treatments commonly use disease-specific health-related quality of life (HRQoL) instruments such as the St. George's Respiratory Questionnaire (SGRQ)[168] and the clinical COPD questionnaire (CCQ).[30] However, preference-based HRQoL measures such as the EQ-5D[72] are often not included in those studies. Nevertheless, data from such studies frequently form the basis of post-hoc cost-utility analyses that aim to estimate the incremental costs per Quality Adjusted Life Year (QALY) gained. To enable the calculation of QALYs in the absence of directly collected EQ-5D data, the SGRQ or CCQ scores from these studies need to be converted to utilities. This can be done with a model or algorithm that maps disease-specific HRQoL data to EQ-5D data. This solution has also been recommended by the National Institute for Health and Care Excellence[244] and is seen as a better approach than judgements of experts.[245] Prior to July 2013, ninety studies estimated 121 mapping models and reported algorithms to allow other researchers to use them to predict EQ-5D values.[246]

A model to map SGRQ scores onto EQ-5D values has been published.[240] However, a model to predict EQ-5D values from CCQ data has not been developed. It is relevant to do so because the CCQ is increasingly used, not only because it is brief and takes little time to complete[93], but also because the 2013 revision of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend the CCQ as one of the options to define symptom level, i.e. one of the 3 components of the COPD classification.[247] This study aims to develop a model to predict EQ-5D values from CCQ scores obtained in clinical trials.

METHODS

Instruments

CCQ. The CCQ is an instrument to measure HRQoL in COPD patients on 3 domains (symptoms, functional state and mental state). The symptom and functional domain contain 4 items each and the mental domain contains 2 items. Patients have to respond to each item on a seven-point scale resulting in over 282 million possible health states. Response options on CCQ items 1-6 are: never / hardly ever / a few times / several times / many times / a great many times / almost all the time. Response options on CCQ items 7-10 are: not limited at all / very slightly limited / slightly limited / moderate limited / very limited / extremely limited / totally limited or unable to do. The total CCQ score and the scores of the domains are calculated by adding up the item scores and dividing this sum by the number of items, where 0 is the best and 6 is the worst score.[30]

EQ-5D. The EQ-5D is a generic HRQoL questionnaire. It consists of 5 dimensions to describe the current health states of patients: mobility, self-care, usual activity, pain/discomfort, anxiety/depression. Each dimension is measured with 1 item and respondents have to respond to each item on a three-point scale (no, some or extreme problems). This results in 243 potential health states. EQ-5D values are calculated by combining the responses on each dimension with off-the-shelf preference-based weights (i.e. a value set). In the base case, we used the Dutch EQ-5D value set to calculate the EQ-5D values of the COPD patients. These EQ-5D values can range from -0.329 to 1, where 0 indicates a health state equivalent to dead and 1 indicates full health.[72,139] In the sensitivity analyses we used UK and US EQ-5D value sets.

Setting and participants

To include a broad range of patients with different severity levels of COPD, we combined the data from three trials: the RECODE trial, a 2-year, cluster-randomized controlled trial with 1086 patients recruited from general practice[165]; the GO-AHEAD trial, a 3-month, multi-centre, randomized trial, with 166 patients hospitalized for a COPD exacerbation[248]; and the MARCH trial, a 6 months, randomized controlled trial with 53 patients recruited from general practice.[249] Patients completed both the CCQ and the EQ-5D at 2 (MARCH), 3 (GO-AHEAD) and 6 (RECODE) time points.

Conceptual similarity

Mapping would only be able to appropriately predict EQ-5D values from the CCQ if there are no major conceptual differences between the CCQ and EQ-5D.[250] Therefore, we first investigated the conceptual (dis)similarities between the EQ-5D dimensions and CCQ items using Spearman rank correlations and principal component analysis (PCA). PCA explores which questions included in the two instruments are related to each other and generate information on the same underlying construct. The CCQ questionnaire may include items related to domains that are not included in the EQ-5D and hence will not be reflected in changes in the patient's EQ-5D value, and vice versa. In the explorative PCA all constructs with an eigenvalue >1 were selected[251] while in the confirmatory PCA the number of constructs was set to five, to investigate whether these five constructs would mirror the five dimensions of the EQ-5D. Eigenvalues of a construct represent the relative share of variance accounted for by the construct. The individual items have meaningful loadings on a construct if their absolute value exceeds 0.40. After extracting the initial constructs, varimax rotation was used to improve the differentiation and the interpretability of the results.[252]

Model development

The dataset was randomly split (50%-50%) into a sample that was used to estimate the model and a sample that was used to validate the estimated model. Thereafter, different types of models were estimated with increasing complexity. We started with simple models that predicted EQ-5D value from the total CCQ score and the CCQ domain scores. We also investigated models that included individual items of the CCQ , either as categorical variables or as dummy variables for the seven possible response options of each CCQ item. We further tested whether the model improved when including polynomial terms, patient characteristics (age, Charlson co-morbidity index[233] and sex), and when the seven-point response scale of the CCQ was collapsed into a three-point scale by combining the response options 1 and 2, 3 and 4, and 5, 6, and 7.

These models were estimated using ordinary least squares (OLS) with backward selection procedures. Variables with a P-value>0.10 were removed. To correct for multiple testing, Bonferroni corrections were applied to the models with dummy variables for the seven possible response options of each CCQ item.

Because OLS regression ignores censoring in the EQ-5D values, we investigated whether Tobit and generalized linear models (GLM) performed better than OLS models.[253] The distribution and link function of these models were selected after comparing the goodness-of-fit of models with different specifications of the distribution and link functions (i.e. normal, inverse gaussian, gamma, poisson distributions in combination with log and identity link). Models that had the lowest Akaike's information criterion (AIC) and Bayesian information criterion (BIC) were selected.[254]

To analyse the effect of using repeated measurements of the same patients as independent observations, we estimated a model based on (I) the baseline data of the RECODE trial and (II) data from all measurements in the RECODE trial. Additionally, we estimated models based on (III) data from the GO-AHEAD trial only (because the patients in that trial are more severely ill) and (IV) data from the combined RECODE, GO-AHEAD and MARCH trials.

Model validation

We validated the models that were developed for each dataset (i.e. dataset I to IV as mentioned above). Firstly, the models were used to predict the EQ-5D values of the patients in the validation sample (internal validation). In addition, the models that were developed using data from one trial were used to predict EQ-5D values in the other trials (external validation). Predicted EQ-5D values were compared to the observed EQ-5D

values. The mean absolute error (MAE) was reported for the overall range of observed EQ-5D values and for observed EQ-5D values in a specific range, i.e. EQ-5D<0.25, 0.25≤EQ-5D<0.50, 0.50≤EQ-5D<0.75, 0.75≤EQ-5D≤1. We also calculated the root mean square error (RMSE) which attaches greater weight to larger errors. A scatter plot of observed and predicted values in the validation sample was provided and we tested whether the mean predicted EQ-5D value significantly differed from the mean observed EQ-5D value. We selected the final models based on the MAE and RMSE when comparing the predicted and observed EQ-5D values from the same trial population (internal validity) and from different trial populations (external validity). This was done for models in which EQ-5D values were based on the Dutch value set and, in sensitivity analyses, for models in which EQ-5D values were based on the US value set and UK value set.

Finally, we assessed the precision of the predicted mean EQ-5D value by applying a bootstrap procedure: (I) we randomly sampled patients, with replacement, to create a group of size 10, 25, 50, 100, 250 and 500; (II) we computed the mean predicted EQ-5D value and the mean predicted error for each of the six group sizes; (III) we repeated step (1) and (2) 1000 times to generate a distribution of the group predicted error for each of the six group sizes.

RESULTS

Descriptive statistics

The patient characteristics are presented in Table 9.1. Observations with missing data on the total EQ-5D and/or CCQ score were excluded, resulting in a study population containing 5751 observations. The patients were mainly elderly (68 years), included slightly more men (55%), and had moderate airflow obstruction. Mean (standard deviation (SD)) CCQ score was 1.66 (1.04) and mean EQ-5D value was 0.75 (0.25) whereas the mean EQ-5D value for a representative sample of the Dutch population has been estimated at 0.89.[255] The distribution of EQ-5D values was left-skewed: 25% of the observations were at 1 (full health), 25% were between 0.8 and 1, 25% were between 0.7 and 0.8 and 25% between -0.3 and 0.7. The CCQ scores also showed skewness towards the severe end of the scale: one percent of the CCQ scores were at 0 (full health), 50% of the observations were between 0 and 1.5, 25% between 1.5 and 2.3, and 25% were between 2.3 and 6. Decreased HRQoL was mainly due to the CCQ items 2, 5, 6 and 7 (Table 9.1 gives a description of these items) and more than 50% of the patients reported some or extreme problems in the EQ-5D dimensions mobility and pain/discomfort. The Charlson co-morbidity index, a weighted sum score of the comorbid conditions of a patient, was lower

(i.e. better) in patients in the GO-AHEAD trial than in patients in the MARCH trial.[256] Despite this, the rank order from best to worst mean HRQoL in the trials was: MARCH, RECODE, GO-AHEAD.

Table 9.1 Patient characteristics at baseline and the average EQ-5D and CCQ scores of all the time points in the different databases

	Total data	RECODE	GO-AHEAD	MARCH
Patients	1303	1084	166	53
Observations (number)	5751	5268	382	101
Age, years	68 (11)	68 (11)	68 (11)	64 (11)
Men, %	55.0	54.0	61.0	58.5
FEV_1, % predicted	65.7	67.8	48.3	75.4
FEV_1 ≥50% predicted	76.2	77.7	41.3	94.3
FEV_1 <50% predicted	23.8	22.3	58.8	5.7
Charlson co-morbidity index	2.27 (1.29)	2.34 (1.26)	1.75 (1.09)	2.56 (1.83)
EQ-5D	0.75 (0.25)	0.75 (0.25)	0.67 (0.25)	0.88 (0.13)
Mobility (no/some/extreme problems),%	48.7/ 50.8/ 0.5	49.7/ 49.9/ 0.5	30.69/ 67.5/ 1.8	67.3/32.7/0
Self-care (no/some/extreme problems),%	79.0/ 19.1/ 1.9	80.9/ 17.5/ 1.6	48.2/ 45.0/ 6.8	96.0/4.0/0
Usual activities (no/some/extreme problems),%	58.3/ 37.5/ 4.2	60.7/ 35.8 /3.5	23.6/ 61.3/15.2	65.3/34.7/0
Pain/discomfort (no/some/extreme problems),%	47.5/ 41.4/ 11.1	46.3/ 41.9/ 11.8	57.9/ 37.7/ 4.5	71.3/27.7/1.0
Depression/anxiety (no/some/extreme problems),%	77.0/ 20.6/ 2.4	78.1/ 19.6/ 2.3	60.7/ 34.6/4.7	82.2/17.8/0
CCQ[1]	1.66 (1.04)	1.61 (1.00)	2.51 (1.17)	1.10 (0.78)
Symptoms	2.13 (1.18)	2.12 (1.18)	2.44 (1.16)	1.68 (1.06)
Functional state	1.69 (1.37)	1.60 (1.30)	3.07 (1.58)	0.92 (0.94)
Mental state	0.65 (1.04)	0.59 (0.99)	1.52 (1.39)	0.29 (0.60)
CCQ-1 Short of breath at rest	1.18 (1.31)	1.16 (1.30)	1.68 (1.37)	0.64 (0.84)
CCQ-2 Short of breath doing physical activities	2.76 (1.73)	2.72 (1.71)	3.54 (1.70)	2.15 (1.62)
CCQ-3 Concerned about getting a cold or your breathing getting worse	0.59 (1.11)	0.53 (1.05)	1.52 (1.55)	0.18 (0.46)
CCQ-4 Depressed (down) because of your breathing problems	0.71 (1.19)	0.66 (1.14)	1.51 (1.56)	0.41 (0.82)
CCQ-5 Cough	2.47 (1.58)	2.47 (1.59)	2.54 (1.45)	2.14 (1.72)
CCQ-6 Produce phlegm	2.11 (1.76)	2.12 (1.76)	2.00 (1.64)	1.78 (1.78)
CCQ-7 Strenuous physical activities	2.82 (1.85)	2.75 (1.82)	4.04 (1.89)	1.92 (1.57)
CCQ-8 Moderate psychical activities	1.87 (1.63)	1.78 (1.57)	3.22 (1.84)	1.02 (1.30)
CCQ-9 Daily activities at home	1.16 (1.48)	1.05 (1.36)	2.92 (1.94)	0.37 (0.86)
CCQ-10 Social activities	0.91 (1.32)	0.83 (1.24)	2.14 (1.72)	0.39 (0.91)

Values are means (S.D.) unless indicated otherwise, FEV_1 = Forced expiratory volume in 1 second; a pulmonary function measurement to indicate the severity of airflow obstruction, CCQ= Clinical COPD Questionnaire, [1] Response options on CCQ items 1-6 are: never (0) / hardly ever (1) / a few times (2) / several times (3) / many times (4) / a great many times (5) / almost all the time (6). Response options on CCQ items 7-10 are: not limited at all (0) / very slightly limited (1) / slightly limited (2) / moderate limited (3) / very limited (4) / extremely limited (5) / totally limited or unable to do (6)

Correlation between CCQ and EQ-5D

The correlation matrix between the two instruments is shown in Appendix 9.1. The correlation between the total CCQ scores and the EQ-5D values was moderate (-0.514). The correlations were negative because a better score is indicated by a higher value on the EQ-5D and a lower value on the CCQ. Correlations between the EQ-5D dimensions and the CCQ total score was mostly lower. Weak correlation (<0.3) was found between the total CCQ score and the EQ-5D dimension pain/discomfort. The highest correlation (0.583) was found between the total CCQ score and the EQ-5D dimension usual activity. The lowest correlations (<0.2) were those between any of the EQ-5D dimensions and the CCQ items 5 and 6 related to cough and phlegm production.

The exploratory PCA showed that 4 constructs had an eigenvalue >1 and explained 69% of the total variance (Appendix 9.2). CCQ items 1, 2, 7, 8, 9, 10, which all related to being active and the impact of being active on breathlessness, and the EQ-5D dimensions mobility, self-care and usual activities all loaded onto the same construct. CCQ items 3 and 4 related to being concerned and depressed loaded on the same construct as the EQ-5D dimension depression/anxiety. CCQ items 5 and 6 related to cough and phlegm production formed a distinct construct, unrelated to any of the EQ-5D items. Likewise, the EQ-5D dimensions pain/discomfort and mobility formed a construct on which none of the CCQ items loaded. Hence, the EQ-5D dimension mobility had a loading > 0.4 on two constructs. The two constructs containing both CCQ and EQ-5D items explained a total variance of 48%.

The confirmatory PCA in which the number of components was fixed at 5 is presented in Appendix 9.3. Construct 1 of the exploratory PCA was split into two constructs: one construct with CCQ items 1, 2, 7, 8, 9 and 10 and one construct with CCQ items 7, 8, 9, 10 and EQ-5D dimensions mobility, self-care and usual activities.

Table 9.2 Mapping algorithm (i.e. regression coefficients) of the recommended models

Model A (Dutch value set)				**Model B (Dutch value set)**			
Variable	**B**	**SE**	**P**	**Variable**	**β**	**SE**	**P**
Intercept	.24995	.06295	.0001	Intercept	.28244	.06506	<.0001
Response 0 or 1 on CCQ-1	.13716	.06105	.0259	Response 0 or 1 on CCQ-1	.16570	.06267	.0089
Response 2 or 3 on CCQ-1	.13146	.05734	.0230	Response 2 or 3 on CCQ-1	.14444	.05742	.0128
Response 0 or 1 on CCQ-4	.14506	.05049	.0046	Response 0 or 1 on CCQ-4	.13021	.05083	.0113
Response 2 or 3 on CCQ-4	.09468	.05243	.0726	Response 2 or 3 on CCQ-4	.08218	.05255	.1196
Response 0 or 1 on CCQ-8	.14845	.05814	.0115	Response 0 or 1 on CCQ-8	.12698	.05897	.0327
Response 2 or 3 on CCQ-8	.06910	.03915	.0793	Response 2 or 3 on CCQ-8	.05938	.03927	.1323
Response 0 or 1 on CCQ-9	.18815	.04875	.0002	Response 0 or 1 on CCQ-9	.18981	.04844	.0001
Response 2 or 3 on CCQ-9	.14164	.03762	.0002	Response 2 or 3on CCQ-9	.14809	.03755	.0001
Male	.06658	.03028	.0292	Male	.08202	.03127	.0095
				Charlson co-morbidity index	-.02427	.01340	.0717
Model C (US value set)				**Model D (UK value set)**			
Variable	**β**	**SE**	**P**	**Variable**	**β**	**SE**	**P**
Intercept	.94682	.03204	<.0001	Intercept	.95497	.04719	<.0001
CCQ symptoms^2	-.00683	.00213	.0016	CCQ symptoms^2	-.01041	.00314	.0011
CCQ functional	-.06249	.00970	<.0001	CCQ functional	-.09133	.01428	<.0001
CCQ mental^2	-.01529	.00684	.0265	CCQ mental^2	-.02242	.01007	.0272
CCQ mental^3	.00293	.00150	.0526	CCQ mental^3	.00449	.00221	.0437
Male	.05102	.02276	.0262	Male	.07866	.03352	.0200

CCQ symptoms^2 = CCQ symptoms * CCQ symptoms, CCQ mental^2 = CCQ mental * CCQ mental, CCQ mental^3 = CCQ mental * CCQ mental * CCQ mental

Models with the Dutch EQ-5D value set

The simplest equation for predicting EQ-5D values using the Dutch value set is the 10-parameter model A in Table 9.2. This model, which was based on the GO-AHEAD dataset, had the lowest MAE and RMSE when comparing the predicted and observed EQ-5D values from the same population and from different trial populations, especially when the observed EQ-5D values were below 0.5 (Appendix 9.4). Therefore, this model was chosen as the best model. Model A was able to predict a mean EQ-5D value that was not significantly different from the observed mean EQ-5D value in the validation dataset (Table 9.3). In the external validation, the model was able to predict a mean EQ-5D value that did not significantly differ from the mean observed EQ-5D value in the MARCH dataset but the model was unable to predict an accurate mean EQ-5D value in the RECODE dataset (Table 9.4). Model A is a classical OLS regression model because that model outperformed the GLM models with different distributions and link functions. Furthermore, performing a Tobit model instead of an OLS model increased the MAE (0.152 vs. 0.161) and the RMSE (0.198 vs. 0.214).

Table 9.3 Internal validity of the recommended models based on the GO-AHEAD database using different EQ-5D value sets.

EQ-5D value set	Dutch Model A		Dutch Model B		US Model C		UK Model D	
	Observed	Predicted	Observed	Predicted	Observed	Predicted	Observed	Predicted
Mean EQ-5D	.6625	.6843	.6625	.6901	.6993	.7134	.6002	.6161
MAE	.1520		.1471		.1211		.1766	
RMSE	.1983		.1963		.1552		.2289	
Mean if observed EQ-5D < 0.25	.1562	.5181	.1562	.5238	.2190	.5184	.0912	.4224
Mean if 0.25 ≤ observed EQ-5D < 0.5	.3513	.5618	.3513	.5567	.3849	.5964	.3101	.5135
Mean if 0.50 ≤ observed EQ-5D < 0.75	.6624	.6530	.6624	.6623	.6364	.6439	.6530	.5939
Mean if 0.75 ≤ observed EQ-5D ≤ 1	.8566	.7753	.8566	.7821	.8425	.7914	.8841	.7875
MAE if observed EQ-5D < 0.25	.3618		.3676		.2994		.3311	
MAE if 0.25 ≤ observed EQ-5D < 0.5	.2113		.2068		.2157		.2283	
MAE if 0.50 ≤ observed EQ-5D < 0.75	.1254		.1215		.0968		.1387	
MAE if 0.75 ≤ observed EQ-5D ≤ 1	.1105		.1027		.0993		.1429	

* Significant (P<0.05), ** Significant (P<0.01), *MAE* Mean Absolute Error, *RMSE* Root Mean Square Error

Table 9.4 External validity of the recommended models based on the GO-AHEAD database using different EQ-5D value sets

Dataset	EQ-5D value set	Dutch Model A		Dutch Model B		US Model C		UK Model D	
		Observed	Predicted	Observed	Predicted	Observed	Predicted	Observed	Predicted
RECODE	mean EQ-5D	.7553	.8088**	.7570	.7907**	.7838	.8259**	.7085	.7788**
	MAE	.1509		.1484		.1224		.1787	
	RMSE	.2235		.2161		.1720		.2592	
MARCH	mean EQ-5D	.8830	.8639	.8807	.8389**	.8904	.8883	.8703	.8627
	MAE	.0933		.0979		.0749		.1010	
	RMSE	.1107		.1179		.0908		.1276	

* Significant (P<0.05), ** Significant (P<0.01), *MAE* Mean Absolute Error, *RMSE* Root Mean Square Error

Scatter plots of the predicted and observed values for model A are shown in Figure 9.1. The scatter plots reveal that the mapping did not produce accurate predictions of the EQ-5D value on an individual level, especially not for the more severe health states (observed EQ-5D values <0.5).

Figure 9.2 shows the results of the bootstrap procedure based on model A. From these graphs we can define the range of certainty of the group mean predicted error by group size: with group size of 10, errors range from +0.3 to -0.2, when group size is 500, errors range from +0.1 to 0. The group mean prediction error decreased when the group mean predicted EQ-5D increased.

We extended model A with the Charlson co-morbidity index to build model B which improved the model and reduced the MAE and RMSE slightly (Table 9.3). We recommend this model when the Charlson co-morbidity index is available. The performance of the other estimated OLS models using the Dutch value set is shown in Appendix 9.5. We investigated the impact of treating repeated measurements from the RECODE dataset as independent observations by comparing a model that was based on the entire dataset with a model that was based on the baseline measurement only. We found that the model based on the entire dataset had better predicted performance (i.e. lower MAE and RMSE) than the model based on the dataset including only the baseline measurements of RECODE. Merging the three different datasets only slightly decreased the MAE from 0.153 (RECODE) to 0.152 (full dataset). The RMSE was the lowest (0.198) when the model was based on the GO-AHEAD trial.

Sensitivity analyses with US and UK EQ-5D value sets

When using US and UK value sets, the models based on the GO-AHEAD dataset had the lowest RMSE and the lowest MAE for patients with an observed EQ-5D value below 0.5. Although the MAE of the models based on GO-AHEAD dataset were somewhat higher than for the other models in case of milder impaired health states, only the GO-AHEAD models predicted a mean EQ-5D value that was not significant different from the observed mean in the MARCH trial. Therefore, the recommended 6 parameter model for the US value set (model C) and the recommended 6 parameter model for the UK value set (model D) are based on the GO-AHEAD dataset. The predicted performances of these models are shown in Table 9.3 and 9.4 and the algorithm can be found in Table 9.2. The predictive ability of the model based on the US value set (MAE 0.121; RMSE 0.155) was slightly better in comparison with the model based on the UK value set (MAE 0.177; RMSE 0.229) and the models based on the Dutch value set (MAE 0.147 and 0.152; RMSE 0.196 and 0.198). The scatter plots of Model C and D look quite similar to the scatterplot of Model A. These plots reveal that we were not able to produce accurate predictions on the individual level. The mapping models underestimated the EQ-5D scores for the mild health states, while they overestimated those for the more severe health states. Appendix 9.6 shows the results of the other estimated models for predicting EQ-5D values based on US and UK value set.

Figure 9.1 Scatter plots of the observed and predicted EQ-5D in Model A based on the GO-AHEAD development data in (I) GO-AHEAD validation dataset (II) RECODE dataset (III) MARCH dataset

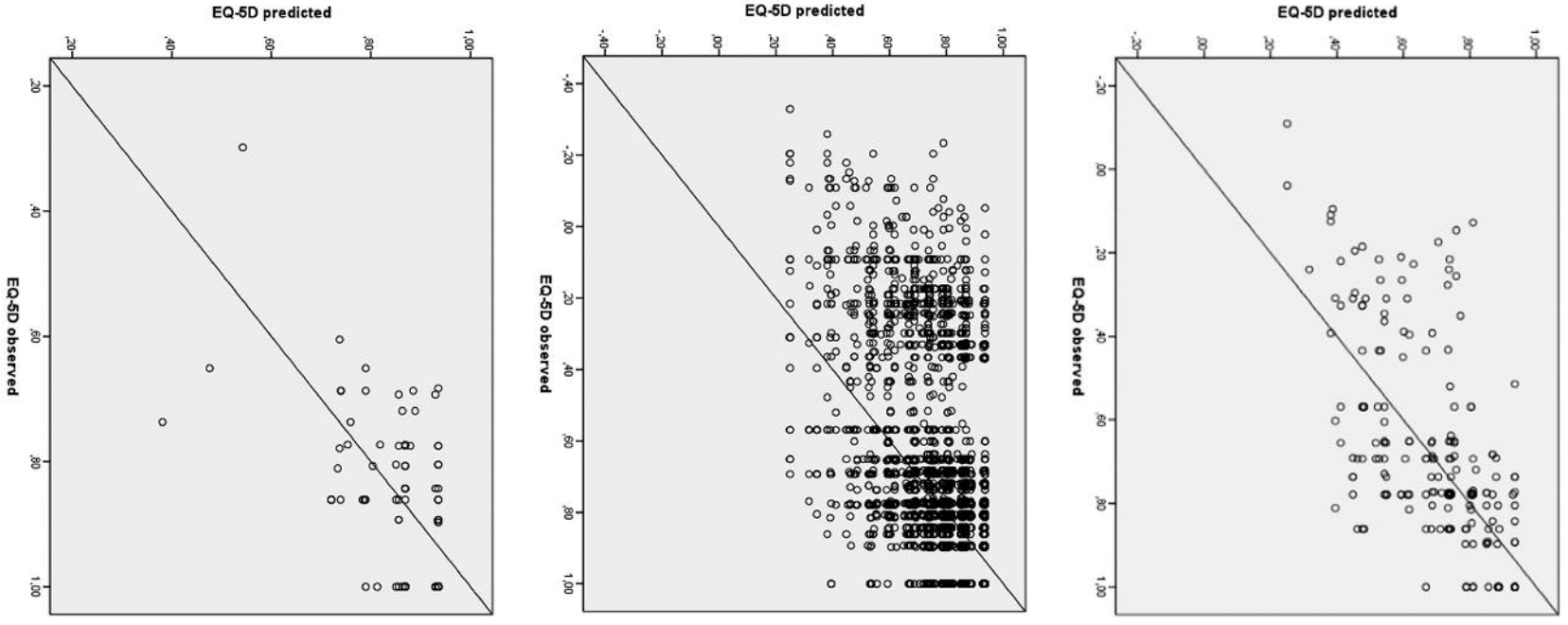
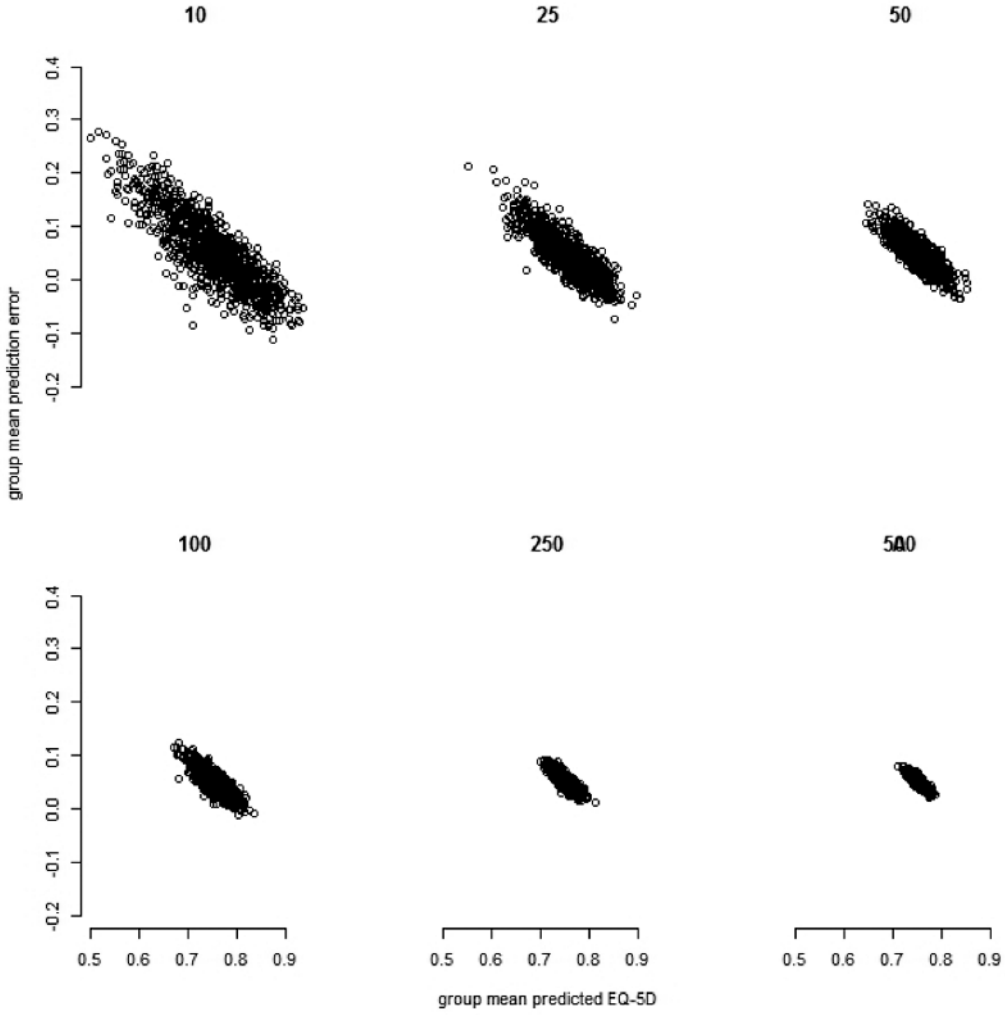


Figure 9.2 Group mean prediction errors, by group size (10, 25, 50, 100, 250, 500) and group mean predicted EQ-5D value



DISCUSSION

This study aimed to develop a model that predicts EQ-5D values from CCQ scores, which can be used in the absence of directly collected EQ-5D data. The recommended models were estimated from the GO-AHEAD dataset because it had the lowest MAE and RMSE, especially for EQ-5D values below 0.5. The main reason is that the GO-AHEAD dataset had the widest variation in EQ-5D values and the highest proportion of severe health states. On a group level, the models predicted mean EQ-5D values that were similar to the mean observed EQ-5D values in the same population (internal validity) and the errors as percentage of the EQ-5D range were lower than the typically found percentage of error of the EQ-5D range up to 15%.[257] However, the predictive ability of the models varied with the severity of HRQoL impairment. The mapping models underestimated the EQ-5D values for the mild health states, while they overestimated those for the more severe health states. This "misfit" is a general problem with mapping studies because of regression to the mean.[257,258] The over- and under estimation may cancel out when predicting the overall mean EQ-5D value. However, the underestimation for patients with good health states is less than the overestimation for patients with more severe health states.[257] This combination of findings may indicate reduced room for improvement in severe health states. In the typical Markov models of COPD, COPD patients are divided into different disease severity states with different EQ-5D values. When using the mapping models to predict EQ-5D values for these states, these predictions are likely to be biased and the overestimation of the low values and underestimation of the high values would probably no longer cancel each other out.

An important cause of the problematic map of the CCQ scores onto EQ-5D values is the conceptual difference between the two instruments. The correlation between the CCQ and the EQ-5D was moderate (-0.514) and PCA suggest that there are differences in the underlying constructs of the CCQ and EQ-5D. The EQ-5D dimension pain/discomfort formed a separate construct on which none of the CCQ items loaded. As this dimension is an important driver of a reduced EQ-5D value in this population, this is an important limitation. Furthermore, CCQ symptom items 5 and 6 related to cough and phlegm production formed a distinct construct, unrelated to any of the EQ-5D items.

If we compare our mapping model, with the mapping model of the SGRQ[240], another frequently used disease-specific HRQoL instrument in COPD, the overall predictive ability is comparable. The MAE and RMSE of the model that predicts EQ-5D values (US value set) from SGRQ scores were 0.124 and 0.172, respectively,[240] and the MAE and RMSE of our model

that predicts EQ-5D values (US value set) from CCQ scores were 0.121 and 0.155, respectively. Unfortunately, we cannot compare the misfit (i.e under- and overestimation of the EQ-5D values) of the model with the SGRQ because a scatter plot of the predicted and observed EQ-5D values is not presented in the SGRQ mapping study.

This is the first mapping study which developed models for EQ-5D value sets of different countries. Because the model coefficients differ between countries, future mapping studies are recommended to account for different value sets of the EQ-5D. Apart from the fact that we investigated a wide range of different models with increasing complexity for different EQ-5D value sets, the strength of our study lies in the large number of observations compared to previous mapping studies [246]. Using repeated EQ-5D measurements of the same patients as unique observations, as previous mapping studies also did, increased the predictive ability of the model. The bootstrap procedure showed to which extend the accuracy of the mapping increases when they are estimated in a larger sample size. These results are consistent with the study from Grootendorst and colleagues.[259] However, the fact that the model estimated from the GO-AHEAD trial performed best, demonstrates that not only the size of the dataset matters but also the variation in EQ-5D values as we mentioned earlier. A wide range of disease severity is a premise for undertaking mapping.[257]

A limitation of this study is that the numbers of patients with an EQ-5D value below<0.5 were relatively small and 25% of the observations were at full health. The final models were based on OLS regression as GLM and Tobit models did not improve the prediction. Some studies suggest that the prediction performance of mapping models may be improved by using more complex models such as the censored least absolute deviation model.[257] However, their use in previous mapping studies was limited (80% of the mapping studies used OLS models[246]) and showed conflicting results on improvement of predictive ability.[257260,261] Recently, latent class analysis showed some promising improvements in the predictive ability of mapping models.[262] For future studies it would be worthwhile to investigate if these new modelling approach will actually lead to better predictability in COPD patients.

CONCLUSION

On a group level, the CCQ mapping models can predict mean EQ-5D values that are similar to the observed mean values, if the patient population is similar to the population in which the algorithm was developed. However, the overestimating of the low observed EQ-5D values and underestimation of the high observed values limits its use in cost-effective-

ness Markov models where utility estimates by disease severity state are required. Therefore, the use of mapping algorithms should be used cautiously.

Appendix 9.1 Correlation matrix between the CCQ and the EQ-5D of the full dataset

Item	Description	EQ-5D	Mobility	Self-care	Usual activities	Pain/ Discomfort	Depression/ Anxiety
CCQ		-0.514	.473	.499	.583	.293	.326
Symptoms	CCQ-1. CCQ-2. CCQ-5. CCQ-6	-0.339	.313	.316	.390	.221	.217
Functional state	CCQ-7. CCQ-8. CCQ-9. CCQ-10	-0.530	.530	.547	.620	.292	.283
Mental state	CCQ-3. CCQ-4	-0.418	.278	.335	.418	.181	.457
CCQ-1	Short of breath at rest	-.375	.314	.315	.409	.214	.228
CCQ-2	Short of breath doing physical activities	-.435	.409	.401	.491	.229	.205
CCQ-3	Concerned about getting a cold or your breathing getting worse	-.337	.225	.286	.363	.140	.361
CCQ-4	Depressed (down) because of your breathing problems	-.414	.265	.327	.397	.179	.468
CCQ-5	Cough	-.178	.116	.130	.159	.125	.116
CCQ-6	Produce phlegm	-.137	.105	.096	.122	.092	.095
CCQ-7	Strenuous physical activities	-.487	.461	.449	.523	.262	.222
CCQ-8	Moderate psychical activities	-.531	.525	.481	.591	.270	.260
CCQ-9	Daily activities at home	-.519	.465	.608	.580	.248	.264
CCQ-10	Social activities	-.445	.379	.455	.506	.220	.283

CCQ Clinical COPD Questionnaire

Appendix 9.2 Overview of the items associated with the four constructs derived from the exploratory principal component analysis of the full dataset

Item	Description	Factor loading	Eigenvalue
Construct 1			
CCQ-1	Short of breath at rest	0.60	4.970
CCQ-2	Short of breath doing physical activities	0.77	
CCQ-7	Strenuous physical activities	0.80	
CCQ-8	Moderate psychical activities	0.86	
CCQ-9	Daily activities at home	0.83	
CCQ-10	Social activities	0.70	
EQ-5D-1	Mobility	0.55	
EQ-5D-2	Self-care	0.64	
EQ-5D-3	Usual activities	0.66	
Construct 2			
CCQ-3	Concerned about getting a cold or your breathing getting worse	0.75	2.174
CCQ-4	Depressed (down) because of your breathing problems	0.77	
EQ-5D-5	Depression/Anxiety	0.77	
Construct 3			
CCQ-5	Cough	0.90	1.832
CCQ-6	Produce phlegm	0.91	
Construct 4			
EQ-5D-1*	Mobility	0.54	1.326
EQ-5D-4	Pain/Discomfort	0.83	

* Item is more strongly associated with Construct 1, CCQ Clinical COPD Questionnaire

Appendix 9.3 Overview of the items associated with the five constructs derived from the confirmatory principal component analysis of the full dataset

Item	Description	Factor loading	Eigenvalue
Construct 1			
CCQ-1	Short of breath at rest	0.72	3.175
CCQ-2	Short of breath doing physical activities	0.81	
CCQ-7	Strenuous physical activities	0.71	
CCQ-8	Moderate psychical activities	0.69	
CCQ-9	Daily activities at home	0.52	
CCQ-10	Social activities	0.50	
Construct 2			
CCQ-7*	Strenuous physical activities	0.41	2.758
CCQ-8*	Moderate psychical activities	0.52	
CCQ-9*	Daily activities at home	0.68	
CCQ-10	Social activities	0.51	
EQ-5D-1	Mobility	0.54	
EQ-5D-2	Self-care	0.84	
EQ-5D-3	Usual activities	0.66	
Construct 3			
CCQ-3	Concerned about getting a cold or your breathing getting worse	0.75	2.147
CCQ-4	Depressed (down) because of your breathing problems	0.77	
EQ-5D-5	Depression/Anxiety	0.77	
Construct 4			
CCQ-5	Cough	0.90	1.769
CCQ-6	Produce phlegm	0.91	
Construct 5			
EQ-5D-1	Mobility	0.54	1.212
EQ-5D-4	Pain/Discomfort	0.83	

* Item is more strongly associated with Construct 1, *CCQ* Clinical COPD Questionnaire

Appendix 9.4 Performance of the best OLS models based on the different databases (Dutch value set)

Estimation & validation dataset	**RECODE Baseline**		**RECODE all measurements**		**GO-AHEAD**		**Full dataset**	
Internal validity	*Observed*	*Predicted*	*Observed*	*Predicted*	*Observed*	*Predicted*	*Observed*	*Predicted*
Mean EQ-5D	.7472	.7333	.7581	.7552	.6625	.6843	.7537	.7525
MAE	.1706		.1531		.1520		.1517	
RMSE	.2274		.2111		.1983		.2093	
Mean if observed EQ-5D < 0.25	.1368	.5835	.1315	.5802	.1562	.5181	.1334	.5832
Mean if 0.25 ≤ observed EQ-5D < 0.5	.3311	.7434	.3396	.6861	.3513	.5618	.3414	.6668
Mean if 0.50 ≤ observed EQ-5D < 0.75	.6809	.6183	.6674	.6618	.6624	.6530	.6669	.6598
Mean if 0.75 ≤ observed EQ-5D ≤ 1	.8833	.7803	.8937	.8051	.8566	.7753	.8927	.8059
MAE if observed EQ-5D < 0.25	.4467		.4491		.3618		.4516	
MAE if 0.25 ≤ observed EQ-5D < 0.5	.4123		.3682		.2113		.3374	
MAE if 0.50 ≤ observed EQ-5D < 0.75	.1329		.1109		.1254		.1122	
MAE if 0.75 ≤ observed EQ-5D ≤ 1	.1210		.1081		.1105		.1074	
Model estimated from	**RECODE Baseline**		**RECODE all measurements**		**GO-AHEAD**		**Full dataset**	
External validity								
RECODE					.7553	.8088**	.7581	.7621
MAE					.1509		.1520	
RMSE					.2235		.2113	
GO-AHEAD	.6734	.5119**	.6725	.5592**			.6600	.5996**
MAE	.2188		.1902				.1611	
RMSE	.2585		.2426				.1994	
MARCH	.8830	.7728**	.8830	.8232**	.8830	.8639	.8656	.8198**
MAE	.1306		.1013		.0933		.1044	
RMSE	.1518		.1189		.1107		.1204	

* Significant (P<0.05), ** Significant (P<0.01), *MAE* Mean Absolute Error, *RMSE* Root Mean Square Error

Appendix 9.5 Performance of the best OLS models based on the different databases, including demographics (e.g. age, gender, lung function, Charlson co-morbidity index in de the models

Estimation & validation dataset	**RECODE**		**GO-AHEAD**		**Full dataset**	
Internal validity	*Observed*	*Predicted*	*Observed*	*Predicted*	*Observed*	*Predicted*
Mean EQ-5D	.7614	.7592	.6625	.6901	.7561	.7560
MAE	.1476		.1471		.1465	
RMSE	.2044		.1963		.2027	
Mean if observed EQ-5D < 0.25	.1304	.5583	.1562	.5238	.1325	.5632
Mean if 0.25 ≤ observed EQ-5D < 0.5	.3384	.6955	.3513	.5567	.3403	.6757
Mean if 0.50 ≤ observed EQ-5D < 0.75	.6674	.6647	.6624	.6623	.6666	.6659
Mean if 0.75 ≤ observed EQ-5D ≤ 1	.8933	.8103	.8566	.7821	.8922	.8098
MAE if observed EQ-5D < 0.25	.4294		.3676		.4317	
MAE if 0.25 ≤ observed EQ-5D < 0.5	.3736		.2068		.3427	
MAE if 0.50 ≤ observed EQ-5D < 0.75	.1088		.1215		.1071	
MAE if 0.75 ≤ observed EQ-5D ≤ 1	.1049		.1027		.1048	
Model estimated from	**RECODE**		**GO-AHEAD**		**Full dataset**	
External validity						
RECODE			.7570	.7907**	.7614	.7639
MAE			.1484		.1469	
RMSE			.2161		.2047	
GO-AHEAD	.6703	.6068**			.6573	.6387
MAE	.1690				.1493	
RMSE	.2204				.1916	
MARCH	.8732	.8079**	.8807	.8389**	.8570	.7986**
MAE	.1062		.0979		.1137	
RMSE	.1222		.1179		.1280	

* Significant (P<0.05), ** Significant (P<0.01), *MAE* Mean Absolute Error, *RMSE* Root Mean Square Error

Appendix 9.6 Performance of the best OLS models based on the RECODE, GO-AHEAD and Full database using different EQ-5D value set

Internal validity	**US**						**UK**					
	RECODE		**GO-AHEAD**		**Full dataset**		**RECODE**		**GO-AHEAD**		**Full dataset**	
	Observed	Predicted	Observed	Predicted	Observed	Predicted	Observed	Predicted	Observed	Predicted	Observed	Predicted
Mean EQ-5D	.7851	.7836	.6993	.7134	.7811	.7812	.7101	.7084	.6002	.6161	.7054	.7057
MAE	.1203		.1211		.1196		.1758		.1766		.1745	
RMSE	.1612		.1552		.1605		.2396		.2289		.2381	
Mean if observed EQ-5D < 0.25	.1634	.5594	.2190	.5184	.1685	.5687	.0703	.5469	.0912	.4224	.0724	.5428
Mean if 0.25 ≤ observed EQ-5D < 0.5	.4022	.6962	.3849	.5964	.4008	.6910	.3029	.6305	.3101	.5135	.3041	.6124
Mean if 0.50 ≤ observed EQ-5D < 0.75	.6624	.6786	.6364	.6439	.6595	.6779	.6655	.6482	.6530	.5939	.6644	.6451
Mean if 0.75 ≤ observed EQ-5D ≤ 1	.8811	.8208	.8425	.7914	.8798	.8202	.9064	.7865	.8841	.7875	.9059	.7885
MAE if observed EQ-5D < 0.25	.3960		.2994		.4003		.4831		.3311		.4753	
MAE if 0.25 ≤ observed EQ-5D < 0.5	.2991		.2157		.2928		.3532		.2283		.3179	
MAE if 0.50 ≤ observed EQ-5D < 0.75	.0941		.0968		.0928		.1075		.1387		.1100	
MAE if 0.75 ≤ observed EQ-5D ≤ 1	.0904		.0993		.0904		.1371		.1429		.1353	
Model estimated from	**RECODE**		**GO-AHEAD**		**Full dataset**		**RECODE**		**GO-AHEAD**		**Full dataset**	
External validity												
RECODE			.7838	.8259**	.7851	.7890			.7085	.7788**	.7101	.7166
MAE			.1224		.1198				.1787		.1747	
RMSE			.1720		.1615				.2592		.2402	
GO-AHEAD	.7104	.6242**			.6992	.6548**	.6138	.4820**			.6001	.5295**
MAE	.1486				.1260		.2209				.1865	
RMSE	.1907				.1592		.2796				.2311	
MARCH	.8904	.8407**	.8904	.8883	.8742	.8374**	.8627	.7902**	.8703	.8627	.8413	.7850**
MAE	.0887		.0749		.0884		.1212		.1010		.1222	
RMSE	.1033		.0908		.1036		.1425		.1276		.1436	

* Significant (P<0.05), ** Significant (P<0.01), *MAE* Mean Absolute Error, *RMSE* Root Mean Square Error

CHAPTER 10

Discussion

This thesis included studies to evaluate the costs and effects of an integrated disease management program for COPD patients (COPD-DM) and studies related to the mechanism of action of such a program. In this final chapter, we will reflect on the most important findings.

Main results cost-effectiveness of COPD-DM

In **chapter 2** a systematic review was performed to evaluate the economic impact of COPD-DM programs. The results of this review suggest that COPD-DM programs reduce hospital admissions, decrease hospital costs and total healthcare costs. They also improve health outcomes, including health-related quality of life (HRQoL). This could stimulate decision makers and payers to implement such programs on a wider scale. However, most of these studies were conducted in patients with more severe COPD than the patients that are treated by general practitioners in the Netherlands. As general practitioners treat the majority of COPD patients, it is of utmost importance to test the cost-effectiveness of these programs in primary care. Therefore, we conducted a large cluster randomised trial (the RECODE trial) with a long-term follow-up (24 months) in which general practices were randomised to a DM program or usual care. The design of this trial was described in **chapter 3**. Contrary to our expectations we found that the RECODE program was not cost-effective for COPD patients in primary care **(chapter 4)**. The intervention costs were €324 per patient. Excluding these costs, the intervention group had €584 (95% CI €86 to €1,046) higher healthcare costs than the usual care group and €645 (95% CI €28 to €1,190) higher costs from the societal perspective. Despite a greater improvement in performance indicators of COPD care in the intervention group than in the usual care group, and the positive impact of some of these indicators on disease-specific and generic HRQoL **(chapter 6)**, health outcomes were similar in both groups, and the number of quality adjusted life years (QALYs) was even a bit less (-0.04 (95% CI -0.07 to -0.01)) in the intervention group. The biggest hurdle turned out to be the implementation of the RECODE program. The study in **chapter 5** showed that the level of implementation of the RECODE program was low and varied widely across different primary care teams. Barriers of the implementation were related to factors at individual (i.e. insufficient motivation of the patients and care providers), social (i.e. variability in adoption of the ICT system between team members), organisational (i.e. small size of the COPD population per team), and broader societal level (i.e. hurdles in the reimbursement). There was little association between level of implementation and improvement in health outcomes.

Policy makers and payers in the Netherlands have taken the decision

to implement integrated DM programs for various chronic diseases, including COPD. As of 2010 this implementation is formally supported through the introduction of a bundled payment system.[83] Hence, one could argue that the most relevant question to answer from a policy perspective is not whether COPD-DM programs are cost-effective compared to usual care, but which type of program is most cost-effective.

Heterogeneity

There are large differences between COPD-DM programs, which hampered the comparison of the results of the RECODE trial with the results of previous studies. This heterogeneity is due to differences in intervention-, patient- and study-characteristics. Firstly, a COPD-DM program includes a mixed package of interventions simultaneously targeting patients, healthcare providers and/or the organization.[192,202] These interventions are often grouped by the six interrelated components of the Chronic Care Model (CCM).[102] These components are: 1) self-management; 2) delivery system design; 3) decision support; 4) clinical information system; 5) community; and 6) organizational support. Secondly, patient-characteristics such as disease severity, health behaviour and comorbidities vary across COPD-DM programs, often resulting from different inclusion- and exclusion criteria. Thirdly, study-characteristics such as the design and duration of the study, the implementation of the interventions, and the starting level of COPD care vary widely.

Intervention characteristics

Chapter 2 showed that COPD-DM programs covering 3 or more components of the CCM had lower rates of hospitalizations and thus lower hospitalisations costs. This is in accordance with previous reviews[4,78] and some recently published studies.[7,11,263,264] In the COPE II study, a two-by-two factorial design was used to evaluate the effectiveness of two interventions (self-treatment of exacerbations and a community-based exercise program [COPE-active]) which are incorporated in a self-management program in comparison with the effectiveness of a self-management program only.[263,264] After one year, the self-treatment of exacerbations group was dominant over the group who received self-management only, i.e. self-treatment lead to lower costs (certainty: 66.5%; average: €154 per patient per year (PPPY)), fewer hospitalisations (certainty: 95.1%; average: 1.14 PPPY) and fewer healthcare contacts (certainty: 74.4%; average: 0.13 PPPY).[263] After two years, patients who received COPE-active had a sustained increase in daily physical activity compared to patients who received a self-management program only, but this was not accompanied by a sustained increase in maximal exer-

cise capacity.[264] Tsiachristas and collegues[265] also found that the implementation of a more comprehensive COPD-DM program compared to a less comprehensive COPD-DM program led to gains in health outcomes (small QALYs gains with 69% certainty) but also a costs increase (certainty: 77%), resulting in a mean incremental cost-effectiveness ratio (ICER) of 127,659 from a healthcare perspective. Considering that the maximum acceptable cost per QALY ratio of €80,000 per QALY gained in the Netherlands would only be applied to diseases with the highest burden, it is unlikely that this would be considered cost-effective.[266] In contrast to these studies which suggest an association between the comprehensiveness of a program and the effectiveness, we found in chapter 5 that there was little association between level of implementation and improved health outcomes. We only found that a higher level of implementation as measured with the PACIC was positively associated with improved self-management capabilities, but not with other outcomes. Moreover, a Cochrane review found no significant difference in effect of pulmonary rehabilitation (PR) between subgroups that received exercise only and those that received exercise plus more complex interventions.[60] Thus, the implementation of a comprehensive program does not guarantee improvements in patients' outcomes and/or lower costs in comparison with a less comprehensive program. Even though most of the single interventions in a COPD-DM program have been proven effective (e.g. smoking cessation support, exercise training, patient education), the challenge is to identify the most optimal mixture of interventions when taking into account the interaction between these interventions and recognizing that there are limits to the capabilities of patients to change multiple habits at the same time.

It has been shown that most COPD-DM programs include mainly patient-oriented interventions and less so professional-directed interventions or organization-directed interventions.[161,162] All evaluated programs in chapter 2 included self-management interventions targeted at patients (i.e. patient education, stimulation of physical therapy and individual treatment plans) and found favourable effects on both health outcomes and costs. Two Cochrane reviews identified exercise as an important success factor of a COPD-DM program.[60,162] In our RECODE study, the translation of a provider-oriented approach into patient-oriented interventions was one of the biggest problems during the implementation of the program. For instance, while the cooperation with physiotherapist(s) in most primary care teams improved, the number of COPD patients referred to physiotherapeutic reactivation was limited. However, in order to maintain the short-term effect of exercise programs in COPD in the long-term, it is increasingly recognised that one should not solely aim

at the improvement of exercise capacity but also at a behavioural change towards exercise and physical activity.[264] In our review study, patient education on psychosocial effects of COPD, increasing the knowledge of the disease COPD and improving self-management skills were interventions frequently included in the programs besides exercise training.

For a structural implementation of large DM programs, it seems that patient-oriented interventions alone are not sufficient. Interventions within the organizational support or community components are essential. For example, financial agreements are potentially powerful tools to stimulate integrated care and influence healthcare expenditure.[63] However, none of our evaluated programs in chapter 2 included these components. It is likely that these studies did not explicitly address these components because of the relatively small-scale on which the programs were implemented or because the organizational, financial and societal conditions necessary to implement DM were already in place. The RECODE primary care teams reported the lack of full reimbursement of smoking cessation and physiotherapy as implementation barrier (chapter 5). The lack of reimbursement of physiotherapy was partly solved by supplementary funding by healthcare insurers for COPD-specific exercise training programs for patients with a MRC Dyspnea score>2, including those without supplementary health insurance. Why this funding was not used very often remains unclear. It could be that uncertainties about the long-term sustainability of reimbursement of physiotherapy have resulted in reluctance to invest in physical reactivation. This is in line with the study from Sunaert and colleagues[267] which found that the uncertainty about sustainability of funding negatively influenced the motivation of healthcare professionals to participate in a DM program and new initiatives for quality improvements were postponed. Changing reimbursement policy for smoking cessation during the RECODE study (i.e. full reimbursement of pharmacological support and counselling in 2011, no reimbursement of pharmacological support in 2012 and conditional reimbursement (only when pharmacological support is combined with counselling) in 2013) did probably also resulted in the limited smoking cessation advice (chapter 6). In accordance, other studies found that reimbursement of smoking cessation support was associated with increased likelihood of initiating of and adherence to pharmacological smoking cessation treatment and led to more successful quitters.[210–212]

Clinical information systems could assure timely access to relevant clinical and quality of life data about individual patients. It is important to assess the cost-effectiveness of these systems, as they are important cost drivers of COPD-DM program.[268] In the RECODE program, about 25% of the intervention costs was due to the ICT system Zorgdraad. Sys-

tematic review studies demonstrated the potential cost-effectiveness of telehealth for patients with COPD.[269,270] However, the studies in these reviews were small and the quality of these studies was low. Hence, the cost-effectiveness of telehealth needs to be demonstrated in routine daily practice on a large scale. In the recently published Whole System Demonstrator Project, the largest pragmatic study to date, telehealth was not a cost-effective addition to standard support of usual care.[271] In the RECODE study, doubts were also raised about the effectiveness of the ICT system, i.e. none of the practices used the ICT system in the second study year. The teams that did use Zorgdraad in the first study year (47%) experienced problems with practicalities and variability in adoption of the system between team members. Furthermore, teams reported unclear instructions and a lack of time or motivation to determine how Zorgdraad worked. All of these problems were probably somehow related to the incompatibility of Zorgdraad with the common GP-information systems; i.e. due to problems with transferring information to the GP-information systems, information was had to be imported in both systems which resulted in delayed or lack of information in either system. A large review indeed corroborates that usefulness, compatibility with work and time were important barriers for implementation of an ICT system.[199] It is a challenge for future studies to develop ICT systems that facilitate the integration of care. These ICT systems should aid healthcare providers in routine daily practice but also aid with the registration and extraction of process and outcomes measures.

Patient characteristics

The room for improvement is higher among a selection of COPD patients with a high disease burden. Accordingly, our review study showed that savings in healthcare costs as well as hospital costs were higher, when patients were more severely ill, i.e. had a higher GOLD stage and a history of exacerbations. However, focussing on more severe COPD reduces the number of patients who participate in the program. Consequently, the motivation of professionals to invest time in optimizing the program and negotiating with health insurers on reimbursement of the program, may decrease. Economies of scale were also reported to be a barrier for improving cooperation with the dietician, the ICT system Zorgdraad and organizing periodically scheduled multidisciplinary meetings. It is a challenge for future programs to find the right balance between a target population that has sufficient room for improvement and economies of scale. In finding this balance, we should take into account that, in the long-term, gains can be increased if we can prevent moderate COPD patients to progress to severe COPD. Moreover, economies of scale can be

improved by combining programs for different patient groups, which require similar types of interventions (e.g. lifestyle related interventions).

The motivation of COPD patients is also an important success factors of COPD-DM programs.[197] It may be very difficult to motivate COPD patients to change their behaviour because they perceive their suboptimal health status as 'normal'; COPD had become a way of life.[197] A review on selection and dropout in randomized controlled trials on pulmonary rehabilitation programs found that patients are selected so that those who are deemed to have the ability and motivation to complete a pulmonary rehabilitation program are more likely to be chosen for participation than patients with poor motivation.[272] For instance, smoking cessation is often a prerequisite to pulmonary rehabilitation[273], and patients who are unmotivated to change their smoking behaviour are therefore less likely to participate. In contrast, the RECODE trial had a limited number of exclusion criteria and the population was found to be representative of the COPD population treated in primary care in the Netherlands. Hence, teams in the RECODE trial need to invest time and effort in motivating patients who may not always be prepared to commit to an intensive integrated care or exercise program. The researchers from the COPE II study did perform an intention-to-treat analyses and a per-protocol analyses in which they excluded 26 patients (35%) who participated in less than 70% of the physiotherapeutic exercise sessions.[264] The per-protocol analyses suggest that patients who adhered were doing better than patients who did not. It can thus be suggested that patients who are motivated to change their health behaviour may increase the (cost-)effectiveness of COPD-DM programs. Specific interventions to change the motivational status of patients are available but need to be used more often.[274]

Study characteristics

Among the many characteristics that vary between studies is the duration of the COPD-DM intervention. The RECODE program did significantly improve physical activity, the coordination/follow-up domain of the PACIC questionnaire and the performance on indicators of COPD care. Considering that improvements in PACIC score were positively associated with improvements in self-management capabilities and some of the performance indicators of COPD care indicators were positively associated with improvements in HRQoL, it is possible that even a duration of the follow-up of two years was too short for changes in health outcomes to become apparent. This hypothesis is supported by the finding from our review study that savings in costs of hospitalizations were greater for studies with a long intervention duration (> 12 months) than

for studies with a short intervention duration (< 12 months). On the other hand, the association between either the coordination/follow-up domain of the PACIC or the performance indicators and health outcomes was relatively weak, making better outcomes when using a longer follow-up not very likely.

The pragmatic nature of the RECODE trial is another study-characteristic that influences the cost-effectiveness of COPD-DM. A review on selection and dropout in RCT on PR found that 75% of the COPD patients suitable for PR programs were omitted due to sampling exclusion and dropout; i.e. most of the study populations were not representative of the target population.[272] In contrast, in the RECODE trial, we have used limited exclusion criteria (only 11% of the registered COPD patients were not eligible to participate), resulting in a broad range of patients with different severity levels of COPD, representative of the primary care COPD population in the Netherlands. Additionally, all teams in the RECODE intervention group were encouraged to write their own reform plan and tailor the implementation strategies. Therefore, the package of interventions that patients received was not only dependent upon their health status, personal needs, and preferences, but also on local adaptation and level of implementation of interventions. This resulted in a low level and a wide variety of implementation across different primary care teams. Although this study design may not evaluate the maximum effect of the RECODE program, the RECODE study probably provided a more realistic estimate of effects than a highly controlled efficacy trial that enrols a homogeneous patient population, defines treatment regimens carefully and requires that they be followed assiduously.[275]

The third characteristic that influences the effects of a COPD-DM program is the starting level of COPD care. In our implementation study we found that teams with a lower starting level implemented, on average, more interventions than teams with a higher starting level. Hence, the teams with a lower starting level had more room for improvement. For example, only a minority of the teams changed smoking cessation support because most teams reported that this was already integrated in their COPD care. The absence of improvements due to already high levels of COPD care in developed countries was pointed out in earlier primary care trials.[12,198] It could be that a program like RECODE would have led to more positive results in settings where the COPD care is less advanced. It might well be that as time passes and quality of COPD care improves, there is less room for improvement. For instance, Bourbeau and colleagues[117,179] demonstrated positive results of a COPD-DM program in patients recruited from 7 hospitals in Canada in 1999, while a similar program in 15 general practices in the Netherlands in 2006[12] found no

long-term benefits and a similar study in the US in 2009 did even find negative results in patients recruited from 20 hospital-based outpatient clinics.[13] Despite these progress in COPD care, there is still room for improvements. For example, the full set of indicators of the COPD care process was completed for only a minority of patients of the RECODE patients (year prior to trial=3%, year1=2%, year2=5%). Moreover, even in the presence of incentivised quality improvement programs like the Quality and Outcome Framework in England, hospital admissions for COPD still occur more frequently among the least well served such as those in deprived areas.[180]

COPD medication adherence

Stimulating appropriate use of inhaled medications is an important element of future COPD-DM programs. Hence, the potential benefits of improving COPD medication adherence are great due to low medication adherence in daily practice, the clearly demonstrated clinical benefits of COPD medication in large controlled clinical trials[276,277] and the due to fact that medication costs are substantial.[54,55] Despite this, **chapter 7** demonstrated that we were unable to find a positive association between COPD medication adherence and HRQoL. Even after adjusting for potential confounders such as demographics, disease severity and healthy lifestyle variables, we did not find a positive relationship. Our analyses demonstrated that the lack of correction for confounders may even result in a reversed association; patients with good COPD medication adherence had a worse HRQoL compared to patients with poor COPD medication adherence. More research is needed to better understand the relationship between medication adherence and HRQoL.

It could be that the promising results that are found in controlled clinical trial settings do not directly reflect effects observed in routine daily practice because in reality patients have to adhere to multiple COPD maintenance medications simultaneously (long-acting ß2-agonists [LABA], long-acting muscarinic antagonists [LAMA], inhaled corticosteroids [ICS], LABA/ICS combinations). In chapter seven we found that when using the maximum proportion of days covered (PDC) if patients used medication from different maintenance medication categories, adherent patients had a worse SGRQ and CCQ score than non-adherent patients while we did not find a relationship between adherence and HRQoL when using the minimum PDC.

Another important issue for further research is the external validity of large pharmaceutical trials. The efficacy of a new COPD medication is commonly tested in trials including severe patients with room for improvements and increasing chance of positive findings.[120,278] However, in

real world, indications for treatment are often broadened. So, the second step should be to study the efficacy in COPD patients without frequent exacerbations and less symptoms, a substantially larger proportion of the COPD population.

GOLD ABCD classification

During the RECODE trial, the strategy document of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) has been updated.[1] In the revised GOLD strategy COPD is not only classified by applying the spirometric 1-2-3-4 grades, but also by symptom level and the risk of COPD exacerbations (group ABCD). This multidimensional GOLD ABCD classification appears to be more strongly related to disease-specific and generic HRQoL and costs than the GOLD 1234 classification **(chapter 8)**. The GOLD ABCD classification raises awareness among physicians that assessment of COPD severity should include multiple components other than lung function. It stimulates patient-centred outcome thinking and is a step towards personalized medicine. The GOLD classification may also have consequences for decision-analytic models that aim to assess the cost-effectiveness of COPD treatments. Currently, most of these models are state-transition models in which the states are defined by airflow obstruction and exacerbations. On the other hand, these models are also moving towards the simulation of individual patients with different characteristics. Adopting the GOLD ABCD classification may be a step towards this, however, there are some important limitations of the ABCD GOLD classification which raise doubts about the usefulness of this classification.

Firstly, debates on the methods and cut-off values of the GOLD ABCD classification are ongoing. Studies have shown that different methods (e.g. MRC or CAT) produce different group classifications.[279–281] The GOLD ABCD classification has been produced by the GOLD committee without rigorously piloting and evaluation and with a failure to involve a wide clinical community in its production.[282]

Secondly, the revision of the GOLD classification did not result in sufficient discriminatory power to be used clinically for risk classification at the individual level.[283] Although, the ABCD GOLD classification predicts exacerbations better than the 1234 GOLD classification[284–286], there is no difference in predicting hospitalizations[287] and it is probably a deterioration for predicting lung function decline.[284] Moreover, a pooled-analysis of 22 COPD cohorts from seven countries demonstrated that the GOLD ABCD classification and the GOLD 1234 classification performed similarly when predicting mortality up to 10 years but neither had a striking discriminatory power.[283]

Thirdly, for personalized medicine, the integrated assessment of COPD severity would require more items such as risk factors, biomarkers, exercise capacity, nutritional status, multi-morbidities, personal goals, illness perceptions, and coping behaviour as is currently advocated by the Dutch and Spanish Care Standard for COPD.[24,288] This is especially relevant for COPD-DM programs because they try to tailor treatments to the specific needs, capacities, and preferences of an individual patient. The GOLD guidelines recommend that any comorbidity should be treated as if the patients do not have COPD, even though COPD coexist with many comorbidities that may have a significant impact on the prognosis of COPD.[14,15] A more integrated assessment of COPD could be done by using for instance the Assessment of Burden of COPD tool (ABC)[289] or the Nijmegen Clinical Screening Instrument (NCSI).[290]

There are still many unanswered questions about the assessment of the disease burden and the prediction of future health outcomes for COPD patients. Future research should be undertaken to investigate individual prediction models (i.e. the prediction of future health outcomes for each COPD patient individually).

Mapping CCQ scores onto EQ-5D values

To compare cost-effectiveness of different treatments for different diseases, generic preference-based measures such as the EQ-5D[72] should be used in the economic evaluation of health interventions. However, studies assessing the effectiveness of new COPD treatments commonly use disease-specific HRQoL instruments such as the CCQ.[30] In our mapping study we determined whether the CCQ scores could be used to predict EQ-5D values **(chapter 9)**. The models from this study predicted mean EQ-5D values that were similar to the observed mean values in the development set, but the predicted EQ-5D values did significantly differ from the observed values in external data sets. The mapping models underestimated the EQ-5D values for mild health states, while they overestimated them in more severe health states. The over- and underestimation may cancel out when predicting the overall mean EQ-5D value. However, the underestimation for patients with good health states is less than the overestimation for patients with more severe health states. This combination of findings indicate reduced room for improvement in severe health states, a diminished treatment effect and biased cost-effectiveness analyses.

The problematic map is mainly due to the conceptual differences between the two instruments. Important items of the CCQ questionnaire (cough / producing phlegm) are not captured by the EQ-5D questionnaire and an important EQ-5D dimension (pain/discomfort) is not captured

by the CCQ questionnaire. These differences between the two instruments do not undermine the merits of either instrument. Given the mapping performance and the conceptual differences between the two instruments it is not recommended to use our mapping models to estimate EQ-5D values from CCQ scores.

For the development of our models, we compared three traditional approaches to estimate the statistical relationship between CCQ and EQ-5D: ordinary least squares (OLS), generalized linear models (GLM) and TOBIT regression. In further studies, we are investigating if these new modelling approaches will actually lead to better predictability of EQ-5D values in COPD patients. The prediction performance of our mapping models may be improved by using more complex model specifications such as mixture models and Bayesian Networks, which not have been tested previously for COPD patients.[262,291] However, even these models cannot solve the problem of conceptual differences between questionnaires.

Instead of mapping COPD-specific questionnaires to utility instruments, we could also try to improve the sensitivity of the utility instruments to clinically relevant changes over time in COPD patients due to treatment. This sensitivity appears limited in stable COPD patients,[292] despite the ability to differentiate between COPD patient groups with different severity of lung function impairment[293] and the ability to detect recovery from moderate COPD exacerbations.[248] We could perhaps improve the sensitivity of the EQ-5D by adding a COPD/respiratory dimension to the current five dimensions of the EQ-5D, e.g. a bolt-on. Further research is ongoing to investigate the added value of a COPD/respiratory domain in terms of the additional utility decrement. Earlier studies developed a 'sleep', 'hearing', 'vision', 'tiredness' and 'psoriasis' bolt-on and demonstrated no substantial decrement in overall values these bolt-ons.[294–297] However, the impact of a bolt-on in terms of the additional utility decrement seems to be dependent on the severity of the EQ-5D health state in combination with the level of the bolt-on dimension.[294]

Recommendations for research

Having investigated the cost-effectiveness of COPD-DM programs and the mechanism of actions of these programs, we remain somewhat puzzled about the ideal DM program in COPD. Although we have identified the patient-, intervention-, and study-determinants that could influence the cost-effectiveness of COPD-DM programs, this thesis raised many questions in need of further investigation.

What is the optimal mixture of interventions for individual patients?

Although the single interventions of COPD-DM have been proven effective, we should recognize that there are limits to the capabilities and motivation of patients and healthcare providers to change multiple habits at the same time. Sunaert and colleagues[267] found that each component of the program requires a specific implementation strategy and follow-up, this complexity has led to some confusion about the aim of the program and further, some components affected each other negatively. Moreover, the mixture of interventions that is optimally comprehensive is likely to vary widely between individual patients. Future studies should address how DM interventions can be tailored to individual patient characteristics. Further studies should also include process outcomes to measure the level of implementation of the interventions per patient (e.g. behavioural changes) and per practice (e.g. organisational changes) in order to identify why one program is more successful than others. For instance, Bucknall and colleagues[182] identified successful self-managers; this group had a significantly reduced risk of COPD readmission, were younger, and were more likely to be living with others.

What is the ideal implementation strategy of COPD-DM?

Further research should be undertaken to develop a successful implementation strategy. In order to determine the conditions for successful implementation and sustainability of COPD-DM, we should evaluate the implementation of new programs and identify the facilitators of and barriers to implementation. For instance, in our implementation study of the RECODE trial, we identified barriers and facilitators at individual, social, organisational, and broader societal level.[189] Part of a successful implementation strategy could be the inclusion of patient-oriented interventions such as motivational interviewing, education, and exercise training. Furthermore, there should be a payment system that provides the right financial incentives to stimulate healthcare providers to implement COPD-DM programs. Since 2010, Dutch healthcare insurers purchase integrated care from care groups by negotiating a fixed price per patient per year for all multidisciplinary COPD care required by a patient. However, bundled payment is disease specific and COPD is often accompanied by cardiovascular, metabolic, musculoskeletal, cancer and mental health conditions.[15,31] To overcome inefficiencies and double payment while stimulating prevention, a combination of global payment and pay-for-performance seems to be the best alternative.[63,298] Accordingly, since 2015 there is a three-tier payment system for general practices introduced in the Netherlands.[208] In this new system there are specific financial incentives for innovations and quality (covering approximately 5-10% of the total practice costs), which deserve careful evaluation.

What should be the time horizon of the evaluation?

On the short term, we could identify changes due to COPD-DM on intermediate outcomes (e.g. changes in health behavior and quality of care) but it is not expected that changes in terms of HRQoL and mortality could be measured on the short-term. Hence, the gains from preventing patients with moderate COPD to progress to severe COPD are likely to be detected only in the long run. Two recently published study evaluated the longitudinal implementation of COPD-DM programs and did find positive results. Over a six year follow-up period, Hernandez and colleagues[11] found that a community-based integrated care program in frail COPD patients improved clinical outcomes including survival and decreased the emergency department visits. Additionally, over a 10-year follow-up period, Lisspers and colleagues[7] demonstrated that structural management of COPD in primary care resulted in fewer experienced exacerbations and hospitalizations, and decreased overall treatment costs substantially. These long-term effects require a long-term vision and commitment, and probably calls for long-term contracts between providers and payers.

SUMMERY

In the past, Chronic Obstructive Pulmonary Disease (COPD) treatment was primarily based on the severity of the airflow limitation, but the acknowledgement of the heterogeneity of the disease has created a worldwide movement towards a more personalized, holistic and integrated approach. Disease management (DM) is such an integrated care approach and is seen as a potentially powerful means to increase health outcomes, improve patients' experience with care and slow down the growth in healthcare expenditure. The purpose of this thesis was to investigate the cost-effectiveness of DM programs for COPD patients (herein, COPD-DM) as well as issues related to the mechanism of action of these programs.

A systematic review was performed in chapter 2 to evaluate the economic impact of COPD-DM programs. Sixteen papers describing 11 studies were included (7 randomized control trials (RCT), 2 pre-post, 2 case-control). Meta-analysis showed that COPD-DM led to savings in costs of hospital admissions of €1060 (95% CI: €80 to €2040) per patient per year and savings in total healthcare utilization of €898 (95% CI: €231 to €1566) (excl. operating costs of the programs). In these health economic studies small but positive results on health outcomes were found. This could stimulate decision makers and payers to implement such programs on a wider scale. However, there was great variability in DM interventions-, study- and patient-characteristics of the COPD-DM programs. Most of the studies were conducted in patients with more severe COPD than the patients that are treated by general practitioners in the Netherlands. As general practitioners treat the majority of COPD patients, it is of utmost importance to test the cost-effectiveness of these programs in primary care.

Therefore, we conducted a large cluster randomised trial (the RECODE trial) with a long-term follow-up (24 months) in which 40 clusters of primary care teams (including 1086 COPD patients) were randomised to a DM program or usual care. The design and baseline results of this trial are presented in chapter 3. Contrary to our expectations we found that the RECODE program was not cost-effective for COPD patients in primary care (chapter 4). The intervention costs were €324 per patient. Excluding these costs, the intervention group had €584 (95% CI €86 to €1,046) higher healthcare costs than the usual care group and €645 (95% CI €28 to €1,190) higher costs from the societal perspective. Despite a greater improvement in performance indicators of COPD care in the intervention group than in the usual care group, and the positive impact of some of these indicators on disease-specific and generic health-related quality-of-life (HRQoL) (chapter 6), health outcomes were similar in both groups, and the number of quality adjusted life years (QALYs) was even

a bit less (-0.04 (95% CI -0.07 to -0.01)) in the intervention group. The biggest hurdle turned out to be the implementation of the RECODE program. The study in chapter 5 showed that the level of implementation of the RECODE program was low and varied widely across different primary care teams. Barriers of the implementation were related to factors at individual, social, organisational, and broader societal level. There was little association between level of implementation and improvement in health outcomes.

Because the RECODE cluster randomized controlled trial is the largest trial of a COPD-DM program to date, it provided a unique opportunity to investigate issues related to the mechanism of action of COPD-DM in more detail in the second part of this thesis. We first concentrated on the performance indicators of the COPD care process (chapter 6) because the measurement of these indicators is based on the assumption that there is a positive association between these indicators and health outcomes. The study in chapter 6 showed that COPD performance indicators improved over time and these improvements were higher in the integrated care group than in the usual care group, indicating improved quality of care. Four indicators (registered BMI, physical activity, functional status, and spirometry test) were associated with an immediate improvement (in the same year) in disease-specific HRQoL. The latter indicator and the indicator 'inhalation technique checked' had a delayed impact on HRQol (improvement in the next year).

Next, we addressed adherence to medication. Because COPD medication is proven to be effective in reducing symptoms, reduce the frequency and severity of exacerbations, and improving health status and exercise tolerance, stimulating appropriate use of medications is an important element of COPD-DM programs. Despite this, chapter seven demonstrated that we were unable to find a positive association between COPD medication adherence and HRQoL. Even after adjusting for potential confounders such as demographics, disease severity and healthy lifestyle variables, we did not find a positive relationship.

The large number of patients in the RECODE trial also provided a unique opportunity to compare the 2007 GOLD classification of COPD with the 2011 GOLD classification with respect to their association with HRQoL and costs (chapter 8). In the revised GOLD strategy COPD is not only classified by applying the spirometric 1-2-3-4 grades, but also by symptom level and the risk of COPD exacerbations (group ABCD). This multidimensional GOLD ABCD classification appears to be more strongly related to disease-specific and generic HRQoL and costs than the GOLD 1234 classification. Furthermore, people with GOLD-C had a better HRQoL than people with GOLD-B, but their costs did not differ.

In chapter 9 we investigate the possibility to predict EQ-5D utilities from scores on the Clinical COPD Questionnaire (CCQ), which is a widely-used disease-specific questionnaire to assess the effectiveness of COPD treatments. The models from this study predicted mean EQ-5D values that were similar to the observed mean values in the development set, but the predicted EQ-5D values did significantly differ from the observed values in external data sets. The mapping models underestimated the EQ-5D values for mild health states, while they overestimated them in more severe health states. The problematic map is mainly due to the conceptual differences between the two instruments. Given the mapping performance and the conceptual differences between the two instruments it is not recommended to use our mapping models to estimate EQ-5D values from CCQ scores.

In the general discussion the main findings of this thesis are presented and discussed. It was brought forward that the most relevant question to answer from a policy perspective is not whether COPD-DM programs are cost-effective compared to usual care, but which type of COPD-DM program is most cost-effective. This is because policy makers and payers in the Netherlands have already taken the decision to implement integrated DM programs for various chronic diseases, including COPD several years ago. This thesis contributes to the current body of evidence of COPD-DM and identified patient-, intervention-, and study-determinants of the cost-effectiveness of COPD-DM programs.

SAMENVATTING

De behandeling van Chronic Obstructive Pulmonary Disease (COPD) was in het verleden hoofdzakelijk gebaseerd op de longfunctie van de patiënt, maar de erkenning van de heterogeniteit van de ziekte heeft wereldwijd tot een meer persoonlijke, holistische en integrale aanpak geleid. Disease management (DM) is een voorbeeld van een integrale aanpak en wordt gezien als een potentieel krachtige manier om gezondheidsuitkomsten en patiënten ervaringen te verbeteren, als wel als de groei in zorgkosten te verminderen. Het doel van dit proefschrift is om de kosteneffectiviteit van DM programma's voor COPD (hierna, COPD-DM) patiënten als wel als issues gerelateerd aan de mechanische werking van deze programma's te onderzoeken.

Als eerste is in hoofdstuk 2 een systematische review uitgevoerd om de economische impact van COPD-DM programma's te evalueren. Zestien artikelen die 11 studies omschrijven zijn hierin geïncludeerd (7 gerandomiseerd control trials, 2 voor-na studies, 2 case-control). De meta-analyse laat zien dat COPD-DM leidt tot een besparing in ziekenhuiskosten van €1060 (95% BI: €80 tot €2040) per patiënt per jaar en een besparing in totale zorgkosten van €898 (95% BI: €231 tot €1566) (excl. programma kosten). In deze gezondheidseconomische studies werden verder kleine maar positieve resultaten op gezondheidsuitkomsten gevonden. Deze resultaten kunnen de beleidsmakers en financierders stimuleren om zulke programma's te implementeren op een grotere schaal. Maar uit de review blijkt ook dat er grote variatie is in de DM interventie-, studie-, en patiënten-kenmerken van de COPD-DM programma's. De meeste studies zijn uitgevoerd met patiënten met een ernstigere vorm van COPD dan dat er gemiddeld in de huisartsenpraktijk in Nederland worden behandeld. En aangezien huisartsen het merendeel van de COPD patiënten behandelen is het uitermate belangrijk om de kosteneffectiviteit van deze programma's in de eerste lijn te testen.

Daarom hebben we een grote cluster gerandomiseerde trial (RECODE trial) met een lange follow-up (24 maanden) uitgevoerd waarin 40 clusters van eerstelijns teams (1086 COPD patiënten) werden gerandomiseerd tot een DM programma of usual care. De opzet en baseline resultaten van deze trial zijn gepresenteerd in hoofdstuk 3. In tegenstelling tot onze verwachtingen vonden we dat de RECODE programma niet kosteneffectief was (hoofdstuk 4). De interventiekosten waren €324 per patiënt. Zonder deze kosten had de interventiegroep €584 (95% BI €86 tot €1,046) hogere zorgkosten dan de usual care groep en €645 (95% BI €28 tot €1,190) hogere kosten vanuit maatschappelijk perspectief. Ondanks de verbetering in de COPD prestatie indicatoren in de interventie groep in vergelijking met de usual care groep en de positieve impact van deze indicatoren op ziekte-specifieke en generieke gezondheids gerelateerde kwaliteit van

leven (KvL) (hoofdstuk 6) waren de gezondheidsuitkomsten vergelijkbaar in beide groepen en het aantal voor kwaliteit gecorrigeerde levensjaren (QALYs) zelfs een beetje kleiner (-0.04 [95% BI -0.07 tot -0.01]) in de interventie groep. De belangrijke obstakel bleek de implementatie van het programma. De studie in hoofdstuk 5 laat zien dat het niveau van implementatie van het RECODE programma laag was en dat er veel variatie was tussen de eerstelijns teams. Implementatie barrières waren gerelateerd aan factoren van het individu (bijv. onvoldoende motivatie van de patiënt en hulpverlener), sociale netwerk (bijv. de variatie in gebruikt van het ICT systeem tussen de team leden), organisatorisch (bijv. de kleine COPD populatie per team) en vanuit een breder maatschappelijk niveau (bijv. de financiering). Er was een kleine relatie tussen de mate van implementatie en verbetering in gezondheidsuitkomsten.

Aangezien de RECODE cluster gerandomiseerde gecontroleerde trial de grootste COPD-DM trial tot nu toe is biedt het een unieke mogelijkheid om ook issues gerelateerd aan de mechanische werking van COPD-DM in meer detail uit te werken in het tweede deel van dit proefschrift. We hebben ons als eerste geconcentreerd op de COPD prestatie indicatoren (hoofdstuk 6) omdat het meten van deze indicatoren is gebaseerd op de assumptie dat er een positieve relatie bestaat tussen deze indicatoren en gezondheidsuitkomsten. De studie in hoofdstuk 6 laat zien dat COPD prestatie indicatoren verbeteren in de loop van de tijd en dat deze verbeteringen groter zijn in de RECODE groep dan in de usual care groep, dus een verbetering in kwaliteit van zorg. Vier indicatoren (geregisterde BMI, fysieke activiteit, monitoren van de functionele status en spirometrie test) waren geassocieerd met een onmiddellijke verbetering (in het zelfde jaar) in ziekte-specifieke KvL. De laatste indicator en de indicator 'inhalatietechniek gecontroleerd' waren geassocieerd met een vertraagd effect op KvL (verbetering in het jaar erna).

Vervolgens hebben we de therapietrouwheid van medicatie onderzocht. Aangezien het bewezen is dat COPD medicatie effectief is in het verminderen van symptomen, verminderen van de frequentie en ernst van exacerbaties, verbeteren van gezonheidsuitkomsten en beweging tolerance, het stimuleren van goed gebruik van medicatie is een belangrijke element van COPD-DM programma's. Desalniettemin heeft hoofdstuk 7 laten zien dat we niet in staat waren om een positieve associatie te vinden tussen therapietrouwheid van medicatie en KvL. Zelfs na correctie van mogelijk confounders zoals variabelen gerelateerd aan de demografie, ernst van de ziekte en levensstijl vonden we geen positieve relatie.

Het grote aantal patiënten in de RECODE trial was ook een unieke mogelijkheid om de GOLD 2007 classificatie van COPD te vergelijken met

de GOLD 2011 classificatie van COPD in termen van associatie met KvL en kosten (hoofdstuk 8). In de herziende versie van de GOLD classificatie is COPD niet alleen gecategoriseerd aan de hand van de spirometische 1-2-3-4 graden, maar ook aan de hand van het niveau van symptomen en het risico van COPD exacerbaties (groep ABCD). Deze multidimensionale GOLD ABCD classificatie blijkt sterker gerelateerd te zijn aan ziekte specifieke en generieke KvL en kosten dan de GOLD 1234 classificatie. Daarnaast hadden mensen met GOLD-C een betere KvL dan mensen van GOLD-B, maar de kosten verschilden niet.

In hoofdstuk 9 hebben we een model gemaakt om de EQ-5D utiliteit scores te voorspellen aan de hand van de klinische COPD vragenlijst (CCQ), een vaak gebruikte vragenlijst om de effectiviteit van verschillende COPD behandelingen te meten. De modellen van deze studie voorspelde een gemiddelde EQ-5D score die vergelijkbaar was aan de geobserveerde EQ-5D score, maar de voorspelde EQ-5D waarden verschilden significant van de geobserveerde waarden in externe data sets. De mapping modellen onderschatte de EQ-5D waarden voor milde gezondheidstoestanden en overschatte de slechtere gezondheidstoestanden. Deze problematische voorspelling komt voornamelijk door de conceptuele verschillen tussen de twee instrumenten en het is daarom niet aan te raden om deze mapping functies te gebruiken om EQ-5d waarden te schatten van CCQ scores.

In de discussie zijn de belangrijkste bevindingen van dit proefschrift besproken en bediscussieerd. Er kwam naar voren dat het voor beleidsmakers niet relevant is om te onderzoeken of COPD-DM kosteneffectief is, maar welk COPD-DM programma meer kosteneffectief is ten op zichtte van de gebruikelijke zorg. Dit is omdat beleidsmakers en financierders in Nederland hun beslissing hebben genomen om DM programma's te implementeren voor verschillende chronische ziekten, inclusief COPD. Dit proefschrift draagt bij aan de huidige wetenschappelijke kennis van COPD-DM en identificeerde patiënt-, interventie-, en studie-determinanten van de kosteneffectiviteit van COPD-DM programma's.

PHD PORTFOLIO

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Boland MRS, Kruis AL, Tsiachristas A, Assendelft WJ, Gussekloo J, Blom C, Chavannes NH, Rutten-van Mölken MPMH. Cost-effectiveness of integrated COPD care: the RECODE cluster randomized trial. BMJ open (in press)

Boland MRS, Kruis AL, Huygens SA, Tsiachristas A, Assendelft WJ, Gussekloo J, Blom C, Chavannes NH, Rutten-van Mölken MPMH. Exploring the variation in implementation of a COPD disease management program and its impact on health outcomes: a post-hoc analysis of the RECODE cluster randomized trial

Boland MRS, van Boven JF, Kocks JW, van der Molen T, Goossens LM, Chavannes NH, Rutten-van Molken MPMH. Mapping the Clinical Chronic Obstructive Pulmonary Disease Questionnaire onto Generic Preference-Based EQ-5D Values. Value in Health 2015; 18(2): 299-307.

Kruis AL, **Boland MRS**, Assendelft WJ, Gussekloo J, Tsiachristas A, Stijnen T, Blom C., Sont JK, Rutten-van Mölken MPMH, Chavannes NH. Effectiveness of integrated disease management for primary care chronic obstructive pulmonary disease patients: results of cluster randomised trial. BMJ 2014; 349: g5392.

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Tsiachristas A, Dikkers C, **Boland MRS**, Rutten-van Molken MPMH. Exploring payment schemes used to promote integrated chronic care in Europe. Health Policy 2013; 113(3): 296-304.

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Kruis AL, **Boland MRS**, Schoonvelde CH, Assendelft WJ, Rutten-van Mölken MPMH, Gussekloo J, Tsiachristas A, Chavannes NH. RECODE: design and baseline results of a cluster randomized trial on cost-effectiveness of integrated COPD management in primary care. BMC Pulm Med. 2013; 23(3)13:17

Boland MRS, Tsiachristas A, Kruis AL, Chavannes NH, Rutten-van Mölken MPMH. The health economic impact of disease management programs for COPD. A systematic literature review and meta-analysis. BMC Pulmonary Medicine 2013; 13(1):40.

PUBLICATIONS IN DUTCH

Kruis AL, **Boland MRS**, Assendelft WJ, Gussekloo J, Tsiachristas A, Stijnen T, Sont JK, Rutten-van Mölken MPMH, Chavannes NH. Effectiviteit van geïntegreerde COPD-zorg, Ned Tijdschr Geneeskd. 2015;159:A8593

Kruis AL, **Boland MRS**, Rutten-van Mölken MPMH, Chavannes NC. (2013) Welke klinische fenotypen zijn relevant voor de eerstelijnsbehandeling van COPD? Spreekuur Huisartsengeneeskunde. 4(3): 2013

Boland MRS., Tsiachristas A., Kruis AL, Chavannes NC., Rutten-van Mölken MPMH. (2013) Is disease management van COPD kosteneffectief ? Spreekuur Huisartsengeneeskunde. 3(14): 2012

PRESENTATIONS AT CONFERENCES

2015 Does registration of performance indicators improve health outcomes in COPD, European Respiratory Society (ERS), Amsterdam, Netherlands

2015 Cost-effectiveness of a pragmatic integrated COPD care program: the RECODE cluster randomized trial, International Health Economic Association (IHEA), Milan, Italy

2015 Kosteneffectiviteit van integrale COPD zorg: de RECODE cluster gerandomiseerde trial, COPD en Astma Huisartsen Advies Groep (CAHAG), Utrecht, Netherlands

2014 Cost-effectiveness of an integrated care program for COPD: the RECODE cluster randomized trial, European Respiratory Society (ERS), Munich, Germany

2014 Is integrated disease management of COPD effective? Results of the recode cluster randomized controlled trial in real world patients? Nederlandse Huisartsen Genootschap (NHG) wetenschapsdag, Groningen, Netherlands

2014 Implementing a COPD disease management program in daily practice: the RECODE trial, International Foundation of Integrated Care (IFIC), Brussel, Belgium

2013 Mapping the Clinical COPD Questionnaire onto the EQ-5D (im)possible? International Society For Pharmacoeconomics and Outcomes Research (ISPOR), Dublin, Ireland

2013 Does the 2011 GOLD strategy improve the association with health status and costs? COPD en Astma Huisartsen Advies Groep (CAHAG), Utrecht, Netherlands

2012 The health economic impact of disease management programs for COPD: a systematic literature review and meta-analysis, European Respiratory Society (ERS), Vienna, Austria

2012 The health economic impact of disease management programs for COPD: a systematic literature review and meta-analysis, International Primary Care Respiratory Group (IPCRG), Edinburgh, England

POSTER PRESENTATIONS AT CONFERENCES

2015 COPD performance indicators in an integrated care program and its impact on health outcomes: the RECODE cluster randomized trial, International Society For Pharmacoeconomics and Outcomes Research (ISPOR), Milan, Italy

2014 Cost-effectiveness of an integrated care program for COPD: the RECODE cluster randomized trial, International Society For Pharmacoeconomics and Outcomes Research (ISPOR), Amsterdam, Netherlands

2013 Relating the new GOLD classification of COPD severity to quality of life and costs in a primary care population, European Respiratory Society (ERS), Barcelona, Spain

2012 The health economic impact of disease management programs for COPD: a systematic literature review and meta-analysis, International Society For Pharmacoeconomics and Outcomes Research (ISPOR), Berlin, Germany

AWARDS AND FUNDING

2015	Travel grant for international conference, Erasmus Trustfonds
2015	Nominated for best abstract 'Kosteneffectiviteit van integrale COPD zorg: de RECODE cluster gerandomiseerde trial' at CAHAG, Utrecht, Netherlands
2015	Nominated for best abstract in primary care 'Cost-effectiveness of an integrated care program for COPD: the RECODE cluster randomized trial' at ERS, Munchen, Germany
2013	Research grant 'Mapping the Clinical Chronic Obstructive Pulmonary Disease Questionnaire onto Generic Preference-Based EQ-5D Values.' Funding Source: Boehringer Ingelheim International
2013	Best student podium presentation 'Mapping the Clinical COPD Questionnaire onto the EQ-5D (im)possible?' ISPOR, Dublin, Ireland
2012	Highly commended primary care abstract 'The health economic impact of disease management programs for COPD: a systematic literature review and meta-analysis', ERS Vienna, Austria

TEACHING

2012-present	Master thesis supervision Master Health Economics, Policy and Law, Erasmus University Rotterdam
2015-present	Quality and Efficiency Bachelor Health Policy and Management, Erasmus University Rotterdam
2015-present	Advanced Research Methods Master Health Care Management, Erasmus University Rotterdam
2014-2015	Methods and techniques 3 Bachelor Health Policy and Management, Erasmus University Rotterdam
2014-2015	Methods and techniques 4 Bachelor Health Policy and Management, Erasmus University Rotterdam
2013-2014	Statistics A Pre-master, Health Policy and Management, Erasmus University Rotterdam

2013-2014	Financial Management Master Health Care Management, Erasmus University Rotterdam
2011-2013	Introduction in health care. Bachelor Health Policy and Management, Erasmus University Rotterdam

SHORT COURSES

2015	English speaking skills, Erasmus University Rotterdam
2015	English writing skills, Erasmus University Rotterdam
2013	Repeated Measurements, Netherlands Institute for Health Science
2013	Academic writing in English, Erasmus University Rotterdam
2012	Feedback & examination, Erasmus University Rotterdam
2012	Group dynamics, Erasmus University Rotterdam
2011	Problem based learning, Erasmus University Rotterdam
2011	Regression analysis, Netherlands Institute for Health Science
2011	Survival analysis, Netherlands Institute for Health Science
2011	Finished within four years, Erasmus University Rotterdam

CURRICULUM VITEA

Melinde Boland was born in Rotterdam on May 21th 1988. After obtaining her Bsc in Health Policy and Management in 2009, she did a master Health Economics Policy and Law (HEPL), with a specialization in Health Economics. After graduation, she started as a PhD candidate at the Institute for Medical Technology Assessment and Institute of Health Care Policy and Management (iBMG/IMTA) of the Erasmus University Rotterdam. She has a broad research interest in the field of health economics, cost-effectiveness analyses, integrated care, quality of life measures, and finance of integrated care, with a specialization in respiratory diseases. Besides her PhD project, she has worked on several research projects related to the economic evaluation of integrated care. In addition, she has taught various bachelor and masters courses at the institute of Health Policy and Management.

DANKWOORD

Met veel plezier kijk ik terug naar de afgelopen jaren waarin ik bij het instituut Beleid en Management voor de Gezondheidszorg mijn promotieonderzoek heb kunnen uitvoeren. Een resultaat (proefschrift) waar ik ontzettend trots op ben, maar ook een startschot van een nieuwe periode. Dit proefschrift was niet tot stand gekomen zonder de samenwerking en hulp van anderen. Dank aan iedereen die hier een grote en kleine rol in heeft gespeeld. In dit laatste stuk van het proefschrift wil ik gebruik maken om een aantal mensen speciaal hiervoor te bedanken.

Allereerst wil ik Prof. Maureen Rutten bedanken. Maureen, van jou heb ik heb de ruimte gekregen om me te ontwikkelen als onderzoeker, bedankt voor dit vertrouwen. Met je enorme hoeveelheid aan kennis, discipline, inspiratie, open houding om meer te leren, maar ook je met je charmes en bescheidenheid ben ik enorm trots dat jij mijn promotor bent. Bedankt voor alles en we gaan zeker nog meer memorabele en grappige momenten meemaken zoals het "gouden standaard" moment op ISPOR en het "muggen incident" op IHEA.

Prof. Niels, bedankt voor je hulp, begeleiding en inzet. Dankzij jou heb ik geleerd om ook vanuit een klinische hoek naar de zorg te kijken en heb ik veel geleerd over de ziekte COPD. Daarnaast heb je me geïntroduceerd aan (huisarts-)onderzoekers in de eerste lijn. Als gezondheidseconoom voel ik me hier nu ook echt thuis.

Apostolos, met jou samenwerken is geweldig. Ik kan me nog goed herinneren dat je me de eerste werkdag stond op te wachten en gelijk een rondleiding op de afdeling gaf. Jouw kennis, drive en humor blijken een succesvolle formule te zijn voor het schrijven en publiceren van artikelen. Ik vind het jammer dat je naar Oxford bent gegaan, maar ik ben erg blij dat we desondanks nog steeds samenwerken. Op naar meer publicaties!

Annemarije, dankzij jouw samenwerking is het RECODE onderzoek een succes geworden! Met jouw klinische en mijn gezondheidseconomische invalshoek vulden we elkaar goed aan. Ook toen je je huisartsenopleiding deed kon ik je altijd mailen of bellen. Een bewondering hoe jij kan timemanagen. Bedankt voor deze fijne samenwerking en natuurlijk je gezelligheid.

Professoren Pim Assendelft en Jacobijn Gussekloo hadden ook een belangrijk aandeel in het RECODE-team. Bedankt voor jullie inzet, discussies en input. Ik heb veel van jullie geleerd.

Graag wil ik nog een aantal mensen van het RECODE-team bedanken. Allereerst de medewerkers van Zorgdraad onder leiding van Coert. Dank voor het bouwen van de applicatie en hulp bij de extracties. De onderzoeksmedewerkers en secretaresses van het LUMC en van het iBMG, bedankt

voor jullie hulp bij het verzamelen van de data. En om niet te vergeten: de studenten Ineke en Simone bedankt voor jullie hulp bij het baseline en implementatie paper.

Ondanks een goed onderzoeksteam was de RECODE studie niet tot stand gekomen zonder de inzet van patiënten, huisartsen en eerstelijns teams. Heel erg bedankt voor jullie deelname.

Alle collega's van het iBMG bedankt voor jullie betrokkenheid, gezelligheid en interesses. Met name mijn kamergenoten Maartje, Ellen, Annemieke, Siok Swan en Leander. Daarnaast wil ik Lucas, Martine, Maria en Fenna bedanken voor jullie teamwork in verschillende projecten.

Job, bedankt voor de fijne samenwerking. De geografische afstand tussen Groningen en Rotterdam of Rotterdam en Mallorca is voor jou geen barrière om bereikbaar te zijn voor vragen en uitgebreide discussies. Op naar nog meer uitdagingen en mooie publicaties.

De leden van de promotiecommissie wil ik bedanken voor het lezen en beoordelen van mijn proefschrift en alvast het opponeren bij de verdediging.

Marc, bedankt voor de grafische vormgeving van dit proefschrift. Jij weet als geen ander van tekst een boek te maken.

Mijn ouders, familie en vrienden. Jullie hebben mij altijd gesteund. Dank voor deze steun, maar ook jullie interesse. Ik vind het super dat jullie aanwezig zijn bij de verdediging. Ook dank aan Hans, Geeske en Pim. Jullie voelen al als familie.

Last but not least, Marco! Marco, zonder jouw liefde, betrokkenheid en humor had ik het niet gered. Als ik 's avonds laat nog mijn presentatie aan het oefenen was, was jij mijn vaste publiek (inclusief grapjes over mijn pronounciation). Ik word blij als ik aan jou denk en we gaan samen nog een mooie toekomst tegemoet!

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