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Integrated disease management interventions for patients with chronic obstructive pulmonary disease (Review)

Poot CC, Meijer E, Kruis AL, Smidt N, Chavannes NH, Honkoop PJ

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[Intervention Review]

Integrated disease management interventions for patients with chronic obstructive pulmonary disease

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ABSTRACT

Background

People with chronic obstructive pulmonary disease (COPD) show considerable variation in symptoms, limitations, and well-being; this often complicates medical care. A multi-disciplinary and multi-component programme that addresses different elements of care could improve quality of life (QoL) and exercise tolerance, while reducing the number of exacerbations.

Objectives

To compare the effectiveness of integrated disease management (IDM) programmes versus usual care for people with chronic obstructive pulmonary disease (COPD) in terms of health-related quality of life (QoL), exercise tolerance, and exacerbation-related outcomes.

Search methods

We searched the Cochrane Airways Group Register of Trials, CENTRAL, MEDLINE, Embase, and CINAHL for potentially eligible studies. Searches were current as of September 2020.

Selection criteria

Randomised controlled trials (RCTs) that compared IDM programmes for COPD versus usual care were included. Interventions consisted of multi-disciplinary (two or more healthcare providers) and multi-treatment (two or more components) IDM programmes of at least three months' duration.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data. If required, we contacted study authors to request additional data. We performed meta-analyses using random-effects modelling. We carried out sensitivity analyses for the quality of included studies and performed subgroup analyses based on setting, study design, dominant intervention components, and region.

Main results

Along with 26 studies included in the 2013 Cochrane Review, we added 26 studies for this update, resulting in 52 studies involving 21,086 participants for inclusion in the meta-analysis. Follow-up periods ranged between 3 and 48 months and were classified as short-term (up to 6 months), medium-term (6 to 15 months), and long-term (longer than 15 months) follow-up. Studies were conducted in 19 different countries. The mean age of included participants was 67 years, and 66% were male. Participants were treated in all types of healthcare settings, including primary (n =15), secondary (n = 22), and tertiary care (n = 5), and combined primary and secondary care (n = 10). Overall, the level of certainty of evidence was moderate to high.

We found that IDM probably improves health-related QoL as measured by St. George's Respiratory Questionnaire (SGRQ) total score at medium-term follow-up (mean difference (MD) -3.89, 95% confidence interval (CI) -6.16 to -1.63; 18 RCTs, 4321 participants; moderate-certainty evidence). A comparable effect was observed at short-term follow-up (MD -3.78, 95% CI -6.29 to -1.28; 16 RCTs, 1788 participants). However, the common effect did not exceed the minimum clinically important difference (MCID) of 4 points. There was no significant difference between IDM and control for long-term follow-up and for generic QoL.

IDM probably also leads to a large improvement in maximum and functional exercise capacity, as measured by six-minute walking distance (6MWD), at medium-term follow-up (MD 44.69, 95% CI 24.01 to 65.37; 13 studies, 2071 participants; moderate-certainty evidence). The effect exceeded the MCID of 35 metres and was even greater at short-term (MD 52.26, 95% CI 32.39 to 72.74; 17 RCTs, 1390 participants) and long-term (MD 48.83, 95% CI 16.37 to 80.49; 6 RCTs, 7288 participants) follow-up.

The number of participants with respiratory-related admissions was reduced from 324 per 1000 participants in the control group to 235 per 1000 participants in the IDM group (odds ratio (OR) 0.64, 95% CI 0.50 to 0.81; 15 RCTs, median follow-up 12 months, 4207 participants; high-certainty evidence). Likewise, IDM probably results in a reduction in emergency department (ED) visits (OR 0.69, 95%CI 0.50 to 0.93; 9 RCTs, median follow-up 12 months, 8791 participants; moderate-certainty evidence), a slight reduction in all-cause hospital admissions (OR 0.75, 95%CI 0.57 to 0.98; 10 RCTs, median follow-up 12 months, 9030 participants; moderate-certainty evidence), and fewer hospital days per person admitted (MD -2.27, 95% CI -3.98 to -0.56; 14 RCTs, median follow-up 12 months, 3563 participants; moderate-certainty evidence).

Statistically significant improvement was noted on the Medical Research Council (MRC) Dyspnoea Scale at short- and medium-term follow-up but not at long-term follow-up. No differences between groups were reported for mortality, courses of antibiotics/prednisolone, dyspnoea, and depression and anxiety scores. Subgroup analysis of dominant intervention components and regions of study suggested context- and intervention-specific effects. However, some subgroup analyses were marked by considerable heterogeneity or included few studies. These results should therefore be interpreted with caution.

Authors' conclusions

This review shows that IDM probably results in improvement in disease-specific QoL, exercise capacity, hospital admissions, and hospital days per person. Future research should evaluate which combination of IDM components and which intervention duration are most effective for IDM programmes, and should consider contextual determinants of implementation and treatment effect, including process-related outcomes, long-term follow-up, and cost-effectiveness analyses.

PLAIN LANGUAGE SUMMARY

Integrated disease management for people with chronic obstructive pulmonary disease

What are the effects of integrated disease management (IDM) programmes on quality of life, ability to exercise, and number of lung attacks compared to usual care in people with chronic obstructive pulmonary disease (COPD)?

Background

Chronic obstructive pulmonary disease (COPD) is a chronic lung disease and is a major cause of ill health worldwide. People with COPD feel the impact of the disease in their daily life through symptoms such as breathlessness and coughing and acute worsening of symptoms in lung attacks.

Different healthcare providers, such as doctors, nurses, and physiotherapists, typically provide different types of care to people with COPD (e.g. prescribe medication, guide self-management, provide education, present exercise training). Previously, people with COPD could visit one or more different healthcare providers, and these providers would work independently. The goal of an integrated disease management (IDM) programme is to include different components of care by which different healthcare providers are co-operating and collaborating to provide more efficient care of better quality.

Study characteristics

We evaluated 52 studies involving 21,086 people with COPD. These studies were conducted in 19 countries spread all over the world. The average age of participants was 67 years, and 66% of participants were men. Some studies took place in general practices, some in hospitals, and some in both settings.

Key results

We found that people who participate in an IDM programme probably have better quality of life and their ability to exercise is probably improved compared to those receiving usual care. It is likely that people in an IDM programme have fewer hospital admissions for lung attacks and make fewer visits to an emergency department. When hospitalised, the total number of days people have to spend in hospital is reduced by two days. IDM programmes probably do not help to reduce the number of patients who die. The variety of available programmes makes it difficult to say if one IDM programme is the best.

Future studies should look at the most important components and the ideal length of the programme.

Certainty of the evidence

Overall, the certainty of our evidence was moderate to high but sometimes with large differences between studies.

This plain language summary is up-to-date as of February 2021.

Summary of findings 1. Integrated disease management interventions compared to usual care for patients with chronic obstructive pulmonary disease

Integrated disease management interventions compared to usual care for patients with chronic obstructive pulmonary disease

Patient or population: patients with chronic obstructive pulmonary disease
Setting: 15 studies in primary care, 22 studies in secondary care, 5 studies in tertiary care, 10 studies combination of primary and secondary care. 4 studies performed in North America, 9 studies in Northwestern Europe, 5 studies in Southern Europe, 3 studies in Oceania, 4 studies in East Asia, 3 studies in West Asia
Intervention: integrated disease management interventions
Comparison: usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care	Risk with integrated disease management interventions				
Health-related quality of life assessed with SGRQ (total) Scale from 0 to 100 (lower scores indicate better quality of life) Follow-up: range 9 to 14 months; median 12 months	Mean change in SGRQ in control groups ranged from -6.77 to 6.24 points	**MD 3.89 points lower** (6.16 lower to 1.63 lower)	-	4321 (18 RCTs)	⊕⊕⊕⊖ MODERATE[a,b]	MCID for SGRQ is -4 points. Effect is not observed longer than 12 months
Functional exercise capacity assessed with 6MWD Follow-up: range 9 to 14 months; median 12 months	Mean change in 6MWD in control groups ranged from -45.0 to 37.4 metres	**MD 44.69 metres more** (24.01 more to 65.37 more)	-	2071 (13 RCTs)	⊕⊕⊕⊖ MODERATE[a,c]	MCID is 35 metres. The observed effect is consistent over time and is noticeable longer than 12 months
Respiratory-related hospital admissions Follow-up: range 3 to 36 months; median 12 months	Study population		OR 0.64 (0.50 to 0.81)	4207 (15 RCTs)	⊕⊕⊕⊕ HIGH	
	324 per 1000	235 per 1000 (193 to 280)				
Hospital admissions, all causes Follow-up: range 6 to 48 months; median 12 months	Study population		OR 0.75 (0.57 to 0.98)	9030 (10 RCTs)	⊕⊕⊕⊖ MODERATE[d]	
	517 per 1000	445 per 1000 (379 to 512)				

Hospital days per patient, all causes Follow-up: range 3 to 24 months; median 12 months	Mean hospital days per patient ranged from 1.6 to 25.5 days	**MD 2.27 days fewer** (3.98 fewer to 0.56 fewer)	-	3563 (14 RCTs)	⊕⊕⊕⊖ MODERATE[a]	Mean change in hospital days ranged between an increase of 3.3 days and a reduction of 10.8 days
ED visits Follow-up: range 3 to 48 months; median 12 months	Study population		OR 0.69 (0.50 to 0.93)	8791 (9 RCTs)	⊕⊕⊕⊖ MODERATE[a]	
	412 per 1000	326 per 1000 (259 to 394)				

*The basis for the assumed risk is provided in the footnotes. **The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the usual care group and the **relative effect** of the intervention (and its 95% CI).

6MWD: six-minute walking distance; **CI:** confidence interval; **ED:** emergency department; **IDM:** integrated disease management; **MCID:** minimum clinically important difference; **MD:** mean difference; **OR:** odds ratio;**RCT:** randomised controlled trial;**SGRQ**: St. George's Respiratory Questionnaire.

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

[a]Downgraded one level because pooling showed substantial heterogeneity between studies, which could not or could only partially be explained by differences in the quality of studies.
[b]Subgroup analysis on the dominant component and region suggested intervention- and context-specific effects.
[c]Pooling of high-quality studies showed a smaller non-statistically significant difference of 6.51 metres (95% CI -7.53 to 20.55).
[d]Downgraded one level because pooling showed considerable heterogeneity and inconsistency in direction of effect between studies with statistical significantly fewer hospitalisations, with more hospitalisations, or with no differences between groups.

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) is a heterogeneous, systemic condition characterised by restricted airflow that is not fully reversible. It is a major cause of morbidity because people with COPD experience chronic and progressive respiratory symptoms (i.e. dyspnoea and coughing) (GOLD 2020). The prevalence of COPD is currently estimated at 11.7% and is expected to increase substantially in the coming decades due to ageing of the world's population, continued use of tobacco, and exposure to indoor biomass pollution (GOLD 2020; Lopez 2006; Lozano 2012). According to the World Health Organization (WHO), COPD is the fourth leading cause of death in the world (Lopez 2006; WHO 2020). Additionally, COPD has important financial consequences, with high reported direct costs (e.g. healthcare resources, medication prescriptions) and indirect costs (e.g. absence from paid work, consequences of disability) (Britton 2003; FIRS 2017; Guarascio 2013).

Optimal management of COPD is complex as it is a multi-component disease. Clinical, functional, and radiological presentations vary greatly from patient to patient, although patients may have a similar degree of airflow limitation (Agusti 2010; GOLD 2009; GOLD 2020; Wedzicha 2000). Previously, the sole focus in disease management lay on the degree of airflow limitation as a measure of disease severity (in the 2007 Global initiative for Chronic Obstructive Lung Disease (GOLD) classification of disease severity). This turned out to be a poor predictor of other important negative features of COPD, including health-related quality of life (HRQoL) and exercise tolerance (Agusti 2010; Burgel 2010). These patient-oriented outcomes are more important for people with COPD, given that COPD has a profound impact on HRQoL and exercise tolerance, even among those with modest airflow limitation (Engstrom 1996). Furthermore, impaired HRQoL (as shown in Domingo-Salvany 2002, Fan 2002, and Martinez 2006) and exercise tolerance (as reported in Gerardi 1996 and Pinto-Plata 2004) are associated with mortality (Cote 2009).

Some people are more prone than others to episodes of acute exacerbation, which is an important additional cause of morbidity, mortality, hospital admission, and impaired health status (Calverley 2003; Seemungal 1998; Wedzicha 2000). Although exacerbations become more severe and occur more frequently with increased severity of COPD, this is not always the case. There is evidence for a 'frequent-exacerbation' phenotype (or group of people) with exacerbation more often than would be expected given disease 'severity' as predicted by lung function testing (Hurst 2010; Le Rouzic 2018).

Description of the intervention

Given that COPD is a disease with a clinically heterogeneous picture characterised by multiple disease components, treatment of patients with COPD requires that these different components of the disease be addressed in a comprehensive programme known as integrated disease management (IDM).

In the previous decade, the concept of IDM was introduced as a means of improving quality and efficiency of care for patients with chronic non-communicable diseases such as COPD, heart failure, and diabetes mellitus. IDM interventions are aimed at reducing symptoms and avoiding fragmentation of care while containing costs. However, although IDM programmes are generally believed to be cost-effective, evidence shows inconclusive results. Several systematic reviews have shown (partly) beneficial results for people with chronic heart failure (Gonseth 2004; Roccaforte 2005), diabetes (Bongaerts 2017; Knight 2005; Norris 2002; Pimouguet 2010), depression (Badamgarav 2003; Neumeyer-Gromen 2004), and COPD (Cronin 2017).

It it important to note that there is no consensus in the literature about the definition of IDM. Several definitions have been proposed since the concept of 'disease management' was introduced. To facilitate communication between researchers, policy makers, and IDM program leaders, Schrijvers proposed a definition based on earlier reported definitions (Faxon 2004): "disease management consists of 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. The goal of chronic disease management is to identify persons at risk for one or more chronic conditions, to promote self-management by patients, and to address the illness or conditions with maximum clinical outcome, effectiveness, and efficiency regardless of treatment setting(s) or typical reimbursement patterns" (Schrijvers 2009). Peytremann-Bridevaux and Burnand adapted the definition as follows: "chronic disease prevention and management consist of a group of coherent interventions, designed to prevent or manage one or more chronic conditions using a community-wide, systematic, and structured multi-disciplinary 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, maximising clinical effectiveness and efficiency regardless of treatment setting(s) or typical reimbursement patterns. Routine process and outcome measurements should allow feedback to all those involved, as well as to adapt the programme" (Peytremann-Bridevaux 2009).

Over the years, IDM programmes combining patient-related, professional-directed, and organisational interventions were developed with the goal of improving effectiveness and economic efficiency of long-term care delivery (Lemmens 2009; Norris 2003; Wagner 2001). Since the previous version of this review of IDM for COPD patients (Kruis 2013), we have seen the advent of technology in IDM programmes, which potentially allows for continuously available and personalised types of patient guidance and monitoring (Kruse 2019).

Technology can be integrated into IDM programmes in different ways, such as use of SMS services, websites, apps, or home monitoring devices. Consequently, several different names are used to describe concepts within this area, such as telehealth, telemonitoring, telerehabilitation, eHealth, and mHealth, which have features that overlap. For the purposes of this systematic review, we adopted the term 'telemonitoring', defined as use of information and communication technologies to monitor and transmit items related to patient health status between geographically separated individuals (Maric 2009). Telemonitoring best describes the different interventions used in clinical studies, and is the term most studies have used themselves to describe their

intervention. Hence, for this update, we have added telemonitoring as a possible additional component of IDM.

How the intervention might work

There is great variation in the symptoms, functional limitations, and degrees of psychological well-being of patients with COPD, as well as in the speed of progression of COPD towards more severe stages (Agusti 2010). This calls for a multi-faceted response, including different elements (e.g. smoking cessation, physiotherapeutic reactivation, self-management, optimal medication adherence) targeted at the patient, the professional, and/or the organisation.

Ideally, COPD care is based on active self-management to slow down progression of the disease, including daily self-care, patient-physician collaboration, and exacerbation management. Information should be tailored to patients' needs, knowledge level, and clinical profile and should be accessible to patients when they need it most (Bourbeau 2013; Tiep 1997)

Another potential benefit of IDM is that without proper self-management, patients often refrain from reporting episodes of exacerbation to healthcare providers (Seemungal 2000). An important reason for this is fear of being sent to the hospital. Unfortunately, neglecting worsening of COPD leads to a negative spiral of increasing dyspnoea, deconditioning, and social deprivation. Eventually, this avoidant behaviour can lead to a respiratory crisis, which necessitates urgent referral to the hospital and might cause further damage to the lungs. To break through this self-reinforcing negative spiral, healthcare professionals must collaborate with their patients. This requires focus on improving and maintaining self-management skills, for example, by urging patients to respond rapidly and seek help to prevent further worsening (Chavannes 2008).

More recently, it has been argued that the addition of telemonitoring to IDM programmes allows for more continuous guidance and might lead to detection of deterioration earlier because of the potential for more frequent assessments. This could lead to more personalised management and prevention of exacerbations (Kruse 2019). However Kruse 2019 also concluded that it is unclear whether this approach enables people with COPD to self-manage more easily. Telemonitoring for pulmonary rehabilitation showed effects similar to those seen with conventional face-to-face, centre-based pulmonary rehabilitation for numerous outcomes (Cox 2021).

Why it is important to do this review

Review authors undertook the original version of this Cochrane Review in 2013 following a number of other (systematic) reviews that described beneficial effects of IDM for the health status of patients with COPD but were unable to draw firm conclusions due to large heterogeneity among interventions, study populations, outcome measurements, and methodological quality. This original review included 26 studies (Kruis 2013), and review authors concluded that IDM improved disease-specific QoL and exercise capacity while reducing hospital admissions and hospital days per person.

An update of the review is required because since that time, many new studies have been conducted to evaluate the effects of IDM programmes on quality of life, exercise capacity, lung function, and exacerbation-related outcomes such as respiratory-related hospital admissions and emergency department (ED) visits. Also, COPD care globally has advanced tremendously. Advancements include greater financial reimbursement for pulmonary rehabilitation programmes and use of technological and digital opportunities. These have altered and potentially improved usual care and have resulted in new studies on the effectiveness of different types of IDM programmes, including telemonitoring interventions. Furthermore, the introduction of telemonitoring has allowed better assessment of actual adherence to IDM programmes due to logging of data entry in apps. This has reinforced the importance of long-term follow-up of outcomes, given that rates of adherence to the IDM programme vary widely and subsequently observed effects can be short-lived (Cheikh-Moussa 2020; Herbert 2018). Finally, the studies included in the previous review provided insufficient data to permit firm conclusions about the long-term effectiveness of IDM.

In summary, in this update of the review, we aimed to summarise and assess evidence of short-, medium-, and long-term effectiveness of IDM compared to usual care among patients with COPD.

OBJECTIVES

To compare the effectiveness of integrated disease management (IDM) programmes versus usual care for people with chronic obstructive pulmonary disease (COPD) in terms of health-related quality of life (QoL), exercise tolerance, and exacerbation-related outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) and cluster-randomised trials in which IDM programmes or interventions were compared with control (i.e. usual care) in people with COPD. We excluded non-randomised controlled trials and other intervention studies.

Types of participants

People with a clinical diagnosis of COPD according to the GOLD criteria were included: people with chronic respiratory symptoms (i.e. coughing, sputum, or dyspnoea) and a limited post-bronchodilator forced expiratory volume in one second (FEV_1)-to-forced vital capacity (FVC) ratio < 0.7. Severity of airflow obstruction was classified by the GOLD stages of 2009 (GOLD 2009). All GOLD stages were accepted. Studies including participants with diagnoses other than COPD were only eligible if results for participants with COPD were available separately.

Types of interventions

We included studies in which the IDM intervention consisted of strategies to improve care for patients with COPD including organisational, professional, patient-directed (e.g. self- management, education), and financial interventions. We classified these according to the Cochrane Effective Practice and Organisation of Care Group (EPOC) taxonomy of interventions (EPOC 2008), complemented with patient-directed interventions. To be included in the review, a study had to include at least two of the following components of the IDM intervention.

1. Education/self-management: education, self-management, personal goals and/or action plan, exacerbation management.
2. Exercise: (home) exercise training and/or strength and/or endurance training.
3. Psychosocial component: cognitive-behavioural therapy, stress management, other psychological assessment and/or treatment.
4. Smoking cessation.
5. Medication: optimisation medication regimen/prescription of medication adherence.
6. Nutrition: dietary intervention.
7. Follow-up and/or communication: structural follow-up and/or communication, case management by nurses, optimal diagnosis.
8. Multi-disciplinary team: active participation and formation of teams of professional caregivers from different disciplines, revision of professional roles, integration of services, local team meetings.
9. Financial intervention: fees/payments/grants for providing IDM.

Furthermore, as IDM included different components, as mentioned above, different healthcare disciplines should be involved in delivery of the IDM programme. Hence, we included a study only if at least two different disciplines of healthcare providers were actively involved in the IDM programme.

Finally, a study should have a minimum duration of the IDM intervention of three months.

For all studies, we determined the dominant component of the programme by verifying with the study authors. If this was not possible, we decided based on the duration and intensity of each component. With the emergence of telemonitoring studies, we added telemonitoring as a separate dominant component post hoc.

Types of outcome measures

We specified the following outcomes a priori.

Primary outcomes

1. Health-related quality of life (HRQoL), as reported by a validated disease-specific questionnaire (e.g. St. George's Respiratory Questionnaire (SGRQ) - Jones 1991; Jones 2005; Clinical COPD Questionnaire (CCQ) - Kocks 2006, van der Molen 2003; Chronic Respiratory Questionnaire (CRQ) - Guyatt 1987; Guyatt 2011; COPD Assessment Test (CAT) - Jones 2009) or a generic quality of life questionnaire (e.g. Short Form-36 (SF-36) - Ware 1992 EuroQol-5D (EQ-5D) - EuroQol Group 1990)
2. Maximal or functional exercise capacity, as reported by peak capacity measured in the exercise laboratory by an incremental exercise test defined according to results of the 6-minute walking distance test (6MWD) - Redelmeier 1997 - or the shuttle run test - Singh 1992
3. Exacerbation-related outcomes, as reported by one of the following: all-cause hospital admissions, respiratory-related hospital admissions, all-cause hospital days, emergency department (ED) visits, patients with at least one exacerbation and patients with at least one prescription for prednisone and at least one for antibiotics. These outcomes follow the latest definitions of moderate and severe COPD exacerbations in the GOLD guideline and are also used in the two latest Cochrane Reviews assessing exacerbations as a primary outcome (GOLD 2020; Threapleton 2019; Walsh 2019)

Secondary outcomes

Clinical outcomes

1. Dyspnoea, as measured by the Medical Research Council (MRC) Dyspnea Scale - Bestall 1999 - or the Borg Scale - Borg 1970
2. Survival (mortality)
3. Lung function (FEV_1, FVC)
4. Depression, as measured by the Hospital Anxiety and Depression Scale (HADS) - Zigmond 1983 - or the Beck Depression Inventory (BDI) - Beck 1961

Process-related outcomes

1. Coordination of care (e.g. accessibility of care, rate of patient participation in the disease management programme, patients' and healthcare professionals' satisfaction with the programme, extent to which disease management was implemented, from the perspective of the patient (PACIC) - Glasgow 2005)

We evaluated outcomes at (1) short-term (up to 6 months), (2) medium-term (6 to 15 months), and (3) long-term (longer than 15 months) endpoints, if possible.

Search methods for identification of studies

Electronic searches

The previously published version of this Review included studies up to April 2013. For the current update, we identified studies using the Cochrane Airways Group Register of trials; the Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library; MEDLINE (Ovid SP); Embase (Ovid SP); and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO).

We used specific medical subject headings (from MeSH) and additional keywords to identify all trials on IDM in COPD patients. The search strategy was developed and conducted in collaboration with the Cochrane Airways Information Specialist. The initial strategy was developed for MEDLINE and was adapted for use in the other databases.

Complete search strategies for the database searches are provided in the appendices (MEDLINE - Appendix 1; Embase - Appendix 2; CINAHL - Appendix 3; CENTRAL - Appendix 4; Airways Register - Appendix 5). The search period for this update covers April 2013 to September 2020. This includes an initial search on 4 January 2017 and updates in March 2018 and March 2019. We ran a final update search in September 2020.

Searching other resources

To identify all possible studies, we carried out an additional search for systematic reviews in the Cochrane Database of Systematic Reviews. We also screened reference lists of included studies and systematic reviews for potential studies for inclusion in the current review. To identify ongoing or new studies, we searched databases of ongoing studies, including ClinicalTrials.gov (up to September 2020) and the WHO International Clinical Trials Registry Platform (ICTRP) (up to March 2019). See Appendix 6 for those search terms.

Data collection and analysis

Selection of studies

The lead review author (CP) and one of two other review authors (EM, PH) independently assessed the title and abstract of each identified citation. If there was any doubt, we retrieved the full-text article and examined it for inclusion eligibility. Disagreements were discussed during a consensus meeting. When consensus could not be reached, the third review author (AK - the first author of the original 2013 review) adjudicated. Subsequently, the full text of the potential eligible abstract was read by two review authors (CP and EM or PH) before a decision was made regarding its inclusion in the review.

Data extraction and management

For the current update, we used Covidence to extract data and assess risk of bias for each included study (Covidence). The lead review author (CP) extracted data from all papers identified for inclusion using a digital data extraction form. Two other review authors (EM, PH) independently extracted data from an equal share of the same studies. We collected the following information: (1) study design (e.g. randomisation method, sample size, blinding); (2) participant characteristics (e.g. age, sex, COPD diagnosis); (3) interventions (i.e. setting, number of professionals involved, elements of IDM programme/intervention, frequency and duration of intervention); (4) outcome measures and timing of outcome assessment; and (5) results (e.g. loss to follow-up, outcomes). Any discrepancies in data extraction between review authors were resolved through discussion. In case of missing data, we contacted the authors of these studies to request additional information or clarification.

Assessment of risk of bias in included studies

The lead review author (CP) assessed the risk of bias for all included studies using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Two other review authors (EM, PH) independently assessed risk of bias for an equal share of the same studies. Disagreements were resolved through discussion. The following risk of bias items were assessed.

1. Random sequence generation.
2. Concealment of allocation.
3. Blinding of participants and personnel, in relation to the intervention.
4. Blinding of outcome assessment (i.e. patient-reported outcome, other outcomes).
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

As cluster-randomised trials were also included, we added the following design-related domains for these types of studies.

1. Recruitment bias (i.e. whether individuals were recruited after clusters had been randomised).
2. Baseline imbalance between groups (i.e. whether risk of baseline differences was reduced by using stratified or pair-matched randomisation of clusters).
3. Loss of follow-up of clusters (i.e. whether missing clusters and missing outcomes for individuals within clusters could lead to a risk of bias in cluster-randomised trials).
4. Methods of analysis adequate for cluster-randomised controlled trials (i.e. whether clustering was taken into account in the analysis) (Higgins 2011).

We judged all items as having high, low, or unclear risk of bias and provided a quote from the study and/or a justification for our decision.

Measures of treatment effect

We analysed results of the studies in RevMan 5, using random-effects modelling. We used forest plots to compare results across trials. When possible, results were related to the minimum clinically important difference (MCID) for the respective variable. We undertook meta-analysis only when this was meaningful, that is, when treatment, participants, and the underlying clinical question were similar enough for pooling to make sense, and when the results of at least two RCTs were available.

We used intention-to-treat data or the 'full analysis set' whenever reported. We used per-protocol analysis when neither was reported. Normally, outcome measures that have been adjusted for baseline differences produce the most reliable outcomes. However, these can be analysed only by generic inverse variance (GIV). Also, we noted significant variation in the number of parameters adjusted for between studies. Hence, we used unadjusted values in our random-effects modelling for studies with an RCT design, and values adjusted for potential clustering effects for studies with a cluster-RCT design.

When multiple trial arms were reported in a single study (e.g. hospital-based pulmonary rehabilitation and home-based pulmonary rehabilitation), we included all relevant trial arms. We halved the control group in these cases to avoid double-counting, as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 16.5.4) (Higgins 2019a).

Unit of analysis issues

When a study used a cluster-RCT design, we calculated the estimate of effect by using the GIV whenever possible. We used the mean difference (MD) and the 95% confidence interval (CI) reported by study authors when the appropriate analyses were used and authors had adjusted for cluster effect. We calculated a dummy mean change and standard deviation (SD) based on the MD and its 95% CI for cluster-RCT studies, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 23.1.3) (Higgins 2019b).

In case of a unit of analysis error in cluster-RCTs, we adjusted for the design effect by reducing the size of the trial to its "effective sample size" (Rao 1992). The effective sample size of a single intervention group in a cluster-randomised trial is its original sample size divided by a quantity called the 'design effect'. The design effect is 1 + (M - 1) * ICC, where M is the average cluster size, and ICC is the intra-cluster correlation coefficient. For dichotomous data, both the total number of participants and the number of participants experiencing the event were divided by the design effect. For continuous data, for which the GIV method could not be used, only sample sizes were reduced, and means and SDs were left unchanged (Higgins 2011).

Dealing with missing data

When a study paper missed important statistical information required for analysis, or required additional calculations that needed to be clarified, we attempted to contact study authors to gather the required information. When authors had not calculated relevant statistics but presented supporting data, we conducted calculations using methods described in the 2019 *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019a). When studies did not report SDs for change from baseline but did provide information on means, standard errors (SEs), 95% CIs, P values, and population sizes across groups, we calculated SDs for change from baseline using the RevMan 5 internal calculator.

When we could not directly calculate the SD for change from baseline, we imputed the SD using a correlation coefficient as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 6.5.2.8) (Higgins 2019a). We calculated the correlation coefficient by using the weighted mean (based on size of the study) of two or more studies that reported results for the respective variable in sufficient detail.

In the case that fewer than two studies provided sufficient information, a weighted mean correlation coefficient could not be calculated. In that case, we used data on post-intervention measurements, as they are considered to be more precise.

For studies that reported a median instead of a mean, we estimated the mean and the SD using the method and open-access calculator provided in Wan 2014.

Assessment of heterogeneity

We assessed heterogeneity in each meta-analysis both visually through inspection of forest plots and statistically using tau^2, I^2, and the T statistic (Higgins 2019). We regarded heterogeneity as substantial when I^2 was greater than 50% or a low P value (< 0.10) was reported for the Chi^2 test for heterogeneity. We reported heterogeneity and explored the possible causes. In cases of substantial (I^2 > 50%) or considerable (I^2 > 75%) heterogeneity, we investigated sources for heterogeneity by conducting subgroup analyses (see Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

The likelihood of publication bias was investigated by preparing a funnel plot only if ten or more studies were included in the meta-analysis. Based on visual inspection, the likelihood of publication bias was evaluated. When asymmetry was observed, we attempted to identify possible reasons by considering the quality of the studies, the particular interventions included, and the contexts in which interventions were implemented.

Data synthesis

We performed statistical analyses using Review Manger software 5.3 (RevMan 5) and RevMan Web 2019 (RevMan Web 2019).

We pooled study results using the random-effects model. For continuous data, we recorded mean change from baseline to endpoint and SD for each group and calculated the MD. For dichotomous data, we recorded the number of participants with each outcome event and calculated the odds ratio (OR). We used all results reported at short-, medium-, and/or long-term follow-up. Given that all interventions had a duration of 12 weeks at minimum, we analysed available data at 6 months for the short term. We analysed data measured most medial to the other time points (i.e. for medium term, we used results at 12 months when 9 and 12 months were given). When possible, we discussed the intervention effect estimate in the context of its MCID. If the meta-analysis led to statistically significant overall estimates, we transformed these results back into measures that are clinically useful in daily practice, such as the number needed to treat for an additional beneficial outcome (NNTB).

Subgroup analysis and investigation of heterogeneity

To explain heterogeneity among study results, we planned the following subgroup analyses a priori (when data were available) to determine if outcomes differed among:

1. settings of the IDM intervention (e.g. primary, secondary, or tertiary care);
2. study designs (individually randomised patients versus cluster-randomised patients); and
3. intervention groups, with regard to different components as listed by the EPOC classification (EPOC 2008).

We performed an additional post-hoc subgroup analysis based on the region in which the study was conducted (i.e. North America, South America, Northwestern Europe, Southern Europe, East Asia, Central Asia) to account for regional differences in usual care and customs regarding hospitalisation, which proved to be large in Kessler 2018. The previous review authors planned to include an additional subgroup on disease severity (Kruis 2013), but they were unable to do so due to the poor quality of reporting. Also, Kruis 2013 performed an additional subgroup analysis based on control group (i.e. no treatment, treatment with one healthcare provider, treatment with one component, other disease management interventions). In the past decade, regular care has evolved in such a way that multiple individual 'intervention components' (e.g. exercise advice, educational flyers) are delivered to patients with COPD; therefore, classification would be too ambiguous, depending largely on what is reported. Hence, this review does not include different control groups as a subgroup analysis.

Sensitivity analysis

We performed sensitivity analyses on the basis of the methodological quality of studies. We did so by repeating our analysis among only studies judged to be of 'high quality'. For the purposes of this review, 'high-quality studies' were defined as studies with low or unclear risk of bias due to allocation concealment, low or unclear risk of bias due to incomplete outcome data, and, in the case of cluster-RCTs, studies with adequate analysis methods.

Summary of findings and assessment of the certainty of the evidence

We presented the main results of this review in a 'Summary of findings' table, which includes an overall rating of the evidence using the GRADE approach, in accordance with recommendations laid out in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). This involves making separate ratings for quality of evidence for each patient-important outcome by identifying five factors that can

lower the quality of evidence, including study limitations, indirectness of evidence (also called clinical heterogeneity with regard to study population, intervention, control group, and outcomes), unexplained heterogeneity or inconsistency of results (i.e. statistical heterogeneity), imprecision of results (i.e. due to small sample sizes and few events), and high probability of publication bias. However, other factors can increase the quality of evidence; these include large magnitude of effect; plausible confounding, which could reduce the demonstrated effect; and the dose-response gradient (GRADE Working Group 2004). We have presented footnotes to justify decisions made and have provided comments to support readers' understanding of this review.

We intended to present short-, medium-, and long-term outcomes for all of our primary outcomes in the 'Summary of findings' table. However, because we were limited to a maximum of seven outcomes, we decided to present dichotomous outcomes for all time points and continuous outcomes for medium-term follow-up only, being most clinically relevant. For all outcomes, we presented the range and the median follow-up.

RESULTS

Description of studies

See Characteristics of included studies.

Results of the search

Our literature search yielded 6900 citations after duplicates were removed with potential for inclusion (see Figure 1). We excluded 6543 citations during the initial screening of titles and abstracts and assessed full texts of 357 citations. Eleven studies were ongoing at the time of this review (Ali 2020; Bourne 2017; Ding 2019; Drennan 2014; Foot 2017; Hajizadeh 2020a; Hansen 2017; NCT04136418; NCT04416295; NCT04533412; Steed 2017). One study had finished data collection, but as the results were not yet published, study authors wished to withhold results until after publication (Bourne 2017). A further seven provided insufficient detail to allow a decision on eligibility. We were unable to establish contact with the study authors, so some studies are still awaiting classification (Baumann 2012; Borji, 2018; Carcereny, 2016; Mao 2020; NCT04256070; Reguera 2017; Xu 2010). Thus, 26 new studies (57 citations) were added to this review, in addition to the 26 studies already included in the previous version of the review.

Figure 1. Study flow diagram

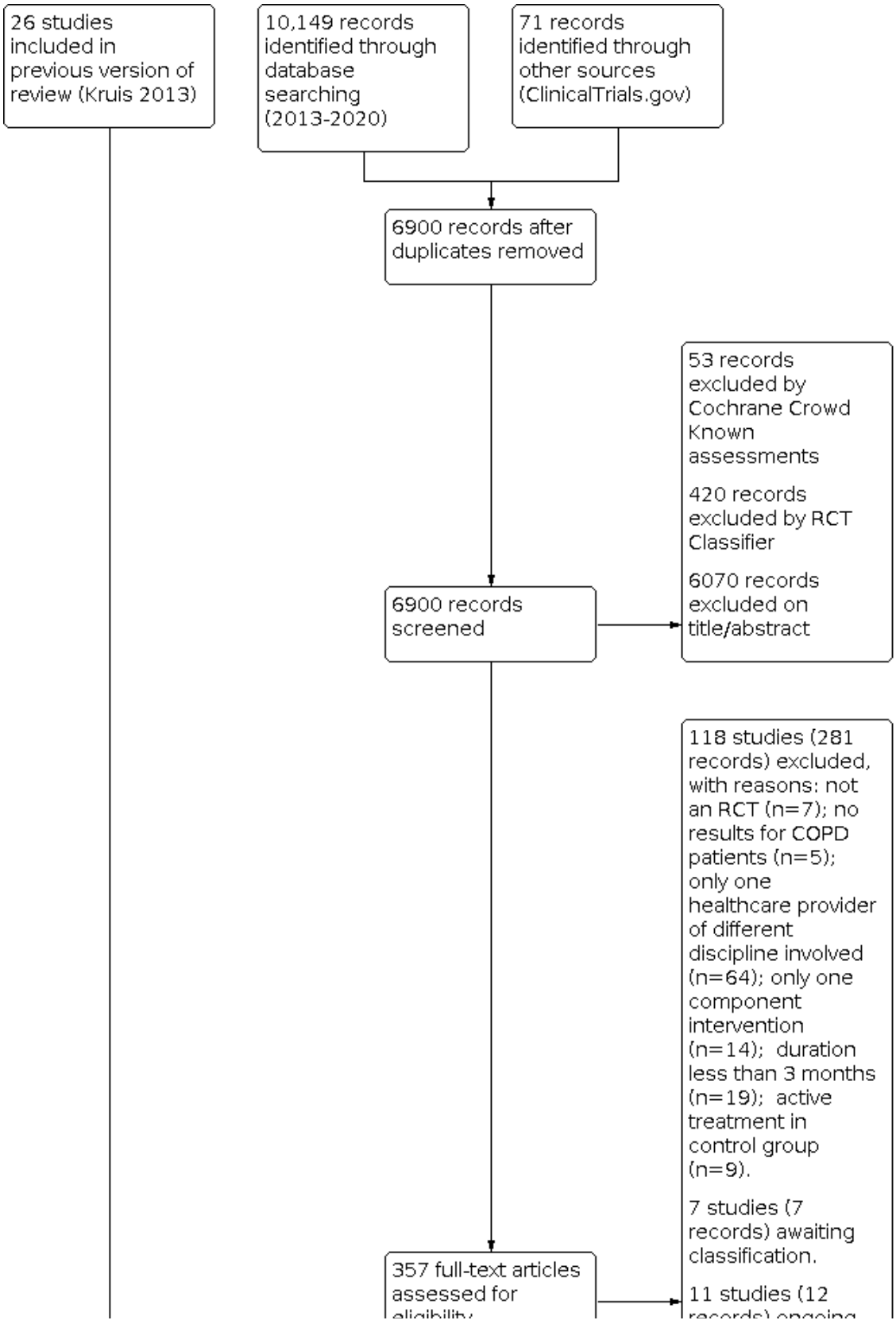
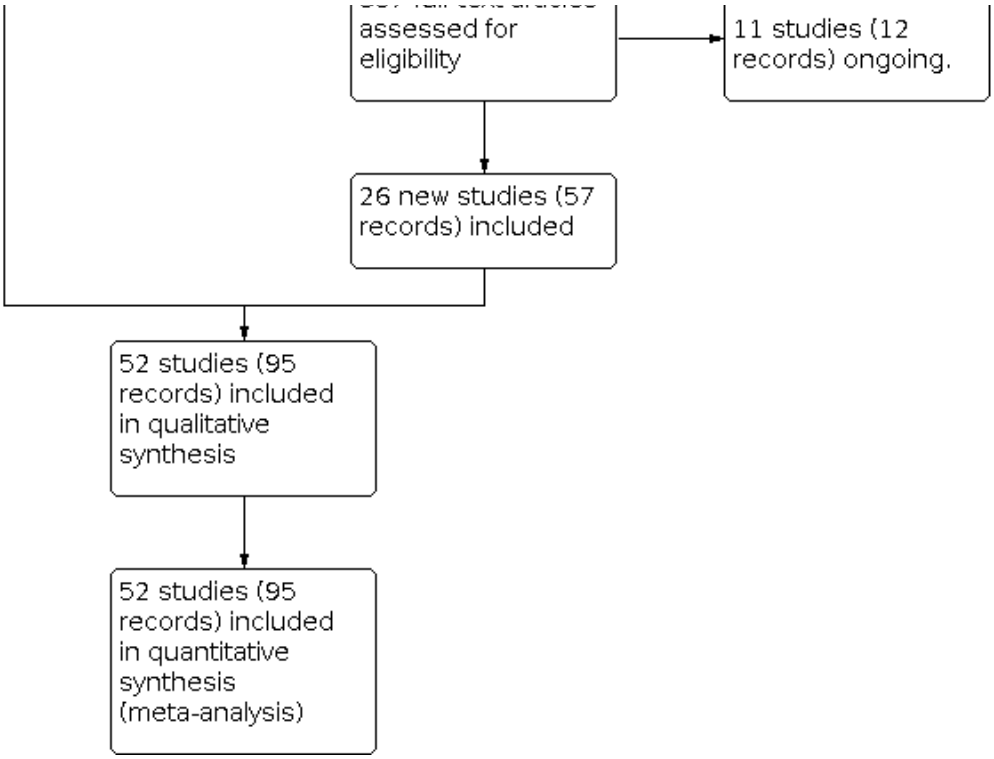


Figure 1. (Continued)



Included studies

We included the 26 RCTs from the 2013 version of the Cochrane Review (Kruis 2013). A total of 52 studies (represented by 95 citations) contributed to the current meta-analysis, including 26 new studies (Aboumatar 2019; Bernocchi 2017; Fan 2012; Freund 2016; Haesum 2012; Jimenez-Reguera 2020; Kalter-Leibovici 2018; Kennedy 2013; Kessler 2018; Khan 2019; Ko 2016; Kruis 2014; Lenferink 2019; Lilholt 2017; Lou 2015; Öztürk 2020; Rose 2017; Sanchez-Nieto 2016; Silver 2017; Tabak 2014; Titova 2017; Vasilopoulou 2017; Vianello 2016; Wang 2017; Zhang 2020; Zwar 2016). The newly included studies were published between 2014 and 2020 and originated from across the globe. Four studies originated from China (Ko 2016; Lou 2015; Wang 2017; Zhang 2020), three from the USA (Aboumatar 2019; Fan 2012; Silver 2017), and one from Canada (Rose 2017). A total of nine studies were performed in Northwestern Europe - three in the Netherlands (Kruis 2014; Lenferink 2019; Tabak 2014), two in Denmark (Haesum 2012; Lilholt 2017), and one each in Germany (Freund 2016), the UK (Kennedy 2013), and Norway (Titova 2017). Kessler 2018 was a multi-national multi-centre study performed in Germany, France, Italy, and Spain. Five studies were performed in Southern Europe - Italy (Bernocchi 2017; Vianello 2016), Spain (Jimenez-Reguera 2020; Sanchez-Nieto 2016), and Greece (Vasilopoulou 2017). Three studies were performed in Western Asia - one in Israel (Kalter-Leibovici 2018), one in Pakistan (Khan 2019), and one in the Asian part of Turkey (Öztürk 2020). One study originated from Australia (Zwar 2016).

Of the 52 studies that met eligibility criteria, nine used a cluster-RCT design, with general practices or healthcare regions as the unit of randomisation (Freund 2016; Kennedy 2013; Khan 2019; Kruis 2014; Lilholt 2017; Lou 2015; Rea 2004; Wood-Baker 2006; Zwar 2016). All but two trials randomly assigned participants to either IDM or usual care. The other two trials had two different intervention groups and one usual care group (Vasilopoulou 2017; Wijkstra 1994). We included both intervention groups as separate comparisons and split the usual care group in half.

A description of the included studies is provided in Table 1 Table 2, and Characteristics of included studies.

Participants

A total of 21,086 COPD patients were randomised in the 52 studies, with a range of 29 to 8171 patients per study. Of these, 16,390 (84%) patients completed the studies (range 23% to 100%). At the moment of inclusion, the mean age of the intervention population was 67.1 years (SD 9.27), with 65% male (range 25% to 99%). In the usual care group, mean age was 67.2 years (SD 9.26) and 67% (range 30 to 100%) were male.

Interventions

Patients were treated in all types of healthcare settings: primary care (15 studies), secondary care (22 studies), tertiary care (5 studies), and a combination of primary and secondary health care (10 studies). The numbers of healthcare professionals involved ranged from 2 to 7, with a mean number of 3. The number of components per programme ranged from 2 to 8, with a mean number of 4. Interventions also varied in terms of duration - between 3 and 48 months - with varying intensity of separate intervention components. Some interventions consisted of a clearly defined intensive intervention period and a subsequent maintenance or structural follow-up period (Bourbeau 2003; Fan 2012; Gottlieb 2011; Güell 2000; Jimenez-Reguera 2020; Ko 2016; Sridhar 2008; van Wetering 2010; Vasilopoulou 2017). One study

had an intervention with a variable duration of 2 years minimum and 5 years maximum (Kalter-Leibovici 2018).

Following the subgroup analysis performed in the previous version of this review, we determined the dominant component of the IDM programme from all newly included studies. The dominant component could be determined directly from the objective or title of the study for eight studies (Aboumatar 2019; Bernocchi 2017; Fan 2012; Haesum 2012; Kruis 2014; Öztürk 2020; Vasilopoulou 2017; Zwar 2016). For the remaining 18 studies, we contacted study authors to ask what they considered the dominant intervention component. Eleven study authors did not provide a response. Of the seven who responded, three indicated that the intervention did not have a dominant component. To perform a subgroup analysis on types of interventions, we chose the dominant component as the component with the greatest intensity in terms of duration. Given the increased use of telemonitoring and its distinguished features to monitor patients from a distance, we decided to include telemonitoring as a separate dominant component. In Vasilopoulou 2017, usual care was compared to two types of interventions: home-based and hospital-based pulmonary rehabilitation. As interventions were characterised by different dominant components (telemonitoring and structural follow-up, respectively), we included both as separate interventions.

Including the dominant components identified by Kruis 2013, we arrived at the following categories of dominant components of IDM programmes.

1. Exercise (13 studies: Bendstrup 1997; Boxall 2005; Cambach 1997; Engstrom 1999; Fernandez 2009; Gottlieb 2011; Güell 2000; Güell 2006; Mendes 2010; Strijbos 1996; Theander 2009; van Wetering 2010; Wijkstra 1994).
2. Self-management with an exacerbation action plan (12 studies: Aboumatar 2019; Bourbeau 2003; Jimenez-Reguera 2020; Kennedy 2013; Koff 2009; Kruis 2014; Lenferink 2019; Öztürk 2020; Rice 2010; Sanchez-Nieto 2016; Trappenburg 2011; Wood-Baker 2006).
3. Structured follow-up with healthcare professionals, including case management (15 studies: Aiken 2006; Dheda 2004; Farrero 2001; Freund 2016; Kalter-Leibovici 2018; Kessler 2018; Khan 2019; Ko 2016; Lilholt 2017; Littlejohns 1991; Rose 2017; Smith 1999; Titova 2017; Vasilopoulou 2017; Zhang 2020).
4. Individualised educational sessions (5 studies: Fan 2012; Lou 2015; Silver 2017; Wakabayashi 2011; Zwar 2016).
5. Telemonitoring (6 studies: Bernocchi 2017; Haesum 2012; Tabak 2014; Vasilopoulou 2017; Vianello 2016; Wang 2017).

In addition, Kruis 2013 identified two studies that each had two dominant components. Sridhar 2008 included two components on which most of the intervention time was spent (i.e. exercise and self-management with action plan). Rea 2004 included two dominant components: self-management with action plan and structured follow-up. Therefore we included these two studies in separate categories, namely, exercise and self-management and self-management and structural follow-up.

Outcomes

We combined the outcomes of 26 recently included studies with the 26 already included studies. We recorded the number of studies reporting a specific outcome as follows.

1. Quality of life (46 studies).
2. Exercise capacity (28 studies).
3. Exacerbation-related outcomes: measured by numbers of exacerbations, hospital admissions, hospitalisation days, emergency department (ED) visits, prednisolone or antibiotics courses (32 studies).
4. Lung function (21 studies).
5. Survival, mortality (15 studies).
6. Depression (10 studies).
7. Dyspnea (13 studies).
8. Process-related outcomes (14 studies).

Details of the included studies and outcomes are provided in Characteristics of included studies, Table 3 Table 4, Table 5, and Table 6.

We requested additional data from 21 study authors; 14 (67%) responded. Nine studies provided additional data that we used in the analysis (Bernocchi 2017; Kalter-Leibovici 2018; Kennedy 2013; Kessler 2018; Khan 2019; Lenferink 2019; Titova 2017; Vasilopoulou 2017; Wang 2017. Seven studies provided sufficient data for calculation of correlation coefficients used to impute missing data (Aboumatar 2019; Engstrom 1999; Fan 2012; Kalter-Leibovici 2018; Lilholt 2017; Sridhar 2008; Vasilopoulou 2017) (see Dealing with missing data).

Excluded studies

We excluded 118 full-text articles from the current update during the full-text screening process. The Characteristics of excluded studies table provides full details on reasons for exclusion.

Risk of bias in included studies

Results of the risk of bias assessment are presented in Figure 2. All but one of the included studies were judged to be at high risk of bias for blinding of participants, which is a result of the nature of the intervention. With regard to the other domains, the likelihood that bias was present (high risk of bias) varied across studies, from 4% for random sequence generation (selection bias) to 27% for blinding of outcome assessment (detection bias).

Figure 2. 'Risk of bias' summary: review authors' judgments about each risk of bias item for each included study.

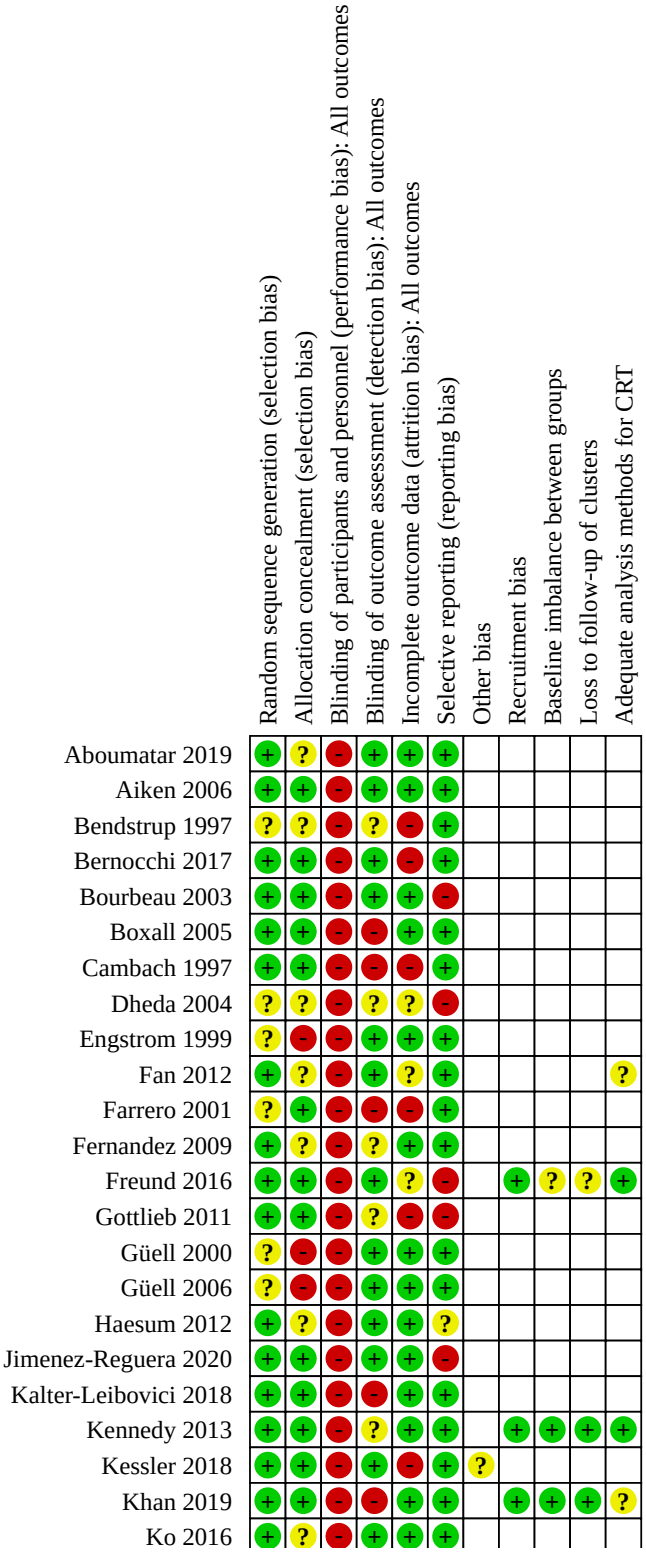
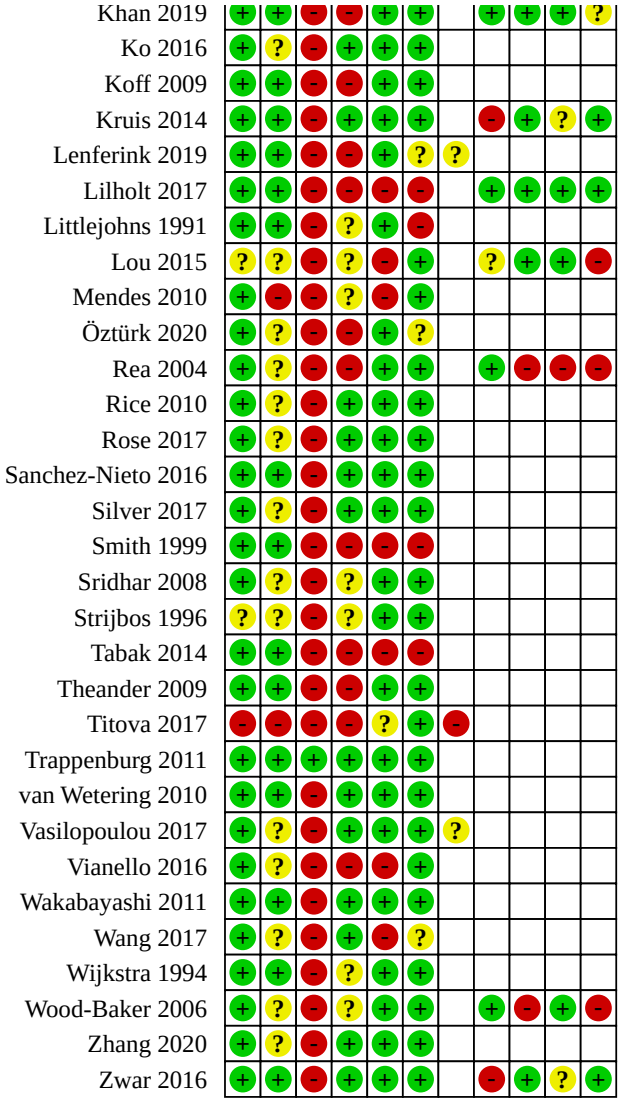


Figure 2. (Continued)



Allocation

We judged 43 included studies as having low risk of bias in sequence generation (Aboumatar 2019; Aiken 2006; Bernocchi 2017; Bourbeau 2003; Boxall 2005; Cambach 1997; Fan 2012; Fernandez 2009; Freund 2016; Gottlieb 2011; Haesum 2012; Jimenez-Reguera 2020; Kalter-Leibovici 2018; Kennedy 2013; Kessler 2018; Khan 2019; Ko 2016; Koff 2009; Kruis 2014; Lenferink 2019; Lilholt 2017; Littlejohns 1991; Mendes 2010; Öztürk 2020; Rea 2004; Rice 2010; Rose 2017; Sanchez-Nieto 2016; Silver 2017; Smith 1999; Sridhar 2008; Tabak 2014; Theander 2009; Trappenburg 2011; van Wetering 2010; Vasilopoulou 2017; Vianello 2016; Wakabayashi 2011; Wang 2017; Wijkstra 1994; Wood-Baker 2006; Zhang 2020; Zwar 2016). Information from eight studies was insufficient to permit a decision (Bendstrup 1997; Dheda 2004; Engstrom 1999; Farrero 2001; Güell 2000; Güell 2006; Lou 2015; Strijbos 1996). One study was judged to have high risk of bias, as participants were randomised based on district (Titova 2017). With regard to allocation bias, we judged 27 studies as having low risk of bias and five studies as having high risk of bias. For the remaining 20 studies, provided information was insufficient to permit a firm conclusion (unclear risk of bias).

Blinding

The nature of the intervention makes blinding of participants and healthcare providers delivering the intervention impossible. Hence, we judged all studies, except Trappenburg 2011, which kept patients unaware of the primary study aim (postponed information), as having high risk of performance bias. Although blinding of patients and/or healthcare providers is impossible, outcome assessors in some cases could be blinded to participants' allocation. Twenty-five studies were judged as having low risk. These studies had outcome assessors that were adequately blinded for allocation, reported only on outcomes that were objective (i.e. mortality, hospitalisations), or had an outcome committee judging the outcomes. This made risk of detection bias highly unlikely. Outcome assessors were unblinded in 15 studies (Boxall 2005; Cambach 1997; Farrero 2001; Kalter-Leibovici 2018; Khan 2019; Koff 2009; Lenferink 2019; Lilholt 2017; Öztürk 2020; Rea 2004; Smith

1999; Tabak 2014; Theander 2009; Titova 2017; Vianello 2016), posing a high risk of bias. Twelve studies provided insufficient information and were judged as having unclear risk (Bendstrup 1997; Dheda 2004; Fernandez 2009; Gottlieb 2011; Kennedy 2013; Littlejohns 1991; Lou 2015; Mendes 2010; Sridhar 2008; Strijbos 1996; Wijkstra 1994; Wood-Baker 2006). For the remaining 25 studies, outcome assessors were blinded to group allocation.

Incomplete outcome data

We judged 35 studies as having low risk of bias, as they had low dropout rates, or dropout rates were balanced across groups for similar reasons. We considered 13 studies to have high risk of bias (Bendstrup 1997; Bernocchi 2017; Cambach 1997; Farrero 2001; Gottlieb 2011; Kessler 2018; Lilholt 2017; Lou 2015; Mendes 2010; Smith 1999; Tabak 2014; Vianello 2016; Wang 2017). Four of these 13 studies had larger dropout in the control group than in the intervention group. In Lou 2015, 1217 participants dropped out from the control group compared to 779 from the intervention group. Reasons were death and inability to perform the walking test. In Bernocchi 2017, larger dropout rates in the control group were due to increased hospitalisations as a result of heart failure.

Selective reporting

We judged 39 studies to have low risk of reporting bias, meaning that all outcomes mentioned in the protocol or the clinical trial register were reported. Nine studies selectively reported outcomes specified in the protocol and/or in the methods section (Bourbeau 2003; Dheda 2004; Freund 2016; Gottlieb 2011; Jimenez-Reguera 2020; Lilholt 2017; Littlejohns 1991; Smith 1999; Tabak 2014), or they changed operationalisation of the outcome (i.e. Physical Component Summary (PCS) subscore instead of SF-36 score to measure QoL) (Lilholt 2017). In three studies (Bourbeau 2003; Dheda 2004; Öztürk 2020), the authors observed no statistically significant differences in outcomes and therefore did not present data. In Tabak 2014, outcomes were reported for only 3 months - not for 6 and 9 months - in contrast to the study protocol. This all points to the risk of selective outcome reporting.

With the exception of one outcome (hospital admission (in days)), funnel plots did not indicate that publication bias is likely. Observed asymmetry of the funnel plot for hospital admission is probably caused by the poor methodological quality of Farrero 2001.

Other potential sources of bias

We included nine cluster-randomised trials, three of which introduced bias (Lou 2015; Rea 2004; Wood-Baker 2006). In Wood-Baker 2006, there was noticeable imbalance in differences between groups at baseline. Wood-Baker 2006 and Lou 2015 did not account for clustering in statistical analyses of dichotomous outcomes. This may lead to over-precise results and can result in much more weight in a meta-analysis (Higgins 2011). Therefore, in our meta-analyses, we adjusted for the design effect by reducing the size of the trial to its "effective sample size" for all dichotomous outcomes (Rao 1992), and we used the adjusted MD via the GIV approach for all continuous outcomes. In Rea 2004, there was loss to follow-up of five clusters (four control and one intervention cluster). Other potential sources of bias were found in Titova 2017 Kessler 2018 Lenferink 2019 Vasilopoulou 2017 Vianello 2016, and Lou 2015. Lou 2015 was performed across four geographically distinct regions and based randomisation on geographical location, thereby potentially introducing cluster effects.

Effects of interventions

See: **Summary of findings 1** Integrated disease management interventions compared to usual care for patients with chronic obstructive pulmonary disease

Primary outcomes

1. Quality of life

Of the 52 studies included, 46 studies measured quality of life, that is, health-related quality of life (34 studies), generic quality of life (four studies), or both (eight studies). In total, 11 different instruments were used (see Table 3).

Health-related quality of life

1. St. George's Respiratory Questionnaire (SGRQ) (25 studies)
2. Chronic Respiratory Questionnaire (CRQ) (nine studies)
3. Clinical COPD Questionnaire (CCQ) (three studies)
4. COPD Assessment test (CAT) (six studies)
5. Body mass index (BMI), airflow obstruction, dyspnoea, and exercise capacity index (BODE) (six studies)
6. Barthel score (one study)
7. Dartmouth Primary Care Co-operative Quality of Life Questionnaire (COOP) (one study)

Generic quality of life

1. Short Form-36 (SF-36) or Short Form-12 (SF-12) (eight studies)
2. EQ-5D (four studies)
3. Sickness Impact Profile (SIP) (two studies)
4. York Quality of Life Questionnaire (YGLQ) (one study)

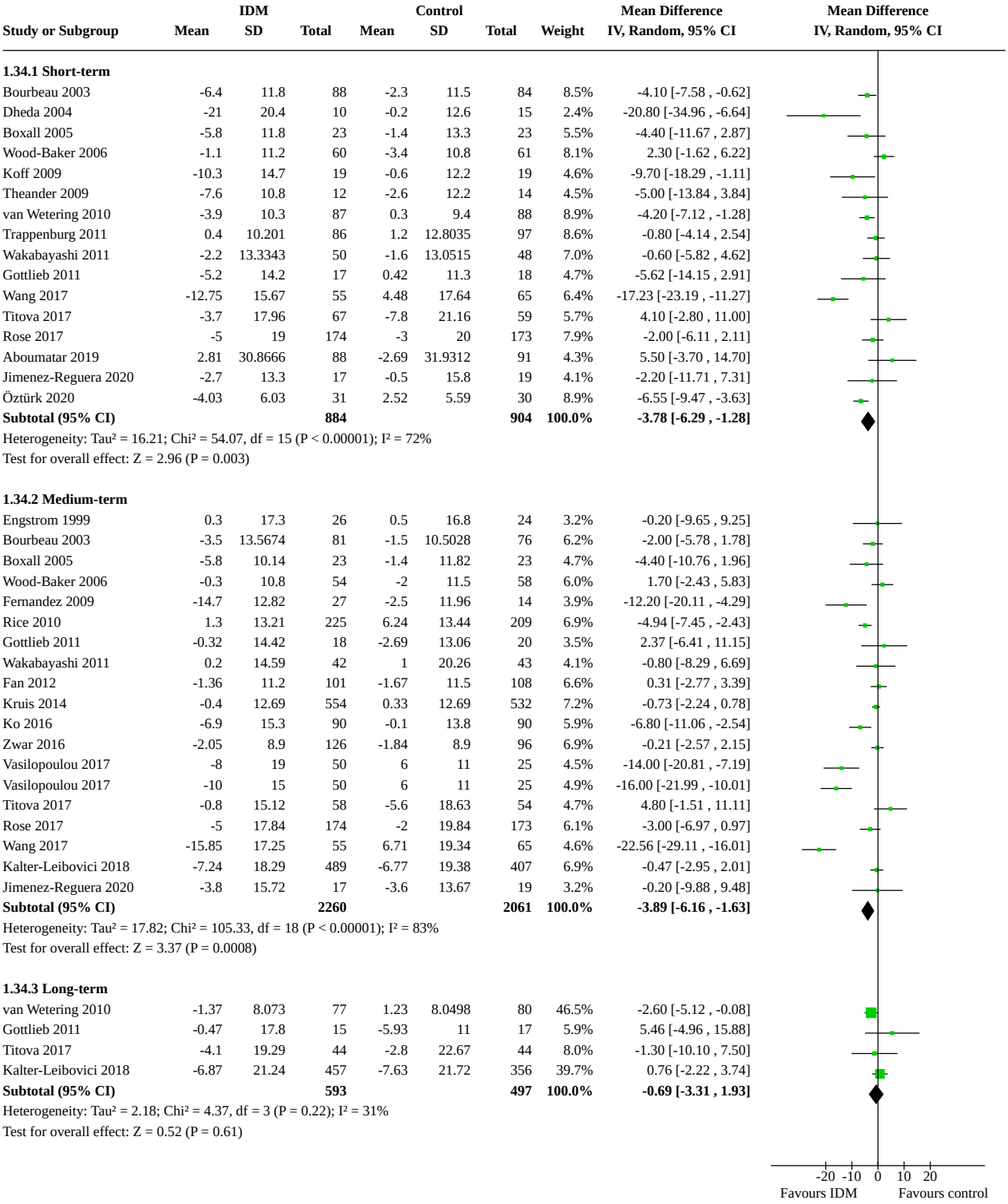
We performed a meta-analysis combining the results of some or all of these questionnaires. The SGRQ and the CRQ are respiratory-specific quality of life questionnaires and have become the recognised standards of HRQoL assessment amongst patients with COPD. However, pooling of these instruments into a meta-analysis was impossible, as the CRQ is more responsive than the SGRQ (Puhan 2006). Furthermore, the included generic quality of life questionnaires (SF-36, SIP, and COOP) measure other dimensions of generic quality of life; therefore combining these data in a meta-analysis across tools is not recommended.

1.1. SGRQ total score (short-term)

The SGRQ is a disease-specific, validated questionnaire with a scale from 0 (good health) to 100 (worst health status). A negative sign on this questionnaire indicates improvement, and the minimum clinically important difference (MCID) is -4 points (Jones 1991). Sixteen studies with a total population of 1788 participants provided data on the SGRQ total score with follow-up to 6 months (Aboumatar 2019; Bourbeau 2003; Boxall 2005; Dheda 2004; Gottlieb 2011; Jimenez-Reguera 2020; Koff 2009; Öztürk 2020; Rose 2017; Theander 2009; Titova 2017; Trappenburg 2011; van Wetering 2010; Wakabayashi 2011; Wang 2017; Wood-Baker 2006). The pooled mean difference (MD) in SGRQ total score was -3.78 (95% confidence interval (CI) -6.29 to -1.28) in favour of IDM. Pooling indicated substantial heterogeneity (I^2 = 72%) (Analysis 1.1; Figure 3). Heterogeneity could be explained in part by differences in the quality of the studies (I^2 = 46%). Sensitivity analysis of 'high-quality studies' showed a comparable effect (MD -3.65, 95% CI -5.66 to

-1.64), indicating a robustness of the overall effect estimate in favour of IDM.

Figure 3. Forest plot of comparison: 1 Integrated disease management versus control, update, outcome: 1.34 SGRQ total score.



1.2. SGRQ total score (medium-term)

Eighteen studies with a total population of 4321 participants provided data on the SGRQ total score with follow-up between 6 and 15 months (Bourbeau 2003; Boxall 2005; Engstrom 1999; Fan 2012; Fernandez 2009; Gottlieb 2011; Jimenez-Reguera 2020; Kalter-Leibovici 2018; Ko 2016; Kruis 2014; Rice 2010; Rose 2017; Titova 2017; Vasilopoulou 2017; Wakabayashi 2011; Wang 2017; Wood-Baker 2006; Zwar 2016). Kessler 2018 used a COPD-specific SGRQ, which could not be pooled. The pooled MD in SGRQ total score (MD -3.89, 95% CI -6.16 to -1.63) favoured IDM (Analysis 1.2; Figure 3). In other words, those treated with IDM reported 3.89 out of 100 points for improved quality of life. Pooling did indicate considerable heterogeneity (I^2 = 83%). Sensitivity analysis performed on high-quality studies still showed a statistically significant effect in favour of IDM (MD -3.95, 95% CI -6.06 to -1.84). This effect was even more pronounced, indicating the robustness of our results. Sensitivity analysis of high-quality studies only did not change the level of heterogeneity (I^2 = 79%). Pre-defined and post-hoc subgroup analyses were performed to investigate heterogeneity (see below).

1.2.1. Subgroup analysis based on setting

Six studies reporting on SGRQ total score were performed in primary care (Boxall 2005; Fernandez 2009; Gottlieb 2011; Kruis 2014; Wood-Baker 2006; Zwar 2016), nine studies in secondary care (Bourbeau 2003; Engstrom 1999; Fan 2012; Jimenez-Reguera 2020; Kalter-Leibovici 2018; Rice 2010; Rose 2017; Titova 2017; Wakabayashi 2011), and three studies in tertiary care (Ko 2016; Vasilopoulou 2017; Wang 2017). A test for subgroup differences showed a statistically significant difference between subgroups (P = 0.001). Studies performed in primary and secondary care showed no statistically significant differences between IDM and control, and pooling of tertiary care studies showed a clinically and statistically significant improvement in favour of IDM (MD -14.58, 95% CI -21.56 to -7.61; Analysis 1.4). However, pooling indicated considerable heterogeneity for all three subgroups. Hence, results of the subgroup analysis should be interpreted with caution.

1.2.2. Subgroup analysis based on study design

We performed subgroup analysis based on study design and compared RCTs (total 2865 participants) with cluster-RCTs (total 1420 participants) (Analysis 1.5). Tests for differences showed a statistically significant difference between both groups. Heterogeneity within the RCT remained considerable (I^2 = 83%).

1.2.3. Subgroup analysis based on dominant component of the programme

Two studies (total 294 participants) included individualised education as the dominant component (Fan 2012; Wakabayashi 2011), five studies (total 1825 participants) included self-management as the dominant component (Bourbeau 2003; Jimenez-Reguera 2020; Kruis 2014; Rice 2010; Wood-Baker 2006), four studies (total 175 participants) included exercise as the dominant component (Boxall 2005; Engstrom 1999; Fernandez 2009; Gottlieb 2011), and five studies (total 1610 participants) included structural follow-up as dominant component (Kalter-Leibovici 2018; Ko 2016; Rose 2017; Titova 2017; Vasilopoulou 2017). Post hoc, we identified telemonitoring as an important dominant component in two studies (Vasilopoulou 2017; Wang 2017). Tests for subgroup differences showed a statistically significant result (Chi^2 = 17.89, df = 4, P = 0.001) indicating differences in effect between subgroups based on the dominant component. A statistically significant difference was found only in the group with telemonitoring as the dominant component (MD -18.33, 95% CI -26.72 to -9.94) (Analysis 1.6). However, the subgroup included only two studies. Also, heterogeneity remained moderate within subgroups. Hence, results should be interpreted with caution.

1.2.4. Subgroup analysis based on region of study

Four studies (total 1147 participants) were performed in North America (Bourbeau 2003; Fan 2012; Rice 2010; Rose 2017), four in Northwestern Europe (total 1286 participants) (Engstrom 1999; Gottlieb 2011; Kruis 2014; Titova 2017), three in Southern Europe (total 227 participants) (Fernandez 2009; Jimenez-Reguera 2020; Vasilopoulou 2017), three in Oceania (total 380 participants) (Boxall 2005; Wood-Baker 2006; Zwar 2016), three in East Asia (total 385 participants) (Ko 2016; Wakabayashi 2011; Wang 2017), and one in Western Asia (total 896 participants) (Wakabayashi 2011). Tests for subgroup differences showed a statistically significant difference in effect between groups (Chi^2 = 16.88, df = 5, P = 0.005) (Analysis 1.7). Closer inspection of the subgroups showed no differences between IDM and control for the Northwest Europe and Oceania subgroups. Heterogeneity remained substantial in the North America subgroup (I^2 = 56%) and the Southern Europe subgroup (I^2 = 61%) and were considerable in the East Asia subgroup (I^2 = 91%). Results for these subgroups should therefore be interpreted with caution.

1.3. SGRQ total score - long-term

Four studies including 1090 participants measured the long-term effect on SGRQ total score at 18 months (Gottlieb 2011), or at 24 months (Kalter-Leibovici 2018; Titova 2017; van Wetering 2010). No statistically significant difference was noted between IDM and usual care (MD -0.69, 95% CI -3.31 to 1.93; I^2 = 31%) (Analysis 1.3; Figure 3).

1.4. SGRQ domain scores - short-term

Eleven studies with a total population of 1320 to 1327 participants reported scores on the SGRQ domains of symptoms, activity, and impact. For all domains, heterogeneity was substantial (I^2 between 46% and 71%) (Analysis 1.1). We found the following results: symptoms domain (MD -1.56, 95% CI -6.66 to 2.53), activity domain (MD -3.04, 95% CI -5.80 to -0.28), and impact domain (MD -3.76, 95% CI -5.94 to -1.57). Sensitivity analysis with only high-quality studies showed a statistically significant effect in favour of IDM for the activity domain (MD -3.63, 95% CI -5.66 to -1.61; I^2 = 0%) and for the impact domain (MD -4.1, 95% CI -6.30 to -1.90; I^2 = 31%) of the SGRQ. There was no significant effect on the SGRQ symptoms domain (MD -1.94, 95% CI -5.26 to 1.38; I^2 = 41%). A portion of the heterogeneity could be explained by the difference in quality of studies, as heterogeneity decreased significantly across all domains when only high-quality studies were pooled (Table 7).

1.5. SGRQ domain scores - medium-term

Twelve studies with a total population of 2608 to 2628 participants reported scores on the SGRQ domains after 6 to 15 months' follow-up. We found the following results: symptoms domain: MD -3.88, 95% CI -7.75 to -0.02; I^2 = 79%; activity domain: MD -2.57, 95% CI -5.53 to 0.38; I^2 = 71%; and impact domain: MD -3.34, 95% CI -6.26 to -0.41; I^2 = 0%. Sensitivity analysis did not explain the heterogeneity observed (I^2 between 71% and 79%) but did show a statistically significant effect in favour of IDM. Effects were statistically significant for all domains (Analysis 1.2; Table 7).

1.6. SGRQ domain scores - long-term

Three studies measured the long-term effect on SGRQ domains at 18 months (Gottlieb 2011), or at 24 months (Titova 2017; van Wetering 2010). As with the SGRQ total score, pooled effects did not show a statistically significant long-term difference between both groups (Analysis 1.3).

1.7. CRQ domain scores - short-term

The Chronic Respiratory Disease Questionnaire (CRQ), with a scale from 0 to 7 and MCID of 0.5, was reported in nine studies (Bendstrup 1997; Cambach 1997; Farrero 2001; Güell 2000; Güell 2006; Lenferink 2019; Rea 2004; Sridhar 2008; Wijkstra 1994). Farrero 2001 administered the CRQ only to the first 40 consecutive patients, and therefore outcomes were not published. Bendstrup 1997 and Rea 2004 reported insufficient data to compute an estimation of effect and therefore were not included in the meta-analysis. Wijkstra 1994 did not report on the dyspnoea dimension of the CRQ and compared two IDM interventions with usual care. We included both study arms in the meta-analysis. Pooled results for the CRQ up to 6 months included 277 participants for the CRQ Dyspnea dimension and 314 for the other domains. There was no statistically significant difference between IDM and control for any dimension (Analysis 1.8). Heterogeneity was substantial for all dimensions (I^2 between 72% and 86%). Sensitivity analysis for CRQ Dyspnoea was not performed, as this would include only one high-quality study. Sensitivity analysis for the other CRQ dimensions did not change the results but smaller heterogeneity was observed (I^2 between 0% and 35%). Thus, heterogeneity could be explained in part by the quality of the studies (see Table 7).

1.8. CRQ domain scores - medium-term

Three of the four studies that reported CRQ up to 6 months also reported CRQ outcomes after 6 months (Güell 2000; Lenferink 2019; Wijkstra 1994). Pooled results, including 2 studies and 219 participants for the CRQ dyspnoea dimension, showed no statistically significant differences between IDM and control groups (MD 0.29, 95% CI -0.88 to 1.46). There also were no statistically significant differences between groups for the CRQ fatigue domain (MD 0.37, 95% CI -0.53 to 1.26), the CRQ emotion domain (MD 0.36, 95% CI -0.84 to 1.57), and the CRQ mastery domain (MD 0.76, 95% CI -0.41 to 1.94) (Analysis 1.9).

1.9. CRQ domain scores - long-term

Three studies reported on long-term effects on the CRQ at 24 months' follow-up, with a total of 184 participants (Güell 2000; Sridhar 2008; Wijkstra 1994) (Analysis 1.10). Pooled data showed no differences between groups on the CRQ dyspnoea domain (MD 0.47, 95% CI -0.31 to 1.25). In contrast, pooled data on the CRQ fatigue domain showed a statistically significant difference in favour of IDM (MD 0.46, 95% CI 0.06 to 0.85). Also, a significant difference in favour of IDM was observed for CRQ emotion (MD 0.53, 95% CI 0.10 to 0.95) and CRQ mastery (MD 0.83, 95% CI 0.41 to 1.26). With an MCID of 0.5, the differences were also clinically significant. Sensitivity analysis revealed that when Güell 2000 was excluded due to inadequate concealment of allocation, pooled differences on CRQ fatigue, emotion, and mastery remained in favour of IDM; however CRQ fatigue was not statistically significant (MD 0.42, 95% CI -0.05 to 0.89) (Table 7).

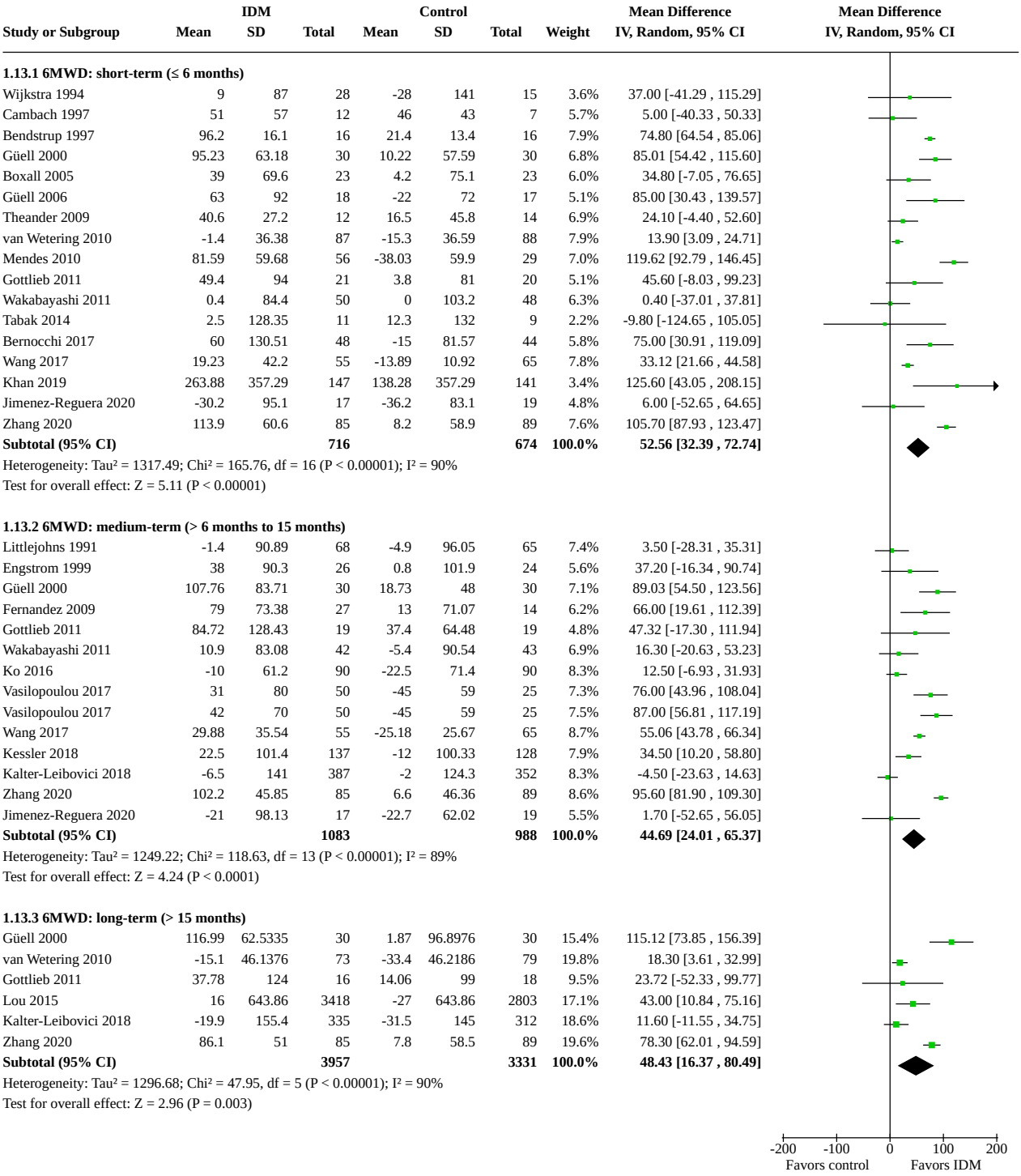
1.10. General health-related QoL

General HRQoL was measured with the SF-36 in six studies (Aiken 2006; Kruis 2014; Lilholt 2017; Öztürk 2020; Rea 2004; Vianello 2016), or with the shorter SF-12 in two studies (Fan 2012; Kalter-Leibovici 2018). Aiken 2006 did not provide us with sufficient information and did not respond to our emails. Rea 2004 and Öztürk 2020 reported only on the separate dimensions of the SF-36 and therefore could not be used for pooling. For the remaining studies, we pooled composite scores from the SF-36 and the SF-12. Hence, we pooled the data from studies for the Mental Component Summary (MCS) score with a total population of 3699 participants and of the Physical Component Summary (PCS) score with a total population of 3704 participants. Pooled MD on the MSC score showed no significant differences between both groups (MD 0.36, 95% CI -0.38 to 1.11; I^2 = 0%). Also no significant differences were observed on the PCS score (MD 1.06, 95% CI -0.67 to 2.79; I^2 = 84%). Substantial heterogeneity observed for the PCS score was due in part to differences in the quality of the studies. Sensitivity analysis excluding Vianello 2016 and Lilholt 2017 showed similar non-significant effects (see Table 7). Two studies measured QoL with the Sickness Impact Profile (SIP) (Engstrom 1999; Littlejohns 1991) (Analysis 1.12). No between-group differences were found in any domain of the SIP.

2. Exercise capacity

Twenty-eight studies measured functional or maximum exercise capacity. Functional exercise capacity was measured through the 6MWD (26 studies) or the shuttle test (1 study). Maximal exercise capacity was measured using the cycle ergometer test expressed as W-max (5 studies), leg fatigue score (1 study), and grip strength (1 study). The MCID on the 6MWD is estimated at 35 meters (Puhan 2008). No MCID for the cycle ergometer test is reported in the current literature. Results are shown in Figure 4.

Figure 4. Forest plot of comparison: 1 Integrated disease management versus control, update, outcome: 1.13 Functional exercise capacity: 6MWD.



2.1. Functional exercise capacity - short-term

We pooled data from 17 studies using the 6MWD including 1390 participants (Bendstrup 1997; Bernocchi 2017; Boxall 2005; Cambach 1997; Gottlieb 2011; Güell 2000; Güell 2006; Jimenez-Reguera 2020; Khan 2019; Mendes 2010; Tabak 2014; Theander 2009; van Wetering 2010; Wakabayashi 2011; Wang 2017; Wijkstra 1994; Zhang 2020). One study could not be pooled, as study authors reported no data because there was no significant difference between groups at 12 months' follow-up (Bourbeau 2003). The pooled MD on the 6MWD outcome was 52.56 in favour of IDM (95% CI 32.39 to 72.74) and exceeded the MCID of 35. In other words, patients treated in an IDM programme were able to walk 52 meters

more, on average, than those who received usual care. Pooling did indicate considerable heterogeneity (I^2 = 90%). Sensitivity analysis performed on high-quality studies showed a smaller but still statistically and clinically significant effect in favour of IDM (MD 41.00, 95% CI 4.40 to 77.60, I^2 = 92%).

2.2. Functional exercise capacity - medium-term

Thirteen studies with a total population of 2071 participants provided data on the 6MWD after a medium-term follow-up period (between 6 and 15 months) (Engstrom 1999; Fernandez 2009; Gottlieb 2011; Güell 2000; Jimenez-Reguera 2020; Kalter-Leibovici 2018; Kessler 2018; Ko 2016; Littlejohns 1991; Vasilopoulou 2017; Wakabayashi 2011; Wang 2017; Zhang 2020). Pooled MD showed a statistically and clinically significant effect of 44.69 in favour of IDM. The observed effect was statistically significant (95% CI 24.01. to 65.37) and exceeded the MCID of 35 meters. Sensitivity analysis showed that our results were robust (MD 40.49, 95% CI 9.71 to 71.27). However, heterogeneity remained substantial (I^2 = 92%). The heterogeneity among high-quality studies and the large confidence interval for the pooled results of all studies indicate there may be substantial methodological or clinical differences between studies. Pre-defined and post-hoc subgroup analyses were performed to further investigate the existing heterogeneity (see below).

2.2.1. Subgroup analysis based on type of setting

Of the studies reporting 6MWD at 12 months, two were conducted in primary care (Fernandez 2009; Gottlieb 2011), seven in secondary care (Engstrom 1999; Güell 2000; Jimenez-Reguera 2020; Kalter-Leibovici 2018; Kessler 2018; Littlejohns 1991; Wakabayashi 2011), and four in tertiary care (Ko 2016; Vasilopoulou 2017; Wang 2017; Zhang 2020). Tests for subgroup differences showed no difference in effect based on setting (Chi^2 = 4.49, df = 2, P = 0.11). However, heterogeneity remained considerable for the secondary care subgroup (I^2 = 80%) and for the tertiary care subgroup (I^2 = 87%). Therefore, results for these groups should be interpreted carefully (Analysis 1.14).

2.2.2. Subgroup analysis based on dominant component of intervention

Four studies (102 participants) reporting on the 6MWD had some kind of exercise training as their dominant component (Engstrom 1999; Fernandez 2009; Gottlieb 2011; Güell 2000). In six studies, structural follow-up was considered the dominant component (Kalter-Leibovici 2018; Kessler 2018; Ko 2016; Littlejohns 1991; Vasilopoulou 2017; Zhang 2020). One study provided individualised education as the dominant component (Wakabayashi 2011), and another study included self-management as the dominant component (Jimenez-Reguera 2020). Therefore, these could not be pooled. A test for subgroup differences showed a statistically significant difference (Chi^2 = 10.56, df = 4, P = 0.03; Analysis 1.14).

Subgroup analysis for exercise training as the dominant component showed that the 6MWD improved by 68.21 metres (95% CI 44.75 to 91.68; I^2 = 3%). This effect was almost twice the MCID of 35 metres. Also, studies with telemonitoring as the dominant component showed a large improvement of 59.94 metres (95% CI 42.59 to 77.29; I^2 = 32%). Studies with structural follow-up as the dominant component showed statistically significant differences in favour of IDM (MD 35.14, 95% CI 2.83 to 67.45). However, heterogeneity remained substantial.

2.2.3. Subgroup analysis based on region of study

Three studies reporting on 6MWD with medium-term follow-up were performed in Northwestern Europe (Engstrom 1999; Gottlieb 2011; Littlejohns 1991), five in Southern Europe (Fernandez 2009; Güell 2000; Jimenez-Reguera 2020; Kessler 2018; Vasilopoulou 2017), four in East Asia (Ko 2016; Wakabayashi 2011; Wang 2017; Zwar 2016), and one in Western Asia (Kalter-Leibovici 2018). A test for subgroup differences indicated statistically significant differences in effect between subgroups (Chi^2 = 19.09, df = 3, P = 0.00003).

Pooling of studies performed in Northwestern Europe showed no statistically significant difference between IDM and control (MD 18.18, 95% CI -7.87 to 44.24; I^2 = 4%). A statistically significant difference was found for the Southern Europe subgroup (MD of 61.73) and the East Asia subgroup (MD of 42.67). Pooling indicated considerable heterogeneity in the subgroup of studies from Southern Europe (I^2 = 68%) and East Asia (I^2 = 90%); results for these subgroups should therefore be interpreted carefully (Analysis 1.16).

2.3. Functional exercise capacity - long-term

Six studies on 7288 participants published long-term results on the 6MWD (Gottlieb 2011; Güell 2000; Kalter-Leibovici 2018; Lou 2015; van Wetering 2010; Zhang 2020). The MD was 48.83 metres in favour of IDM and was of statistically and clinically significant relevance (95% CI 16.37 to 80.49; I^2 = 90%) (Analysis 1.13). Sensitivity analysis could not explain heterogeneity and showed a smaller non-statistically significant mean difference (MD 36.4; I^2 = 94%; Analysis 1.13) noted by a wide CI (95% CI -6.43.97 to 79.24).

2.4. Maximal exercise capacity

Four studies on 298 participants assessed maximum exercise capacity (in Watts) using the cycle ergometer test (Engstrom 1999; Strijbos 1996; van Wetering 2010; Wijkstra 1994). Pooling showed that IDM statistically significantly improved maximal exercise capacity by 7 Watts (MD 6.99, 95% CI 2.96 to 11.02; Analysis 1.17).

3. Exacerbation-related outcomes

3.1. Respiratory-related admissions

Fifteen studies including a total of 4207 participants reported on the number of patients with at least one respiratory-related admission, which could be COPD-related, exacerbation-related, or of a respiratory nature in general. Pooling showed an effect in favour of the IDM intervention (OR 0.64, 95% CI 0.50 to 0.81). In other words, per 1000 patients, 89 fewer (range 131 fewer to 44 fewer) patients had a respiratory-related (re-)hospitalisation compared to patients given usual care (Analysis 1.18 Figure 5).

Figure 5. In the usual care group, 32 out of 100 people had a respiratory-related hospital admission over a period of 3 to 36 months, compared to 23 (95% CI 19 to 28) out of 100 people in the integrated disease management group.

3.2. Respiratory-related admissions - short-term

We pooled data from three studies with 377 patients measuring respiratory-related admissions until 6 months' follow-up (Bernocchi 2017; Koff 2009; Trappenburg 2011). There were no statistically significant differences in the risk of respiratory-related hospital admissions in the short term (OR 0.60; 95% CI 0.30 to 1.22). Studies were homogeneous, but the number of events was too small (ranging from 1 to 11) to allow firm conclusions based on the data.

3.3. Respiratory-related admissions - medium-term

Nine studies with a total of 2449 participants reported on the number of patients with at least one respiratory-related admission at 6 to 15 months' follow-up (Bourbeau 2003; Fan 2012; Lenferink 2019; Rea 2004; Rice 2010; Sanchez-Nieto 2016; Silver 2017; Smith 1999; Vasilopoulou 2017). Pooled estimates showed a statistically significant reduction in admissions in favour of IDM (OR 0.60, 95%CI 0.44 to 0.81). Data showed considerable heterogeneity (I^2 = 57%) (Analysis 1.18). Sensitivity analysis of only high-quality studies showed similar results, with only a small reduction in heterogeneity (I^2 = 48%) (see Table 7). To further explore the reasons for heterogeneity, we performed three subgroup analyses.

3.3.1. Subgroup analysis based on setting

Heterogeneity remained substantial or considerable when we pooled all studies in which the intervention was delivered in a primary care setting (I^2 = 84%) and secondary or tertiary care settings combined (I^2 = 48%). A test for subgroup differences showed no differences between groups (Chi^2 = 0.38, df = 1, P = 0.54). In other words, there seems to be no convincing difference between primary care and secondary or tertiary care that can explain the observed heterogeneity (Analysis 1.19).

3.3.2. Subgroup analysis based on dominant component of the programme

In five studies with a total of 1353 participants, the dominant component was self-management (Bourbeau 2003; Lenferink 2019; Rea 2004; Rice 2010; Sanchez-Nieto 2016). Two studies included education (Fan 2012; Silver 2017), two studies structural follow-up (Smith 1999; Vasilopoulou 2017), and one study telemonitoring as the dominant intervention component (Vasilopoulou 2017). A test for subgroup difference showed no differences between groups (Chi^2 = 3.65, df = 3, P = 0.30). However, these results should be interpreted carefully, as only the self-management subgroup pooled more than two studies, while the other subgroups pooled two or fewer studies. Among studies with self-management as the

dominant component, the effect on respiratory-related admissions favoured IDM ((OR 0.55, 95% CI 0.43 to 0.71; I^2 = 0%) (Analysis 1.20).

3.3.3. Subgroup analysis based on region

Four of the nine studies, with a total of 1788 participants, originated in North America (Bourbeau 2003; Fan 2012; Rice 2010; Silver 2017), two studies in Southern Europe (Sanchez-Nieto 2016; Vasilopoulou 2017), one study in Northwestern Europe (Lenferink 2019), and one study in Oceania (Smith 1999). The effect estimate differed significantly between subgroups (Chi^2 = 10.93, df = 3, P = 0.01). Pooling of studies conducted in North America showed a significant reduction in respiratory-related hospital admissions (OR 0.69, 95% CI 0.50 to 0.94; I^2 = 44), as did pooling of studies conducted in Southern Europe (OR 0.35, 95% CI 0.18 to 0.68; I^2 = 25%). Pooling of studies from Northwestern Europe and Oceania was not possible due to the small numbers (Analysis 1.21) (Lenferink 2019; Smith 1999). In addition to regional differences in effects of IDM on respiratory-related hospital admissions, there was a marked difference in the mean rate of respiratory-related hospital admissions per patient. Among IDM groups, the mean rate per patient was 0.19 admissions per patient in studies from North America, 0.21 per patient from Northwestern Europe, 0.59 per patient for Souhern Europe, and 0.70 per patient from Oceania. Similarly, for controls, the rate from North America was 0.26 per patient, from Northwestern Europe 0.26 per patient, from Southern Europe 0.64 per patient, and from Oceania 0.56 per patient.

3.4. Hospital admissions, all causes

We were able to pool ten studies that reported on patients experiencing at least one hospital admission for all causes and included a total of 9030 participants. Pooling showed an overall statistically significant effect in favour of IDM (OR 0.75, 95% CI 0.57 to 0.98). This means that compared with usual care, there were 72 fewer (range 138 fewer to 5 fewer) hospitalisations per 1000 with IDM. Pooling based on follow-up period indicated slight differences in short-, medium-, and long-term effects (Analysis 1.22).

3.5. Hospital admissions, all causes - short-term

Only one study including 112 participants reported on the number of hospital admissions for all causes after 6 months' follow-up and therefore could not be pooled (Bernocchi 2017). Study authors reported a significant reduction in the number of patients having at least one hospital admission, in favour of the intervention group (OR 0.31, 95% CI 0.14 to 0.67).

3.6. Hospital admissions, all causes - medium-term

Five studies with a total of 1212 participants provided data on the number of participants admitted at least one time for all causes at 6 to 15 months' follow-up (medium-term) (Fan 2012; Kessler 2018; Lenferink 2019; Littlejohns 1991; Rea 2004). Kessler 2018 did not directly report the number of participants, so the number was approximated based on the percentage of people with 0 hospitalisation days. Pooling showed that results were homogeneous and there was no significant difference between groups (OR 0.93, 95% CI 0.71 to 1.21; I^2 = 14%). A sensitivity analysis of only high-quality studies showed a similar result (OR 0.91, 95% CI 0.66 to 1.26; I^2 = 0%).

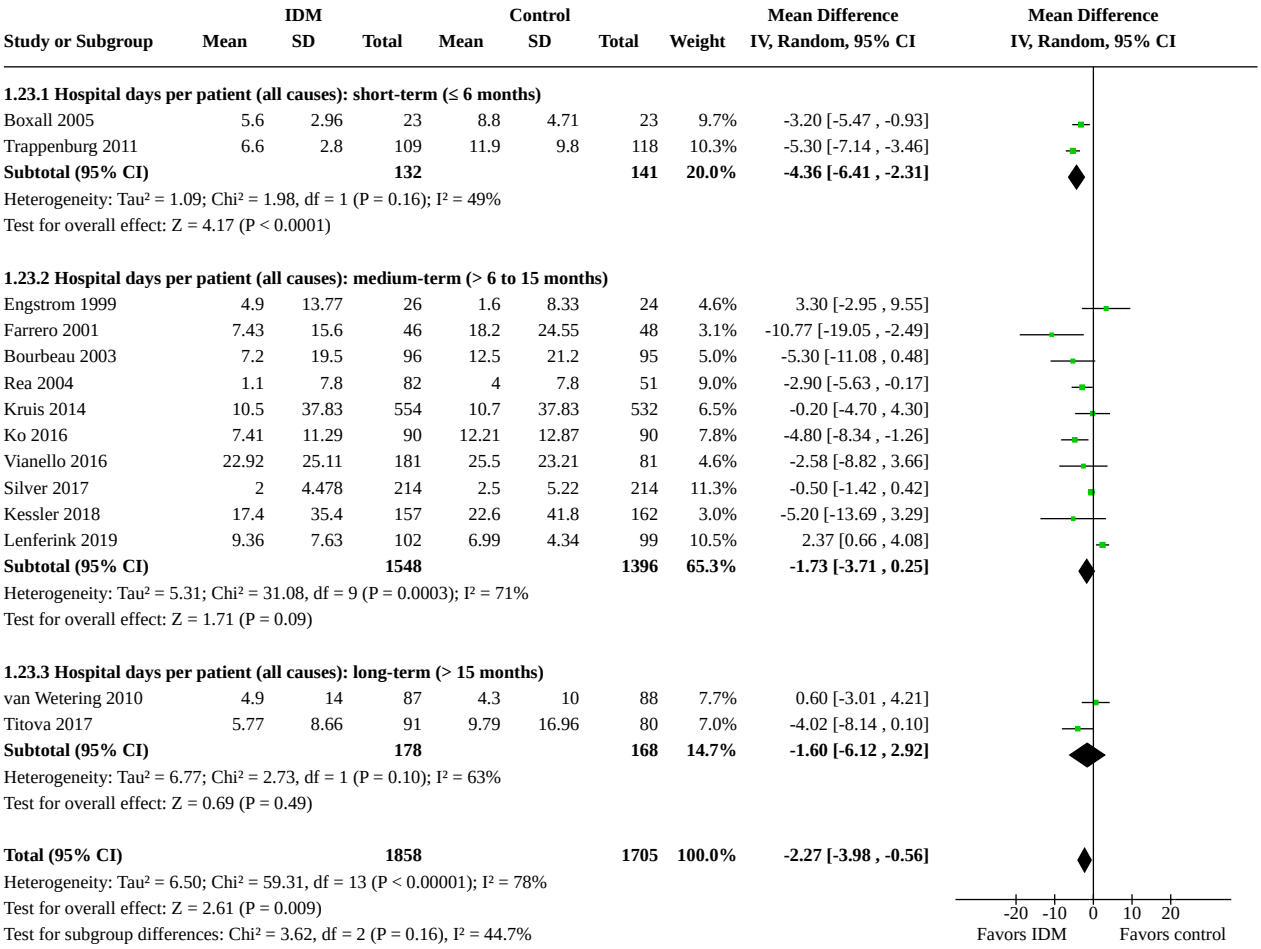
3.7. Hospital admissions, all causes - long-term

Four studies including a total of 7706 participants assessed the number of participants admitted after 15 months' follow-up (Kalter-Leibovici 2018; Lou 2015; Sridhar 2008; van Wetering 2010). Numbers of events and total numbers are lower for Lou 2015, as we reduced the size of the study to its 'effective sample size' to adjust for clustering effects. Pooled meta-analysis showed no significant differences between groups (OR 0.72, 95% CI 0.45 to 1.16). Pooled results showed considerable heterogeneity (I^2 = 75%) and differences in direction of effect. Although Lou 2015 and van Wetering 2010 showed positive effects in favour of IDM, Kalter-Leibovici 2018 and Sridhar 2008 showed no statistically significant differences. The different findings could have resulted from variation in follow-up duration which ranged from 24 months in Sridhar 2008and van Wetering 2010 to 36 months in Kalter-Leibovici 2018 to 48 months in Lou 2015. Finally, heterogeneity could be explained by the large differences in study size ranging from 104 participants in Sridhar 2008 to 6221 participants (435 effective sample size) in Lou 2015. Sensitivity analysis including only high-quality studies did not show a statistically significant effect (OR 0.88, 95% CI 0.61 to 1.27; I^2 = 38%).

3.8. Hospital days per patient

We were able to pool 14 studies that reported on the number of hospital days among those (3563 participants) hospitalised during the study. Pooling showed an overall reduction of 2.27 days spent in the hospital in favour of IDM; this finding was statistically significant (MD -2.27, 95% CI -3.98 to -0.56; I^2 =7 8%) (see Figure 6).

Figure 6. Forest plot of comparison: 1 Integrated disease management versus control, update, outcome: 1.24 Hospital days per patient (all causes).



3.9. Hospital days per patient - short-term

Two studies with a total of 273 participants reported on the difference in mean hospitalisation days per patient per group within the first six months (Boxall 2005; Trappenburg 2011). Pooling showed a significant reduction in days spent in the hospital per patient in favour of IDM (MD -4.36, 95% CI -6.41 to -2.31) (Analysis 1.23).

3.10. Hospital days per patient - medium-term

Ten studies including 2994 participants assessed the difference in mean hospitalisation days per patient per group from 6 to 15 months' follow-up (Bourbeau 2003; Engstrom 1999; Farrero 2001; Kessler 2018; Ko 2016; Kruis 2014; Lenferink 2019; Rea 2004; Silver 2017; Vianello 2016). Pooling showed a non-significant reduction in hospitalisation days in favour of IDM (MD -1.73, 95% CI -3.71 to 0.25), with moderate heterogeneity (I^2 = 71%). Heterogeneity could not be explained by differences in the quality of studies. Three studies showed a significant effect in favour of IDM (Farrero 2001; Ko 2016; Rea 2004), and one study showed a significant effect in favour of control (Smith 1999). Smith 1999 reported increased attention to disease and symptoms by the COPD nurse as a possible explanation. Mean hospitalisation days also varied substantially between studies and within the IDM study groups, with an average hospital stay ranging from 2 days in Silver 2017 to 25.5 days in Vianello 2016 (Analysis 1.23).

3.11. Hospital days per patient - long-term

Two studies with 346 participants reported the difference in mean hospitalisation days after 15 months' follow-up (Titova 2017; van Wetering 2010). There was no significant difference between groups (MD -1.60, 95% CI -6.12 to 2.92) (Analysis 1.23).

3.12. Emergency department

Twelve studies assessed the number of participants with at least one ED visit (Bourbeau 2003; Fan 2012; Farrero 2001; Lou 2015; Rea 2004; Rice 2010; Rose 2017; Sanchez-Nieto 2016; Silver 2017; Smith 1999; Trappenburg 2011; Wakabayashi 2011). To account for clustering, we reduced the study size in Lou 2015 to its 'effective sample size'. We were able to pool the data from nine studies with 8791 participants (Bourbeau 2003; Fan 2012; Lou 2015; Rea 2004; Rice 2010; Rose 2017; Sanchez-Nieto 2016; Silver 2017; Smith 1999), which revealed a significant reduction in the number of participants with at least one ED visit in favour of IDM, with considerable heterogeneity (OR 0.69, 95% CI 0.50 to 0.93; I^2 = 68%) (Analysis 1.24). A sensitivity analysis including only high-quality studies showed that the risk of an ED visit was still significantly reduced

with IDM (OR 0.69, 95% CI 0.50 to 0.94; I^2 = 64%) but could not explain the heterogeneity. Further exploration to assess reasons for heterogeneity revealed that seven trials had decreased risk of ED visits in favour of IDM (Bourbeau 2003; Fan 2012; Lou 2015; Rea 2004; Rice 2010; Sanchez-Nieto 2016; Silver 2017), of which three were statistically significant (Bourbeau 2003; Lou 2015; Rice 2010). Two studies showed a non-significant increase in risk of ED visits for the IDM group (Rose 2017; Smith 1999). Silver 2017 reported in the discussion that lack of effect on ED visits "may be due to the emergency department functioning as an out-patient or rescue clinic for patients with exacerbations of their disease". The fact that most of the participants enrolled in the study lacked access to a primary care provider could explain the observation that the effect was non-significant.

3.13. Number of patients experiencing at least one exacerbation

Seven studies reported on the number of patients experiencing at least one exacerbation during follow-up. The definition of exacerbation differed slightly between studies. Trappenburg 2011 and Bourbeau 2003 defined an exacerbation as an increase in symptoms with deterioration of dyspnoea or purulent sputum. Lenferink 2019 used a similar definition (clear negative change in two symptoms classified as major symptoms (dyspnoea, sputum purulence, sputum volume) or in one major and one minor symptom (coughing, wheezing, fever) from baseline, for 2 or more consecutive days). Vasilopoulou 2017, Kruis 2014, and Sridhar 2008 defined exacerbation as an "unscheduled need for healthcare, or need for steroid tablets, or antibiotics for worsening of their COPD". Vasilopoulou 2017 and Kruis 2014 defined exacerbation based on a visit to the general practitioner or the respiratory physician in combination with a prescription of antibiotics and/or prednisolone; Kruis 2014, Vasilopoulou 2017, and Kessler 2018 made a distinction between moderate and severe exacerbations. If provided, we included the results for severe exacerbations.

Pooling of all studies reporting on the number of participants experiencing at least one exacerbation during follow-up showed no statistically significant difference between groups (OR 0.96, 95% CI 0.65 to 1.42). Pooling based on follow-up periods showed consistent non-significant results for medium-term effects (OR 0.72, 95% CI 0.90 to 1.27; I^2 = 47%) and long-term effects (OR 1.53, 95% CI 0.90 to 2.60; I^2 = 0%; Analysis 1.25). Trappenburg 2011, which reported results at 6 months' follow-up, indicated that although exacerbation rates did not differ between groups, exacerbations within the IDM group were perceived as substantially milder by patients. Sridhar 2008, reporting on the number of participants experiencing at least one exacerbation at 24 months' follow-up (long-term), stated that patients in the intervention group were more likely to have exacerbations treated with oral steroids alone or oral steroids and antibiotics than patients in the control group. The initiator of treatment in the control group was statistically more likely to be the patient rather than the GP, and this could explain the absence of an effect.

3.14. Patients using at least one course of oral steroids

We pooled data from four studies including 433 participants reporting on the number of patients using at least one course of oral steroids during follow-up (12 months) (Farrero 2001; Littlejohns 1991; Rea 2004; Sanchez-Nieto 2016). Pooling showed homogeneity between studies and no differences between groups (OR 1.05, 95% CI 0.66 to 1.64; I^2 = 27%; Analysis 1.26).

3.15. Patients using at least one course of antibiotics

Three studies with 321 participants reported on the number of patients using at least one course of antibiotics (Littlejohns 1991; Rea 2004; Sanchez-Nieto 2016). The number of patients using at least one course of antibiotics was not statistically different between groups (OR 1.46, 95% CI 0.51 to 4.18; I^2 = 53%; Analysis 1.27). A sensitivity analysis of high-quality studies showed decreased heterogeneity (I^2 = 53%) and significantly increased risk when a course of antibiotics was received by people in the IDM group (OR 2.35, 95% CI 1.02 to 5.42). Further exploration of these studies revealed that they provided the same follow-up (12 months) but represented very different settings, as Rea 2004 was a cluster-randomised trial in a primary care setting, and Littlejohns 1991 and Sanchez-Nieto 2016 were RCTs conducted in a secondary care setting.

Secondary outcomes

4. Dyspnoea

Fifteen studies reported on modified MRC Dyspnoea Scale scores as an outcome for dyspnoea (Bernocchi 2017; Gottlieb 2011; Kalter-Leibovici 2018; Khan 2019; Ko 2016; Kruis 2014; Lenferink 2019; Lou 2015; Mendes 2010; Öztürk 2020; van Wetering 2010; Vasilopoulou 2017; Wakabayashi 2011; Wang 2017; Zhang 2020). Gottlieb 2011 did not publish any results, and results from Wang 2017 could not be included due to a reporting error. Outcomes were reported after 3 months, 4 months, 6 months, 12 months, and/or 24 months. The data allowed us to calculate the MRC Dyspnoea Scale score at short-, medium-, and long-term follow-up. Pooling showed significant improvement in favour of IDM for short-term follow-up (MD -0.33, 95% CI -0.52 to -0.15). Pooling of mMRC Dyspnoea Scale scores at medium- and long-term follow-up showed heterogeneity (I^2 = 96%) too large to be permit conclusions based on the results (Analysis 1.28). Dyspnoea as measured by Borg Scale score in three studies showed no differences between groups (MD 0.14, 95% CI -0.70 to 0.98; I^2 = 39%) (Boxall 2005; Gottlieb 2011; Güell 2000).

5. Mortality

Fifteen studies assessed mortality as an outcome or as part of patient safety assessment. Of these studies, two assessed mortality at 6 months' follow-up (Aboumatar 2019; Bernocchi 2017), nine at 12 months' follow-up (Fan 2012; Farrero 2001; Kessler 2018; Littlejohns 1991; Rice 2010; Rose 2017; Sanchez-Nieto 2016; Smith 1999; Vianello 2016), and four after more than 15 months' follow-up (Kruis 2014; Lou 2015; Sridhar 2008; Titova 2017). The numbers for Lou 2015 are lower, taking clustering into account. Fan 2012 was temporarily stopped because all-cause mortality was higher in the intervention group than in the usual care group. A thorough investigation of the circumstances of death by an independent and blinded panel showed that death was unrelated to the intervention, and a minority of deaths were due to COPD. Pooling of death events in IDM and control groups across all studies showed a non-statistically significant effect in favour of the intervention (OR 0.86, 95%CI 0.59, to 1.25). Heterogeneity was substantial and could not be explained by duration of follow-up, as outcomes were comparable after medium-term (OR 0.80, 95% CI 0.45 to 1.43) and long-term follow-up (OR 0.87, 95% CI 0.48 to 1.57) (Analysis 1.30).

6. Lung function

Lung function was expressed as FEV_1 in litres and as FEV_1% predicted. Following Kruis 2013, we pooled data from a total of

six studies for FEV_1 (litre) (Bourbeau 2003; Kalter-Leibovici 2018; Öztürk 2020; Sridhar 2008; Wood-Baker 2006; Zhang 2020), and from 14 studies for FEV_1% predicted (Farrero 2001; Fernandez 2009; Güell 2000; Jimenez-Reguera 2020; Kalter-Leibovici 2018; Khan 2019; Ko 2016; Lenferink 2019; Littlejohns 1991; Lou 2015; van Wetering 2010; Wakabayashi 2011; Wood-Baker 2006; Zhang 2020). Wang 2017 and Wood-Baker 2006 reported on short-term effects on FEV_1 in litres, but data from Wang 2017 could not be pooled due to reporting error. Pooling of FEV_1 in litres showed no differences between groups for medium- and long-term follow-up (Analysis 1.31). Pooled MDs in FEV_1% predicted showed a short-term effect in favour of the IDM group (MD 2.88, 95% CI 1.35 to 4.40). This effect was statistically significant but was not clinically significant. Medium-term effects were less pronounced and were not statistically significant (MD 0.95, 95% CI -0.20 to 2.11). After 24 months, there was no difference between groups (MD 1.18, 95% CI -0.82 to 3.18). Results were homogeneous across studies (Analysis 1.32). However, except for Lou 2015, 95% confidence intervals for the different studies were consistently large, suggesting large between-patient variation.

7. Anxiety and depression

Ten studies assessed depression, anxiety, or both as an outcome (Engstrom 1999; Güell 2000; Kessler 2018; Lenferink 2019; Littlejohns 1991; Öztürk 2020; Rose 2017; Titova 2017; Trappenburg 2011; Vianello 2016). Engstrom 1999 used the Mood Adjective Check List (MACL), and Güell 2006 used a Revised Symptom Checklist. Kessler 2018 used the Hospital Anxiety and Depression Scale (HADS) but reported only the combined score. The other studies reported depression and anxiety scores from the HADS, and results were pooled. Pooled data from the anxiety domain of the HADS showed no differences between groups (MD 0.09, 95% CI -0.30 to 0.47; I^2 = 38%). Pooled data for the depression domain of the HADS showed a non-significant effect in favour of the intervention group (MD -0.20, 95% CI -0.45 to 0.05; I^2 = 38%: Analysis 1.33).

8. Process-related outcomes

8.1. Compliance/Adherence

Patient adherence to the programme or to intervention uptake was evaluated in five studies by review of programme attendance rate and programme completers (Bernocchi 2017; Rose 2017; Tabak 2014; Vasilopoulou 2017; Zwar 2016). Bernocchi 2017 reported a high adherence rate, with 93% of participants performing activities at home as part of the programme. Rose 2017 reported that 29% of participants were fully compliant and 22% were non-compliant (< 50% compliant with separate components). In addition, only 7% of study participants attended respiratory rehabilitation despite this being a component of usual care. Study authors also noted that 38% of intervention group participants who met the eligibility criteria for pulmonary rehabilitation were unable to attend due to unavailability of classes. Tabak 2014 monitored use of the web portal and separate intervention modules and observed that use of the web portal differed greatly among participants; some used the diary almost every day, others used it on only half of the days. Varying levels of implementation were also reported by Kennedy 2013 and Zwar 2016. Zwar 2016 particularly reported low implementation rates by practitioners and low response to questionnaires caused by limited time.

8.2. Satisfaction

Eight studies assessed patient satisfaction with the IDM programme in some way (Bernocchi 2017; Fan 2012; Koff 2009; Kruis 2014; Littlejohns 1991; Rose 2017; Tabak 2014; Zwar 2016). Various questionnaires, either validated or self-developed, were used to measure patient satisfaction; this made pooling impossible. Rose 2017 and Tabak 2014 used the eight-item Client Satisfaction Questionnaire (CSQ-8) (Attkisson 2004). Tabak 2014 measured lower satisfaction with the telehealth programme compared to usual care, and Rose 2017 found no differences between groups. Likewise, Fan 2012 found no differences between groups on the 21-item Seattle Outpatient Satisfaction Questionnaire, and Littlejohns 1991 found no differences on its self-developed questionnaire. Both Bernocchi 2017 and Koff 2009 reported high satisfaction scores for IDM, except for use of the pedometer, but did not compare satisfaction scores with those of the control group. Bernocchi 2017 saw that patients reported high satisfaction on all items of the self-developed questionnaire, including service as a whole, use of the devices, and healthcare professionals' willingness to respond to patient needs. Zwar 2016 included patient satisfaction as a secondary outcome in its protocol paper but for unknown reasons did not report on this.

8.3. Co-ordination of care

Two studies assessed co-ordination of care (Kruis 2014; Zwar 2016). Kruis 2014 measured the level of care integration from the view of patients using the Patient Assessment Chronic Illness Care (PACIC) and found a statistically significant increase and difference in favour of the IDM group (Glasgow 2005). Zwar 2016 included in its protocol the Collaborative Practice Scale to assess 'interactions between nurses and GPs that enable synergistic influence of patient care' (WEISS 1985). For unknown reasons, these results were not reported.

DISCUSSION

Summary of main results

This review summarised and meta-analysed the results of 52 studies involving 21,086 participants with chronic obstructive pulmonary disease (COPD) who were randomly allocated to usual care or to an integrated disease management (IDM) programme with a minimum duration of 12 weeks. This review is an update of the review performed in 2013 (Kruis 2013). Studies were conducted in 19 different countries across multiple healthcare settings. All studies investigated an IDM programme. Studies differed in terms of intervention components, duration of intervention, healthcare professional involvement, follow-up window, number of participants, and outcome reporting. Nonetheless, we were able to pool data on all primary outcomes for short-term (up to 6 months), medium-term (6 to 15 months), and long-term (longer than 15 months) follow-up. Results of the previous review support IDM for management of COPD. Results of this update reinforce these findings, providing evidence of higher certainty and including evidence on long-term effects (up to 48 months).

First, this review showed that IDM probably improves health-related quality of life (HRQoL) as indicated by a change in St. George's Respiratory Questionnaire (SGRQ) overall score by 3.89 points after 12 months without reaching the minimum clinically important difference (MCID) of -4 points. This improvement was more pronounced among high-quality studies only, indicating the

robustness of our conclusions. This effect was not observed after 15 months (mean difference (MD) -0.69). IDM probably leads to improvement after 12 months in the symptoms domain (MD -3.88) and in the impact domain (MD- 3.34) but not in the activity domain of the SGRQ. Across all outcomes, we observed considerable heterogeneity, which could be explained in part by differences in the quality of studies. Subgroup analysis suggested context-specific effects with no differences among studies performed in Northwestern Europe and Oceania. Pooling of data from the Chronic Respiratory Questionnaire (CRQ), another measurement for HRQoL, showed statistically significant long-term effects in favour of IDM in fatigue (MD 0.46), emotion (MD 0.53), and mastery (MD 0.83) domains. No significant effects were found for short- and medium-term follow-up, nor for generic quality of life.

Second, IDM probably results in a large improvement in maximum and functional exercise capacity as measured by the six-minute walking distance test (6MWD), which exceeds the MCID of 35 metres. At short-term follow-up, pooling showed improvement of 48 metres. This effect was sustained over time, as shown by pooled data after 12 months (MD 44.69) and after 15 months' follow-up (MD 60.41). Subgroup analysis indicated a considerable intervention-specific effect, with a larger effect in studies with exercise, structural follow-up, or telemonitoring as the dominant intervention component.

Third, the total number of patients with at least one respiratory-related hospital admission receiving an IDM programme, after median follow-up of 12 months, was on average 235 per 1000 patients compared to 324 per 1000 receiving usual care. Likewise the number of all-cause hospital admissions decreased from 517 per 1000 for usual care to 445 per 1000 for IDM. Within the group of patients admitted to the hospital, IDM likely reduces the length of stay by 2.3 days after median follow-up of 12 months. However, length of stay differed considerably between studies, ranging from a reduction of 10.8 days to an increase of 3.5 days in the IDM group compared to the usual care group. In terms of the number of emergency department (ED) visits, IDM probably reduces the number of visits by 86 per 1000 ED visits.

Effects on the aforementioned primary outcomes and details on level of certainty are summarised in Summary of findings 1. In addition to effects on our primary outcomes, we found a statistically significant improvement in lung function parameters without clinical relevance and in dyspnoea. We found no statistically significant differences between IDM and usual care in terms of generic quality of life (i.e. Short Form (SF)-12/36 score), courses of antibiotics/prednisolone, mortality, or depression and anxiety scores.

Overall completeness and applicability of evidence

With the addition of 26 new studies resulting from the search update for the 2020 review, the number of people with COPD in this review increased from 2997 to 21,086. The large increase in terms of studies and participants has resulted in better precision and better generalisability of findings. In addition, we were able to distinguish short-, medium-, and long-term effects. Unfortunately, we observed large heterogeneity within the primary analysis for almost all primary outcomes. Although part of the observed heterogeneity could probably be explained by variation in the quality of studies in some cases, our results are also marked by large clinical and methodological variations. Accordingly, the applicability of our evidence warrants some comments.

The COPD population in the included studies ranged from those with mild to very severe COPD, and trials were conducted across all types of healthcare settings in a range of different countries, each with a unique healthcare system. This improves generalisability and makes (parts of) the results of this review applicable to a large proportion of COPD patients worldwide. However, one should bear in mind that the precise applicability will depend on the context of the specific healthcare setting and the type of COPD patient. The IDM programmes included in this review also differed in types of healthcare providers involved, types of intervention components, and intervention duration and intensity, reflecting the diversity of daily practice. Overall, with subgroup analysis, we noticed intervention-specific effects, that is, IDM programmes focused mainly on exercise probably result in greater improvement in exercise capacity, and programmes with self-management as the dominant component probably lead to fewer respiratory-related hospital admissions.

Besides clinical heterogeneity, our review also deals with significant methodological heterogeneity. We included studies with differences in duration and intensity of follow-up. By dividing the follow-up duration into short-, medium-, and long-term follow-up, we aimed to assess groups of studies with sufficient homogeneity. However, the intensity of the intervention could still differ between included studies. Also, it should be noted that an observed effect at long term does not necessarily indicate a sustained effect of the intervention because for some studies, the interventions continued throughout the study. Hence, further research is required to define the optimal combination, intensity, and duration of components of IDM programmes, taking into account the importance of methodological factors.

Our subgroup analysis results point towards beneficial effects among telemonitoring-based IDM interventions in terms of health-related quality of life, exercise capacity, and respiratory-related hospital admissions. However, given the small number of studies (5 studies) including telemonitoring, no decisive conclusions or recommendations can be made regarding the overall beneficial effects of telemonitoring as an IDM programme. Future research should shed light on the beneficial effects of telemonitoring and its use in practice.

Also, the applicability of evidence depends on the healthcare context in which the IDM programme is implemented, which differed greatly among studies included in this review. Studies were conducted in many different countries across five different continents. Subgroup analysis pointed towards a context-specific effect. This is in line with recent findings from the COMET study performed in Germany, France, Italy, and Spain (Kessler 2018), which reported significant country-specific differences between study settings. Kessler attributed these to differences in routine care, such as country-specific differences in baseline hospitalisation practices, admission criteria, and bed availability. Hence, effectiveness varying between study regions is likely related to variations in usual care that occur over time and are driven by national changes in policy and healthcare financing.

Also, country-specific differences in terms of cultural and societal norms may play a role in terms of implementation fidelity and therefore outcomes (Marsiglia 2015). For example, the four-year

study in which the IDM group received a monthly one-hour health lecture, performed by Lou 2015 in China, reported dropout (other than death) of only 7%, and noted that 87% of the study population attended all 48 COPD lectures.

Furthermore, the period in which included studies were published spanned 30 years, with the earliest published in 1991 and the latest in 2020. The clinical applicability of more recent studies is larger, given the embedding of IDM programmes into the healthcare system and the evolution of healthcare systems nationally and internationally. Hence, it would be worthwhile to investigate the relationship between advancements in usual healthcare over time and additional beneficial effects of IDM. Furthermore, it would be interesting to explore ways in which more weight could be given to more recent studies or older studies with limited applicability for current health care could be left out in a legitimate way.

Quality of the evidence

There was clinical and methodological heterogeneity among studies, which likely results (at least in part) from the complexity of IDM interventions. We have incorporated heterogeneity into estimated effects by using random-effects analyses. Using the GRADE approach, we specified levels of quality of the evidence (high, moderate, low, and very low) in our 'Summary of findings' table. According to this approach, we checked whether included trials had limitations in terms of design, indirectness of evidence, unexplained heterogeneity or inconsistency of results, imprecision of results, or high probability of publication bias. Such limitations may impact the certainty of evidence for all outcomes that are relevant to guideline formation, health policy development, and clinical guidance.

We deemed the quality of evidence for HRQoL (as measured by the SGRQ) as moderate, and we observed a consistent effect in favour of the intervention group for all SGRQ domains at medium-term follow-up. We downgraded the quality of evidence due to large heterogeneity between studies. For outcomes of functional and maximum exercise capacity, we downgraded the certainty of evidence owing to large heterogeneity that may be caused by an intervention-specific effect (i.e. IDM programmes with exercise as the dominant component showed more positive results for exercise capacity). We deemed the quality of evidence for respiratory-related hospital admissions as high. We downgraded one level for all-cause hospital admissions because of considerable heterogeneity and inconsistency in direction of effect. We also downgraded the certainty of evidence for outcomes of hospital days per patient and ED visits due to inconsistency in effects.

Potential biases in the review process

Several methodological strengths minimised the risk of bias in this review. As definitions of IDM are still under debate, we strictly determined the inclusion criteria for an IDM programme a priori and published this in our review protocol (Kruis 2011). Our definition was derived from definitions published in the literature (Peytremann-Bridevaux 2009; Schrijvers 2009). Overall, researchers reported on "multiple interventions, designed to manage chronic conditions, with a focus on a multidisciplinary approach". Furthermore, these definitions suggest that IDM interventions should "focus on maximum clinical outcome, regardless of treatment setting(s) or typical reimbursement patterns". As a result, we chose to include all interventions, independent of treatment setting, and to keep our definition as simple as possible, to be easily understandable for readers and easy to use when readers check on all relevant literature. Therefore, we restricted included trials to multi-component, multi-disciplinary programmes of at least 12 weeks' duration. Furthermore, we performed comprehensive searches to identify possible studies, leading to identification of more than 10,000 potentially relevant abstracts. Subsequently, three different assessors assessed the abstracts. We reached consensus on all included studies. Final decisions of course are open to interpretation or criticism. However, we have applied a systematic approach to including and excluding studies in this review, have followed the criteria pre-specified in the protocol, and have used robust methods for data collection and 'Risk of bias' assessment.

We were able to retrieve additional data from 17 study authors but did not receive a response from eight authors despite multiple reminders. This may have introduced bias. Another limitation of this review is inconsistent reporting in the included studies, in terms of adjusting for baseline differences. We decided on a conservative approach, using unadjusted mean differences for all randomised controlled trials (RCTs) and adjusted only values corrected for clustering effects, to overcome inconsistency between study authors' corrections. Inconsistency in reporting also resulted in the need for computing standard deviations of the mean change using appropriate analysis methods. Last, there may have been large heterogeneity in control groups, resulting from country-specific healthcare systems and COPD regulations for COPD treatment (i.e. reimbursements). Because the level of detail in reporting usual care varied greatly between studies (possibly also due to journal guidelines), we decided it was more informative to further investigate differences between regions instead of differences between types of usual care, as was performed in the previous version of this review (Kruis 2013).

Agreements and disagreements with other studies or reviews

This review adds to the results of six earlier systematic reviews analysing IDM for COPD patients (Adams 2007; Lemmens 2009; Lemmens 2013; Niesink 2007; Peytremann-Bridevaux 2008; Peytremann-Bridevaux 2014). The current review brings together new trials that were not included in any of these reviews, and it provides an overview of multiple outcomes. Adams 2007 examined the effectiveness of programmes for COPD patients, including chronic care model components, and pooled six trials including at least two components. Pooled results did not demonstrate statistically significant differences on the SGRQ. Adams 2007 showed lower rates of hospitalisation and shorter length of stay in the intervention group, comparable to our results. Lemmens 2009 pooled data based on the number of components used in IDM and compared these to usual care. The effect on the SGRQ was optimal if three components of IDM were used (MD -4.69), which is comparable to our effect in the medium term (MD -3.89). Review authors also showed a decrease in the number of respiratory-related hospitalisations for studies with multiple intervention components, with a pooled odds ratio (OR) of 0.58, which is comparable to the OR of 0.64 found in the current review. Niesink 2007 described the results of several studies that evaluated quality of life in IDM programmes among COPD patients. Five out of 10 studies showed clinically relevant improvement in quality of life. Peytremann-Bridevaux 2008 examined the effectiveness of

IDM in COPD patients for exercise tolerance, quality of life, hospital admissions, and mortality. Only data on hospital admissions and exercise tolerance were pooled. In line with the current review, positive effects on exercise capacity were found, but no significant effects were found for hospital admissions. Review authors demonstrated mean improvement of 32 metres on the 6MWD in five studies. Although we found overall improvement of 45 metres, this is largely attributable to the IDM programmes with a dominant exercise component. Furthermore, the pooled odds ratio of 0.85 (95% confidence interval (CI) 0.54 to 1.36) for mortality reported by review authors is comparable to that in our review (OR 0.86, 95% CI 0.59 to 1.25). Lemmens 2013 performed a meta-analysis on existing reviews that focused on IDM programmes with two or more components for adult patients with COPD. They showed statistically significant improvements on the SGRQ in favour of IDM ($P < 0.01$) with moderate heterogeneity. In contrast to our review, these review authors did not find any significant changes in all-cause hospitalisations (OR 0.95, 95% CI 0.76 to 1.14) or in numbers of ED visits (OR -0.11, 95% CI -0.26 to 0.04). Peytremann-Bridevaux 2014 performed an additional analysis of studies in the previous version of this Cochrane systematic review, in which they specifically assessed potential differences in mortality between IDM and usual care. They found no effects of IDM on mortality (OR 1.00, 95% CI 0.79 to 1.28), which is in line with our current findings. Some of the observed differences can be explained by the fact that nearly all reviews used different definitions of IDM. Also, all aforementioned systematic reviews included study designs other than RCTs, except Peytremann-Bridevaux 2014.

In addition to other reviews that assessed the effectiveness of IDM in COPD as described above, multiple systematic reviews have assessed the effectiveness of different components of IDM programmes.

Exercise

Two Cochrane Reviews examined pulmonary rehabilitation programmes for COPD patients in which the dominant component is generally exercise training. McCarthy 2015 assessed the effectiveness of pulmonary rehabilitation for COPD in general, although Puhan 2016 specifically assessed the effectiveness of pulmonary rehabilitation following an exacerbation of COPD. Similar to our review, McCarthy 2015 demonstrated statistically significant improvement in quality of life and exercise capacity (6MWD) in favour of pulmonary rehabilitation (SGRQ overall score MD -6.89; 6MWD MD 43.93 metres). Only one study in our review, Ko 2016, is also included in Puhan 2016, probably because of its selection of COPD patients with a recent exacerbation. The review authors also showed significant improvement in quality of life and exercise capacity in favour of pulmonary rehabilitation (SGRQ MD 7.80; 6MWD MD 62 metres) and a reduction in hospital admissions (OR 0.44).

Telemonitoring

The effectiveness of telemonitoring among COPD patients was assessed in a systematic review and meta-analysis of 27 studies (Hong 2019). In contrast to results from our subgroup analysis with telemonitoring as the dominant component, Hong 2019 found no difference in SGRQ (MD -0.21; our review MD -18.33) or in hospitalisations (all-cause and respiratory-related). However, our analyses are based on a small number of studies, which makes it impossible to draw firm conclusions. Another recent systematic literature review showed inconclusive results for the effectiveness of telemonitoring in COPD (Kruse 2019). These review authors did not perform a meta-analysis but described 29 articles, of which 13 (45%) showed favourable results, five (17%) negative outcomes, and 11 (38%) no differences in outcomes.

Self-management

Two Cochrane systematic reviews reported on self-management-based interventions in COPD. Zwerink 2014 assessed self-management training, which should allow patients to successfully manage their own disease. Follow-up ranged between 2 and 24 months. Lenferink 2017 focused on self-management interventions that are personalised and included action plans for the management of exacerbations. In line with our results, both reviews found significant improvement in HRQoL in favour of the intervention (Zwerink 2014 SGRQ overall score MD -3.51; Lenferink 2017 MD -2.69). In these reviews, respiratory-related hospital admissions were assessed as the number of people with at least one respiratory-related hospital admission. Still, both studies showed similar significantly reduced risk in favour of the intervention (Zwerink 2014 OR 0.57; Lenferink 2017 OR 0.69). It is interesting to note that in our review, we did not find a difference in the number of people prescribed at least one course of oral corticosteroids (OR 1.05), whereas in both of the other reviews, odds ratios appeared to be much higher in the intervention group, albeit with non-statistically significant findings (Zwerink 2014 number of courses of steroids OR 4.42; Lenferink 2017 OR 4.38). This might have to do with the nature of the action plans incorporated into self-management programmes, which stimulate patients to start a course of prednisolone in case of increased symptoms.

Education

A Cochrane systematic review from 2016 assessed the effectiveness of action plans with brief patient education for exacerbations in COPD (Howcroft 2016). Review authors showed that the intervention reduced the combined rate of hospitalisations and ED visits (rate ratio 0.59, 95% CI 0.44 to 0.79) and led to small but significant improvement in quality of life (SGRQ MD -2.8. 95% CI -4.8 to -0.8). One recent systematic review explored the effects of health coaching for people with COPD (Long 2019). According to the definition used in this review, health coaching programmes aim to improve self-management and healthy behaviour by teaching and motivating patients to achieve personalised goals. Long 2019 showed that health coaching had a significantly positive effect on the SGRQ (MD -0.69). These review authors also found a significant reduction in COPD-related hospital admissions (OR 0.45). In contrast to both of these reviews, our subgroup analysis on studies with education as the main component did not find significant differences in SGRQ (MD 0.15) nor in respiratory-related hospital admissions (OR 0.83). This might be related to the content of the education, suggesting that action plans need to be an integral part of any educational component in IDM to be of benefit for patient outcomes. Additionally, as shown by Long 2019, education has a larger beneficial effect when it is personalised and includes motivational techniques and goal-setting.

It is hard to draw conclusions on our subgroup analysis of the dominant component and the findings of earlier reviews because of the limited number of studies per dominant component and considerable variation among studies in terms of intervention

duration. However, our findings suggest that to improve exercise capacity, IDM programmes with an exercise focus or with use of telemonitoring components are best suited. IDM programmes using telemonitoring can provide large benefit with regard to respiratory-related admissions by monitoring the patient's symptoms, providing tailored and individualised self-management support (i.e. delivery of coping skills), and managing unexpected patient hospitalisations. For quality of life, most reviews on different components show improvement. Overall, this suggests that a multi-component approach, such as that used in IDM programmes, should result in optimal benefit for multiple important outcomes.

Finally, when compared to pharmaceutical treatments such as long-acting beta-agonist (LABA)/long-acting muscarinic antagonist (LAMA) treatment or use of phosphodiesterase-4 inhibitors, our findings from the SGRQ showed improvement of comparable magnitude. Our review showed that IDM resulted in improvement of 3.89 points on the SGRQ compared to 4.08 points for LABA/LAMA treatment (Maqsood 2019), as well as 1.06 points for phosphodiesterase-4 inhibitors (Janjua 2020). Although the confidence interval for IDM was wider (95% CI -6.16 to -1.63) compared to the confidence interval for LABA/LAMA treatment (95% CI -4.80 to -3.36), our results indicate clinical significance of the effects of IDM for a large group of patients.

AUTHORS' CONCLUSIONS

Implications for practice

This review and meta-analysis provides evidence that integrated disease management (IDM) programmes of at least 12 weeks' duration are generally effective for people with chronic obstructive pulmonary disease (COPD) and result in clinically beneficial outcomes. Effects are most pronounced on the short term and in the medium term. For the long term only, effects on six-minute walking distance (6MWD) persist, although this may be explained in part by the smaller number of studies. Also, the effect size differs between studies and interventions. In practice, this means there is no one size fits all solution, and interventions should always be carefully designed and evaluated.

We calculated that 89 hospital admissions related to respiratory problems can be prevented for every 1000 patients treated with IDM, leading to a number needed to treat for additional beneficial outcome (NNTB) of 12 patients to prevent one from being admitted over follow-up of 12 months. Although the numbers of patients admitted to hospital for all causes differed slightly between groups, time spent in the hospital decreased by two days in patients treated with IDM compared to those receiving usual care. This is of utmost importance, as hospitalisations contribute to the highest burden and costs among patients with COPD.

In our review, we do not provide the ideal combination of components that represent the optimal IDM programme. Rather, our results indicate that different dominant components of IDM have beneficial effects for specific outcomes. Our dominant component analysis showed that telemonitoring improves quality of life, whereas exercise tolerance is improved by IDM programmes with a dominant component of exercise, structural follow-up, or telemonitoring, and respiratory-related admissions are improved by self-management. This means that IDM programmes should consist of several different components to reach the highest potential. Ideally, components of the IDM programme should be linked to personal goals of the patient.

Previously, Kessler 2018 and Marsiglia 2015 showed important differences in usual care between countries, and our review also found differences between regions. These differences might stem from a disparity in local availability of different components, from differences in the healthcare system, or from different customs. Furthermore, they are dependent on available resources and costs of interventions. Therefore, we suggest that policy makers and healthcare leaders should assess local needs and available interventions and use this overview to develop and implement an IDM programme in a context-sensitive manner. This review suggests that an IDM programme with a combination of exercise training, self-management, telemonitoring, and personalised education implemented in the right context should result in the best outcomes.

Implications for research

Well-designed and appropriately conducted studies are still needed to minimise bias, to allow measurement of the true intervention effect. Specifically, consistent reporting on exacerbation outcomes and on severity of exacerbations may overcome the difficulties we encountered in this review, for which we found a myriad of exacerbation definitions. Researchers are encouraged to use recent Global initiative for Chronic Obstructive Lung Disease (GOLD) guidelines to provide unambiguous definitions of disease severity and to evaluate effects of IDM programmes on mild, moderate, and severe exacerbations (GOLD 2020).

Subgroup analyses undertaken as part of this update stimulate new questions in relation to IDM and its contextual embedding. Differences in subgroups based on the dominant intervention component call for further research to identify which intervention component, or which combination of components, is most effective in IDM programmes, and for which patient groups. Similarly, the context-specific effects we observed in the subgroup analysis suggest that the country in which the IDM programme is embedded and the level of usual care it is compared to greatly impact the magnitude of effect. This still means that the individual components of IDM programmes are important and will improve patient outcomes, as shown in this review. However, the contrast of a new IDM programme versus usual care becomes smaller when usual care itself already routinely contains several of the components. Other factors that remain uncertain are the optimal duration and intensity of the intervention and the combination of healthcare providers involved. These questions can be examined in a meta-regression analysis, which could shed light on the contribution of each individual factor or combination of factors to observed treatment effects.

Although the observed effect of - 3.89 on the SGRQ did not reach the proposed MCID of -4 points for medium-term follow-up, there could be a proportion of patients in the intervention group that does exceed the 4 points of improvement. These so called 'responders' would clinically benefit more from IDM than from usual care. In our review, only Bourbeau 2003 reported the proportion of people who improved by 4 points or more on the SGRQ. Hence, we echo Cates 2015 and urge trialists to also report, besides the mean difference, the spread of individual responses to the intervention or treatment.

This information can be used for more complete assessment of clinical importance and helps to reveal the population benefit.

Last, process-related outcomes raised issues that require consideration beyond this current review. For example, special attention should be given to evaluating the actual implementation of IDM programmes in existing healthcare structures, which should include outcomes related to patient satisfaction, feasibility, programme compliance, and assessment of personal and contextual determinants of implementation and treatment effects. Pragmatic, real-life RCTs including both clinical and process-related outcomes and qualitative assessment with long-term follow-up are needed to evaluate IDM programmes as comprehensive packages in routine primary and secondary care practice. As part of this, cost-effectiveness remains an important outcome, to allow for reimbursement and to inform health policy development and clinical guidance.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aboumatar 2019

Study characteristics	
Methods	RCT; follow-up: 6 months; control group: usual care
Participants	Eligible: 417 Randomised: 240, I: 120, C: 120 Completed: 187, I: 93, C: 94 Mean age (SD): I: 63.9 years; C: 66.0 years Sex (% male): I: 40, C: 37 *Inclusion criteria:* hospitalised patients and their family-caregivers who were admitted with a COPD-related condition. Additional eligibility criteria included age 40 years or older; history of smoking more than 10 pack-years; understands English language; has no terminal illness (< 6 months' life expectancy) unless end-stage COPD; no severe cognitive dysfunction (able to follow simple instructions) *Major exclusions:* severe cognitive dysfunction; terminal illness (< 6 months' life expectancy) that is non-COPD-related; homelessness
Interventions	Hospital-initiated programme that combines transition and long-term self-management support to patients and their family caregivers (the BREATHE programme). The BREATHE transitional care programme, which was co-developed with COPD patients, family-caregivers, and stakeholders

Aboumatar 2019 *(Continued)*

	Intervention components - Tailored hospital-to home transition support - Individualised COPD self-management education and support - Facilitated access to community programmes and healthcare services The intervention is delivered by a new team member called "COPD Nurse Transition Guide". The new team member works with both hospital and outpatient care teams, is a registered nurse with home care service experience, and has received additional training in COPD self-management and motivational interviewing. The nurse meets participants in the hospital and then follows up with them via home visits and phone calls. The intervention involves both patients and family caregivers (if available), is literacy adapted, and follows a tailored approach based on patient needs, priorities, and preferences Invervention duration: 3 months Disciplines involved: COPD nurse, treating physician Dominant component: none
Outcomes	Combined number of COPD-related hospitalisations and ED visits per participant at 6 months (primary outcome); quality of life (SGRQ); combined number of 'all-cause' hospitalisations and ED visits and individual components (hospital and ED visits separately); time to first event (re-hospitalisation, first ED visit death); dyspnoea (mMRC); anxiety and depression; patient activation score; self-efficacy and self-care behaviours; patient perceptions of family-caregivers' support; family-caregivers' preparedness for caregiving and coping
Notes	This article was retracted and re-published due to programming error and other errors that affected the results of our article. This article was re-published with complete corrected findings. These findings have been used in this review Dominant component: self-management (investigator's judgement)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "participants were randomised in a 1:1 ratio to either study group based on a pre-generated sequence of assignments. Randomization was stratified by hospital unit, and a computer algorithm was used to perform blocked randomisation assignment..."
Allocation concealment (selection bias)	Unclear risk	Quote: "participants were randomised in a 1:1 ratio to either study group based on a pre-generated sequence of assignments" Comment: unclear whether people screening for eligibility were aware of pre-generated sequence of study group assignment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "...due to the nature of the intervention, participants and clinicians were not blinded" Comment: plausible that people being aware of group allocation could have biased results on SGRQ outcome, being more subjective. As noted by investigators, "increased communications with clinicians about exacerbation signs might have led to increased referrals to the emergency department (and subsequent hospitalizations)"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: "data collectors and outcomes assessors were blinded to group allocation"

Aboumatar 2019 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: loss to follow-up balanced across arms (27 in intervention arm and 25 in usual care arm). Reasons for loss to follow-up comparable between groups
Selective reporting (reporting bias)	Low risk	Comment: all reports specified in protocol reported on. Additional post-hoc analysis well supported by arguments.

Aiken 2006

Study characteristics	
Methods	RCT; follow-up: unknown; control group: usual care, which means patients receiving care from managed care organisations (MCOs)
Participants	Eligible: 192 (COPD and congestive heart failure) Randomised COPD: 61, I: 33, C: 28 Completed COPD: I; 14, C: 7 Mean age/sex: not reported separately for COPD patients *Inclusion criteria:* COPD or congestive heart failure, palliative treatment residing at home, receiving care by MCO, mean life expectancy 2 years, saturation < 88%, oxygen usage, marked limitation of physical functioning, recent exacerbation
Interventions	Phoenix Care palliative intervention services were added to treatment services of local MCOs. Registered nurse case managers (serving 30 to 35 patients) provided the intervention service. These nurses worked with protocols and held contact with attending physicians. Furthermore, they developed care plans, provided education to patients, and tailored self-management of the disease. They supported services including assessing psychological and spiritual needs. During exacerbation episodes, nurses assessed medical status, implemented a symptom control intervention, and contacted the physician Intervention duration: 6 months Disciplines involved: GP, nurse case manager
Outcomes	SF-36, medical utilisation
Notes	Main component of programme: structured follow-up with nurses/GP

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomization was carried out within diagnosis, in blocks of 30 patients (15 intervention, 15 control) by a member of the project administration staff"
Allocation concealment (selection bias)	Low risk	Quote: "sealed-envelopes, colour-coded by diagnosis and containing the assignment to condition, were shuffled and assigned to participants in order of shuffling... the enroller, blinded to condition, opened the sealed envelope that identified the patients' study condition"
Blinding of participants and personnel (performance bias)	High risk	Comment: participants and treating therapists not likely to have been blinded to group allocation

Aiken 2006 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "all participants received an interview administered by a professional interviewing firm; interviewers were blind to condition and diagnosis"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: s tudy authors performed an attrition analysis according to the Jurs and Glass procedure
Selective reporting (reporting bias)	Low risk	Comment: all outcomes reported

Bendstrup 1997

Study characteristics	
Methods	RCT; follow-up: 24 weeks; control group: no treatment
Participants	Randomised: 47, I: 22, C: 20 Completed: 32, I: 16, C: 16 Mean age: I: 64 years, C: 65 years Sex (% male) both groups: 56 *Inclusion criteria:* diagnosis of COPD according to GOLD, FEV_1 25% to 55% of predicted value, Tiffeneau index < 70%, stable condition for 4 weeks (no change in exercise status, sputum colour/quantity, no change in medication) *Major exclusions:* heart disease, musculoskeletal disease limiting exercise, intermittent claudication limiting exercise
Interventions	Comprehensive outpatient rehabilitation programme - Exercise training (strength training, backwards/sideways walking, endurance training): 3 times per week for 1 hour during 12 weeks. Patients were encouraged to train at home - Occupational therapy: 2 group sessions - Education: 12 sessions, including proper administration, inhalation techniques, psychological education, socioeconomic problems, and nutrition - Smoking cessation: free nicotine patches, education Intervention duration: 12 weeks Involved disciplines: practice nurse, physiotherapist, dietician, psychologist, occupational therapist, social worker, physician
Outcomes	CRDQ, YQLQ, 6MWD, lung function, patient attendance, staff working hours
Notes	Dominant component: exercise
Risk of bias	
Bias	**Authors' judgement** **Support for judgement**

Bendstrup 1997 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "the patients were randomly allocated to either an intervention or a control group" Comment: no information on allocation procedure provided
Allocation concealment (selection bias)	Unclear risk	Comment: methods used to conceal the sequence of treatment group allocation were not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: participants and treating therapists not likely to have been blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: we could not ascertain how and whether outcome assessors were blinded to treatment group assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: high dropout rate (31%)
Selective reporting (reporting bias)	Low risk	Comment: study protocol is not available, but it is clear that published reports include all expected outcomes, including those that were pre-specified

Bernocchi 2017

Study characteristics	
Methods	RCT; follow-up: 6 months; control: usual care, multi-centre (n = 3)
Participants	Eligible: 319 Randomised: 112, I: 56, C: 56 Completed: 80, I: 45, C:35 Mean age: I: 71 years, C: 70 years Sex (% male): I: 88, C: 75 *Inclusion criteria:* older patients with COPD and cardiovascular heart disease: COPD new GOLD classification (B, C, and D classes) and spirometry in the previous year and systolic and/or diastolic CHF defined at least by an echocardiogram performed in clinical stability; II, III, and IV NYHA class and optimised drug therapy *Major exclusions:* physical activity limitations caused by non-cardiac and/or pulmonary problems; obstructive cardiomyopathies and/or myocarditis; non-cardiac and/or pulmonary pathologies that would cause the death of the patient during the study; poor adherence and compliance of the patient
Interventions	Home-based telehealth and rehabilitation programme Intervention components - Scheduled calls initiated by nurse (weekly) - Unscheduled calls initiated by patients or caregivers through the service centre (24 hours/24 hours) to report any clinical problems in case of signs or symptoms - Telemonitoring: during calls, patients can transmit via landline or mobile phone recordings from the 1-lead ECG to a service centre, and talk to the nurse or doctor

Bernocchi 2017 *(Continued)*

	- Home visit performed by therapist 7 days after hospital discharge by setting the daily physical activity and other home visits in case of need Home-based rehabilitation programme - Individual rehabilitative programme including ≥ 3 sessions/week of mini-ergometer and exercises and 2 sessions/week of walking with pedometer - Scheduled calls initiated by therapist performed weekly aimed at increasing workload and evaluating proper execution of exercises Duration intervention: 12 weeks Disciplines involved: nurse, therapist, treating physician
Outcomes	6MWD, mMRC, PASE score, Barthel score, CAT score, number of hospitalisations total, hospitalisation - respiratory-related, mortality
Notes	Dominant component: telerehabilitation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “a computer generated tables to allocate patients in fixed blocks of 4” (Bernocchi 2016)
Allocation concealment (selection bias)	Low risk	Quote: “in order to prevent selection bias, the allocation sequence was concealed from the investigators enrolling and assessing patients, in sequentially numbered, opaque, sealed envelopes" (Bernocchi 2016)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: “due to the nature of the intervention, neither the patients nor the physicians were blinded to patients’ group allocation” Comment: primary outcome functional exercise capacity, likely to be biased by difference in performance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: outcome assessors and data analysts were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: missing outcome data were greater in control group (21/56) compared to intervention group (11/56). More loss to follow-up in control group due to hospitalisation caused by heart failure. Loss to follow-up likely to be related to intervention
Selective reporting (reporting bias)	Low risk	Comment: a secondary outcome in protocol defined as (1) reduction of hospitalisations for cardiovascular and/or respiratory disease; and (2) reduction of hospitalisations for all causes, in outcome paper reported as reduction to time-to-event, combining hospitalisation and mortality. Reasons for change in outcome paper not provided. Explanation sought and provided by study authors: "incidence of death was very low and we considered that the inclusion of the two events (hospitalisations and deaths) best described the effect of the treatment" Also feasibility measure adherence to ≥ 70% proposal rehabilitative sessions not reported; instead crude outcome reported. Unlikely to have biased outcomes

Bourbeau 2003

Study characteristics	
Methods	RCT; follow-up: 12 months; control group: usual care
Participants	Eligible: 469 Randomised: 191, I: 95, C: 95 Completed: 165, I: 79, C: 86 Mean age: I: 69 years, C: 70 years Sex (% male): I: 52, C: 59 *Inclusion criteria:* stable COPD with ≥ 1 hospitalisation for an exacerbation in preceding year, age ≥ 50 years, pack-years ≥ 10 years, FEV_1% predicted (post-bronchodilator): 25% to 70%, FEV_1/FVC < 70% *Major exclusions:* no previous diagnosis of asthma or left congestive heart failure, terminal disease, dementia, uncontrolled psychiatric disease, no pulmonary rehab < 1 years ago, no long-term facility stays
Interventions	Disease-specific self-management programme (Living Well With COPD) of 7 to 8 weeks' follow-up including - Individual sessions of education by an experienced health professional at the patient's home - Content of education: COPD knowledge, breathing and coughing techniques, energy conservation during day-by-day activities, relaxation exercises; preventing and controlling symptoms through inhalation techniques, understanding and using a plan of action for acute exacerbation, adopting a healthy lifestyle, leisure activities and travelling, a simple home exercise programme. and long-term home oxygen therapy - An action plan for acute exacerbations was customised for each patient Intensity: education 1 hour per week during 7 to 8 weeks, follow-up first 2 months' weekly telephone calls, then once-a-month telephone call. Exercise evaluation (not mandatory): 3 times per week, 30- to 45-minutes/session + exercise teaching Intervention duration: 8 weeks followed by 10 months maintenance Involved disciplines: nurse, physiotherapist, physician, pulmonologist
Outcomes	SGRQ, exacerbations, spirometry, FEV_1 (L), forced vital capacity, hospital admissions, symptoms, emergency room visits, outpatients visits, 6MWD, walking distance
Notes	Dominant component: self-management (including action plan)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "patients underwent randomisation with the use of a central computer-generated list of random numbers. Randomization was stratified per centre and in blocks of 6, and patients were assigned to the self management program (intervention group) or to usual care"
Allocation concealment (selection bias)	Low risk	Quote: "the blocking factor was not known by the investigators or their staff in each participating centre"
Blinding of participants and personnel (performance bias)	High risk	Quote: "since a double-blind design was impossible ..."

Bourbeau 2003 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: ".. an independent evaluator unaware of the patient assignment was responsible for the evaluation process in each centre. The evaluator was cautioned not to ask about the workbook modules and types of contact"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "an intention to treat analysis included all available study patients"
Selective reporting (reporting bias)	High risk	Comment: data on the 6MWD not presented but stated only as "not statistically significant"; study authors cannot provide us with additional data

Boxall 2005

Study characteristics	
Methods	RCT; follow-up: 12 weeks; control group: usual care
Participants	Eligible: not clear Randomised: 60, I: 30, C:30 (started intervention: I: 28, C: 26) Completed: 46, I: 23, C: 23 Mean age: I: 78 years, C: 76 years Sex (% male): I: 48, C: 65 *Inclusion criteria:* diagnosis of COPD by a respiratory specialist, age > 60 years, dyspnoea on exertion, live locally, motivated to exercise daily unsupervised, stable for 2 weeks, functionally housebound *Major exclusions:* attending outpatient-based PR, restricted shoulder movement, living in nursing home, previous lung volume surgery, pain limiting mobility
Interventions	12-week home-based pulmonary rehabilitation programme - Exercise consisting of walking (level 1 to 10) and arm exercises (1 to 18) + educational sessions. Patients were required to carry out exercise daily. Weekly physiotherapy visits were scheduled for the first 6 weeks, and then visits were made until Week 12 of the programme. Visits were used to monitor exercise performance and progress in exercises, to retest 6MWD at regular intervals (Weeks 1, 4, 6, 8, and 12 of the programme) and to provide encouragement to patients - Educational sessions for patients and carers were conducted by physiotherapists, nurses, and occupational therapy staff in their homes. Sessions covered anatomy and physiology of the lungs, use of respiratory devices, medications, breathing techniques, secretion removal techniques, energy conservation, use of adaptive aids, and stress management. Patients received on average 11 home visits during the programme Intervention duration: 12 weeks Disciplines involved: physiotherapist, nurse, occupational therapist
Outcomes	SGRQ, 6MWD, hospital admission, average length of stay, dyspnoea Borg Scale
Notes	Dominant component: exercise
Risk of bias	

Boxall 2005 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomised to equal groups using computer-generated random numbers"
Allocation concealment (selection bias)	Low risk	Quote: "random numbers were coded into opaque envelopes by a person independent from the study, they retained the envelopes until initial assessment was completed"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "neither assessors nor participants were blinded to group assignment in this study"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "neither assessors nor participants were blinded to group assignment in this study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: m issing outcome data balanced in numbers (23/23 analysed in both groups) across intervention and control groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	Comment: study protocol is not available, but it is clear that published reports include all expected outcomes, including those that were pre-specified

Cambach 1997

Study characteristics	
Methods	RCT with cross-over design; follow-up: 6 months; control group: drug treatment only
Participants	Eligible (asthma and COPD) : 89 Analysed (COPD) : 23 (COPD) , I: 15, C: 8 Mean age: I: 62 years, C: 62 years Sex (% male): I: 47, C: 75 *Inclusion criteria:* diagnosis of asthma or COPD according to guidelines, evidence of dyspnoea and decreased exercise tolerance as a result of obstructive lung disease, 18 to 75 years of age, ability to travel independently to the physiotherapy practice, medication prescribed by a pulmonary physician, motivation to improve self-care, informed consent *Major exclusions:* manifested cardiac complaints, hypercapnia and/or hypoxia
Interventions	3-month rehabilitation programme including drug treatment Exercise group sessions of 3 to 4 participants including techniques of breathing retraining and evacuation of mucus, exercise training, patient education, relaxation techniques, and recreational activities. Training was provided 3 days a week for 90 minutes. Exercise training was performed twice a week on a cycle ergometer and by stair-walking. Recreational activities were provided once a week for 45 minutes. Educational sessions were provided every week for 45 minutes Intervention duration: 12 weeks Involved disciplines: nurse, physiotherapist

Cambach 1997 *(Continued)*

Outcomes	6MWD, incremental cycle ergometer test, CRQ
Notes	Dominant component: exercise

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "block randomisation procedure; four closed envelopes for condition RC and four closed envelopes for condition CR"
Allocation concealment (selection bias)	Low risk	Quote: "four closed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: participants and treating therapists not likely to have been blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: outcome assessors not likely to have been blinded to intervention, as patients were tested for exercise capacity in their practices, by their treated physiotherapist, who was probably not blinded to group allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: “data obtained from patients who did not return for one or more of the assessments (i.e. baseline (t0), after 3 months (t3) and/or after 6 months (t6), or patients who were not measured within 3 weeks (from t0, t3 and t6) were excluded from data analysis" Comment: exclusion of non-responders may have affected outcome data
Selective reporting (reporting bias)	Low risk	Comment: study protocol is not available, but it is clear that published reports include all expected outcomes, including those that were pre-specified

Dheda 2004

Study characteristics

Methods	RCT; follow-up: 6 months; control group: primary care follow-up
Participants	Eligible: 33 Completed: 25, I: 10; C: 15 Mean age: I: 68 years, C: 71 years Sex (% male) both groups: unknown *Inclusion criteria:* diagnosis of COPD according to B TS guidelines, first admission to hospital with progressive symptoms, smoking history > 20 pack-years *Major exclusions:* another dominant medical condition, mandatory reason for hospital follow-up
Interventions	Intensive outpatient follow-up program me following BTS guidelines Respiratory nurse and/or chest physician reviewed the intervention group ≥ 4 times in the 6-month period (at 6, 8, 12, or 16 weeks). The following interventions were provided at some or all of these visits: spirometry with reversibility, review of inhaler technique and peak flow diary, ambulatory oxygen as-

Dheda 2004 *(Continued)*

	sessment, smoking cessation advice, steroid trial, nebuliser assessments, review of medication, advice about nutrition and exercise, and introduction to a patient support group Intervention duration: 6 months Involved disciplines: nurse, chest physician
Outcomes	SGRQ, SF-36
Notes	Dominant component: structured follow-up with nurse/GP

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Comment: methods used to conceal the sequence of treatment group allocation were not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: participants and treating therapists not likely to have been blind to group allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not reported; therefore unclear who scored outcome assessments (patients, caregivers, or outcome assessors)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: not clear whether results in SGRQ were described in the total population, as well as in patients who withdrew (n = 8) from the study
Selective reporting (reporting bias)	High risk	Comment: not all outcome measurements are given in measures; some are reported only as "there was no significant difference at 6 months in FEV1"

Engstrom 1999

Study characteristics

Methods	RCT; follow-up: 12 months; control group: usual outpatient care
Participants	Eligible: 58 Randomised: 55 Completed: 50, I: 26, C: 24 Mean age: I: 66 years, C: 67 years Sex (% male): I: 54, C: 50 *Inclusion criteria:* clinical diagnosis of COPD, developing after ≥ 10 years of smoking, FEV_1 < 50%, debut of symptoms after 40 years of age, dyspnoea mainly elicited by exercise or infection, no allergy *Major exclusions:* disabling or severe disease, coexistence of other causes of impaired pulmonary function

Engstrom 1999 *(Continued)*

Interventions	12-month rehabilitation programme including - Exercise training sessions (bicycle, arm, and breathing techniques), 2/week for 6 weeks, once weekly for 6 weeks, once every second week for 6 weeks, and then once a month for remaining period. Every session: 45 minutes. Furthermore, instructions for daily walks and an individualised daily 30-minute home training programme - Individualised educational programme with outpatient team (nurse and physician) on visit every 3 months - Occupational therapist gave 2 group sessions about energy-saving techniques and 2 global educational sessions - Dietician gave information about nutrition for COPD patients and intervened in malnutrition Intervention duration: 12 months Involved disciplines: physiotherapist, nurse, physician, dietician, occupational therapist
Outcomes	SGRQ, 6MWD, W-max, days in hospital, SIP, MACL
Notes	Dominant c omponent: exercise

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information reported
Allocation concealment (selection bias)	High risk	Quote: "patients with COPD were recruited consecutively and, when a sufficient number had been collected, randomised to produce a rehab group and a control group of equal size"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: participants and treating therapists not likely to have been blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "all the physiological and QOL assessments were blinded, except the walking test, which was performed by the nurse in the rehabilitation team"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: missing outcome data balanced in numbers across intervention and control groups (2 vs 3 persons)
Selective reporting (reporting bias)	Low risk	Comment: study protocol is not available, but it is clear that published reports include all expected outcomes, including those that were pre-specified

Fan 2012

Study characteristics

Methods	RCT; intended follow-up: 12 months (terminated early, mean follow-up 250 days); control: usual care (general information booklet COPD)

Fan 2012 *(Continued)*

Participants	Eligible: 426 Randomised: 426, I: 209, C: 217 Completed: 126, I: 197, C: 193 Mean age: I: 66.2 years, C: 65.8 years Sex (% male): I: 97.6, C: 96.3 *Inclusion criteria:* hospitalised for COPD in the 12 months before enrolment, post-bronchodilator ratio of FEV_1 to FVC < 0.70 with FEV_1 < 80% predicted, older than 40 years, current or past history of cigarette smoking (> 10 pack-years), ≥ 1 visit in the past year to a primary care or pulmonary clinic at a Veterans Affairs (VA) medical centre, no COPD exacerbation in the past 4 weeks, ability to speak English, access to a telephone *Major exclusions:* primary diagnosis of asthma or any medical condition that would impair ability to participate in the study or to provide informed consent
Interventions	Comprehensive care management programme - COPD education during 4 individual 90-minute weekly sessions and 1 group session - Action plan for identification and treatment of exacerbations and scheduled proactive telephone calls for case management Patients in both intervention and usual care groups received a COPD informational booklet specially designed for the study; primary care providers received a copy of COPD guidelines and were advised to manage patients according to these guidelines Intervention duration: 4 week s followed by 11 months ' structural follow-up Disciplines involved: primary care physician, case manager (nurse)
Outcomes	Time to first COPD hospitalisation (primary outcome); all-cause hospitalisations; self-reported COPD exacerbations; number of COPD exacerbations treated with prednisone/antibiotic; delay to prednisone/antibiotic treatment; all-cause mortality; COPD-related mortality; SGRQ; Veterans Medical Outcomes Study Short Form-12; Patient Health Questionnaire (depressive symptoms); COPD-related knowledge; self-efficacy questionnaire
Notes	Dominant component: self-management Trial was stopped early when a safety monitoring board noted more deaths in the intervention group. Deaths due to COPD accounted for the largest difference: 10 in the intervention group vs 3 in the usual care group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the Cooperative Studies Program Coordinating Center in Boston, Massachusetts, randomly assigned eligible patients in equal numbers to 2 groups, stratifying patients by site to allow for possible regional differences in patient characteristics and clinical practice patterns"
Allocation concealment (selection bias)	Unclear risk	Comment: unclear whether investigators had access to randomisation lists
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "the 2 groups differed on the basis of a complex behavioral intervention that made blinding impossible"

Fan 2012 *(Continued)*

		Comment: majority of outcomes are self-reported and may be affected by performance bias. However, not all outcomes (hospitalisation, mortality) are likely to be affected by performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "research staff blinded to study group contacted patients every 2 months to determine whether they developed symptoms of a COPD exacerbation, along with details of treatment and health care use"; "3 blinded pulmonologists reviewed discharge summaries and other available information to determine the primary cause of all hospitalisations and classified them as COPD-related (exacerbation or pneumonia), cardiovascular, or other"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "citing serious safety concerns, the data monitoring committee terminated the intervention before the trial's planned completion after 426 (44%) of the planned total of 960 patients were enrolled"; "available data could not fully explain the excess mortality in the intervention group. Ability to assess the quality of the educational sessions provided by the case managers was limited" Comment: study was terminated before planned 12-month follow-up period. However, based on computed data, results are likely to be the same if the study would have been continued
Selective reporting (reporting bias)	Low risk	Comment: health care-related costs, health service use, and medication adherence were not reported in the paper. Selective reporting probably due to early termination of the study. Given negative findings that were reported, it appears unlikely that selective reporting influences the conclusions reached. Full protocol requested from investigators but not received
Adequate analysis methods for CRT	Unclear risk	,

Farrero 2001

Study characteristics	
Methods	RCT; follow-up: 12 months; control group: usual care
Participants	Randomised: 122, I: 60, C: 62 Completed: 94, I: 46, C: 48 Mean age: I: 69 years, C: 69 years Clinical diagnosis of COPD, requiring oxygen for ≥ 6 months, with willingness to participate in a hospital-based home care programme, and with residence within easy reach of the hospital
Interventions	Hospital-based home care programme of 12 months with the aim of combining home care management and easy access to hospital resources. Programme included - Monthly telephone calls and 3-monthly home visits from a nurse, working closely with a physician. Patients could also request an immediate response, which varied according to a home visit, a hospital visit, telephone advice, or a control visit Intervention duration: 12 months Involved disciplines: nurse and physician
Outcomes	CRQ, spirometry, mortality, hospital admissions, hospital days, ED visits

Farrero 2001 *(Continued)*

Notes	Dominant component: structured follow-up with nurses

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "after this initial evaluation, informed consent was obtained and patients were allocated randomly to the HCP treatment group or to the control group" Comment: unclear if patients were randomised by sequence generated or based on, for example, date of admission
Allocation concealment (selection bias)	Low risk	Quote: "codes of randomisation were kept in sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: participants and treating therapists not likely to have been blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "patients in the control group were evaluated by the HCP team at the outpatient department in the initial visit, and after 1 year" Comment: as the HCP team was the intervention team and was not blinded to which group a patient was randomised, it is likely that assessment can be influenced by no blinding of the outcome assessor
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "quality of life was investigated in the first 40 consecutive patients included in the study (..) applied before the study and after 3 months and 12 months" Comment: reason for missing outcome data likely to be related to true outcome, with imbalance in numbers
Selective reporting (reporting bias)	Low risk	Comment: study protocol is not available, but it is clear that published reports include all expected outcomes, including those that were pre-specified

Fernandez 2009

Study characteristics

Methods	RCT; follow-up: 12 months; control group: education (mono-disciplinary intervention)
Participants	Eligible: 50 Randomised: 50, I: 30, C: 20 Mean age: 66 years, C: 70 years Sex: 100% male (both groups) *Inclusion criteria:* GOLD IV patients; younger than 80 years of age; stable COPD defined as a period of 2 months without any exacerbations, defined as signs of acute dyspnoea requiring medical attention, changes in the quantity and characteristics of sputum, an increase in pulmonary noise or an increase in the necessity for medication; correct administration of pharmacological treatment according to GOLD; home treatment with oxygen for ≥ 6 months before commencement of the study

Fernandez 2009 *(Continued)*

	Major exclusions: severe cardiovascular pathology, unstable angina, acute myocardial infarction, cerebral vascular accident, physical or psychological disorder that impedes the practice of physical exercise
Interventions	Rehabilita tion programme of 11 months At the start: two 1-hour sessions of respiratory re-education in the hospital, where exercises at home were taught Home-rehab programme - One hour of exercise per day (respiratory re-education, muscular inspiratory training, muscular training of upper and lower limbs) - First 2 months: attendance of physiotherapist at home (who visited twice monthly for 1 hour) - Months 2 to 9: single-monthly visits to physiotherapist, including resistance training, respiratory re-education, isotonic training, training of respiratory muscles - Three respiratory education sessions by nursing staff (handling of inhalers, knowledge of illness, what to do in the event of an attack) Intervention duration: 11 months Disciplines involved: nurse, physiotherapist
Outcomes	Pulmonary function, SGRQ, 6MWD
Notes	Dominant component: exercise

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "50 patients were prospectively randomised to block of 5 patients and randomly divided into 2 groups"
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: participants and treating therapists not likely to have been blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: dropout rates between groups comparable
Selective reporting (reporting bias)	Low risk	Comment: all outcomes in methods section provided

Freund 2016

Study characteristics	
Methods	Cluster-RCT (115 clusters); follow-up: 24 months; control: usual care
Participants	Eligible: 3065 Randomised: total 2076, I: 1093, C: 983 Randomised: COPD: 543, I: 321, C: 222 Completed: total 1718, I: 874, C: 844 (24-month follow-up) Completed: COPD: not reported Mean age: I: 71.6 years, C: 72.4 years Sex (% male): I: 48, C: 48 *Inclusion criteria*: 18 years or older and received medical treatment for ≥ 1 of the following index conditions at time of inclusion: type 2 diabetes mellitus, COPD, or chronic heart failure ; risk for future hospitalisation (i.e. predicted likelihood of hospitalisation within the upper quartile of the total population of health plan patients, as determined by analysis of data from the preceding 18 months *Major exclusion criteria*: active cancer (cancer diagnosis and current receipt of radiotherapy or chemotherapy), moderate to severe dementia, permanent residency in a nursing home, participation in a concurrent clinical trial (including telemonitoring studies), severe physical and mental disorders (such as dementia, psychotic disorder, or palliative care needs), other problems that hindered active participation in the intervention (such as language barriers), as assessed by the primary care physician
Interventions	Protocol-based care management, including structured assessment, action planning, and monitoring delivered by medical assistants Intervention components were self-management (education, action planning, exacerbation management), assessment of medical and non-medical needs and resources, goal-setting, follow-up/communication tailored to patients' heath status (minimum every 6 weeks), case management, multi-disciplinary teams. PCPs and HCAs were trained jointly in communication techniques and goal-setting to enhance communication within the care management team, weekly review of patient progress between primary care physician and medical assistant practice teams received $135 per enrolled patient per year to cover staff costs as financial incentive Duration intervention: 12 months Involved disciplines: primary care physician, GP or general internist, medical assistant
Outcomes	Number of all-cause hospitalisations at 12 months at the patient level (primary outcome); number of days in the hospital; hospitalisations related to index conditions; patient-reported quality of life (SF-12); general health (EQ-5D); all-cause mortality Intervention costs (estimation based on g standard wages for medical assistants' and physicians' working time). Only number of all-cause hospitalisations (12 months, 24 months) reported for COPD separately
Notes	Unpublished data on COPD patients sought but not received Dominant component: self-management

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "we used computer generated randomisation lists (SAS Version 9.2). Separate randomisation lists were prepared for urban and rural practices. A re-

Freund 2016 *(Continued)*

		search assistant who was not otherwise involved in the project performed the central randomisation"
Allocation concealment (selection bias)	Low risk	Quote: "we concealed the allocation to intervention or control groups until each practice completed patient enrolment and baseline assessment"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "because of the nature of the intervention, blinding primary care physicians, medical assistants, and patients was not possible" Comment: unlikely to affect primary outcome (number of hospitalisations derived from insurance data) but may affect some of the secondary outcomes (e.g. self-reported quality of life)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "we blinded the assessment of the primary and secondary end points as well as the responsible statistician to study group allocation"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "for the quality-of-life measures, we performed analyses for the available cases (reported here) and used multiple imputation for incomplete data"; "results of the per protocol analysis and the multivariable models were similar to the results of the intention-to-treat analysis" Comment: furthermore, no missing data for 2 important outcome measures (all-cause hospitalisation, number of days in hospital). Not all outcomes reported for participants with COPD specifically. Hence, impossible to conclude if missing outcome data are balanced in numbers across intervention and control groups
Selective reporting (reporting bias)	High risk	Comment: the PACIC, medication adherence, depression, self-management capabilities, physical activity, activities of daily living, healthcare utilisation, total healthcare costs, blood pressure, MRC dyspnoea, forced expiratory volume, and number of exacerbations were mentioned in the protocol but were not reported in the results
Recruitment bias	Low risk	Quote: “we concealed the allocation to intervention or control groups until each practice completed patient enrolment and baseline assessment”; "we informed physicians about their allocation via an official letter and asked them to inform participating patients"
Baseline imbalance between groups	Unclear risk	Comment: practice and patient characteristics were similar between groups at baseline, with the exception of a slightly higher proportion of patients with COPD in the intervention group and a higher proportion from ethnic minorities in the usual care group. Investigators stratified randomisation according to population density of participating practice sites (urban vs rural) to minimise effects of population density on hospitalisation
Loss to follow-up of clusters	Unclear risk	Comment: study authors describe a 10% attrition rate (see point 10 attrition), but loss to follow-up of clusters is not mentioned, nor do study authors confirm that all clusters were present at follow-up
Adequate analysis methods for CRT	Low risk	Quote: "we accounted for clustering within practices but were unable to account for clustering within physician/medical assistant teams within a practice (each of which had up to 2 teams)" Comment: intercluster correlation taken into account for sample size estimation

Gottlieb 2011

Study characteristics	
Methods	RCT; follow-up: 18 months; control group: usual care
Participants	Eligible: 133 Randomised: 61 , I: 35, C: 26 (started study I:22, C:20) Completed: 26, I: 16, C: 18 Mean age: I: 74 years, C: 73 years Sex (% male): I: 32, C: 35 *Inclusion criteria:* diagnosis of moderate COPD, $FEV_1/FVC < 0.7$ and $50\% \leq FEV_1 < 80\%$ with motivation for pulmonary rehabilitation *Exclusion criteria:* comorbidity contraindicating rehabilitation, participation in PR within the last year, cognitive disorder limiting ability to participate in physical training and educational sessions
Interventions	Programme of intensive training for 7 weeks, with maintenance programme for 6 months, including - Intensive 7-week physical training and educational phase led by a multi-disciplinary team. Furthermore, smoking cessation counselling given on an individual basis and a dietary intervention consisting of group cookery classes and individual sessions - Final interview following completion of the programme, in which participants' achievements were compared to original goals - Maintenance programme for 6 months, including a 90-minute monthly session focusing on ways of incorporating exercise in daily life, 2 sessions on exercise activities in the local community, and another 2 sessions on exercise as well as on repetition of relevant topics Intervention duration: 7 weeks followed by 6 months ' maintenance Involved disciplines: multi-disciplinary team, not further specified. Study authors were unreachable for further information
Outcomes	SGRQ, 6MWD, MRC, Borg Dyspnoea Scale, Sit-to-Stand test
Notes	Dominant component: exercise

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "subjects were randomised 1:1 to pulmonary rehabilitation and control"
Allocation concealment (selection bias)	Low risk	Quote: "randomization was performed using sealed opaque envelopes randomly assigned to participants"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: p articipants and treating therapists not likely to have been blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: w e could not ascertain how and whether outcome assessors were blinded to treatment group assignment

Gottlieb 2011 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: d ropout rate equally divided: 39% intervention group, 23% control group
Selective reporting (reporting bias)	High risk	Comment: r esults on MRC Dyspnea Scale not reported in results section

Güell 2000

Study characteristics	
Methods	RCT; follow-up: 24 months; control group: usual care
Participants	Eligible: 65 Randomised: 60, I: 30, C: 30 Completed (24 months): 47, I: 23, C: 24 Mean age: I: 66 years, C: 64 years Sex (% male) both groups: 100 *Inclusion criteria:* age ≤ 75 years, FEV_1 < 70%, FEV_1/FVC < 65%, PaO_2 > 55 mmHg at rest with no indication for prescribing home oxygen therapy *Major exclusion criteria:* clinically apparent heart disease, bone or joint disease; exacerbation or hospitalisation in previous month
Interventions	Outpatient pulmonary rehabilitation programme, followed by a 6-month maintenance programme - First 3 months: two 30-minute sessions each week: breathing retraining, combined with low-level home exercise programme. If indicated, patients also received chest physiotherapy, which involved teaching effective cough and postural drainage. Patients attended educational sessions on anatomy and basic physiology of the respiratory system as well as on the nature of their disease and of PR - Months 3 to 6: exercise training programme of five 30-minute sessions weekly on a stationary cycle ergometer. During this period, patients also began a programme of home exercise with either 30 minutes of pedaling on a stationary cycle or 1 hour of walking - Months 6 to 12: single weekly session in groups during which patients performed exercises for breathing and leg-arm co-ordination - Months 12 to 24: instructed to do home exercises without supervision Intervention duration: 6 months followed by 6 months ' maintenance Disciplines involved: nurse, physiotherapist, pulmonologist
Outcomes	Lung function, 6MWD, cycle ergometer, VAS, MRC, CRQ, exacerbations, hospital admissions
Notes	Dominant component: exercise

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Güell 2000 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "randomization was done at inclusion of consecutive patients"
Allocation concealment (selection bias)	High risk	Quote: "randomization was not concealed"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "same physician saw patients at each visit" It is unlikely that the healthcare professional was blinded to treatment group allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the technicians, who collected data for outcome measures at every visit, as explained below, were blinded to a patient's allocation to PR or control groups"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: m issing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	Comment: study protocol is not available, but it is clear that published reports include all expected outcomes, including those that were pre-specified

Güell 2006

Study characteristics	
Methods	RCT; follow-up: 4 months; control group: usual care
Participants	Randomised: 40, I: 20, C: 29 Completed: 35, I: 18, C: 17 Mean age: I: 68 years, C: 66 years Male: I: 88%, C: 100% *Inclusion criteria:* age ≤ 75 years, FEV_1 < 70%, FEV_1/FVC < 65%, PaO_2 > 55 mmHg at rest with no indication for prescribing home oxygen therapy *Exclusion criteria:* psychiatric disturbance; no heart, bone, or joint disease; exacerbation or hospitalisation in previous 2 months
Interventions	Pulminary rehabilitation programme of 4 months, including - First 2 months: two 30-minute sessions each week, including relaxation techniques, breathing retraining, and chest wall and abdominal muscle wall work. Patients attended four 45- to 60-minute educational sessions - Month 2 to 4: five 30-minute sessions weekly exercise training on cycle ergometer Intervention duration: 4 months Disciplines involved: nurse, physiotherapist, pulmonologist
Outcomes	MBHI, Revised Symptom Checklist (SCL-90-R), 6MWD, CRQ
Notes	Dominant component: exercise

Güell 2006 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomization was done at inclusion of consecutive patients" Comment: it is not clear how the sequence was generated
Allocation concealment (selection bias)	High risk	Quote: "randomization was not concealed"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "neither patients nor clinicians were blinded to allocation"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the technicians who collected the data were blinded to patient allocation, as were the data analysts, until the analysis was deemed complete"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: l oss to follow-up comparable between groups (2 vs 3)
Selective reporting (reporting bias)	Low risk	Comment: a ll outcomes reported

Haesum 2012

Study characteristics	
Methods	RCT of a telerehabilitation programme; control: usual care (home exercises); follow-up: 10 months
Participants	Eligible: 114 Randomised: 111, I: 60, C: 51 Completed: 105, I: 57, C: 48 Mean age: I: 68 years, C: 68 years Sex (% male): 42.85 *Inclusion criteria:* over 18 years; can understand oral and written trial information; diagnosed COPD in stage III or IV (severe or very severe COPD); COPD as primary cause of reduction in function *Major exclusion criteria:* heart disease that could limit physical function; mental illness; terminal malignant disease; severe rheumatoid arthritis; pregnancy; living outside Aalborg Municipality
Interventions	Telerehabilitation with a telehealth monitoring device Intervention components: telemonitoring, home exercise, advice from healthcare professionals on disease and training, team video meetings with healthcare professionals from primary and secondary care (to co-ordinate and discuss COPD patients' individual rehabilitation programme) Duration intervention: 4 months Involved disciplines: GP, district nurse, nurse and doctor at healthcare centre or hospital

Haesum 2012 *(Continued)*

Outcomes	Admission rate per patient over a 10-month period (primary outcome); cost of admission per patient (based on ambulatory contacts, GP contacts, emergency physician contacts, utilisation of other primary services, medicine consumption), SF-36
Notes	Domi n ant component: telemonitoring ; SF-36 not yet published

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "after confirming eligibility and obtaining written informed consent, the patients drew envelopes to see which group they would attend"
Allocation concealment (selection bias)	Unclear risk	Quote: "the envelopes were sealed and therefore the allocation was blinded for health-care professionals, patients and researchers" Comment: it remains unclear whether envelopes were sequentially numbered and opaque
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: blinding of participants and personnel is not mentioned by study authors but is unlikely in light of the nature of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: outcome assessors were blinded to group allocation (unpublished data)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: missing outcome data due to loss to follow-up are balanced between groups (3 in intervention group, 3 in control group). Unlikely to have caused attrition bias
Selective reporting (reporting bias)	Unclear risk	Comment: according to study authors, QoL (SF-36) will be reported in future publication

Jimenez-Reguera 2020

Study characteristics

Methods	RCT; follow-up: 10 months post rehabilitation ; control group: usual care following 8 weeks PR
Participants	Eligible: 44 Randomised: 44, I: 20, C: 24 Completed: 36; I: 17, C: 19 Mean age: I: 68 years, C: 68 years Sex (% male): I: 41, C: 59 *Inclusion criteria:* COPD patient, between 55 and 85 years of age, with degree of severity II, III, or IV of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) scale, in a stable clinical situation (no exacerbations in the last 6 weeks) *Major exclusion criteria:* unstable cardiovascular disease or muscular or nervous system impairments that prevented performance of rehabilitation programme or evaluation tests; cognitive impairment that makes it difficult to understand the educational program and to manage the HappyAir system
Interventions	10-month PR maintenance programme following an integrated care plan using a mobile device with pulmonary care web-based app (HappyAir app)

Jimenez-Reguera 2020 *(Continued)*

	HappyAir app comprised 2 components - Educational programme providing patients advice about their disease - Component for data collection for physical activity, medication intake, and disease HappyAir integrated plan was designed as a model of a therapeutic programme based on communication that introduced the figure of the therapeutic educator (physiotherapist or respiratory coach). Therapeutic educators had access to the platform for clinical evaluation assessment, recording weekly and monthly goals. Pulmonologist, physiotherapist had access to the platform to enter clinical data, communicate with therapeutic educator. Patients were made responsible for their self-care and for management of their illness. Patient and educator shared responsibility Intervention duration: 8 weeks PR (both group); 10 months' maintenance programme Disciplines involved: physiotherapist or respiratory coach, pulmonologist
Outcomes	Adherence to maintenance program me (primary outcome); adherence to physical activity (Morisky-Green Test) ; CAT; SGRQ; EQ-5D; 6MWD
Notes	Power calculation based on primary outcome (adherence to maintenance program me); likely to be underpowered for other outcomes Dominant component: self-management

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "p atients were recruited by convenience sampling through face-to-face interviews at participating hospitals. The recruitment of subjects was performed from patients attending pneumology consultations at the rehabilitation service of the hospitals participating in the study " Quote: "w e used a computer-generated simple randomisation procedure, using the online randomisation tool Research Randomizer " Comment: selecti on preceded an initial face-to-face interview. Initial sel e ction of study pop ulation may be biased by willingness to participate in the interview. Adequate randomisation procedures used, so unlikely that selection bias was introduced between groups
Allocation concealment (selection bias)	Low risk	Quote: "b efore the beginning of the study, distribution was made in two groups through the Research Randomizer program, and a list of patients designated to each group was drawn up, considering a homogeneous distribution of groups for each hospital. This listing was sequentially numbered and coded "
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "d ue to the characteristics of the intervention, healthcare professionals and patients could not be blinded to the group assignment "
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: " t he follow-up assessment of outcome measures of both groups was carried out by a blinded assessor "
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: s tudy dropout is balanced between groups (5/17 intervention; 5/19 control). Reasons for dropout are more or less comparable. Unclear if reasons are related to study allocation

Jimenez-Reguera 2020 *(Continued)*

Selective reporting (reporting bias)	High risk	Comment: study protocol is not available. Lung function outcomes (FEV_1, FVC, FEV_1/FVC ratio) and VAS results reported that were not specified in the trial registration

Kalter-Leibovici 2018

Study characteristics

Methods	RCT; follow-up: 24 months; control group: usual care; multi-centre
Participants	Eligible: 1333 Randomised: 1202, I: 600, C: 602 Completed: 992, I: 500, C: 492 Mean age: I: 66.7 years, C: 68.3 years Sex (% male): I: 69, C: 73 *Inclusion criteria:* aged 40 years or older; COPD patients with GOLD Stage III or IV (see table-1), or patients with GOLD Stage II COPD, with past or current history of cigarette smoking, not history of childhood asthma, and with unstable disease (≥ 1 hospital admission or 2 visits to internal wing of emergency department for COPD exacerbation during past 12 months) *Major exclusion criteria:* permanent tracheostomy; heart failure with left ventricular ejection fraction < 40%; severe comorbidity; significant functional or cognitive impairment; communication problems; substance abuse; participating in another trial
Interventions	Disease management intervention delivered by trained COPD nurses in addition to recommended care Intervention components - Face-to-face session with COPD nurse during visits; remote contact in between visits - Symptom and adherence to treatment monitoring by COPD nurse, exacerbation management, lifestyle advice, treatment plan, and education - Co-ordination of care - On-call disease management nurse outside office hours Duration of intervention: duration of follow-up; minimum 2 years, maximum 5 years Disicplines involved: trained COPD nurse, disease management nurse, programme director
Outcomes	Total number hospitalisation days (all-cause and COPD-related), number of patients with ≥ 1 hospitalisation (all-cause and COPD-related), hospitalisation rate, 6MWD, mMRC, SF-12 MCS, SF-12 PCS, SGRQ - total, FEV_1% predicted
Notes	Dominant component: structured follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "after completing eligibility and baseline assessment and providing signed informed consent, patients were randomly assigned either to the study intervention or to the control intervention, using a computerized randomisation program with permuted-block design linked to the patients' electronic medical record"

Kalter-Leibovici 2018 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "after completing eligibility and baseline assessment and providing signed informed consent, patients were randomly assigned either to the study intervention or to the control intervention"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "the study personnel at the COPD centres were not blinded to the patients' assigned intervention during follow-up assessments" Comment: primary outcomes less subjective; outcomes on health-related quality of life, SGRQ, and depression symptoms may be biased by performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "hospital admissions were classified by two independent investigators, blinded to the patients' assigned intervention" Comment: outcomes on hospitalisation assessed blinded to allocation. However, all other outcomes assessed by unblinded personnel at COPD centre with knowledge of allocation, likely to have biased results
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "all analyses were performed according to the intention-to-treat principle" Comment: 1 in 6 patients in both groups lost to-follow up. Numbers and reasons for loss to-follow-up balanced between groups. In the control group, number of deaths (n = 91) slightly greater compared to control group (n = 72). Unlikely to have biased results
Selective reporting (reporting bias)	Low risk	Comment: all outcomes specified in protocol reported. Protocol published as appendix to article

Kennedy 2013

Study characteristics	
Methods	Cluster-RCT (44 clusters); follow-up: 6 and 12 months; control group: usual care
Participants	Eligible (diabetes, COPD, irritable bowel syndrome): 13,053, I: 5578, C: 7475 Randomised COPD: 1634, I: 1009, C: 625 Randomised total (diabetes, COPD, irritable bowel syndrome): 5599, I: 2295, C: 3304 Complete COPD: 1146, I: 424, C: 722 Completed total (diabetes, COPD, irritable bowel syndrome): 4076, I: 1649, C: 2427 Mean age: I: 68.89 (SD 10.08), C: 69.37 (SD 9.85) Sex COPD (% male): I: 51.0, C: 47.8 *Inclusion criteria:* patients with diabetes, COPD, or irritable bowel syndrome *Major exclusions:* under 18, insufficient English language, receiving palliative care, insufficient capacity to give written consent
Interventions	Practice level training in a whole systems approach to self-management support. Practices were trained to use a range of resources: a tool to assess the support needs of patients, guidebooks on self-management, and a web-based directory of local self-management resources Duration of intervention: cannot be defined

Kennedy 2013 *(Continued)*

	Disciplines involved: GP, practice nurse
Outcomes	EQ-5D, COPD-specific quality of life, general health subscale of the Medical Outcomes Survey, healthcare utilisation, self-efficacy, Medical Outcomes Survey (social or role limitations; energy and vitality; psychological well-being; self-care activity), COPD scale, Patient Enablement Questionnaire, enablement, HCCQ
Notes	Dominant component: s elf-manag e ment (investigator's judg e ment)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "we used a wait list comparator group. Using a minimisation procedure based on practice size, area deprivation (the area index of multiple deprivation), and contractual status (contracted either to the National Health Service or to the local primary care trust), we allocated practices 1:1 to intervention or control groups"
Allocation concealment (selection bias)	Low risk	Quote: "research staff recruiting practices are unaware of the next allocation in the sequence at the time of recruitment"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no blinding of patients or personnel. Unclear whether patients were aware of allocation of practice
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "… and with the analyst (DR) blind to practice allocation" Comment: blinding of outcome assessor ensured
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "we did not impute missing follow-up data but used multivariate logistic regression to identify baseline covariates predictive of missing data and included these (disease, age, general health, deprivation index, and home ownership) as covariates"
Selective reporting (reporting bias)	Low risk	Comment: authors reported on a range of outcomes that did not show an effect. All primary outcomes and most secondary outcomes are reported. Primary and secondary outcomes for COPD study population were provided upon request
Recruitment bias	Low risk	Quote: "we intended to recruit patients before allocation, but this proved logistically impractical. Recruitment was through electronic health records rather than by professional invitation, but practitioners could exclude patients after identification" Comment: initial patient selection proceeded via existing disease registers. Recruitment could be influenced only by a request for exclusion of a patient. Proportion of excluded patients comparable between intervention and control
Baseline imbalance between groups	Low risk	Quote: "the two trial arms were well balanced on all variables at the patient level, although practices in the intervention group were o n average slightly smaller"
Loss to follow-up of clusters	Low risk	Quote: "three practices randomised to the intervention group withdrew before data collection, leaving 19 intervention and 22 control practices" Comment: no practice were lost to follow-up after the start of the trial

Kennedy 2013 *(Continued)*

Adequate analysis methods for CRT	Low risk	Quote: "each outcome was subjected to analysis of covariance within a multi - level regression framework. A 2-level mixed model was used to account for clustering of patients within practices"

Kessler 2018

Study characteristics	
Methods	RCT, multi-centre (n = 33), France (12), Germany (8), Italy (6), and Spain (7); follow-up: 12 or 24 months; control group: usual care
Participants	Randomised: 345, I: 172, C: 173 Completed: 265, I: 137, C: 128 Mean age: I: 67.3 years, C: 66.9 years Sex (% male): I: 69.4, C: 69.8 *Inclusion criteria:* COPD patients aged 35 years or older with post-bronchodilator forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio ≤ 70%; FEV_1 < 50% of predicted value; 10 pack-year smoking history or more; ≥ 1 severe exacerbation in the previous year *Major exclusions:* not expected to survive longer than 6 months; cognitive/psychiatric disease; continuous treatment > 10 mg per day prednisone or equivalent longer than 6 weeks; living in a nursing home; unable to read or speak the country language
Interventions	Multi-component home-based COPD disease management intervention, specifically developed for patients with Gold III/IV COPD Intervention components - Patient education (based on “Living Well With COPD”) and motivation by case managers, with the goal of attaining sustainable self-management skills and behavioural changes - Action plan to prevent exacerbations, with decision-making and actions to be taken in case symptoms worsen - Self-monitoring of FEV_1, arterial oxygen saturation measured by pulse oximetry, and heart rate (HR). For patients on long-term oxygen therapy, daily oxygen use and respiration rate (RR) were recorded by the NOWOX in-line monitoring device - Care co-ordination through an e-health platform for early detection of exacerbations by registration of status of well-being, worsening, or alarm - Reference to the investigator for same-day medical assessment and follow-up when confirmed alarm status - During follow-up consultation with physician, every 3 months Duration intervention: 12 or 24 months Disciplines involved: case manager, physician
Outcomes	Primary outcome: total number of all-cause hospital days over 1 year Secondary outcome: COPD-related hospital days, number of moderate to severe exacerbations, healthcare utilisation, death, HADS score, SGRQ, HRQoL, spirometry, ECG, 6MWD, BODE Index, fatal SAE cost-effectiveness
Notes	Dominant component: structured follow-up
Risk of bias	

Kessler 2018 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “patients were allocated to groups in a 1:1 fashion according to a pre-specified randomisation list generated before the study by a partial-minimisation computer algorithm under supervision of the study sponsor”
Allocation concealment (selection bias)	Low risk	Quote: “patients were assigned a randomisation number by study staff at each centre in sequential numerical order through a telephone-based interactive voice response system"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: “for practical reasons, the study was open; neither the patients nor the investigators were blinded to the COPD management strategy”
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “hospitalisations were rigorously and blindly reviewed by the end-point validation committee (EVC) and followed-up with additional enquiries if necessary, ensuring the reliability of the outcomes”; "EVC members were 3 respiratory physicians independent from the sponsor and investigational sites” Comment: primary outcome assessed blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: missing outcome data were greater in control group (34/162) compared to intervention group (20/157). In control group patient death 23 compared to 3 in intervention group. Differences in missing outcome data potentially related to (absence) intervention. In addition, 23 patients in intervention group lost to follow-up due to major protocol violations. Likely that outcomes are biased by loss to follow-up, related to intervention
Selective reporting (reporting bias)	Low risk	Comment: all outcomes pre-defined in protocol paper reported. However in addition, reported outcomes on smoking habits, daily use of LTOT, days to first exacerbation, number of patients who improved on 6MWD
Other bias	Unclear risk	Comment: main conclusions based on PP analysis instead of ITT. Analysis performed with ITT and PP populations. Potentially high risk of attrition bias with outcomes and reasons for missing data related to intervention. Multiple supportive outcomes that were not pre-defined in protocol or trial register. ITT based on population at start of follow-up period, after run-in (5 weeks with intervention), instead of population at randomisation

Khan 2019

Study characteristics	
Methods	Cluster-RCT (30 clusters); follow-up: 6 months
Participants	Eligible: not specified Randomised: 313, I: 159, C: 154 Completed: 288 , I: 147, C: 141 Mean age: I: 48 years, C: 48 years Sex (% male) : I: 77, C: 72

Khan 2019 *(Continued)*

	Inclusion criteria: newly diagnosed COPD given consent to participate in the trial, aged 18 years, currently residing (and expected to continue residing for the next 12 months) in the catchment area of the participating health facility *Major exclusions:* contraindication for trial procedures (e.g. people not fit for 6-minute walk, advanced or complicated cases as per stage IV of National Institute for Health and Care Excellence (NICE)/Global Initiative for Chronic Obstructive Lung Disease (GOLD))
Interventions	Intervention components Overall quality of care, including enhanced screening and diagnosis, standardised prescription, follow-up and adherence, referral linkage with district hospital - 2-day training of staff on screening, diagnosis, maintaining patient record, COPD education, follow-up care, use of desk guides for staff - Patient education using pictorial flipcharts on preventive measures - Smoking cessation support - Provision of free-of-charge inhalers and optimisation of medication Duration intervention: 6 months Disciplines involved: doctor and allied staff
Outcomes	BODE Index (primary outcome), COPD control, smoking status, follow-up adherence. FEV, mMRC, 6MWD (elements of BODE Index), unpublished data
Notes	Dominant component: structured follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the selection of the 30 trial facilities was carried out by listing all 41 eligible facilities in sealed opaque envelopes before shuffling and randomly selecting 30 of them. Then randomisation of the selected facilities (after obtaining district and communal consent) was done by again placing their names into sealed opaque envelopes and shuffling them, before a staff member of the provincial directorate randomly picked 15 envelopes for each treatment arm and opened them
Allocation concealment (selection bias)	Low risk	Quote: "...randomisation of the selected facilities (after obtaining district and communal consent) was done by again placing their names into sealed opaque envelopes and shuffling them, before a staff member of the provincial directorate randomly picked 15 envelopes for each treatment arm and opened them"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "owing to the nature of the trial, it was not possible to blind individual patients or healthcare providers"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "the facility doctor recorded the clinical data (that is, the diagnosis and prescription); 'paramedic' staff recorded basic data (for example, name, age, sex, weight, height, peak expiratory flow rate result, and residential address)" Comment: outcomes assessed by facility staff, who were aware of allocation. Data analyst blinded to allocation

Khan 2019 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: missing outcome data were balanced in numbers across intervention (12/159) and control groups (13/154). Reasons for loss to follow-up are unknown
Selective reporting (reporting bias)	Low risk	Quote: "the three secondary outcomes, which were all added post-protocol..." Comment: outcomes were added post-hoc. All outcomes specified in the protocol paper were reported
Recruitment bias	Low risk	Comment: patients were recruited after clusters were randomised. Patients and personnel were aware of the allocation. Unlikely that this has biased the results, as patients could not choose between facilities (region-bound) and all new COPD cases aged 18 were eligible for participation
Baseline imbalance between groups	Low risk	Comments: mean cluster size was comparable, no large imbalances between groups
Loss to follow-up of clusters	Low risk	Comment: no clusters were lost to follow-up
Adequate analysis methods for CRT	Unclear risk	Quote: "to analyse the data, robust methods (suitable for cluster trials with relatively few clusters per arm) were used. For the continuous primary outcome, a crude analysis was initially carried out by calculating cluster-level outcome values based on the mean of all outcome scores in each cluster. An independent t-test was then used to estimate the treatment effect as the mean difference in the cluster level outcome values between treatment arms (intervention minus control), with the associated 95% CI and P value. To adjust for potentially confounding covariates, a two-stage approach was used. First, a linear regression model was fitted to the individual-level outcome data to adjust for covariates of interest, but excluding the treatment effect. A covariate adjusted difference-residual for each cluster was then calculated from the model by calculating the mean difference between the observed and model predicted outcomes for each cluster. An independent t-test was then used to estimate the covariate-adjusted treatment effect as the mean difference in the cluster-level difference-residuals between treatment arms, with the associated 95% CI and P value"

Ko 2016

Study characteristics	
Methods	RCT, single-centre; follow-up: 12 months; control group: usual care
Participants	Eligible: 230 Randomised: 180, I: 90, C: 90 Completed: 142, I: 73, C: 69 Mean age: I: 75 years, C: 75 years Sex (% male): I: 94, C: 97 *Inclusion criteria:* COPD patients who had been admitted with AECOPD. AECOPD defined as presentation with ≥ 2 major symptoms (increased dyspnoea, increased sputum purulence, increased sputum volume) or 1 major and 1 minor symptom (nasal discharge/congestion, wheeze, sore throat, cough) for ≥ 2 consecutive days

Ko 2016 *(Continued)*

	Major exclusions: age < 40 years; asthma; chronic lung disease other than COPD; very severe medical illness that would affect patient's ability to participate in this study
Interventions	Comprehensive COPD programme Intervention components - Individualised care plan - 1-hour educational session from a respiratory nurse. Education included anatomy and physiology of the respiratory system, pathophysiology of COPD, smoking cessation, technique of using medications, dyspnoea management, nutrition, self-management and exacerbation reduction skills, coping with psychological distress and relaxation techniques - Social and community support - Physiotherapist support for short-course outpatient pulmonary rehabilitation or physical training programme to perform at home - 3-monthly telephone calls by a respiratory nurse over 1 year, and follow-up at a respiratory clinic with a respiratory specialist once every 3 months for 1 year Durtion intervention: 12 months Disciplines involved: respiratory nurse, physiotherapist, respiratory specialist
Outcomes	Hospital re-admission rate at 12 months (primary outcome); hospital days; health-related quality of l ife (SGRQ); lung function (FEV_1% predicted, FVC% predicted, FEV_1/FVC ratio); exercise capacity (6MWD); dyspnoea (m mMRC), mortality
Notes	Dominant component: structural follow-up (author judgement)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a random number generator was used to assign the patient to the intervention or control group. A computer programme (allocation by minimisation) was used to assist the randomisation of subjects..." Comment: computer random number generator used with minimisation of age, sex, length of hospital admission, 6MWD, and predicted FEV_1
Allocation concealment (selection bias)	Unclear risk	Comment: no details on concealment of allocation provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "owing to the nature of the intervention, this was an open study for the patients and therapists" Comment: participants and personnel were not blinded (QoL outcome might be influenced by this)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the research assistant performing the lung function, walking tests and questionnaire tests was neither involved in the delivery of patient care nor aware of the randomisation process"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "analyses were conducted according to the intention-to-treat principle" Comment: missing outcome data were more or less balanced in numbers across intervention (17/90) and control groups (21/90), with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	Comment: published report includes all primary and secondary outcomes that were pre-specified. However additional outcomes such as exacerbations

Ko 2016 *(Continued)*

	(treated with oral steroids or antibiotics), ED visits (obtained from participants and verified with medical record), m MRC, length of stay in hospital for COPD, length of stay for other causes reported on but not mentioned in trial register. No protocol published

Koff 2009

Study characteristics	
Methods	RCT; follow-up 3 months; control group: usual care
Participants	Eligible: 40 Randomised: 40, I: 20, C: 20 Completed: 38, I: 19, C: 19 Mean age: I: 67 years, C: 65 years Sex (% male): I: 45, C: 50 *Inclusion criteria:* clinical diagnosis of COPD, GOLD 3+4, with telephone land line *Exclusion criteria:* active treatment for lung cancer, illiteracy, non-English-speaking, inability to complete 6MWD
Interventions	Integrated self-man a gement education al program me wit h proactive remote disease monitoring - Disease-specific education, by respiratory therapist at enrolment and daily by Health Buddy System (telehealthcare). Education included disease description, medications and their use, nutrition, breathing techniques - Teaching of self-management skills (use of an oximeter and increased awareness of clinical changes/problems). Patients could contact the co-ordinator in case of deterioration - Patients were remotely monitored 5 days per week with the Health Buddy system for changes in symptoms, saturation, 6MWD, and lung function. Study co-ordinator reviewed these results and patients were contacted if they were at high risk for exacerbation, when they started exacerbation management or had contact with respiratory physician/GP Intervention duration: 3 months Disciplines involved: physician, pulmonologist
Outcomes	SGRQ, 6MWD, exacerbations, hospitalisations, ED visits, equipment satisfaction, number of calls
Notes	Dominant component: self-management

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "patients randomly selected their group assignment (by choosing a blinded envelope that contained a group indicator"
Allocation concealment (selection bias)	Low risk	Quote: "patients randomly selected their group assignment (by choosing a blinded envelope that contained a group indicator"

Koff 2009 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "because of the type of intervention, it was not possible to blind the subjects or investigators as to whether they were randomised to the treatment or control arms of the trial"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "primary end-point was collected by the coordinator, and analysed by R.H. Jones" The co-ordinator was also responsible for the intervention and therefore was not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: dropout rates balanced in numbers across groups
Selective reporting (reporting bias)	Low risk	Comment: all outcomes reported

Kruis 2014

Study characteristics	
Methods	Cluster-RCT (40 clusters); follow-up: 24 months; control: usual care; 40 clusters of primary care teams
Participants	Eligible: 22698 Randomised: 1086, I: 554, C: 532 Completed: 810, I: 419, C: 391 Mean age: I: 68 years, C: 68 years Sex (% male): 54, I: 51, C: 57 *Inclusion criteria:* clinical diagnosis of COPD according to GOLD criteria, if possible and necessary (no spirometry data available) verified by available spirometry data or spirometry assessment *Major exclusion criteria:* terminally ill patients, dementia or cognitive impairment, inability to fill in Dutch questionnaires, hard drug or alcohol abuser
Interventions	Two-day training of multi-disciplinary team on all IDM components of intervention before implementation intervention. During training, the team redesigns the care process and defines responsibilities of different caregivers, and is trained in how to use feedback on process and outcome data to implement guideline-driven integrated health care. The team sets up a time-contingent individual practice plan, agreeing on steps to be taken to integrate a COPD IDM programme into daily practice. Practice-tailored feedback reports are provided at baseline and at 6 and 12 months to each team. After 6 and 12 months, a refresher course is provided for all teams simultaneously to enable them to learn from each other's experiences. Intensity of the IDM programme for individual patients depended on health status, personal needs, and preferences Intervention components - Access to patient healthcare provider portal for process and outcome measures - Optimal medication adherence - Proper diagnosis - Motivational interviewing

Kruis 2014 *(Continued)*

	- Smoking cessation - Self-management - Dietary intervention Duration intervention: 12 months Disciplines involved: GP, practice nurse, physiotherapist and dietician, consulting pulmonary physician
Outcomes	CCQ, SGRQ-C, EQ-5D, SF-36, smoking behaviour (guided smoking attempts), IPAQ, SMAS-30, MRC Dyspnoea, number of moderate exacerbations, number of severe exacerbations, level of care integration (PACIC and ACIC), satisfaction with healthcare providers, costs, healthcare utilisation, costs of productivity loss
Notes	Dominant component: self-management Additional comment: practices affiliated to Primary Care Research Network - signed agreement to collaborate in scientific research

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the same blinded researcher randomised matched clusters in pairs by using a computer generated list in four blocks of 10"
Allocation concealment (selection bias)	Low risk	Quote: “the clusters were matched and randomised by a researcher who was blinded to the identity of the practices”
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "because of the nature of the intervention, participating healthcare providers and patients could not be blinded"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "blinded research nurses assessed outcomes to minimise detection bias. Patients were instructed not to report on their type of management to these research nurses"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: missing outcome data was balanced in numbers across intervention (n = 135) and control groups (n = 141), with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	Comment: all outcomes included in the protocol were reported, with the exception of ACIC (assessment of chronic illness care) and level of healthcare providers' satisfaction (intervention group only). Missing of outcomes most probably does not impact the quality of the evidence
Recruitment bias	High risk	Quote: “the GPs checked the selected patients against the formal inclusion and exclusion criteria before the recruitment procedure started” Comment: study flowchart suggests that patients were recruited after the cluster had been randomised
Baseline imbalance between groups	Low risk	Comment: most baseline characteristics did not differ significantly between intervention group and usual care group, although participants in the intervention group were significantly less likely to be male and had significantly higher functional CCQ scores

Kruis 2014 *(Continued)*

Loss to follow-up of clusters	Unclear risk	Comment: insufficient information provided on practice level
Adequate analysis methods for CRT	Low risk	Quote: “we used linear mixed model analyses to assess differences within and between groups for all continuous outcomes, correcting for baseline scores, age, sex, proportion of patients with MRC score above 2, and clustering of patients per general practice. We used baseline scores as a dependent variable, the cluster was represented by a random effect, and the within patient covariance structure was unstructured. For dichotomous outcomes, we used logistic link generalised linear mixed models for repeated measurements to analyse differences within and between groups at all time points, correcting for the same covariates"

Lenferink 2019

Study characteristics	
Methods	RCT, multi-centre (Netherlands (n = 2), Australia (n = 3)); follow-up: 12 months; control group: usual care
Participants	Eligible: 226 Randomised: 201, I: 102, C: 99 Completed: 169, I: 85, C: 84 Mean age: I: 69 years, C: 68 years Sex (% male): I: 65, C: 63 *Inclusion criteria:* diagnosis of COPD (GOLD criteria) with 1 to 5 highly prevalent comorbidities (i.e. ischaemic heart disease (history of myocardial infarction, angina pectoris)); heart failure; diabetes mellitus; active symptoms of anxiety and/or depression (≥ 11 Hospital Anxiety and Depression Scale (HADS) and/or anxiety or depression symptoms treated at the time of inclusion); ≥ 3 COPD exacerbations,defined as respiratory problems that required a course of oral corticosteroids/antibiotics; ≥ 1 hospitalisation for respiratory problems in the 2 years preceding study entry; ≥ 40 years of age *Major exclusions:* terminal cancer, end stage of COPD or another serious disease with expected survival < 12 months; other serious lung disease (e.g. α1-antitrypsin deficiency; interstitial lung disease); cognitive impairment (MMSE < 24)
Interventions	Patient-tailored multi-disease exacerbation action plan Intervention components - Depending on comorbidities 2 to 3 1- to 2-hour group sessions (1 to 2 hours); 2 times individual hospital-based self-management session (1 hour) by trained case manager (respiratory nurse) and supported by cardiac, mental health, and/or diabetes nurses (first month) - Group sessions including knowledge regarding COPD and comorbidities; symptom recognition and monitoring; self-treatment (action plan linked to diary); breathing and relaxation exercises; extra session on how to check (and regulate) (Dutch patients only); blood glucose levels when necessary (diabetes patients); dietary and lifestyle behaviours - Individual session: individualised action plan set for COPD and each comorbid symptom with colour coding, what are my “usual” symptoms card; diary training; exacerbation action plan training; mastery of skills (e.g. correct inhaler techniques; early recognition of exacerbations, self-initiating correct and proper actions) - Follow-up phone calls by case manager to reinforce self-management skills (Weeks 8, 20, 36) Duration intervention: 9 months

Lenferink 2019 *(Continued)*

	Disciplines involved: respiratory nurse (case manager); cardiac, mental health, and/or diabetes nurse
Outcomes	Total number of COPD exacerbation days/patient/year (primary outcome); number of COPD exacerbations/patient/year; duration per COPD exacerbation/patient/year; severity of COPD exacerbation day (symptom diary); FEV_1, FEV_6, FVC; CAT; mMRC; health-related QoL(EQ-5D; VAS); Chronic Respiratory Diesease Questionnaire (CRQ); Fatigue (ICFS); Anxiety and Depression (HADS); Confidence and Competence (CSES, CRQ mastery domain); self-management behaviour and knowledge (PIH); cost and healthcare utilisation; healthcare utilisation for COPD, all-cause respiratory, cardiac, and diabetes; GP visits; specialist consultations and other services; number of hospitalisations; number of in-hospital days; travel; costs of usual care; adherence qualitative outcomes
Notes	Dominant component: self-management with exacerbation plan

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “after baseline measurements, patients were allocated to self-management or UC by an independent research assistant who was masked to treatment assignment and randomisation schedule, using a computerised minimisation program. Allocation was stratified per hospital for smoking status, modified Medical Research Council dyspnoea (mMRC) score, number of comorbidities, and being on a waiting list for pulmonary rehabilitation”
Allocation concealment (selection bias)	Low risk	Comment: concealment of allocation after baseline measurement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: “blinding of patients and personnel to treatment group was not possible. Wherever possible, though, assessors of outcomes were blinded to treatment group”
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: “wherever possible, though, assessors of outcomes were blinded to treatment group" Comment: COPD exacerbation data (primary outcome) collected from symptom diary. Outcome self-reported, hence outcomes likely to be biased by unb l inding of assessment of primary outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: “if patients have less than three months of complete diary data over the course of the year they will be excluded from the analysis of the daily diaries”; “analyses were conducted on an intention-to-treat basis” Comment: missing outcome data were more or less balanced in numbers across intervention (17/102) and control groups (15/99), with similar reasons for missing data across groups
Selective reporting (reporting bias)	Unclear risk	Comment: all primary and secondary outcomes specified in protocol paper have been reported on. In addition, investigators report on analysis of COPD exacerbations and hospitalisations. Data on hospitalisation in protocol collected only for cost-effectiveness
Other bias	Unclear risk	Comment: timely recognition of exacerbations through symptom diaries and tailored action plan - part of intervention. So can be expected that number of reported exacerbations would be higher in intervention group than in usual care group (missed actual exacerbations). Outcomes may not present actual benefit of intervention

Lilholt 2017

Study characteristics	
Methods	Cluster-RCT (13 clusters per study arm); follow-up: 12 months; control group: usual care
Participants	Eligible: not reported Randomised: 1125, I: 578, C: 647 Completed: 574, I: 258, C: 316 Mean age: I: 70 years, C: 70 years Sex (% male): I: 48; C: 43 *Inclusion criteria:* primary diagnosis of COPD based on spirometry, Medical Research Dyspnoea Council Scale (MRC) score ≥ 3 or modified Medical Research Dyspnoea Council Scale (mMRC) score ≥2 or COPD Assessment Test score ≥ 10, or ≥ 2 exacerbations during past 12 months; telephone connection; permanent residence; enrolled with participating GP; speaking Danish or living with Danish-speaking relatives for support in use of telehealthcare system *Major exclusions:* cognitive impairment; no phone line or GSM coverage; inability to understand Danish to the extent allowing completion of study questionnaires
Interventions	Telehealthcare in addition to standard treatment and care Intervention components - Self-measurement of blood pressure, pulse, blood oxygen saturation, and weight - Wireless transmission of vital health data to web portal, accessible to patients, relatives, and trained municipality healthcare personnel - Monitoring of vital health data by trained municipality healthcare personnel (i.e. community nurses) based on individually determined threshold values. Monitoring frequency daily (first 2 weeks), once or twice weekly - Contact by healthcare personnel with adverse changes in patient's vital health values and responses (1-way communication) - Contact by healthcare personnel if measurements were not carried out as agreed or were not received as expected - Follow-up visit 3 to 4 weeks to review threshold values and tablet use Duration intervention: 12 months Disciplines involved: GP, healthcare personnel (i.e. community nurse)
Outcomes	Health-related QoL (SF-36) (primary outcome); mortality; diastolic blood pressure, systolic blood pressure, pulse, oxygen saturation, and weight; cost-effectiveness ratio (ICER); cost per QALY
Notes	Dominant component: self-management (investigator judgement)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "the municipality districts were matched 1:1 by the following variables: the total population size of the districts, the proportion of people with a higher education, the sum of the district's total income, unemployment and the estimated number of patients with COPD"; "the districts were distributed randomly by a blinded volunteer with no relation to the trial, who performed the randomisation by throwing a dice"

Lilholt 2017 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: “the identification and recruitment of patients took place prior to random allocation of clusters in order to minimise biased recruitment" Comment: use of sealed envelope method by person not affiliated with the trial
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: nature of intervention does not allow blinding. Primary outcome as subjective self-reported measure likely to have biased outcomes
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: primary outcome subjective measure based on patient self-report. Highly likely that knowledge of study allocation could have biased outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: “reasons for withdrawing from the TeleCare North trial included complicated technology, concomitant health problems, not interested, leaving local geographical area, does not trust the equipment or disappointed over not being a part of the telehealth intervention” Comment: large proportion loss to follow-up. 210/579 for intervention and 177/647 for control. Reason for loss to follow-up for an intervention related to intervention (n = 101). Attrition rate at 12 months 53%, 110 interventions, 154 controls; patients had incomplete data. Analysis based on imputed data
Selective reporting (reporting bias)	High risk	Quote: “the primary outcome for theme 1 (effectiveness) is the change in health-related quality of life (SF-36) at the individual level from baseline to follow-up at 12 months” (protocol paper)"; “the primary outcome measure was the adjusted mean differences in PCS summary scores between treatment groups at 12 month follow-up" Comment: change in primary outcome with PCS as a subscore within SF-36. No reason for change provided. No data on mortality
Recruitment bias	Low risk	Quote: “the identification and recruitment of patients took place prior to random allocation of clusters” Comment: in protocol paper: “the randomisation will not be undertaken until after all general practitioners have sent their lists of patients eligible for inclusion from their practice, and after all patients have given written consent to participation and completed baseline physical measurements and questionnaires”
Baseline imbalance between groups	Low risk	Comment: investigators minimised baseline imbalances through stratification on total population size of districts, proportion of people with a higher education, sum of district’s total income, unemployment and estimated number of patients with COPD. Baseline comparison provided. No large imbalances between groups
Loss to follow-up of clusters	Low risk	Comment: no clusters lost to follow-up
Adequate analysis methods for CRT	Low risk	Quote: “the clusters were assumed to be represented as random effects, and the models had robust covariance structures. ICC estimates of patient-reported outcome variables were calculated for measurement of the variability within and across the clusters. The subgroup analyses applied the same statistical models and covariates as above, but with added treatment-by-covariate interaction for each subgroup” Comment: appropriate analysis applied to take clustering into account

Littlejohns 1991

Study characteristics	
Methods	RCT; follow-up: 12 months; control group: usual care
Participants	Eligible: 166 Randomised: 152; I: 73, C: 79 Completed (12 months): 133, I: 68, C: 65 Mean age: I: 63 years, C: 63 years Sex (% male): I: 67, C: 63 *Inclusion criteria:* COPD diagnosed by spirometry, according to guidelines; age 30 to 75 years; pre-bronchial FEV_1% < 60%; stable state; no change in medication for ≥ 6 weeks before recruitment; no other major disease
Interventions	Intervention group received care from the respiratory health worker while continuing with routine outpatient appointments during 12 months. Health worker provided - Health education directed at the patient and the primary care team - Monitoring of treatment compliance and optimising treatment by ensuring correct inhalation techniques and supervision of domiciliary oxygen - Monitoring of the results of spirometry and of patients' symptoms to enable acute exacerbations and worsening heart failure to be detected and treated early - Liaison between GP and hospital-based services (including domiciliary physiotherapy services and social services) Intervention duration: 12 months Disciplines involved: GP, respiratory health worker
Outcomes	Mortality, spirometry, 6MWD, step test, MRC chronic bronchitis questionnaire, HADS, SIP, hospital admissions, drug prescriptions, visits to GP or clinic, satisfaction
Notes	Dominant component: structured follow-up with respiratory health worker

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "random numbers were generated by tables in permuted blocks of four, stratified by age and sex"
Allocation concealment (selection bias)	Low risk	Quote: "the groups to which successive patients were to be allocated were noted in sealed, numbered envelopes, which were kept centrally"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "the physician was aware which group the patient was in"
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: no information provided

Littlejohns 1991 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: dropout rates comparable between groups
Selective reporting (reporting bias)	High risk	Comment: outcomes on MRC chronic bronchitis questionnaire not reported

Lou 2015

Study characteristics	
Methods	Cluster- RCT; follow-up: 4 years; control: usual care; 14 healthcare centres in rural areas of Xuzhou City, China
Participants	Eligible: 8217 Randomised: 8171, I: 4172, C: 3999 Completed: 6221, I: 3418, C: 2803 Mean age: I: 62 years, C: 61 years Sex (% male): I: 48, C: 48 *Inclusion criteria:* clinical diagnosis of COPD according to GOLD criteria, verified by spirometry assessment *Major exclusion criteria:* presence of fever, active tuberculosis, changes in radiographic images or medication in the 4 weeks immediately preceding recruitment, primary diagnosis of asthma or obvious bronchiectasis, cystic fibrosis, interstitial lung disease, previous lung volume reduction surgery, lung transplantation, pneumonectomy, uncontrolled or serious conditions that could potentially affect spirometry tests, refusal to fill out psychological questionnaires
Interventions	Prior to implementation, health management intervention 2-day training of GP. Training components included general information on COPD, pathogenesis, risk factors, clinical manifestations, clinical assessment, exacerbations, stable stages of treatment and rehabilitation of COPD, providing smoking cessation support, self-management skills Intervention components - Individual health management plan (based on baseline measurements) - Attendance at educational lecture along with caregiver (every 2 weeks, 40 to 60 minutes per session): total 48 lectures (information on COPD, observation of inhaler techniques, medication, hospitalisation, smoking cessation, vaccination, exercise encouragement, rehabilitation, hand hygiene) - Psychological counselling - Face-to-face follow-up visit (every 2 weeks) on treatment compliance: delivered by GP - Monthly report by GP on patient condition for professional team (pulmonologist, psychiatrist, rehabilitation specialist, nutritionist, respiratory nurse), which provides feedback to GP on focus of action and supervises quality of care - Meeting between professionals (every 2 months) Duration intervention: 48 months

Lou 2015 *(Continued)*

	Disciplines involved: GP, pulmonologist, psychiatrist, rehabilitation specialist, nutritionist, respiratory nurse
Outcomes	BODE index, FEV_1% predicted, mMRC D yspnoea Scale, 6MWD, BMI, COPD knowledge, COPD-related deaths, HADS, number of hospital admissions, number of ED visits, change in medication regimen
Notes	Dominant component: e ducation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: “centers with experience and those without were then randomly allocated separately into the health management and control groups…” Comment: insufficient detail on randomisation procedure
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient detail on allocation procedure; additional information sought but not received
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: insufficient detail provided on blinding procedure; given nature of the intervention, participants and treating therapist not likely to have been blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not enough information provided to determine whether assessor was blinded to group allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: “reasons for dropping out after randomisation were refusal to continue participation (25 subjects in the management group and 21 in the control group), lost to follow-up (19 subjects in the management group and 32 in the control group), and death (610 subjects in the management group and 946 in the control group): Comment: statistically significant larger dropout rate in control group (1217) compared to intervention group (779). Reasons for dropout in control group were death, inability to perform walking test, and incomplete lung function test
Selective reporting (reporting bias)	Low risk	Comment: study protocol in not available; published reports include all expected outcomes that were pre-specified
Recruitment bias	Unclear risk	Comment: insufficient detail on whether people involved in recruitment knew about allocation. Additional information sought but not received
Baseline imbalance between groups	Low risk	Quote: "health-care centers were classified into 2 groups: those with previous experience with health management counseling and those without" Comment: healthcare cent r es were stratified on experience to prevent baseline imbalance. No significant difference s between groups on healthcare cent r e level
Loss to follow-up of clusters	Low risk	Comment: no clusters were lost to follow-up
Adequate analysis methods for CRT	High risk	Comment: inadequate analysis for dichotomous outcomes, not accounting for possible clustering effects

Mendes 2010

Study characteristics	
Methods	RCT; follow-up 12 weeks; 2 intervention groups (at-home PR vs outpatient PR); 1 control group: usual care
Participants	Eligible: 117 Randomised: 117 (intervention I: 42, intervention II: 46, control: 29) Analysed: 85 (intervention group I: 33, intervention II: 23, control: 29) Mean age: intervention I: 66 years, intervention II: 71, control: 71 Sex (% male): intervention I: 82, intervention II: 83, control: 66 *Inclusion criteria:* diagnosis of COPD according to GOLD, stable at inclusion *Major exclusions:* hospitalisation or COPD instability; presence of neuromuscular disease, associated respiratory disease, orthopaedic or neurological disease that affected gait; recent impairment due to comorbidities such as myocardial infarction, heart failure, stroke, or neoplasm; prior pneumonectomy or other thoracic surgery
Interventions	Home - based or outpatient self-monitored pulmonary rehabilitation program me - Both intervention groups received 1 session of education about COPD, treatment and relevance of PR - Both intervention groups trained 3 mornings a week for 3 months, with aerobic and strengthening exercises. Patients in the outpatient clinic trained under supervision; patients who trained at home were instructed in the clinic and received support through telephone calls Intervention duration: 3 months Disciplines involved: physiotherapist, pulmonologist
Outcomes	6MWD, MRC, FEV_1, BMI, all included in BODE index (body mass, obstruction, dyspnoea, exercise tolerance)
Notes	Dominant component: exercise

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomised electronically by a computer"
Allocation concealment (selection bias)	High risk	Comment: distribution of patients was unequal: 42 in at-home group, 46 in outpatient group vs 29 in control group
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: participants and treating therapists not likely to have been blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "two duly trained health care professionals were responsible for the evaluations, which were performed by the same evaluators for all patients"

Mendes 2010 *(Continued)*

		Comment: not clear whether these professionals were blinded to group allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "19 out of 46 of outpatient intervention group were lost to follow up, compared to 7 out of 42" Comment: reasons for missing outcome data likely to be related to true outcome, with imbalance in quantities of missing data
Selective reporting (reporting bias)	Low risk	Comment: study protocol is not available, but it is clear that published reports include all expected outcomes, including those that were pre-specified

Öztürk 2020

Study characteristics	
Methods	RCT; follow-up: 3 months; control group: usual care
Participants	Eligible: 80 (consecutive inclusion) Randomised: 80, I: 40, C: 40 Completed: 63, I: 31, C: 30 Mean age: I: 65 years, C: 61 years Sex (% male): I: 94, C: 83 *Inclusion criteria:* aged 45 to 75 years with moderate and/or severe COPD *Major exclusion criteria for patients:* psychiatric, neurological, muscular, or decompensated chronic disease (congestive heart failure, chronic renal insufficiency, diabetes mellitus), mild COPD, respiratory disease other than COPD, acute exacerbation of COPD, exacerbation of COPD in the last 1 month
Interventions	Structure d self-management educational programme provided by specified education team Intervention components - 1 group educational session on activity and nutrition training (5 or fewer patients) - Structural follow-up by a chest disease specialist every 2 weeks, using motivational sentences and action plans - Psychological assessment by a psychologist, on coping with chronic illness, leisure time, redirect to mental health support unit Duration intervention: 12 weeks Disciplines involved: chest disease specialist, physiotherapist, psychologist, dietician
Outcomes	CAT, SGRQ, SF-36, HADS, mMRC
Notes	Dominant component: self-management
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

Öztürk 2020 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "by using the random number table, 40 patients each were assigned to the self-management training (case) and standard care (control) groups"
Allocation concealment (selection bias)	Unclear risk	Comment: not enough detail provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no details provided; considering the nature of the study, unlikely that participants and personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "a chest physician interviewed all included patients, and pulmonary function test, short form-36 (SF-36), St George's respiratory questionnaire (SGRQ), and modified British Medical Research Council (mMRC) dyspnea scale were performed" Comment: no details provided; outcome assessors were the same personnel as those delivering the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "9 from the case and 10 from the control groups did not participate in the post-training evaluation; therefore, 31 case and 30 control patients were included in the study" Comment: loss to follow-up was balanced between groups; reason for loss to follow-up was unclear but occurred prior to intervention period; therefore unlikely to be related to the intervention
Selective reporting (reporting bias)	Unclear risk	Quote: "in our study, we also found no significant differences between the two groups in terms of mortality and hospital readmission rates after one year" Comment: n o trial registration or protocol paper available; mortality and hospital admission rates not defined as outcomes in methods section of the paper. Reported only in the discussion

Rea 2004

Study characteristics	
Methods	Cluster RCT; follow-up: 12 months; control: conventional care
Participants	Eligible: 158 Randomised: 135; I: 83, C: 52 Completed: 117 Mean age of both groups: 68 years Sex (% male) of both groups: 41.5 *Inclusion criteria:* COPD diagnosed by ICD-9-CM codes and GP records for a clinical diagnosis of moderate to severe COPD *Major exclusion criteria for patients:* chronic asthma, bronchiectasis, comorbidity more significant than COPD, unable to give informed consent, prognosis < 12 months, long-term oxygen therapy or too unwell, deceased

Rea 2004 *(Continued)*

	Major exclusion criteria GP: no longer enrolled with participating GP practice or moved out of area, unable to contact patient, insufficient practice nurse resource
Interventions	Chronic disease management programme was implemented including - An action plan, which was implemented by patient's own GP and practice nurse, with advice from respiratory nurse and specialist physician. The plan comprised a timetable for regular maintenance checks and achievable goals set for lifestyle changes - Patients visited the nurse monthly, the GP 3-monthly and at other times if worsening symptoms demanded more visits - Patients received education about smoking cessation, medication. Annual influenza vaccination and pulmonary rehabilitation were recommended Intervention duration: 12 months Disciplines involved: GP, nurse, pulmonologist
Outcomes	Health status, SF-36, CRQ, shuttle walk test, spirometry, hospital admissions, medication, courses of oral steroids, courses of antibiotics, smoking cessation Randomisation at cluster level, analysis at patient level
Notes	Dominant component: self-management/action plan and structured follow-up by GP/nurse

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "practices were randomised, using a set of computer-generated numbers"
Allocation concealment (selection bias)	Unclear risk	Comment: no information available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: participants and healthcare providers not likely to have been blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: healthcare providers involved in the programme administered outcome measurements at visit
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: missing outcome data balanced between groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	Comment: all outcomes reported
Recruitment bias	Low risk	Quote: "written information about the trial was provided to patients and consent was obtained before patients knew whether they belonged to an intervention or control practice"
Baseline imbalance between groups	High risk	Comment: no stratified or pair-matched randomisation was used, resulting in baseline imbalance of 99 eligible patients in the intervention group and 59 patients in the control group

Rea 2004 *(Continued)*

Loss to follow-up of clusters	High risk	Quote: "after randomisation, two practices declined to participate, and in three, changes of either GP's or practice nurses prevented participation before enrolment had begun"
Adequate analysis methods for CRT	High risk	Comment: inadequate methods of analysis: randomisation done at level of GP practice, analysis performed at level of patients

Rice 2010

Study characteristics	
Methods	RCT; follow-up: 12 months; control: single intervention (1 page of information and telephone number)
Participants	Eligible: 743 Randomised: 743, I: 372, C: 371 Completed: 743, I: 323, C: 336 Mean age: I: 69 years, C: 71 years Sex (% male): I: 98, C: 98 *Inclusion criteria:* COPD diagnosed by spirometry; high risk for hospitalisation as predicted by 1 or more of the following during previous year; hospital admission or ED visit for COPD; long-term home oxygen use or course of systemic corticosteroids for COPD *Major exclusion criteria:* any condition that might preclude effective participation in the study or that would reduce life expectancy to less than a year; no access to a telephone
Interventions	Chronic disease management programme of 12 months, including - Group session (1-1, 5-hour): general information about COPD, medication, smoking cessation, vaccinations, and exercise - All patients received an individualised written action plan including prescriptions for prednisone and antibiotics with contact information for a case manager. Participants were in possession of action plan medications at all times and were to refill prescriptions immediately upon initiating the action plan - Case manager made monthly telephone calls Intervention duration: 12 months Disciplines involved: case manager, pharmacist
Outcomes	ED and hospital admissions related to COPD, SGRQ, mortality, number of telephone contacts
Notes	Dominant component: self-management/action plan

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "we assigned subjects in equal proportions to each of the two treatment arms by permuted Block randomisation"
Allocation concealment (selection bias)	Unclear risk	Comment: information not available

Rice 2010 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: participants and treating therapists not likely to have been blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "blinded pulmonologists independently reviewed all discharge summaries and ED reports and assigned a primary cause for each"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all outcome data reported; concordance between outcome observers was tested in subsets and was 96.5%
Selective reporting (reporting bias)	Low risk	Comment: no missing outcome data

Rose 2017

Study characteristics	
Methods	RCT, multi-centre (n = 2); follow-up: 12 months; control group: usual care
Participants	Eligible: 780 Randomised: 475, I: 237, C: 238 Completed: 398, I: 207, C: 191 Mean age: I: 71 years, C: 71 years Sex (% male): I: 44; C: 50 *Inclusion criteria:* COPD diagnosis (GOLD criteria) and published Canadian reference values confirmed by a respirologist or internist; 50 years of age or older; 1 of more ED visits or hospital admissions for COPD exacerbation in previous 12 months; 2 or more prognostically important COPD-associated comorbidities (as defined by GOLD and Canadian Thoracic Society Guidelines) identified via medical record screening *Major exclusions:* primary diagnosis of asthma; terminal diagnosis; dementia; uncontrolled psychiatric illness; inability to understand English; no telephone access; inability to attend follow-up; resident in a long-term care facility; enrolled in provincial tele-home monitoring programme; no family physician
Interventions	Multi-component, case manager-led intervention Intervention components - Trained case manager delivered 40-minute standardised educational session based on Living Well With COPD during study enrolment - Individualised care and action plans for COPD exacerbation recognition, self-management, and management of comorbidities - Case manager-initiated telephone consultations (12 weekly, monthly for subsequent 9 months; 21 sessions) comprising standardised reinforcement/motivational interviewing focused on health behaviours; action plan teach-back sessions; assessment of symptoms/symptom monitoring, problems and problem solving strategies - Ongoing case manager communication with family physicians and with hospital specialists including respirologists - Priority access to ambulatory outpatient clinics Duration intervention: 9 months

Rose 2017 *(Continued)*

	Disciplines involved: case manager, family physician, hospital specialist such as respirologist
Outcomes	Number of ED visits at 1 year after randomisation (primary outcome); time to first ED presentation; number of hospital admissions and number of hospitalised days at 1 year; mortality; BODE (body mass index, airflow obstruction, dyspnoea, and exercise capacity) index; health-related QoL (EQ-5D-3L); disease-specific QoL (SGRQ); Anxiety and Depression Scale (HADS), COPD Self-Efficacy Scale (SES), Client Satisfaction Questionnaire-8; Caregiver Impact Scale; adherence to chronic disease management measures; smoking cessation and vaccination status
Notes	Dominant component: case management (investigator's judgement)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomisation was performed according to a centralised, computer generated 1:1 randomisation schedule stratified by study site"
Allocation concealment (selection bias)	Unclear risk	Comment: no details on concealment of allocation provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "because of the nature of the intervention and co-location of research staff within the respiratory clinics, healthcare providers, patients and outcome assessors were not blinded, though treating respirologists were not informed of study allocation"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "outcome assessors were not blinded" Comment: unlikely to affect primary outcome (number of ED visits) but may affect some secondary outcomes (e.g. self-reported quality of life, HADS). Analysis performed by an independent statistician. Not explicitly stated but probably blinded to study allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "intention-to-treat analysis according to a pre-specified analysis plan" Comment: larger dropout in control group due to death; may by related to intervention but unlikely to have influenced outcomes
Selective reporting (reporting bias)	Low risk	Quote: "analysis according to a pre-specified analysis plan" Comment: all pre-specified outcomes are reported, except satisfaction with programme and caregiver impact. Reason provided by study authors is missing responses

Sanchez-Nieto 2016

Study characteristics

Methods	RCT; multi-centre (n = 2); follow-up: 12 months; control: usual care
Participants	Eligible: 124 Randomised: 96, I: 54, C: 45 Completed: 85, I: 47, C: 38 Mean age: I: 69 years, C: 68 years

Sanchez-Nieto 2016 *(Continued)*

	Sex (% male): I: 6, C: 11 *Inclusion criteria:* clinical stability (at least in the 3 months before randomisation, with no change in medication or usual symptoms); active smoker or prior history of smoking of ≥ 10 pack-years; post-bronchodilator FEV_1/FVC ratio 70%; normal cognitive status to read and understand written texts and receive training in inhalation techniques or self-care education sessions; physical status that allows for regular walking or exercise; no diagnosis of asthma, advanced heart failure, unstable ischaemic heart disease, terminal disease, dementia, or uncontrolled psychiatric disorders; ability to read texts; no participation in any pulmonary rehabilitation programme in previous year *Major exclusion criteria:* none reported (included in inclusion criteria)
Interventions	Self-management programme consisting of several components - Education: group education session on main characteristics COPD, specially designed for the SMP-COPD programme - Individual training session on inhalation techniques - Written action plan with colour-coded treatment instructions including recommendations for physical exercise, exacerbations - Visit by respiratory nurse to check correct use of treatment instructions and inhalation techniques. Duration intervention: 12 weeks Disciplines involved: nurse, physiotherapist, medical specialist in respiratory medicine
Outcomes	Hospitalisation for COPD exacerbation (primary outcome), days at risk (primary outcome), A&E visits for COPD exacerbation, length of stay, antibiotic or glucocorticoid treatment, all-cause mortality
Notes	Dominant component: self-management

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “simple randomisation was carried out separately at each site by means of a list of computer-generated random numbers, assigning the patients to two groups”
Allocation concealment (selection bias)	Low risk	Quote: “simple randomisation was carried out separately at each site by means of a list of computer-generated random numbers, assigning the patients to two groups”
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: due to the nature of the intervention, blinding of personnel and participants was not possible
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “because double-blinding was not possible, an independent evaluator, who did not know the patients’ group assignments, was responsible for evaluating the outcome variables”
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: missing data on outcomes and reasons for loss to follow-up are balanced between groups
Selective reporting (reporting bias)	Low risk	Comment: study protocol in not available; published reports include all expected outcomes that were pre-specified

Silver 2017

Study characteristics	
Methods	RCT; follow-up:6 months, control group: usual care
Participants	Eligible: 574 Randomised: 428, I: 214, C: 214 Completed: 423, I: 211, C: 212 Mean age: I: 50 years, C: 57 years Sex (% male): I: 44, C: 50 *Inclusion criteria:* between 18 and 65 years of age; diagnosis of COPD based on $FEV_1/FVC < 0.7$ or FEV_1 < 80% predicted (performed before bronchodilator administration); at high risk for repeat hospitalisations or emergency department visits as predicted by hospital admission or emergency department visit in previous 12 months for a COPD exacerbation; long-term home use of oxygen or treatment with a course of systemic corticosteroids in preceding 12 months *Major exclusions:* not expected to survive the hospitalisation; metastatic cancer, bed-bound; non-English-speaking; inability to provide informed consent
Interventions	Respiratory therapist disease management transition team Intervention components - 1-hour educational in-service by trained respiratory therapist case manager. Education included general information about COPD, direct observation of inhaler techniques, review and adjustment of outpatient COPD medications, smoking cessation counselling, recommendations concerning influenza and pneumococcal vaccinations, encouragement of regular exercise, instruction in hand hygiene - Discussion with case manager and treating physician on need for pharmacotherapy - Verification of COPD diagnosis with bedside spirometry if necessary - Individualised written action plan - Scheduled follow-up telephone calls with case manager to address specific patient needs, concerns, and questions Duration intervention: 6 months Disciplines involved: respiratory therapist (case manager), treating physician
Outcomes	Combined number of non-hospitalised ED visits and hospital admissions for a COPD exacerbation (primary outcome); ED visits for COPD exacerbations; hospital admissions for COPD exacerbations; ED visits for other causes; hospital admissions for other causes; ICU days; hospital days; all-cause mortality
Notes	Dominant component: s tructured follow-up with c ase manager (investigator 's judgement)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: “study subjects were randomly assigned to treatment groups in a 1:1 ratio using blocked randomisation (n = 4/block)
Allocation concealment (selection bias)	Unclear risk	Comment: n o details on concealment of allocation provided

Silver 2017 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "we cannot exclude some form of bias in terms of the outcome assessment because this was not a blinded study" Comment: outcomes less subjective; however knowledge of allocation may have influenced participants' behaviour with regard to ED visit and other outcomes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: study not blinded; however primary outcomes extracted from automated medical records and bi-monthly telephone calls by study co-ordinator to determine if participants had recent hospital or ED visits and medical indications for admission/ED visit. Outcome less subjective and based mostly on EHR, so unlikely to have biased results
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: quantity of missing data minimum (3/214 intervention and 2/214 control) and balanced between groups
Selective reporting (reporting bias)	Low risk	Comment: all pre-defined outcomes reported on. Reported on more than specified in trial register. For all outcomes, also reported on (1) number of participants with ≥ 1 COPD ED visit/non-COPD ED visit/hospital admission; (2) median (IQR) per subject COPD ED visit/non-COPD ED visit/hospital admission; (3) number of participants with ≥ 1 COPD ED visit/non-COPD ED visit/hospital admission

Smith 1999

Study characteristics	
Methods	RCT; follow-up: 12 months; control: usual care
Participants	Eligible: 105 Randomised: 96, I: 48, I: 48 Completed: 36 (data completed only for intervention group) Mean age: I: 70 years, C: 70 years *Major inclusion criteria:* COPD diagnosis according to guidelines, age > 40 years, $FEV_1/FVC < 60\%$, stable state, carer involved in management, able to speak and read English and give written consent *Major exclusion criterion:* no other active illness
Interventions	Intervention of 12 months including - Follow-up planning for inpatients and outpatients with a nurse in shared care approach with GP and medical staff. Nurses discussed with GP goals for discharge and needs and facilitated involvement of domiciliary service. Goals were inserted into patient notes - During 12 months every 2 to 4 weeks, there was a home visit including education, spirometry, optimal medication, exacerbation management, smoking cessation, and fitness advice Included HCPs: nurse, GP, social worker, hospital medical officer
Outcomes	COOP (HRQoL), mortality, hospital admissions, lung function
Notes	Dominant component: structured follow-up with nurse/GP

Smith 1999 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomised as they were enrolled, following discharge from hospital (..), into the HBNI or control groups from two lists of randomly computer generated numbers"
Allocation concealment (selection bias)	Low risk	Quote: "patients were randomised as they were enrolled, following discharge from hospital"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "this study was unblinded"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "this study was unblinded"
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "attempts to perform questionnaires in the control subjects were unsuccessful due to a combination of (I) these subjects perceived no immediate benefit of the trial; and (ii) the burden of participating in a study" Comment: no outcomes reported in control group
Selective reporting (reporting bias)	High risk	Comment: 1 or more primary outcomes in the review (COOP, spirometry) are reported incompletely, so they cannot be entered into a meta-analysis

Sridhar 2008

Study characteristics	
Methods	RCT; 104 weeks; control group: usual care
Participants	Eligible: 297 Randomised: 122, I: 61, C: 61 Completed: 104, I: 55, C: 49 Mean age both groups: 70 years Sex (% male): both groups: 49 *Inclusion criteria:* diagnosis of COPD and admitted between 2000 and 2004 with acute exacerbation of COPD *Exclusion criteria:* significant comorbidity (severe heart disease or cancer, or any condition that would preclude participation in physical therapy component of PR programme)
Interventions	Nurse-led intermediate care package - Patients started with PR programme for 4 weeks, including general education about disease and treatment, and physical training programme - After 4 weeks, patients received a home visit, including a written COPD action plan for exacerbations. GPs provided medication

Sridhar 2008 *(Continued)*

	- Patients received monthly telephone calls and a home visit every 3 months until 24 months' follow-up. Calls reinforced advice regarding treatments, smoking cessation, need to continue exercise therapy; reinforced self-management education Intervention duration: 24 months Disciplines involved: GP, nurse, physiotherapist
Outcomes	CRQ, mortality, exacerbations, hospital admissions, lung function
Notes	Dominant component: exercise and action plan

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "122 patients were suitable and were recruited and randomised by the use of random numbers to the intervention and control group"
Allocation concealment (selection bias)	Unclear risk	Comment: n o information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: p articipants and treating therapists not likely to have been blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: n o information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: d ropout rates comparable between groups
Selective reporting (reporting bias)	Low risk	Comment: study protocol is not available, but it is clear that published reports include all expected outcomes, including those that were pre-specified

Strijbos 1996

Study characteristics

Methods	RCT; 18 months; intervention group 1: hospital-based PR, intervention group 2: home-based PR, control group: usual care
Participants	Eligible: 50 Randomised: 50, I group 1: 18, I group 2: 17, C: 15 Completed: 41, I group 1: 15, I group 2: 15, C: 15 Mean age: I 1: 61 years, I 2: 60 years, C: 63 Sex (% male): I 1: 93, I 2: 80, C: 80 *Inclusion criteria:* diagnosis of COPD as evidenced by history, physical examination, chest radiograph, and pulmonary function test results; $PaCO_2$ at rest < 6.5 kPa, and PaO_2 at rest > 7.5 kPa; FEV_1 < 65% predicted

Strijbos 1996 *(Continued)*

	Major exclusion: ischaemic heart disease, musculoskeletal disorder or other disabling disease that could restrict rehab therapy
Interventions	12-week rehabilitation programme - Both groups: exercise twice a week during 12 weeks, 1 hour each session - In hospital group, exercise was administered by a physiotherapist (1 hour twice a week) and patients were instructed to practise daily exercise for ≥ 15 minutes. Patient education 3 times/1 hour by a respiratory nurse - In home care group, exercise was carried out at home by local physiotherapist and home care nurse, under supervision of GP. Patients received individualised exercise programme from physiotherapist of 30 minutes (24 sessions) and were instructed to exercise ≥ 15 to 30 minutes. They received 3 times education by a nurse and 3 times visit by physician or GP - Both groups were intended to continue exercise daily at home, after completion of the programme Intervention duration: 12 weeks Involved disciplines: nurse, physiotherapist, GP or pulmonologist
Outcomes	4-minute walking test (4MWT), cycle test (measured as maximum watts, W-max), interviews
Notes	Dominant component: exercise

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly assigned to intervention or control group". Information is insufficient to be confident that the allocation sequence was genuinely randomised
Allocation concealment (selection bias)	Unclear risk	Comment: n o information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: p articipants and treating therapists not likely to have been blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: w e were unable to ascertain whether outcome assessors were blinded to treatment group assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: c omparable low dropout rates in both groups
Selective reporting (reporting bias)	Low risk	Comment: study protocol is not available, but it is clear that published reports include all expected outcomes, including those that were pre-specified

Tabak 2014

Study characteristics

Tabak 2014 *(Continued)*

Methods	RCT; follow-up: 9 months; control: usual care (control group also received an activity sensor to register activity levels)
Participants	Eligible: 101 Randomised: 29, I: 15, C: 14 Completed: 12, I: 10, C: 2 Mean age: I: 64 years, C: 63 years Sex (% male): 50, I: 50, C: 50 *Inclusion criteria:* COPE II criteria (e.g. no exacerbation in the month prior to enrolment and 3 or more exacerbations or 1 hospitalisation for respiratory problems in the 2 years preceding study entry), access to computer with Internet connection *Major exclusion criteria:* serious other disease with low survival rate; other disease influencing bronchial symptoms and/or lung function (e.g. cardiac insufficiency, sarcoidosis); uncontrolled diabetes mellitus during COPD exacerbation in the past or hospitalisation for diabetes mellitus in the 2 years preceding the study; need for regular oxygen therapy (> 16 hours per day or pO2 < 7.2 kPa); maintenance therapy with antibiotics; known alpha$_1$-antitrypsin deficiency; impaired hand function causing inability to handle the application
Interventions	Components of telehealth programme - Web-based exercise programme (breathing exercise, relaxation, mobilisation, resistance and endurance training, muscle clearance) with individual exercise schemes created by physiotherapist, with feedback option for patients - Individualised activity coach to monitor daily activity via an accelerometer-based activity sensor and smartphone with encouraging motivational individualised daily messages - Self-management module on the web portal that enables patients to treat exacerbations themselves following a decision tree. Before use of self-management module, attendance at 2 self-management teaching sessions (90 minutes each) provided by nurse practitioner. Patients received recipes for their medication. Access to patient diary by chest physician and nurse practitioner - Teleconsultation module allowing questions and comments between physiotherapist and patient Duration intervention: 9 months Disciplines involved: primary and secondary care professionals (physiotherapist, practice nurse, chest physician)
Outcomes	Adherence to intervention (primary outcome), satisfaction with received care (primary outcome), number of hospitalisations, duration of hospitalisations, number of ED visits, number of exacerbations, activity level (activity sensor), self-perceived activity levels (Baecke Physical Activity Questionnaire), 6MWD, MFI (fatigue), CCQ, MRC Dyspnoea, EuroQol-5D
Notes	Dominant component: telemonitoring

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “patients were randomised using a computer-generated randomisation list where randomisation was applied in random blocks of two and four. Participants were allocated by a data manager in order of inclusion following the randomisation list”

Tabak 2014 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "participants were allocated by a data manager in order of inclusion following the randomisation list, placed in a sealed envelope"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: due to the nature of the intervention, it is not likely that participants and treating healthcare providers were blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: not enough information provided to determine whether assessor was blinded to outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: large imbalance in dropout rates between intervention (n = 5) and control (n = 12) and reasons for missing data. Reasons for missing outcome data likely to be related to true outcome, being satisfied with received care
Selective reporting (reporting bias)	High risk	Quote: “data in Table 4 (clinical outcomes) are descriptive only, and present T0–T2” Comment: clinical outcomes reported only up to 3 months, not for 6 and 9 months Quote: “exacerbation data were not available for the control group”; “the temporary unavailability of one physiotherapy practice, were also a reason not all measurements were assessed. This made us unable to report the number of exacerbations in the control group” Comment: exacerbations/relapses reported for telehealth and usual care Comment: due to scope of study (pilot RCT) and size of groups, no statistical tests were performed. Furthermore MRC Dyspnoea was reported only for T1 (1 month). Hence, study fails to report all study outcomes as specified in the protocol

Theander 2009

Study characteristics	
Methods	RCT; 3 months; control group: usual care
Participants	Eligible: 30 Randomised: 30, I: 15, C: 15 Completed: 26, I: 12, C: 14 Mean age: I: 66 years, C: 64 years Sex (% male): I: 25, C: 71 *Inclusion criteria:* diagnosis of COPD according to British guidelines, with FEV_1 between 60% and 25% post bronchodilation, age ≤ 75 years *Major exclusions:* disabling or severe disease other than COPD, impaired pulmonary function due to other disease, long-term oxygen therapy, $alpha_1$-antitrypsin deficiency, cancer disease, untreated obstructive sleep apnoea syndrome, no COPD-related symptoms affecting activities of daily life
Interventions	Multi-disciplinary programme

Theander 2009 *(Continued)*

	- Physiotherapy 2 days per week (1 hour) for 12 weeks, with additional home training after 1 month - Dietician support (3 sessions of 1 hour): education and, if needed, additional nutritional supplementation - Occupational therapist: education and teaching - Nurse (2 sessions of 1 hour): education and self-care advice Intervention duration: 3 months Disciplines involved: physiotherapist, dietician, occupational therapist, nurse
Outcomes	BMI, FEV_1, fatigue impact scale, 6MWD, grip strength, SGRQ, SF-36
Notes	Dominant component: exercise

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "for the randomisation we prepared 80 sealed opaque envelopes with assignment information: 40 for the rehabilitation group and 40 for the control group"
Allocation concealment (selection bias)	Low risk	Quote: "randomization procedures were performed by an independent person from the research group, who took a random envelope from the prepared box with sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: p articipants and treating therapists not likely to have been blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "the data collection was performed by members of the rehabilitation group. The data collection was not blinded to the data collector"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: c omparable dropout rates
Selective reporting (reporting bias)	Low risk	Comment: study protocol is not available, but it is clear that published reports include all expected outcomes, including those that were pre-specified

Titova 2017

Study characteristics

Methods	RCT, single-centred; follow-up: 3 years (initially 2 years planned); control: usual care
Participants	Eligible: 199 Randomised:172, I: 91, C: 81 Completed: 100, I: 51, C: 49 Mean age: I: 74 years, C: 72 years

Titova 2017 *(Continued)*

	Sex (% male): I: 43, C: 43 *Inclusion criteria:* admission due to COPD exacerbations; clinical diagnosis of COPD with GOLD stage III or IV; living in Trondheim municipality; ability to communicate in Norwegian; ability to sign informed consent *Major exclusions:* serious disease that might cause a very short life span (expected survival time < 6 months)
Interventions	Intervention components of COPD - home intervention - Call centre for support and communication with patients, home care nurses, co-ordination between various levels of care - Educational session for home care nurses and interactive e-learning programme for patients - Individualised self-management plan for patients - Joint visits at patients‘ homes by a specialist nurse who repeated the core element of the educational programme and reinforced specific health behaviours, as well as making necessary changes to patient's treatment programme Duration intervention: 24 months Disciplines involved: home care nurse, specialised nurse, GP
Outcomes	Number of hospital admissions caused by AECOPD (primary outcome), number of in-hospital days due to AECOPD, all-cause mortality, COPD-related mortality, SGRQ, HADS, Patient Activation Measurement (PAM), use of medication, lung function, cost-effectiveness
Notes	Dominant compone n t: stru c tured follow-up Study temporarily stopped after 2 years' follow-up for 8 months due to increased mortality rates in intervention group. REC concluded that mortality was not related to intervention. Follow-up continued, intervention not continued

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: “it was decided by lottery that participants from District Pair 1 were assigned to the UC group, and participants from District Pair 2 were assigned to the IC group”; "the demography is quite similar according to age and disease panorama, i.e. the number of inhabitants 55–79 years old are the same in the two district pairs (Lerkendal/Heimdal; 15 800 and Østbyen/Midtbyen 15 200) Comment: randomisation was performed on district level, matched based on district size
Allocation concealment (selection bias)	High risk	Quote: "they were randomly allocated to either integrated care (IC) or usual care (UC) based on address of permanent residence Comment: insufficient detail on allocation concealment provided. Considering randomisation procedure on district level and following hospitalisation, it seems unlikely that participants and investigators could not foresee assignment to intervention or control conditions
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "the study was a prospective, open, single-centre intervention study"

Titova 2017 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "the study was a prospective, open, single-centre intervention study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: “an increased number of deaths were registered among the patients in the IC group compared to the UC group.”; “data on the causes of death were analysed, and the REC concluded that the increased number of deaths in the IC group was not related to the COPD-home intervention, but could be explained by pre-study poorer health status and higher age” Comment: imbalance in number of deaths could have resulted in overall healthier health status among intervention group members at follow-up. Insufficient details provided to be conclusive regarding effect on true outcome
Selective reporting (reporting bias)	Low risk	Comment: published reports include all expected outcomes that were prespecified, with the exception of lung function and cost-effectiveness as included in the clinical trial register
Other bias	High risk	Comment: not defined as cluster-RCT; however potential clustering effect, considering that level of randomisation is region (4 clusters)

Trappenburg 2011

Study characteristics	
Methods	RCT; follow-up 6 months; control group: usual care
Participants	Eligible: 391 Randomised: 233, I: 111, C: 122 Completed: 193, I: 91, C: 102 Mean age: I: 66 years, C: 65 years Sex (% male): I: 65, C: 69 *Inclusion criteria:* COPD diagnosed by spirometry, age > 40 years, smoking history > 20 years or 15 pack-years, diagnosis of COPD as a major functionally limiting disease, current use of bronchodilator therapy *Major exclusions:* primary diagnosis of asthma, primary diagnosis of cardiac disease, presence of disease that could affect mortality or participation in the study
Interventions	6-month self-management/action plan programme - Individualised action plan with treatment prescriptions related to color-coded symptom status to enhance adequate response to periods of symptom deterioration - Action plan included ongoing support of case manager, in concordance with GP/respiratory physician. 2 reinforcement sessions provided by telephone at 1 and 4 months Intervention duration: 6 months Disciplines involved: GP, nurse, pulmonologist
Outcomes	Exacerbation rate and recovery time; SGRQ; HADS; courses of antibiotics, corticosteroids; ED visits for exacerbation; CCQ score during exacerbation

Trappenburg 2011 *(Continued)*

Notes	Dominant component: self-management/action plan

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomisation was carried out using the minimization technique to balance the control and intervention groups for centre and gender"
Allocation concealment (selection bias)	Low risk	Quote: "to conceal the assignment sequence, a central web-based service was used"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "an informed consent to postponed information procedure is used, keeping the patient unaware of the AP being the major study aim. This implies that all patients are informed about the fact that, besides the outcome assessment aiming at gaining more insight in daily symptom variations, the study has another purpose. Patients are told that they will be informed about this additional research question only after follow up because informing during recruitment would affect study results"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "investigators were blinded to allocation"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "monthly discontinuation rates and reasons for withdrawal are comparable in both study arms"
Selective reporting (reporting bias)	Low risk	Comment: study protocol is not available, but it is clear that published reports include all expected outcomes, including those that were pre-specified

van Wetering 2010

Study characteristics

Methods	RCT; follow-up: 24 months, control group: usual care
Participants	Eligible: 199 Randomised: 199, I: 102, C: 97 Completed: I: 77, C: 81 Mean age: I: 66 years, C: 67 years Sex:: I: 71%, C: 71% *Inclusion criteria:* diagnosis of COPD according to guidelines, other inclusion criteria: impaired exercise capacity, W-max < 70%, GOLD 2 + 3, clinically stable at inclusion *Major exclusion criteria:* prior rehabilitation, patients with serious comorbidity that precluded exercise therapy
Interventions	Community-based COPD management programme - Intensive 4-month standardised, supervised physiotherapy 2/week (30 minutes), with home-based exercise

van Wetering 2010 *(Continued)*

	- Participation in an individualised education programme - All smokers were offered smoking cessation counselling - Nutritionally depleted patients received counselling from a dietician - During 20-month active maintenance phase, patients were instructed to train at home and visited the physiotherapist once a month. Dietician support was continued Intervention duration: 16 weeks followed by 20 months ' maintenance Involved disciplines: nurse, physiotherapist, dietician
Outcomes	SGRQ, total score, number of exacerbations, mMRC, exercise performance (measured as maximum Watts: W-max), 6MWD, muscle strength, isometric quadriceps peak torque, maximum inspiratory mouth pressure, fat-free mass, lung function
Notes	Dominant component of programme: exercise

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomised to INTERCOM or usual care using a computerised procedure with concealed patient allocation"
Allocation concealment (selection bias)	Low risk	Quote: "patients were randomised to INTERCOM or usual care using a computerised procedure with concealed patient allocation"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: p articipants and treating therapists not likely to have been blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "all outcome measurements were assessed single blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: results were analysed by intention-to-treat
Selective reporting (reporting bias)	Low risk	Comment: study protocol is not available, but it is clear that published reports include all expected outcomes, including those that were pre-specified

Vasilopoulou 2017

Study characteristics

Methods	RCT; follow-up: 14 months, control group: usual care (all study arms have 2 months' pulmonary rehab)
Participants	Eligible: unknown Randomised: 150, I (A): 50, I (B): 50, C: 50 Completed: 147, I (A): 47, I (B): 50, C: 50 Mean age: I (A): 67 years, I (B): 67 years, C: 64 years

Vasilopoulou 2017 *(Continued)*

	Sex (% male): I (A): 94, I (B): 76, C: 74 *Inclusion criteria*: older than 40 years of age, diagnosis of COPD, FEV_1 to FVC < 0.7 with FEV_1 < 80% predicted, with optimal medical treatment according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) without regular use of systemic corticosteroids, history of acute exacerbations of COPD 1 year before entry into the study *Major exclusions:* diagnosis of orthopaedic, neurological, and other conditions that significantly impair exercise tolerance; respiratory disorder other than COPD; cognitive impairment and/or difficulties in managing electronic devices
Interventions	Intervention consisted of 2 months' outpatient rehabilitation followed by a 12-month maintenance rehabilitation programme that is home-based (group A) or hospital-based (group B) **Home-based maintenance telerehabilitation (group A)** Intervention components - Individualised action plan - Individually tailored physical exercise sessions to remote monitoring, adaption of exercise load based on exercise vital sign data (144 sessions) - Self-measurement of exercise vital sign data (heart rate and oxygen saturation) along with ratings related to symptoms of dyspnoea and leg discomfort immediately after completion of home exercise programme - Manual entry of data into tablet and transmission of self-collected data to web-based platform 3 times per week (exercise vital sign data) or 2 times per week (pedometer, spirometry, oximetry, and responses to questionnaires (HRQoL, CAT, HADS, mMRC)) - Review of transmitted data on secure web-based server platform regularly by different healthcare professionals (3 or 4 times per week) - Self-management; psychological support and dietary and self-management advice via scheduled weekly contacts with a physiotherapist, an exercise scientist, a dietician, and a physician through telephone or video conference - Access to a pulmonologist at a call centre 5 days per week, 10 hours per day **Hospital-based maintenance rehabilitation (group B)** Intervention components - Continuation of rehabilitation programme twice weekly for 12 months, including exercise training, physiotherapy, dietary and psychological advice Intervention duration: 14 months (2 months ' outpatient rehabilitation + 12 months ' home-based or hospital-based maintenance rehabilitation) Involved disciplines: physiotherapist, dietician, physician (as case manager for home-based telerehabilitation)
Outcomes	Rate of moderate to severe acute exacerbation (GOLD) (primary outcome), hospitalisations due to acute exacerbation of COPD (primary outcome), ED visits (primary outcome), rate of severe exacerbations (hospitalisations), rate of ED visits due to acute exacerbation of COPD that did not require hospital admission, functional capacity (peak work rate, 6MWD), daily physical activity (activity monitoring via accelerometer), health-related quality of life (SGRQ), respiratory symptoms (CAT, mMRC); compliance with intervention
Notes	Dominant component: (A) telemonitoring, (B) structural follow-up
Risk of bias	

Vasilopoulou 2017 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomised into three groups using a set of computer-generated random numbers"
Allocation concealment (selection bias)	Unclear risk	Comment: no details on allocation concealment provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "our study design was not blinded"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: investigator aware of allocation. However primary endpoint objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: analysis performed per protocol. Dropouts (n = 3) in home-based telerehabilitation group unlikely to affect outcome
Selective reporting (reporting bias)	Low risk	Comment: all outcomes have been reported
Other bias	Unclear risk	Comment: o utcome from baseline (Month 2, after outpatient PR) to 12 months. Usual care group also had no access to outpatient PR. Hence maintenance of benefits might be related to conduct of initial PR

Vianello 2016

Study characteristics	
Methods	RCT; follow-up: 12 months; control: usual care
Participants	Eligible: 458 Randomised: 334, I: 230, C: 104 (allocation using 2:1 ratio) Completed: 262, I: 181, C: 81 Mean age: I: 75.96 years, C: 76.48 years Sex (% male): I: 71.3, C: 73.1 *Inclusion criteria:* clinical diagnosis of class III to IV COPD according to GOLD guidelines, age ≥ 18 years, life expectancy > 12 months according to Multiparametric Prognostic Index (MPI), capability of using telemonitoring equipment *Major exclusion criteria:* concomitant significant lung disease, unwillingness to use telemonitoring technology, negative advice of GP, other serious social problems
Interventions	Tele-self-monitoring system: telemonitoring kit consisting of portable wrist clinic device for clinical parameters measuring heart rate and SpO_2 and gateway device for data transmission to a central data management unit every other day and/or with clinical worsening - Patient-customised threshold level of alert based on baseline values of pulmonary function test during routine visit, before hospitalisation

Vianello 2016 *(Continued)*

	- Self-management education material - Access to data by pulmonary specialist. When alerted, pulmonary specialist contacts patients to verify and undertake appropriate action (e.g. modifying medication, sending district nurse for home visit, setting up office appointment with pulmonary specialist, taking patient to emergency department) Duration intervention: 12 months Disciplines involved: central data management unit operator, pulmonary specialist, nurse (for home visits)
Outcomes	SF-36 PCS and MCS score (primary outcome), HADS, number of hospitalisations due to exacerbation, duration of hospitalisation due to exacerbation, number of hospitalisations for any cause, duration of hospitalisation for any cause, number of re-admissions due to exacerbation, number of re-admissions for any cause, number of appointments with pulmonary specialist, number of ED visits, mortality
Notes	Dominant component: telemonitoring

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “randomisation was performed following standard procedures and checked for incorrect imbalances or meaningful baseline differences in variables using a dedicated algorithm provided by PASS 2008 software that took into account patient’s age and gender” Comment: randomisation to intervention or control group using 2:1 allocation. insufficient information about sequence generation process but imbalance checked using appropriate methods
Allocation concealment (selection bias)	Unclear risk	Quote: “randomisation was performed following standard procedures” Comment: insufficient information provided about concealment of allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: “a pragmatic unblinded, parallel-group, two arm, 12 month randomised controlled trial (RCT) was carried out”
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: unblinded study design. Some outcomes were extracted from regional records and were less prone to detection bias (hospital admissions, healthcare service use including consultations with a pulmonary specialist and visits to ED service) and mortality
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: “out of the 230 patients allocated to the study group, 19 did not actually participate in the study (and did not receive the TM equipment) for the following reasons: death (n = 1), withdrawal of consent (n = 9), administrative problems (n = 7), moving to a nursing home (n = 1), and another reason (n = 1)”
Selective reporting (reporting bias)	Low risk	Comment: published reports include all expected outcomes that were prespecified

Wakabayashi 2011

Study characteristics

Wakabayashi 2011 *(Continued)*

Methods	RCT; follow-up 12 months; control group: single intervention (education)
Participants	Eligible: 102 Randomised: 102; I: 52, C: 50 Completed: 85; I: 42, C: 43 *Inclusion criteria:* clinical diagnosis of COPD, > 65 years, exclusively visited clinic with monthly scheduled appointments, history of cigarette smoking *Exclusion criteria:* history of atopy or any apparent asthmatic features, illiterate or with cognitive impairment score < 26 on MMSE, lived in a residential care facility or nursing home, exacerbations during preceding 3 months, other respiratory disease such as bronchiectasis, any type of pulmonary fibrosis or congestive heart failure
Interventions	Patients underwent a programme of educational sessions for 6 months, individually tailored according to their domain scores on the LINQ questionnaire, which was designed to assess the need for information from the patient's perspective. Programme was given by respiratory nurses and pulmonary physicians. There were six domains: (1) understanding of COPD, (2) pharmacological treatments, (3) exercise, (4) avoidance of exacerbations, including action plan with instructions in the event of exacerbation, (5) smoking cessation, (6) nutrition. All patients were provided with a booklet that was used during each session. After intensive education period, each patient was followed up for 6 months in the same way as patients in the usual care group Intervention duration: 6 months Disciplines involved: nurse, pulmonologist
Outcomes	FEV_1, MRC, SGRQ, 6MWD, Lung Information Needs Questionnaire (LINQ), BMI, BODE Index (body mass index, dyspnoea, airflow obstruction, exercise capacity), activities of daily living (ADL), comorbidities, hospitalisations
Notes	Dominant component: self-management/action plan

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a case manager independent of the study randomly assigned patients to either group I or group U using a computer-generated list"
Allocation concealment (selection bias)	Low risk	Quote: "patients' allocations were sealed in numbered envelopes by an independent evaluator, not involved in the interventions"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: p articipants and treating therapists not likely to have been blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "an independent evaluator, who assessed outcomes at the beginning of the study, after initial integrated education (6 months), and after follow-up period (6 months)"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: c omparable dropout rates between groups

Wakabayashi 2011 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: study protocol is not available, but it is clear that published reports include all expected outcomes, including those that were pre-specified

Wang 2017

Study characteristics	
Methods	RCT, multi-centre (n = 2); follow-up: 12 months, control group: usual care
Participants	Eligible: 162 Randomised: 130, I: 62, C: 68 Completed: 120, I: 55, C: 65 Mean age: I: 69 years, C: 72 years Sex (% male) I: 38, C: 55 *Inclusion criteria:* medically confirmed diagnosis of COPD based on Chinese Medical Association diagnostic criteria, including percentage forced expiratory volume for 1 second (FEV_1%) ≤ 80% and forced expiratory volume for 1 second divided by forced vital capacity (FEV_1/FVC) ≤ 70%; ability to speak Mandarin to communicate; discharged to a home where Internet and computer have been installed; ability to be reached by telephone post discharge *Major exclusions*: comorbidities (i.e. allergic rhinitis, myocardial infarction, severe heart failure, and malignant tumour); no access to a computer or Internet at home
Interventions	Web-based coaching programme using EHRs, accessible for patients and medical staff Intervention components - Web-based HER system to allow for input of demographic information, record of admission, discharge, and community information - Ability for patient to manage and control own record and enter health information - Visual presentation of trajectory of disease to medical staff and patient - Access to patient on information about the disease and health education content entered by administrator (medical staff). Health education included information about COPD and pulmonary rehabilitation instructions. Information related to COPD consisted of cause of disease, development, acute exacerbation, prognosis, medication information (name, route, dosage, and adverse reactions), oxygen therapy, diet, importance of smoking cessation - Direct email-like communication with community administrator - Messaging function between medical team and patient (2-way) - Telephone call from research team every 2 weeks Duration intervention: 12 months Disciplines involved: community nurse, medical practitioner, clinical nurse
Outcomes	FEV_1 %, FVC%, FEV_1/FVC, peak expiratory flow and maximum mid-expiratory flow, SGRQ, mMRC, 6MWD
Notes	Dominant component: telemonitoring

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Wang 2017 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "the patients who consented to participate were assigned to the intervention or control group using a computer-generated randomised table"
Allocation concealment (selection bias)	Unclear risk	Comment: n o details on concealment of allocation provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "participants were not blinded to group assignment" Not explicitly mentioned whether medical staff was blinded. However, given nature of intervention, unlikely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: in supplementary material – CONSORT eHEALTH checklist mentioned that all data were collected face-to-face by research assistant, who was blinded to allocation outcome. Researchers were not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: loss to follow-up unbalance d between groups: 7/62 in intervention lost to-follow-up with reason 'could not contact'; 3/68 lost to follow-up in control group. Analysis performed with only complete measurements
Selective reporting (reporting bias)	Unclear risk	Comment: protocol not published nor trial registered in trial registry. All outcomes mentioned in protocol are reported, except FEV_1/FVC. No distinction between primary and secondary outcomes

Wijkstra 1994

Study characteristics	
Methods	RCT; follow-up 12 weeks; control group: no treatment
Participants	Randomised: 45 Completed: 43; I: 28, C: 15 Mean age I: 64 years, C: 62 years Sex (% male): I: 82, C: 93 *Inclusion criteria:* diagnosis of COPD with FEV_1 % < 60%, FEV_1/IVC < 50% *Exclusion criteria:* evidence of ischaemic heart disease, intermittent claudication, musculoskeletal disorder, other disabling disease that could restrict the rehab programme
Interventions	Comprehensive rehabilitation programme at home - Patients were supervised by a multi-disciplinary team: pulmonologist, physiotherapist, nurse, GP - Patients visited physiotherapist twice a week for 12 weeks and programme consisted of conventional physiotherapy, upper limb training, inspiratory muscle training, exercise training. Patients had to practice twice a day for a half hour at home - Furthermore, they received education at home from a nurse (once a month) - They visited the GP once a month, who supervised clinical status and maintenance treatment Intervention duration: 3 months Disciplines involved: GP, physiotherapist, nurse

Wijkstra 1994 *(Continued)*

Outcomes	Lung function, CRQ, cycle ergometer test
Notes	Dominant component: exercise

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were stratified for their FEV_1 % predicted. After this stratification, the patients were randomly allocated"
Allocation concealment (selection bias)	Low risk	Quote: "(after randomisation), they were randomly allocated to one of three groups, each of 15 patients"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: p articipants and treating therapists not likely to have been blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: w e could not ascertain how and whether outcome assessors were blinded to treatment group assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: o nly 2 (out of 30) dropouts in rehabilitation group vs no dropouts in control group
Selective reporting (reporting bias)	Low risk	Comment: a ll outcomes reported

Wood-Baker 2006

Study characteristics

Methods	Cluster-RCT; follow-up 12 months, control group: education + usual care
Participants	Eligible: 218 Randomised: 138; I: 67, C: 72 Completed (12 months): 112; I: 54, C: 58 Mean age: I: 69 years, C: 71 years Sex (% male): I: 49, C: 71 *Inclusion criteria:* COPD diagnosed by spirometry, age > 50 years, tobacco smoking history > 10 pack-years, FEV_1 < 65% predicted *Major e xclusion criterion:* nursing home residents
Interventions	Control + intervention group: COPD information booklet, individual educational session with nurse Intervention group: written self-management plan, which was developed in consultation with the treating GP. Patients were encouraged to make early contact with GP during an exacerbation Intervention duration: 12 months Disciplines involved: GP, nurse

Wood-Baker 2006 *(Continued)*

Outcomes	SGRQ, exacerbations (courses of antibiotics/prednisone), ED visits, hospital admissions, GP consultations, spirometry, mortality, physical exercise (pedometer)
Notes	Before commencement of the randomisation process, only 50% of included GPs attended 1 of a series of educational workshops on management of COPD Dominant component: self-management/action plan

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "practices were randomised to the intervention or control group using a computer generated randomisation software package“
Allocation concealment (selection bias)	Unclear risk	Comment: n o information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: it is not likely that participants and personnel have been blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "baseline, 6- and 12-month assessments involved face to face contact with a research nurse at the GP’s surgery or at patient's home“
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 13 intervention patients vs 14 control patients missing at 6 months; reasons similar
Selective reporting (reporting bias)	Low risk	Comment: study protocol is not available, but it is clear that published reports include all expected outcomes, including those that were pre-specified
Recruitment bias	Low risk	Comment: no information provided
Baseline imbalance between groups	High risk	Comment: baseline imbalance between groups
Loss to follow-up of clusters	Low risk	Comment: no missing clusters
Adequate analysis methods for CRT	High risk	Comment: no adjustments for cluster-randomised trials

Zhang 2020

Study characteristics

Methods	RCT; follow-up 24 months ; control group: u sual care
Participants	Eligible: 702 Randomised: 208; I: 104, C: 104 Completed: 174; I: 85, C: 89 Mean age I: 65 years, C: 66 years Sex (% male): I: 77, C: 75

Zhang 2020 *(Continued)*

	Inclusion criteria: older than 45 years of age; diagnosis of GOLD stage II, III, or IV COPD as documented by pulmonary function testing; current or previous smoker with ≥ 10 pack-years of cigarette smoking; hospitalised for an exacerbation of COPD *Exclusion criteria:* unable to provide accurate information or to follow instructions, unable to walk even during periods of COPD
Interventions	Hospital outreach PR program me after hospital discharge, delivered i n 2 p hases P h ase 1: 3-month intensive intervention with i ntervention components - S upervised physical exercise, 2 × per week, 50 minutes per session - S moking cessation (2 sessions) - S elf-management education, including COPD knowledge, symptom management, instruction on medication intake and adherence, nutritional support. Session every 2 weeks - P sychosocial support (2 sessions) P h ase 2: s tructural follow-up by telephone (once every 1 to 2 weeks) and home visits (once every 1 to 3 months) up to 24 months by a respiratory nurse. Exercise diary to record daily exercise and symptoms Duration intervention: 3 months intensive with up to 24 months structural follow-up Dis c iplines involved: respiratory nurse, physiotherapist, tai chi mentor, psychologist, nutritionist
Outcomes	Healthcare utili s ation costs (admission rates, admission days, ED visits) (primary outcome); lung function (FEV_1, FVC, FEV_1 % predicted; mMRC; 6MWD; CAT (health-related QoL); COPD self-management scale)
Notes	Dominant component: structured follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "block randomization was used. Subjects were randomized after consent and collection of baseline data. Every two patients with the same level of COPD severity were allocated into one block according to their admission dates. In each block, the two patients were further allocated into treatment and control groups randomly based on allocation sequence"
Allocation concealment (selection bias)	Unclear risk	Quote: "patients were informed of the results of randomization in person or by phone after discharge"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "single-blind trial. Given the nature of the intervention, blinding the subjects was not feasible, and the interventionist would also know that those contacted were in the intervention arm"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the statistician was blinded to individual results during the trial, and the allocation-to-trial-arm coding was not revealed until the data set had been sealed. For outcome assessment, the assessor was also blinded to subject allocation"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: c omparable dropout rates between groups (19/104 in intervention, 15/104 in control). Reasons for dropout are comparable between groups

Zhang 2020 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: study protocol is not available; all outcomes from trial registration are reported

Zwar 2016

Study characteristics	
Methods	Cluster-RCT (36 clusters); follow-up: 12 months, control group: usual care (copy COPD treatment guidelines)
Participants	Newly diagnosed COPD patients Eligible: 287, I: 169, C: 118 Randomised: 254, I: 144, C: 110 Completed: 222, I: 126, C: 96 Mean age: I: 67 years, C: 65 years Sex (% male): I: 62 C: 58 *Inclusion criteria:* current and former smokers, aged 40 to 85 years, newly identified as having COPD on post-bronchodilator spirometry (post-bronchodilator $FEV_1/FVC < 0.7$), had attended the practice at least twice with ≥ 1 visit in the preceding 12 months *Major exclusions:* recorded diagnosis of COPD, unable to understand English sufficiently to complete study questionnaires or procedures, cognitive impairment
Interventions	Nurses and GPs in intervention practices were educated to work in partnership to identify patients with COPD and to initiate an evidence-based early intervention programme Intervention components: care plan, education, optimal diagnosis, management of anxiety and depression, medication, influenza and pneumococcal vaccination, referral to PR and/or dietician if necessary/appropriate, smoking cessation advice and resources if necessary. Multidisciplinary teams; professional roles Duration intervention: intervention duration not fixed; expected to be completed within 6 months Disciplines involved: GP, nurse, physiotherapist, dietician
Outcomes	SGRQ, CAT, general health status, post-bronchodilator FEV_1, COPD knowledge score, awareness of diagnosis of COPD, smoking status, immunisation status for influenza and pneumococcus, effective inhaler use (when prescribed), attendance at pulmonary rehabilitation, healthcare utilisation, intervention uptake
Notes	Dominant component: e ducation

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomization and group allocation of GP practices was performed by an independent statistician using a computer-generated randomisation program"

Zwar 2016 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: “allocation concealment will be ensured as group allocation will be conducted at the same time as randomisation. Practices will be informed about their group allocation by fax (Bunker et al, 2012)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: " i n this pragmatic trial , participating GPs, PNs, and patients were not blind to the aims of the study n or to their randomisation group"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “project officers, who collected study outcome measures, and the statistician undertaking analyses were blind to group allocation”
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: “the primary analysis was by intention to treat and relied on the diagnosis of COPD assigned by the PN/GP on the basis of case-finding spirometry” Comment: 34 and 10 patients withdrew from intervention and control groups, respectively. Reasons for withdraw not likely to be related to true outcomes
Selective reporting (reporting bias)	Low risk	Comment: all outcome measures described in the protocol, except patient satisfaction, are reported
Recruitment bias	High risk	Comment: patient inclusion following case-finding procedures were performed after randomisation and group allocation of GP practices
Baseline imbalance between groups	Low risk	Comment: groups did not differ substantially in mean SGRQ nor in other characteristics
Loss to follow-up of clusters	Unclear risk	Comment: 4 practices withdrew after randomisation, and 2 practices merged into 1 during the study period
Adequate analysis methods for CRT	Low risk	Quote: “intra-cluster(practice) correlation coefficients (ICCs) were determined for all primary outcome variables” “The effect of the intervention on outcomes measured on a continuous scale (such as SGRQ score) were estimated and tested using mixed-model analysis of variance in which time and treatment group were fixed effects and GP practice and subject nested within practice were random effects. The effect of the intervention on dichotomous variables was analysed using generalized estimating equations with a logistic link and a model structure that is analogous to that described above"

4MWT: four-minute walking test; 6MWD: six-minute walking distance; ADL: activities of daily living; BMI: body mass index; BTS: British Thoracic Society; COOP: Dartmouth Primary Care Co-operative Quality of Life Questionnaire; COPD: chronic obstructive pulmonary disease; CRDQ: Chronic Respiratory Disease Questionnaire; CRQ: Chronic Respiratory Questionnaire; ED: emergency department; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; GP: general practitioner; HADS: Hospital Anxiety and Depression Scale; HCCQ: Health Care Communication Questionnaire; HRQoL: health-related quality of life; I: intervention; MACL: Mood Adjective Check List; MBHI: Millon Behavioral Health Inventory; MCO: managed care organisation; MMSE: Mini–Mental State Examination; MRC: Medical Research Council; NYHA: New York Heart Association; PR: pulmonary rehabilitation; RCT: randomised controlled trial; SGRQ: St. George's Respiratory Questionnaire; SIP: Sickness Impact Profile; VAS: visual analogue scale; VC: vital capacity; YQLQ: York Quality of Life Questionnaire.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ancochea 2018	Fewer than 2 different healthcare providers included

Study	Reason for exclusion
Arbillaga-Etxarri 2018	Fewer than 2 different healthcare providers included
Bachmann 2018	No results for COPD patients presented
Bachmann 2019	Fewer than 2 component s of intervention
Bal 2016	Fewer than 2 different healthcare providers included
Balaban 2017	Fewer than 2 different healthcare providers included and duration < 3 months
Benzo 2016	Fewer than 2 different healthcare providers included
Benzo 2019	Fewer than 2 different healthcare providers included
Bischoff 2012	No multi-disciplinary intervention
Blumenthal 2014	Fewer than 2 different healthcare providers included
Bringsvor 2018	Duration < 3 months
Budnevskiy 2016	Fewer than 2 different healthcare providers included
Cameron-Tucker 2016	Duration < 3 months
Carrieri 2005	Active treatment in control group
Carron 2017	Not an RCT
Casas 2006	Intervention duration < 3 months
Collins 2019	Fewer than 2 different healthcare providers and fewer than 2 intervention components included
Collinsworth 2018	Fewer than 2 different healthcare providers included
Coultas 2016	Fewer than 2 different healthcare providers included
Cox 2018	Duration < 3 months
Csikesz 2016	Duration < 3 months
De Godoy 2003	Active treatment in control group
Drks 2019	Fewer than 2 different healthcare providers included
Eaton 2009	Intervention duration < 3 months
Effing 2009	Active treatment in control group
Efraimsson 2008	Fewer than 2 different healthcare providers included
Elliott 2004	Fewer than 2 different healthcare providers included
Farmer 2017	Fewer than 2 different healthcare providers included and duration < 3 months
Ferrone 2019	Fewer than 2 different healthcare providers included

Study	Reason for exclusion
Flink 2017	Fewer than 2 different healthcare providers included and duration < 3 months
Folch-Ayora 2018	Fewer than 2 different healthcare providers included
Fu 2018	Fewer than 2 different healthcare providers included
Garcia 2007	Duration of intervention < 3 months
George 2019	Fewer than 2 different healthcare providers included
Gohl 2006	Fewer than 2 different healthcare providers and fewer than 2 components included
Goldstein 1994	Fewer than 2 components of intervention
Guell 2008	Active treatment as control group
Hajizadeh 2020	Fewer than 2 different healthcare providers included
Heidari 2018	Fewer than 2 different healthcare providers included
Hernandez 2004	Duration < 3 months
Hughes 2000	No results solely for COPD
IRCT20160914029817N	Duration < 3 months
Jakobsen 2015	Duration < 3 months
Jiang 2020	Fewer than 2 intervention components
Jolly 2018	Fewer than 2 different healthcare providers included
Jones 2009	Fewer than 2 different healthcare providers included
JPRN-UMIN000034582	Fewer than 2 intervention components (pharmaceutical intervention)
Khdour 2011	Fewer than 2 different healthcare providers included
Lahham 2018	Duration < 3 months
Lainscak 2013	Duration < 3 months
Lavoie 2017	Fewer than 2 components of intervention (same study as Troosters 2017)
Li 2019	Fewer than 2 different healthcare providers included
Liang 2019	Duration < 3 months
Linden 2014	Fewer than 2 different healthcare providers included
Liu 2006	Not an RCT
Liu 2019	Fewer than 2 components of intervention
Lorig 2006	Fewer than 2 different healthcare providers included and duration < 3 months

Study	Reason for exclusion
Ly 2018	Not an RCT
Maltais 2008	No usual care as control group
Markun 2018	Fewer than 2 components of intervention and duration < 3 months
Martin 2004	Fewer than 2 components of intervention
Martinez 2014	Fewer than 2 different healthcare providers included
McGeoch 2006	Fewer than 2 components of intervention
Monninkhof 2003	No usual care as control group
Moy 2014	Fewer than 2 different healthcare providers included
Moy 2016	Fewer than 2 different healthcare providers included
Muelepas 2007	Not an RCT
NCT03794921	Fewer than 2 intervention components
NCT03889054	Fewer than 2 intervention components
NCT04260178	Fewer than 2 different healthcare providers included
NCT04348344	Fewer than 2 intervention components
NCT04437238	Fewer than 2 different healthcare providers included
NCT04459546	Fewer than 2 different healthcare providers included
Nguyen 2019	Fewer than 2 different healthcare providers included
North 2018	Fewer than 2 different healthcare providers included
Nyberg 2017	Fewer than 2 different healthcare providers included
Rabinovich 2017	Fewer than 2 different healthcare providers included
Radini 2017	Not reported for COPD
Rausch-Osthoff 2017	Fewer than 2 different healthcare providers included
RBR-533hht	Fewer than 2 different healthcare providers included and duration < 3 months
Renn 2018	Fewer than 2 different healthcare providers included
Ries 2003	Active treatment as control group
Ringbaek 2015	Fewer than 2 different healthcare providers included
Rixon 2017	Fewer than 2 different healthcare providers included
Robinson 2020	Fewer than 2 different healthcare providers included

Study	Reason for exclusion
Rotter 2017	Not an RCT
Schmidt 2018	Fewer than 2 components of intervention (same study as Troosters 2017)
Scuffham 2018	Fewer than 2 different healthcare providers included
Selzler 2019	Duration < 3 months
Sidhu 2015	Fewer than 2 different healthcare providers included
Soler 2006	Active treatment as control group
Sorensen 2016	Fewer than 2 different healthcare providers included
Soriano 2018	Fewer than 2 different healthcare providers included
Stamenova 2020	Fewer than 2 different healthcare providers included
Steele 2008	Active treatment as control group
Stenlund 2019	Fewer than 2 different healthcare providers included
Steurer-Stey 2018	Not an RCT
Thom 2019	Fewer than 2 different healthcare providers included
Thurber 2018	Not an RCT
Torre 2018	Fewer than 2 different healthcare providers and fewer than 2 intervention components included
Troosters 2016	Fewer than 2 intervention components
van der Weegen 2015	Fewer than 2 different healthcare providers included
Van Genugten 2016	Duration < 3 months and fewer than 2 different healthcare providers included
Varas 2018	Duration < 3 months
Voncken-Brewster 2015	Fewer than 2 different healthcare providers included
Walker 2018	Fewer than 2 different healthcare providers included
Walters 2013	Fewer than 2 different healthcare providers included
Wang 2020	Fewer than 2 different healthcare providers included
Waterhouse 2010	Duration < 3 months and fewer than 2 different healthcare providers included
Welch 2020	Fewer than 2 different healthcare providers included
Weldam 2017	Fewer than 2 different healthcare providers included and duration < 3 months
Wootton 2019	Fewer than 2 different healthcare providers included
Wu 2018	Fewer than 2 intervention components

Study	Reason for exclusion
Xi 2014	Fewer than 2 different healthcare providers included
Yoon 2018	Not reported for COPD
Zakrisson 2019	Duration < 3 months
Zhou 2010	COPD diagnosis not an inclusion criterion
Zhou 2017	Fewer than 2 different healthcare providers and fewer than 2 intervention components included

COPD: chronic obstructive pulmonary disease.
RCT: randomised controlled trial.

Characteristics of studies awaiting classification *[ordered by study ID]*

Baumann 2012

Methods	RCT with 26 weeks ' follow-up to investigate whether relevant improvements in physical capabilities and quality of life for patients with COPD could be achieved by a long-term, low-intensity, once-weekly rehabilitation programme using limited resources 100 patients with moderate to severe COPD were randomised to a continuous outpatient interdisciplinary rehabilitation programme or standard care
Participants	100 patients with moderate to severe COPD
Interventions	Physiotherapy-led supervised outpatient training sessions were performed once weekly in addition to educational elements
Outcomes	6MWD, cycle ergometry, SGRQ
Notes	

Borji, 2018

Methods	RCT with 6 months ' follow-up to determine the effect of the Adaptive Sustainability Care Model on re-admission of patients with COPD
Participants	80 COPD patients, randomised to intervention or routine care
Interventions	Adaptive sustainability model was performed for patients in the intervention group in 4 steps: investigation of the demographic characteristics of family, desensitisation, collaboration, and continuous monitoring during 6 months
Outcomes	R e-admission rate
Notes	Additional details regarding intervention required to determine eligibility

Carcereny, 2016

Methods	RCT with 6 months' follow-up to evaluate the effectiveness of a therapeutic education programme on COPD in preventing exacerbations after discharge (APRENDEEPOC study)
Participants	COPD patients discharged from the hospital
Interventions	A Therapeutic Education Program (TEP) as a key component of the Integrated Care Model
Outcomes	H ospital (re) admissions, ED visits
Notes	Additional details regarding intervention required to determine eligibility

Mao 2020

Methods	RCT with 3 months ' follow-up to evaluate clinical outcomes and quality of life resulting from evidence-based nursing in elderly patients with COPD and heart failure
Participants	120 patients over 60 years of age with COPD or ECG and chest X-ray diagnosed heart failure
Interventions	Evidence-based nursing, which was p erformed by the selection of best evidence-based practice by a multi-disciplinary team, depending on the patient ' s condition. Evidence-based practice included cognitive-behaviour al intervention (i.e. health education, mental health status assessment), oxygen therapy, exercise tolerance, breathing function exercises, and dietary advice
Outcomes	Disease-related adverse events, FVC, FEV_1 /FVC, 6MWD, Minnesota Living With HA Questionnaire (MLWHFQ) , European Heart Failure Self-care Behavior Scale (EHFScBS), nursing satisfaction, intervention compliance
Notes	Additional details regarding intervention required to determine eligibility. We were unable to contact study authors

NCT04256070

Methods	RCT with 3 months ' follow-up to eval u ate the effect of e ducation and teleconsultancy i ntervention based on Watson human care theory on self-efficacy and quality of life of i ndividuals with COPD
Participants	74 participants with COPD randomised to intervention or control
Interventions	Education, counselling , nursing care , and education booklet based on Watson h uman care theory; fixed teleconsultation appointments at 2, 4, 6, 8, and 10 weeks; 24-hour teleconsultat ion if request ed by the individual
Outcomes	Chronic Obstructive Pulmonary Disease Self-Efficacy Scale , SGRQ, FVC, FEV_1, FEV_1 /FVC, number of hospitalisations
Notes	Additional details regarding intervention required to determine eligibility

Reguera 2017

Methods	RCT with 6 and 12 months' follow-up to evaluate the efficacy of an integrated Internet programme (IIP) followed after conventional PR to maintain its benefits
Participants	COPD patients attending an ambulatory PR programme
Interventions	Integrated Internet programme consisting of plan of education, self-care, physical activity, and behavioural modifications
Outcomes	SQRQ, CAT, 6MWD, dyspnoea
Notes	Full text not retrieved. Additional details regarding intervention required to determine eligibility

Xu 2010

Methods	Four-arm RCT with 3, 6, and 12 months' follow-up to observe the efficacy of integrative respiratory rehabilitation training for exercise ability and quality of life of COPD patients in stable phase
Participants	O utpatients and inpatients with COPD from Department of Respiratory Medicine, Taihe Hospital, Yunyang Medical College
Interventions	Eighty outpatients and inpatients with COPD from Department of Respiratory Medicine, Taihe Hospital, Yunyang Medical College, were randomly divided into 4 groups, with 20 patients in each group. Patients in group A received only drug therapy, patients in group B received traditional qigong training, patients in group C received modern rehabilitation training, and patients in group D received integrative respiratory rehabilitation training
Outcomes	CRQ, Borg score, 6MWD
Notes	Full text not retrieved. Additional details regarding intervention required to determine eligibility

6MWD: six-minute walking distance.
CAT: COPD Assessment Test.
COPD: chronic obstructive pulmonary disease.
CRQ: Chronic Respiratory Questionnaire.
ECG: electrocardiogram.
ED: emergency department.
EQ-5D: EuroQol Quality of Life - 5 domains.
FEV_1: forced expiratory volume in one second.
FVC: forced vital capacity.
PR: pulmonary rehabilitation.
RCT: randomised controlled trial.
SGRQ: St. George's Respiratory Questionnaire.

Characteristics of ongoing studies *[ordered by study ID]*

Ali 2020

Study name	Person-centred Care at Distance (PROTECT)
Methods	Open-label RCT with 3, 6, 12, and 24 months ' follow up Aim: to evaluate the effects of person-centred care (PCC) by combined digital platform and structured telephone support for people with COPD and/or chronic heart failure
Participants	People with diagnosis of COP D or chronic heart failure

Ali 2020 *(Continued)*

Interventions	Person-centred care at a distance through an eHealth platform, used by professionals, patients, and relatives
Outcomes	General Self-Efficacy Scale (GSE) , hospitalisation, mortality, healthcare utili s ation, EQ-5D, HADS, shortness of breath in heart failure (SOB-HF), CAT, mMRC
Starting date	Starting date: August 2017; estimated completion date: June 2021
Contact information	Dr. Lilas Ali; lilas.ali@gu.se
Notes	

Bourne 2017

Study name	A Self-Management Programme of Activity Coping and Education - SPACE for COPD(C) - in primary care
Methods	Prospective, multi-site, single-blinded RCT with follow-up at 6 and 9 months
Participants	Patients with COPD; identified from General Practice COPD registers, responding to a poster advertisement displayed at GP practices and hospitals, or participating in previous research at the Respiratory Biomedical Research Unit at University Hospitals of Leicester
Interventions	Community-based, HCP-led, group-based self-management programme based on the Self-Management Programme of Activity Coping and Education (SPACE for COPD(C))
Outcomes	CAT, CRQ-SR, incremental shuttle walk test, physical activity monitor, EQ-5D, PAM, HADS, feasibility, acceptability, efficacy
Starting date	January 2015
Contact information	Bourne@uhl-tr.nhs.uk; clinical trial registration ISRCTN17942821
Notes	Pre-results published in trial register

Ding 2019

Study name	Evaluation of an innovative mobile health program for the self-management of chronic obstructive pulmonary disease (MH-COPD)
Methods	Prospective open RCT with 3 and 6 months ' follow-up Aim: to examine whether an innovative mobile health (mHealth)-enabled care programme (MH-COPD) will improve patient self-management and relevant health outcomes
Participants	Patients with diagnosed COPD with chronic airflow limitation that is not fully reversible (post - bronchodilator FEV_1/ FVC < 70%, FEV_1 < 80% predicted) and current o r former smokers (> 10 pack-years)
Interventions	Innovative mHealth programme for COPD specifically designed to integrate an mHealth system within an existing COPD care service to deliver all core components advocated by evidence-based clinical guidelines in Australia. The MH-COPD programme includes health education, symptom monitoring, an electronic CIPD action plan, physical activity, and smoking cessation support i n cluding automatically generated motivational messages and inhaler technique. All data entries of

Ding 2019 *(Continued)*

	participants recorded via the app, such as symptoms, action plan, and cigarettes, will be automatically uploaded to the online portal, accessible to research staff to mon i t or patient adherence
Outcomes	CAT, SGRQ, mMRC, test of adherence to inhalers, smoking cessation, Global Physical Activity Questionnaire, exacerbation rate, healthcare utilisation (hospital re - admission s as ED visits)
Starting date	Starting date: June 2019; an t icipated end date: December 2021
Contact information	Dr. Hang Ding; hang.ding@csiro.au
Notes	

Drennan 2014

Study name	Expanding Paramedicine in the Community (EPIC) study
Methods	Pragmatic, stratified RCT to compare a community paramedic intervention to standard of care for patients with COPD, heart failure (HF) , or diabetes mellitus (DM)
Participants	Patients with diagnosed DM, HF, or COPD, identified by the Family Health Care Team as being at high risk for hospital admission based on hospital admission rates over 3 years before study enrolment
Interventions	Intervention will consist of an initial visit and 3 follow-up visits at 3-month intervals over 1 year by a paramedic who has received additional training in chronic disease management. Visits include a medical history, a physical examination (recorded on an electronic assessment tool that is e-linked to the patient care record for the entire family healthcare team), and disease-specific education and counselling. If necessary, the community paramedic may initiate treatment in the home based on disease-specific evidence-based medical directives and/or may initiate telephone contact with the primary healthcare physician in accordance with the medical directive Control group: usual care from family healthcare team
Outcomes	Number of hospitalisations per patient after 1 year, number of 911 calls, number of clinical visits, length of hospital admission, mortality, EQ-5D-3L, intervention compliance and safety, cost-effectiveness
Starting date	Starting date: June 2013; estimated completion date: December 2016
Contact information	DrennanI@smh.ca; ClinicalTrials.gov identifier: NCT02034045
Notes	

Foot 2017

Study name	REMAIN HOME - REducing Medical Admissions INto Hospital through Optimising MEdication
Methods	Stepped-wedged, cluster- RCT with 12-month follow-up. There will be 14 clusters, each representing a different general practice medical centre. A total of 2240 participants will be recruited from hospital who attend an enrolled medical centre, take 5 or more long-term medicines, or whose reason for admission was related to heart failure or chronic obstructive pulmonary disease

Foot 2017 *(Continued)*

Participants	Patients in hospital who are considered at risk of re-admission, prescribed ≥ 5 long-term medicines on discharge, or with primary discharge diagnosis of congestive heart failure or exacerbation of COPD
Interventions	A multi-faceted and collaborative service involving a practice pharmacist integrated into a medical centre to assist patients in transitioning back into primary care after hospitalisation. Participants meet with the practice pharmacist and the GP after discharge to review and reconcile their medicines and discuss changes made in hospital. The pharmacist follows up with the participant and liaises with other health professionals involved in the patient's care
Outcomes	Rate of unplanned, all-cause hospital re-admissions; healthcare utilisation; cost-effectiveness
Starting date	May 2017 ; actual end date: 14 April 2019
Contact information	c.freeman4@uq.edu.au
Notes	

Hajizadeh 2020a

Study name	A RCT into a Telehealth Delivered Pulmonary Rehabilitation (TelePR) programme for Hispanic and African Patients hospitalized for COPD exacerbations
Methods	Single-cent r e RCT with 8 weeks ' and 6 months ' follow-up Aim: to test whether a referral to TelePRversus SPR resulted in decreased 6-month re - admission among Hispanic or African American patients hospitalised for COPD exacerbation
Participants	People with moderate COPD, African-American/Hispanic, Spanish/English fluency, who are able to follow basic exercise instructions and use a stationary bike Important exclusion criteria are completion of pulmonary rehabilitation within the last year and weight < 300 lb
Interventions	Telehealth pulmonary rehabilitation, twice/week for 8 weeks Exercise bikes are equipped with software enabling respiratory therapist to remotely conduct pulmonary rehabilitation session with a patient while the patient is at home. Vital signs are continually monitored, and the RT is able to alert 911 (emergency services) if patient is in distress. Educational videos and stretches are also incorporated
Outcomes	Re - hospitalisation following exacerbation of COPD, 2-minute s tep test, CAT, mMRC, Bristol COPD Knowledge Questionnaire, depression, patient adherence, acceptability
Starting date	Starting date: April 2017; estimated completion date: November 2020
Contact information	Prof Negin Hajizadeh; Nhajizadeh@northwell.edu
Notes	

Hansen 2017

Study name	COPD Online Rehabilitation (CORe) - a Randomized, Multicenter Telemedicine Intervention Study

Hansen 2017 *(Continued)*

Methods	Multi-centre (8 hospitals) RCT to compare the effects of supervised COPD online rehabilitation in groups, as delivered by health professionals in the patients' own home via a computer, for patients with severe and very severe COPD with conventional supervised COPD rehabilitation programme Follow-up duration: 12 months
Participants	Patients with severe and very severe (stage III or IV) COPD identified and recruited by respiratory nurses during outpatient COPD control visits at a respiratory and physiotherapy department
Interventions	Supervised online COPD rehabilitation, delivered in groups through a computer screen in the patient's own home. Rehabilitation contains exercise training and educational sessions 3 times per week for a duration of 10 weeks. Each session lasts 60 minutes (60% exercise, 40% education)
Outcomes	6MWD, 30 s sit-to-stand test, EQ-5D, CCQ, CAT, lung function, HADS, hospitalisation, exacerbation, mortality
Starting date	March 2016 ; actual completion date: 31 December 2019
Contact information	Henrik.hansen.09@regionh.dk
Notes	

NCT04136418

Study name	A Randomised Designed Clinical Investigation of the Use of a Personalised Early Warning Decision Support System With Novel Saliva Bio-profiling to Predict and Prevent Acute Exacerbations of Chronic Obstructive Pulmonary Disease
Methods	Multi-centre, open label RCT with 12 months ' follow-up Aim: t o investigate if a smart digital health intervention (COPDPredict™) can be used by both COPD patients and clinicians to improve self-management, predict lung attacks early, intervene promptly, and avoid hospitalisation
Participants	People with clinically diagnosed and confirmed COPD with ≥ 2 acute exacerbations of COPD (AECOPD) in the previous 12 months according to the patient and/or ≥ 1 hospital admission for AECOPD
Interventions	COPDPredict™, which consists of a patient-facing app and a clinician-facing smart early warning decision support system. The app on a mobile device is used by patient s to track the status of their COPD and to inform the patient's care team
Outcomes	AECOPD-related hospital admissions, inpatient days, COPD exacerbations, ED visits, symptom control markers, CAT, EQ-5D, lifestyle choices, FEV_1, C-reactive protein during exacerbations
Starting date	Starting date: September 2020; estimation completion date: September 2022
Contact information	Rachael O'Beney; Rachael.O'Beney@uhcw.nhs.uk
Notes	

NCT04416295

Study name	Selfcare MAnagement InteRvenTion in COPD (SMART COPD)
Methods	Single-cent r e RCT with 6 and 12 months ' follow-up Aim: to eval u ate a digital support and communication platform for COPD patients
Participants	People with diagnosed COPD
Interventions	LifePod: LifePod consists of a web-based E-health platform with 2 interfaces - 1 medical for health-care professionals and 1 patient interface. Patients can enter symptom parameters and vital parameters such as breathing and mucus status, weight, activity, medication, a nd other disease-specific values. Several different validated questionnaires are sent regularly to the patient to obtain information about the patient's mood and activity. The platform contains a chat function between healthcare professionals and patients. A unique health profile is created in which patient s self-report their health. P atient s receive direct feedback through the web application if they are within the interval given for the individual. Medical interfaces are designed so that patients are automatically placed in a priority order where by the person outside the given range is given top priority
Outcomes	mMRC, CAT, VAS, EQ-5D, ho s pitalisations, lengt h of stay, healthcare visits
Starting date	Starting date: Augu s t 2019; estimated completion date: April 2021
Contact information	Sofia Gerwards ; sofia.gerward@med.lu.se
Notes	

NCT04533412

Study name	Comprehensive Self-management Support for COPD Patients (SAMBA COPD)
Methods	Single-cent r e, double - blind RCT with 6 months ' follow-up
Participants	People aged 40 years or older with chart-document severe or very severe COPD (FEV_1 < 50% predicted) or COPD-related ED/hospitalisation ≥ 1 visit within the past 12 month s and smoking history ≥ 10 pack-years
Interventions	For the intervention, community health workers will assess barriers to good self-management behavio u rs that lie within 4 domains: (1) social context, (2) physical health and functioning, (3) cognitive factors, and (4) psychological factors. They will work with participants for 6 months to help them work through their barriers to self-management of COPD. Participants can also participate in home-based pulmonary rehabilitation and can receive emergency pack/action pack medication for COPD exacerbation. The attention control is designed to isolate the impact of screening for self-management barriers. The attention control will consist of 4 visits by a COPD educator who will review a COPD education booklet
Outcomes	CAT, Medication Adherence Report Scale, 6MWD
Starting date	Starting date: August 2020; estimated completion date: April 2022
Contact information	Shynah James; shynah.james@mountsinai.org
Notes	

Steed 2017

Study name	TANDEM study - Tailored intervention for ANxiety and DEpression Management in COPD
Methods	RCT with 6 and 12 months' follow-up to investigate whether a cognitive-behavioural approach (CBA) intervention, delivered prior to PR, can help to improve mild to moderate anxiety and/or depression in those with moderate to very severe COPD and consequently encourage PR uptake/completion (phase III of the TANDEM study)
Participants	Adults living with COPD recruited from primary care, community clinics, or secondary care clinics, or following referral to PR services, who have symptoms of mild to moderate comorbid anxiety or depression on screening; caregivers of patients
Interventions	A tailored, psychological intervention for mild to moderate anxiety and/or depression in people with chronic obstructive pulmonary disease (COPD)
Outcomes	Anxiety, depression (primary outcomes), dyspnoea, health-related quality of life, functional activity, smoking status, process outcomes, cost-effectiveness outcomes
Starting date	April 2016
Contact information	s.j.c.taylor@qmul.ac.uk
Notes	

6MWD: six-minute walking distance.
AECOPD : acute exacerbation of COPD .
ADL: activities of daily living.
BMI: body mass index.
BODE: BMI, airflow Obstruction, Dyspnoea, and Exercise Capacity.
CAT: COPD Assessment Test .
CCQ: COPD Control Questionnaire .
COPD: chronic obstructive pulmonary disease.
DM: diabetes mellitus .
ED: emergency department .
EQ-5D: EuroQol Quality of Life - 5 domain s.
FEV_1: forced expiratory volume in one second .
FVC: forced vital capacity .
GOLD: Global Initiative for Chronic Obstructive Lung Disease.
HADS: Hospital Anxiety and Depression S cale .
HF: heart failure .
IDM: integrated disease management.
m MRC: modified Medical Research Council D yspnoea Scale .
PAM: patient activation measure.
RCT: randomised controlled trial.
VAS: visual analogue scale .

DATA AND ANALYSES

Comparison 1. Integrated disease management versus control, update

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 SGRQ: short-term (≤ 6 months)	16		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1.1 SGRQ: total	16	1788	Mean Difference (IV, Random, 95% CI)	-3.78 [-6.29, -1.28]
1.1.2 SGRQ: symptoms	13	1327	Mean Difference (IV, Random, 95% CI)	-1.56 [-5.66, 2.53]
1.1.3 SGRQ: activity	13	1320	Mean Difference (IV, Random, 95% CI)	-3.04 [-5.80, -0.28]
1.1.4 SGRQ: impact	13	1322	Mean Difference (IV, Random, 95% CI)	-3.76 [-5.94, -1.57]
1.2 SGRQ: medium-term (> 6 to 15 months)	18		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.2.1 SGRQ: total	18	4321	Mean Difference (IV, Random, 95% CI)	-3.89 [-6.16, -1.63]
1.2.2 SGRQ: symptoms	12	2628	Mean Difference (IV, Random, 95% CI)	-3.88 [-7.75, -0.02]
1.2.3 SGRQ: activity	12	2608	Mean Difference (IV, Random, 95% CI)	-2.57 [-5.53, 0.38]
1.2.4 SGRQ: impact	12	2610	Mean Difference (IV, Random, 95% CI)	-3.34 [-6.26, -0.41]
1.3 SGRQ: long-term (> 15 months)	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.3.1 SGRQ: total	4	1090	Mean Difference (IV, Random, 95% CI)	-0.69 [-3.31, 1.93]
1.3.2 SGRQ: symptoms	3	279	Mean Difference (IV, Random, 95% CI)	2.35 [-5.49, 10.19]
1.3.3 SGRQ: activity	3	278	Mean Difference (IV, Random, 95% CI)	-2.87 [-6.17, 0.43]
1.3.4 SGRQ: impact	3	270	Mean Difference (IV, Random, 95% CI)	-2.21 [-4.71, 0.29]
1.4 Subgroup analysis SGRQ (total score, medium-term) based on type of setting	18	4321	Mean Difference (IV, Random, 95% CI)	-3.89 [-6.16, -1.63]
1.4.1 Primary care	6	1545	Mean Difference (IV, Random, 95% CI)	-1.18 [-3.55, 1.20]
1.4.2 Secondary care	9	2326	Mean Difference (IV, Random, 95% CI)	-1.38 [-3.23, 0.47]
1.4.3 Tertiary care	3	450	Mean Difference (IV, Random, 95% CI)	-14.58 [-21.56, -7.61]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5 Subgroup analysis SGRQ (total score, medium-term) based on study design	18	4321	Mean Difference (IV, Random, 95% CI)	-3.89 [-6.16, -1.63]
1.5.1 RCT	15	2901	Mean Difference (IV, Random, 95% CI)	-4.98 [-7.93, -2.02]
1.5.2 Cluster-RCT	3	1420	Mean Difference (IV, Random, 95% CI)	-0.38 [-1.60, 0.83]
1.6 Subgroup analysis SGRQ (total score, medium-term) based on dominant component of intervention	17	4099	Mean Difference (IV, Random, 95% CI)	-4.20 [-6.66, -1.73]
1.6.1 Education	2	294	Mean Difference (IV, Random, 95% CI)	0.15 [-2.70, 3.00]
1.6.2 Self-management	5	1825	Mean Difference (IV, Random, 95% CI)	-1.62 [-4.01, 0.77]
1.6.3 Telemonitoring	2	195	Mean Difference (IV, Random, 95% CI)	-18.33 [-26.72, -9.94]
1.6.4 Exercise	4	175	Mean Difference (IV, Random, 95% CI)	-3.92 [-9.95, 2.11]
1.6.5 Structural follow-up	5	1610	Mean Difference (IV, Random, 95% CI)	-4.19 [-9.48, 1.09]
1.7 Subgroup analysis SGRQ (total score, medium-term) based on region	18	4321	Mean Difference (IV, Random, 95% CI)	-3.89 [-6.16, -1.63]
1.7.1 North America	4	1147	Mean Difference (IV, Random, 95% CI)	-2.50 [-4.98, -0.02]
1.7.2 Northwestern Europe	4	1286	Mean Difference (IV, Random, 95% CI)	-0.12 [-1.98, 1.74]
1.7.3 Southern Europe	3	227	Mean Difference (IV, Random, 95% CI)	-11.42 [-17.38, -5.45]
1.7.4 Oceania	3	380	Mean Difference (IV, Random, 95% CI)	-0.23 [-2.61, 2.16]
1.7.5 East Asia	3	385	Mean Difference (IV, Random, 95% CI)	-10.08 [-21.59, 1.43]
1.7.6 Western Asia	1	896	Mean Difference (IV, Random, 95% CI)	-0.47 [-2.95, 2.01]
1.8 CRQ: short-term (≤ 6 months)	5		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.8.1 CRQ: dyspnoea	4	277	Mean Difference (IV, Random, 95% CI)	0.80 [-0.01, 1.62]
1.8.2 CRQ: fatigue	5	314	Mean Difference (IV, Random, 95% CI)	0.71 [-0.19, 1.62]
1.8.3 CRQ: emotion	5	314	Mean Difference (IV, Random, 95% CI)	0.45 [-0.26, 1.17]
1.8.4 CRQ: mastery	5	314	Mean Difference (IV, Random, 95% CI)	0.72 [-0.08, 1.52]
1.9 CRQ: medium-term (> 6 to 15 months)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.9.1 CRQ: dyspnoea	2	219	Mean Difference (IV, Random, 95% CI)	0.29 [-0.88, 1.46]
1.9.2 CRQ: fatigue	3	255	Mean Difference (IV, Random, 95% CI)	0.37 [-0.53, 1.26]
1.9.3 CRQ: emotion	3	255	Mean Difference (IV, Random, 95% CI)	0.36 [-0.84, 1.57]
1.9.4 CRQ: mastery	3	255	Mean Difference (IV, Random, 95% CI)	0.76 [-0.41, 1.94]
1.10 CRQ: long-term (> 15 months)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.10.1 CRQ: dyspnoea	2	151	Mean Difference (IV, Random, 95% CI)	0.47 [-0.31, 1.25]
1.10.2 CRQ: fatigue	3	184	Mean Difference (IV, Random, 95% CI)	0.46 [0.06, 0.85]
1.10.3 CRQ: emotion	3	184	Mean Difference (IV, Random, 95% CI)	0.52 [0.10, 0.95]
1.10.4 CRQ: mastery	3	184	Mean Difference (IV, Random, 95% CI)	0.83 [0.41, 1.26]
1.11 SF-36	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.11.1 SF-36 MCS score	5	3699	Mean Difference (IV, Random, 95% CI)	0.36 [-0.38, 1.11]
1.11.2 SF-36 PCS score	5	3704	Mean Difference (IV, Random, 95% CI)	1.06 [-0.67, 2.79]
1.12 General health QoL: SIP mean difference	2		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.12.1 SIP total	2	183	Mean Difference (IV, Random, 95% CI)	-1.06 [-3.00, 0.89]
1.12.2 SIP: physical	2	183	Mean Difference (IV, Random, 95% CI)	-2.63 [-5.55, 0.30]
1.12.3 SIP: psychosocial	2	183	Mean Difference (IV, Random, 95% CI)	-0.86 [-3.17, 1.44]
1.13 Functional exercise capacity: 6MWD	25		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.13.1 6MWD: short-term (≤ 6 months)	17	1390	Mean Difference (IV, Random, 95% CI)	52.56 [32.39, 72.74]
1.13.2 6MWD: medium-term (> 6 months to 15 months)	13	2071	Mean Difference (IV, Random, 95% CI)	44.69 [24.01, 65.37]
1.13.3 6MWD: long-term (> 15 months)	6	7288	Mean Difference (IV, Random, 95% CI)	48.43 [16.37, 80.49]
1.14 Subgroup analysis 6MWD (medium-term) based on type of setting	13	2071	Mean Difference (IV, Random, 95% CI)	43.21 [24.97, 61.44]
1.14.1 Primary care	2	79	Mean Difference (IV, Random, 95% CI)	59.65 [21.96, 97.33]
1.14.2 Secondary or tertiary care	7	1368	Mean Difference (IV, Random, 95% CI)	25.01 [-0.20, 50.21]
1.14.3 Tertiary care	4	624	Mean Difference (IV, Random, 95% CI)	60.41 [35.87, 84.96]
1.15 Subgroup analysis 6MWD (medium-term) based on dominant component of intervention	13	2071	Mean Difference (IV, Random, 95% CI)	43.21 [24.97, 61.44]
1.15.1 Education	1	85	Mean Difference (IV, Random, 95% CI)	16.30 [-20.63, 53.23]
1.15.2 Self-management	1	36	Mean Difference (IV, Random, 95% CI)	1.70 [-52.65, 56.05]
1.15.3 Telemonitoring	2	195	Mean Difference (IV, Random, 95% CI)	59.94 [42.59, 77.29]
1.15.4 Exercise	4	189	Mean Difference (IV, Random, 95% CI)	68.21 [44.75, 91.68]
1.15.5 Structural follow-up	6	1566	Mean Difference (IV, Random, 95% CI)	35.14 [2.83, 67.45]
1.16 Subgroup analysis 6MWD (medium-term) based on region	13	2071	Mean Difference (IV, Random, 95% CI)	43.21 [24.97, 61.44]

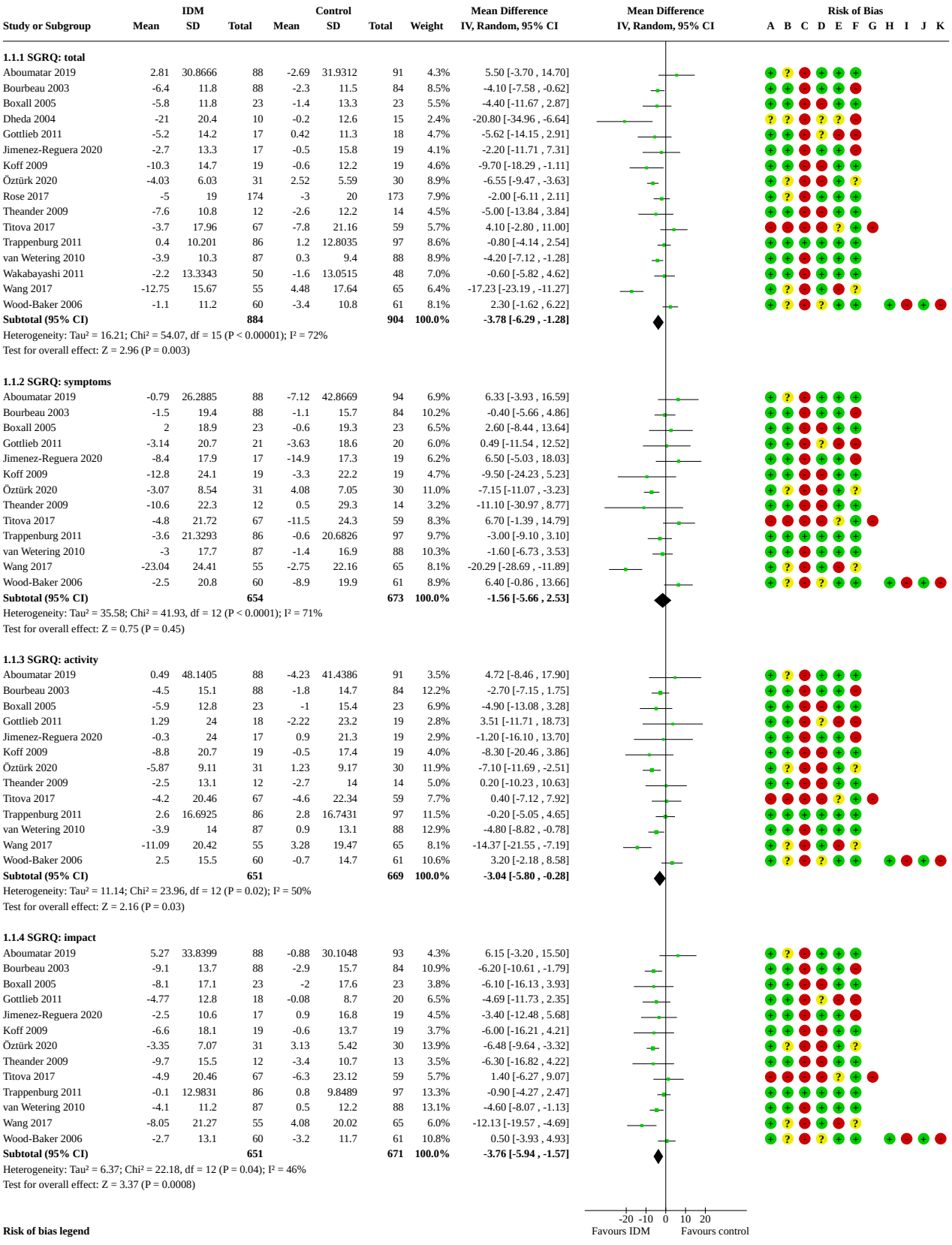
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.16.1 Northwestern Europe	3	221	Mean Difference (IV, Random, 95% CI)	18.18 [-7.87, 44.24]
1.16.2 Southern Europe	5	552	Mean Difference (IV, Random, 95% CI)	61.73 [36.74, 86.71]
1.16.3 East Asia	4	559	Mean Difference (IV, Random, 95% CI)	42.67 [13.94, 71.41]
1.16.4 Western Asia	1	739	Mean Difference (IV, Random, 95% CI)	-4.50 [-23.63, 14.63]
1.17 Maximal exercise capacity: cycle test (W-max)	4	298	Mean Difference (IV, Random, 95% CI)	6.99 [2.96, 11.02]
1.18 Respiratory-related hospital admissions	14	4207	Odds Ratio (M-H, Random, 95% CI)	0.64 [0.50, 0.81]
1.18.1 Respiratory-related hospital admissions: short-term (≤ 6 months)	3	377	Odds Ratio (M-H, Random, 95% CI)	0.60 [0.30, 1.22]
1.18.2 Respiratory-related hospital admissions: medium-term (> 6 to 15 months)	9	2449	Odds Ratio (M-H, Random, 95% CI)	0.60 [0.44, 0.81]
1.18.3 Respiratory-related hospital admissions: long-term (> 15 months)	2	1381	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.59, 1.23]
1.19 Subgroup analysis respiratory-related hospital admissions (medium-term) based on type of setting	9	2449	Odds Ratio (M-H, Random, 95% CI)	0.60 [0.44, 0.81]
1.19.1 Primary care	2	225	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.21, 3.76]
1.19.2 Secondary or tertiary care	7	2224	Odds Ratio (M-H, Random, 95% CI)	0.56 [0.42, 0.76]
1.20 Subgroup analysis respiratory-related hospital admissions (medium-term) based on dominant component of intervention	9	2449	Odds Ratio (M-H, Random, 95% CI)	0.60 [0.44, 0.81]
1.20.1 Education	2	854	Odds Ratio (M-H, Random, 95% CI)	0.83 [0.47, 1.45]
1.20.2 Self-management	5	1353	Odds Ratio (M-H, Random, 95% CI)	0.55 [0.43, 0.71]
1.20.3 Telemonitoring	1	75	Odds Ratio (M-H, Random, 95% CI)	0.27 [0.09, 0.79]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.20.4 Structural follow-up	2	167	Odds Ratio (M-H, Random, 95% CI)	0.65 [0.08, 5.55]
1.21 Subgroup analysis respiratory-related hospital admissions (medium-term) based on region	8	2316	Odds Ratio (M-H, Random, 95% CI)	0.61 [0.44, 0.86]
1.21.1 North America	4	1788	Odds Ratio (M-H, Random, 95% CI)	0.69 [0.50, 0.94]
1.21.2 Northwestern Europe	1	201	Odds Ratio (M-H, Random, 95% CI)	0.43 [0.23, 0.82]
1.21.3 Southern Europe	2	235	Odds Ratio (M-H, Random, 95% CI)	0.35 [0.18, 0.68]
1.21.4 Oceania	1	92	Odds Ratio (M-H, Random, 95% CI)	1.89 [0.80, 4.45]
1.22 All hospital admissions	10	3244	Odds Ratio (M-H, Random, 95% CI)	0.75 [0.57, 0.98]
1.22.1 All hospital admissions: short-term (≤ 6 months)	1	112	Odds Ratio (M-H, Random, 95% CI)	0.31 [0.14, 0.67]
1.22.2 All hospital admissions: medium-term (> 6 months to 15 months)	5	1212	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.71, 1.21]
1.22.3 All hospital admissions: long-term (> 15 months)	4	1920	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.45, 1.16]
1.23 Hospital days per patient (all causes)	14	3563	Mean Difference (IV, Random, 95% CI)	-2.27 [-3.98, -0.56]
1.23.1 Hospital days per patient (all causes): short-term (≤ 6 months)	2	273	Mean Difference (IV, Random, 95% CI)	-4.36 [-6.41, -2.31]
1.23.2 Hospital days per patient (all causes): medium-term (> 6 to 15 months)	10	2944	Mean Difference (IV, Random, 95% CI)	-1.73 [-3.71, 0.25]
1.23.3 Hospital days per patient (all causes): long-term (> 15 months)	2	346	Mean Difference (IV, Random, 95% CI)	-1.60 [-6.12, 2.92]
1.24 ED visits	9	3005	Odds Ratio (M-H, Random, 95% CI)	0.69 [0.50, 0.93]
1.25 Number of patients experiencing ≥ 1 exacerbation	7	1378	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.65, 1.42]

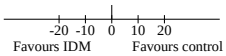
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.25.1 Number of patients experiencing ≥ 1 exacerbation: short-term (≤ 6 months)	1	216	Odds Ratio (M-H, Random, 95% CI)	1.17 [0.68, 1.99]
1.25.2 Number of patients experiencing ≥ 1 exacerbation: medium-term (> 6 months to 15 months)	4	861	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.40, 1.27]
1.25.3 Number of patients experiencing ≥ 1 exacerbation: long-term (> 15 months)	2	301	Odds Ratio (M-H, Random, 95% CI)	1.53 [0.90, 2.61]
1.26 Number of patients using ≥ 1 course of oral steroids	4	433	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.66, 1.64]
1.27 Number of patients using ≥ 1 course of antibiotics	3	321	Odds Ratio (M-H, Random, 95% CI)	1.46 [0.51, 4.18]
1.28 MRC dyspnoea score	13		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.28.1 MRC dyspnoea score: short-term (≤ 6 months)	8	1132	Mean Difference (IV, Random, 95% CI)	-0.33 [-0.52, -0.15]
1.28.2 MRC dyspnoea score: medium-term (> 6 months to 15 months)	7	2753	Mean Difference (IV, Random, 95% CI)	-0.61 [-0.98, -0.23]
1.28.3 MRC dyspnoea score: long-term (> 15 months)	3	7252	Mean Difference (IV, Random, 95% CI)	-0.37 [-0.88, 0.14]
1.29 Borg score	3	145	Mean Difference (IV, Random, 95% CI)	0.14 [-0.70, 0.98]
1.30 Mortality	15	4745	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.59, 1.25]
1.30.1 Mortality: short-term (≤ 6 months)	2	320	Odds Ratio (M-H, Random, 95% CI)	1.10 [0.41, 2.93]
1.30.2 Mortality: medium-term (> 6 months to 15 months)	9	2603	Odds Ratio (M-H, Random, 95% CI)	0.80 [0.45, 1.43]
1.30.3 Mortality: long-term (> 15 months)	4	1822	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.48, 1.57]
1.31 FEV_1 (litre)	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.31.1 FEV_1 (litre): short-term (< 6 months)	2	184	Mean Difference (IV, Random, 95% CI)	0.19 [-0.17, 0.55]
1.31.2 FEV_1 (litre): medium-term (> 6 months to 15 months)	4	1344	Mean Difference (IV, Random, 95% CI)	0.04 [-0.05, 0.12]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.31.3 FEV_1 (litre): long-term (> 15 months)	3	1047	Mean Difference (IV, Random, 95% CI)	0.05 [-0.08, 0.18]
1.32 FEV_1 (% predicted)	15		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.32.1 FEV_1 (% predicted): short-term (≤ 6 months)	7	954	Mean Difference (IV, Random, 95% CI)	2.88 [1.35, 4.40]
1.32.2 FEV_1 (% predicted) medium-term (> 6 to 15 months)	10	1902	Mean Difference (IV, Random, 95% CI)	0.95 [-0.20, 2.11]
1.32.3 FEV_1 (% predicted): long-term (> 15 months)	5	7328	Mean Difference (IV, Random, 95% CI)	1.18 [-0.82, 3.18]
1.33 Anxiety and depression (HADS)	8		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.33.1 HADS: anxiety	8	1580	Mean Difference (IV, Random, 95% CI)	0.09 [-0.30, 0.47]
1.33.2 HADS: depression	8	1584	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.45, 0.05]
1.34 SGRQ total score	25		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.34.1 Short-term	16	1788	Mean Difference (IV, Random, 95% CI)	-3.78 [-6.29, -1.28]
1.34.2 Medium-term	18	4321	Mean Difference (IV, Random, 95% CI)	-3.89 [-6.16, -1.63]
1.34.3 Long-term	4	1090	Mean Difference (IV, Random, 95% CI)	-0.69 [-3.31, 1.93]

Analysis 1.1. Comparison 1: Integrated disease management versus control, update, Outcome 1: SGRQ: short-term (≤ 6 months)



Analysis 1.1. (Continued)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias
(H) Recruitment bias
(I) Baseline imbalance between groups
(J) Loss to follow-up of clusters
(K) Adequate analysis methods for CRT

Analysis 1.2. Comparison 1: Integrated disease management versus control, update, Outcome 2: SGRQ: medium-term (> 6 to 15 months)

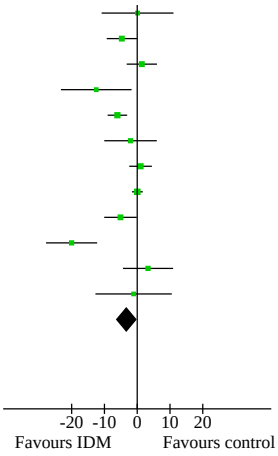
Study or Subgroup	IDM Mean	IDM SD	IDM Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.2.1 SGRQ: total								
Engstrom 1999	0.3	17.3	26	0.5	16.8	24	3.2%	-0.20 [-9.65 , 9.25]
Bourbeau 2003	-3.5	13.5674	81	-1.5	10.5028	76	6.2%	-2.00 [-5.78 , 1.78]
Boxall 2005	-5.8	10.14	23	-1.4	11.82	23	4.7%	-4.40 [-10.76 , 1.96]
Wood-Baker 2006	-0.3	10.8	54	-2	11.5	58	6.0%	1.70 [-2.43 , 5.83]
Fernandez 2009	-14.7	12.82	27	-2.5	11.96	14	3.9%	-12.20 [-20.11 , -4.29]
Rice 2010	1.3	13.21	225	6.24	13.44	209	6.9%	-4.94 [-7.45 , -2.43]
Gottlieb 2011	-0.32	14.42	18	-2.69	13.06	20	3.5%	2.37 [-6.41 , 11.15]
Wakabayashi 2011	0.2	14.59	42	1	20.26	43	4.1%	-0.80 [-8.29 , 6.69]
Fan 2012	-1.36	11.2	101	-1.67	11.5	108	6.6%	0.31 [-2.77 , 3.39]
Kruis 2014	-0.4	12.69	554	0.33	12.69	532	7.2%	-0.73 [-2.24 , 0.78]
Zwar 2016	-2.05	8.9	126	-1.84	8.9	96	6.9%	-0.21 [-2.57 , 2.15]
Ko 2016	-6.9	15.3	90	-0.1	13.8	90	5.9%	-6.80 [-11.06 , -2.54]
Vasilopoulou 2017	-8	19	50	6	11	25	4.5%	-14.00 [-20.81 , -7.19]
Vasilopoulou 2017	-10	15	50	6	11	25	4.9%	-16.00 [-21.99 , -10.01]
Titova 2017	-0.8	15.12	58	-5.6	18.63	54	4.7%	4.80 [-1.51 , 11.11]
Rose 2017	-5	17.84	174	-2	19.84	173	6.1%	-3.00 [-6.97 , 0.97]
Wang 2017	-15.85	17.25	55	6.71	19.34	65	4.6%	-22.56 [-29.11 , -16.01]
Kalter-Leibovici 2018	-7.24	18.29	489	-6.77	19.38	407	6.9%	-0.47 [-2.95 , 2.01]
Jimenez-Reguera 2020	-3.8	15.72	17	-3.6	13.67	19	3.2%	-0.20 [-9.88 , 9.48]
Subtotal (95% CI)			**2260**			**2061**	**100.0%**	**-3.89 [-6.16 , -1.63]**
Heterogeneity: Tau² = 17.82; Chi² = 105.33, df = 18 (P < 0.00001); I² = 83%								
Test for overall effect: Z = 3.37 (P = 0.0008)								
1.2.2 SGRQ: symptoms								
Engstrom 1999	-7.5	23.5	26	-4.1	23	24	5.3%	-3.40 [-16.29 , 9.49]
Bourbeau 2003	-3.1	20.3511	81	-4.9	17.5047	76	9.8%	1.80 [-4.13 , 7.73]
Wood-Baker 2006	-5.7	22.7	54	-4.4	19.2	58	8.4%	-1.30 [-9.11 , 6.51]
Fernandez 2009	-22.8	20.4	27	-9.1	17.3	14	5.8%	-13.70 [-25.59 , -1.81]
Rice 2010	-0.26	20.42	252	5.38	20.92	234	11.4%	-5.64 [-9.32 , -1.96]
Gottlieb 2011	-0.18	20.8	19	-6.33	17.9	20	5.6%	6.15 [-6.06 , 18.36]
Fan 2012	-1.56	14.9	101	1.62	14.7	108	11.2%	-3.18 [-7.20 , 0.84]
Kruis 2014	-0.75	19.84	554	0.22	19.84	532	12.1%	-0.97 [-3.33 , 1.39]
Ko 2016	-10.2	22.5	90	-3.2	21.3	90	9.4%	-7.00 [-13.40 , -0.60]
Wang 2017	-26.05	23.29	55	0.18	20.96	65	8.2%	-26.23 [-34.22 , -18.24]
Titova 2017	-1.8	21.76	58	-5.6	20.62	54	8.3%	3.80 [-4.05 , 11.65]
Jimenez-Reguera 2020	-3.6	24.2	17	-9.8	19	19	4.6%	6.20 [-8.13 , 20.53]
Subtotal (95% CI)			**1334**			**1294**	**100.0%**	**-3.88 [-7.75 , -0.02]**
Heterogeneity: Tau² = 30.65; Chi² = 51.23, df = 11 (P < 0.00001); I² = 79%								
Test for overall effect: Z = 1.97 (P = 0.05)								
1.2.3 SGRQ: activity								
Engstrom 1999	0.7	17.8	26	-0.4	14.2	24	6.3%	1.10 [-7.79 , 9.99]
Bourbeau 2003	0.8	15.8286	81	0.2	14.4414	76	10.6%	0.60 [-4.14 , 5.34]
Wood-Baker 2006	4.3	14.5	54	0.7	15.9	58	9.5%	3.60 [-2.03 , 9.23]
Fernandez 2009	-11.2	13.9	27	0	12.1	14	6.8%	-11.20 [-19.43 , -2.97]
Rice 2010	1.47	14.03	240	5.37	14.13	226	13.1%	-3.90 [-6.46 , -1.34]
Gottlieb 2011	3.32	24.8	19	-6.36	23	20	3.0%	9.68 [-5.35 , 24.71]
Fan 2012	-0.25	20.4	101	-1.31	18.2	108	9.9%	1.06 [-4.19 , 6.31]
Kruis 2014	0	18.07	554	1.25	18.07	532	13.4%	-1.25 [-3.40 , 0.90]
Ko 2016	-6.2	18	90	3.6	19.4	90	9.7%	-9.80 [-15.27 , -4.33]
Titova 2017	-2.2	19.43	58	-3	22.12	54	7.3%	0.80 [-6.93 , 8.53]
Wang 2017	-14.27	24.77	55	3.51	21.98	65	6.6%	-17.78 [-26.23 , -9.33]
Jimenez-Reguera 2020	7.3	22.4	17	5.7	16.3	19	3.8%	1.60 [-11.33 , 14.53]
Subtotal (95% CI)			**1322**			**1286**	**100.0%**	**-2.57 [-5.53 , 0.38]**
Heterogeneity: Tau² = 15.67; Chi² = 38.23, df = 11 (P < 0.0001); I² = 71%								
Test for overall effect: Z = 1.71 (P = 0.09)								
1.2.4 SGRQ: impact								
Engstrom 1999	2.6	19.4	26	2.5	20.1	24	4.6%	0.10 [-10.87 , 11.07]
Bourbeau 2003	-6.1	15.8286	81	-1.4	13.5662	76	10.1%	-4.70 [-9.30 , -0.10]
Wood-Baker 2006	1.2	13.3	54	2.6	11.5	58	10.1%	1.40 [-3.22 , 6.02]

Analysis 1.2. (Continued)

Engstrom 1999	2.6	19.4	26	2.5	20.1	24	4.6%	0.10 [-10.87 , 11.07]
Bourbeau 2003	-6.1	15.8286	81	-1.4	13.5662	76	10.1%	-4.70 [-9.30 , -0.10]
Wood-Baker 2006	-1.2	13.3	54	-2.6	11.5	58	10.1%	1.40 [-3.22 , 6.02]
Fernandez 2009	-14.3	16.3	27	-1.8	16.9	14	4.8%	-12.50 [-23.28 , -1.72]
Rice 2010	1.61	16.16	246	7.66	16.63	223	11.8%	-6.05 [-9.02 , -3.08]
Gottlieb 2011	-1.57	12	18	0.47	13.2	20	6.7%	-2.04 [-10.05 , 5.97]
Fan 2012	-1.92	12.2	101	-2.94	13.2	108	11.3%	1.02 [-2.42 , 4.46]
Kruis 2014	-0.31	13.96	554	-0.35	13.96	532	12.9%	0.04 [-1.62 , 1.70]
Ko 2016	-6.2	17.4	90	-1.1	16.6	90	9.7%	-5.10 [-10.07 , -0.13]
Wang 2017	-11.96	22.3	55	8.06	20.97	65	6.9%	-20.02 [-27.81 , -12.23]
Titova 2017	-0.9	19.82	58	-4.2	21.37	54	7.0%	3.30 [-4.35 , 10.95]
Jimenez-Reguera 2020	-10.2	19.2	17	-9.1	16.1	19	4.3%	-1.10 [-12.75 , 10.55]
Subtotal (95% CI)			**1327**			**1283**	**100.0%**	**-3.34 [-6.26 , -0.41]**

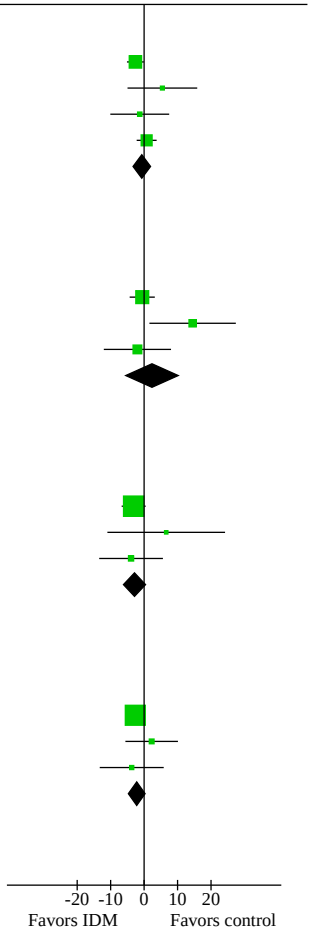
Heterogeneity: Tau² = 16.60; Chi² = 46.83, df = 11 (P < 0.00001); I² = 77%
Test for overall effect: Z = 2.24 (P = 0.03)

Test for subgroup differences: Chi² = 0.54, df = 3 (P = 0.91), I² = 0%

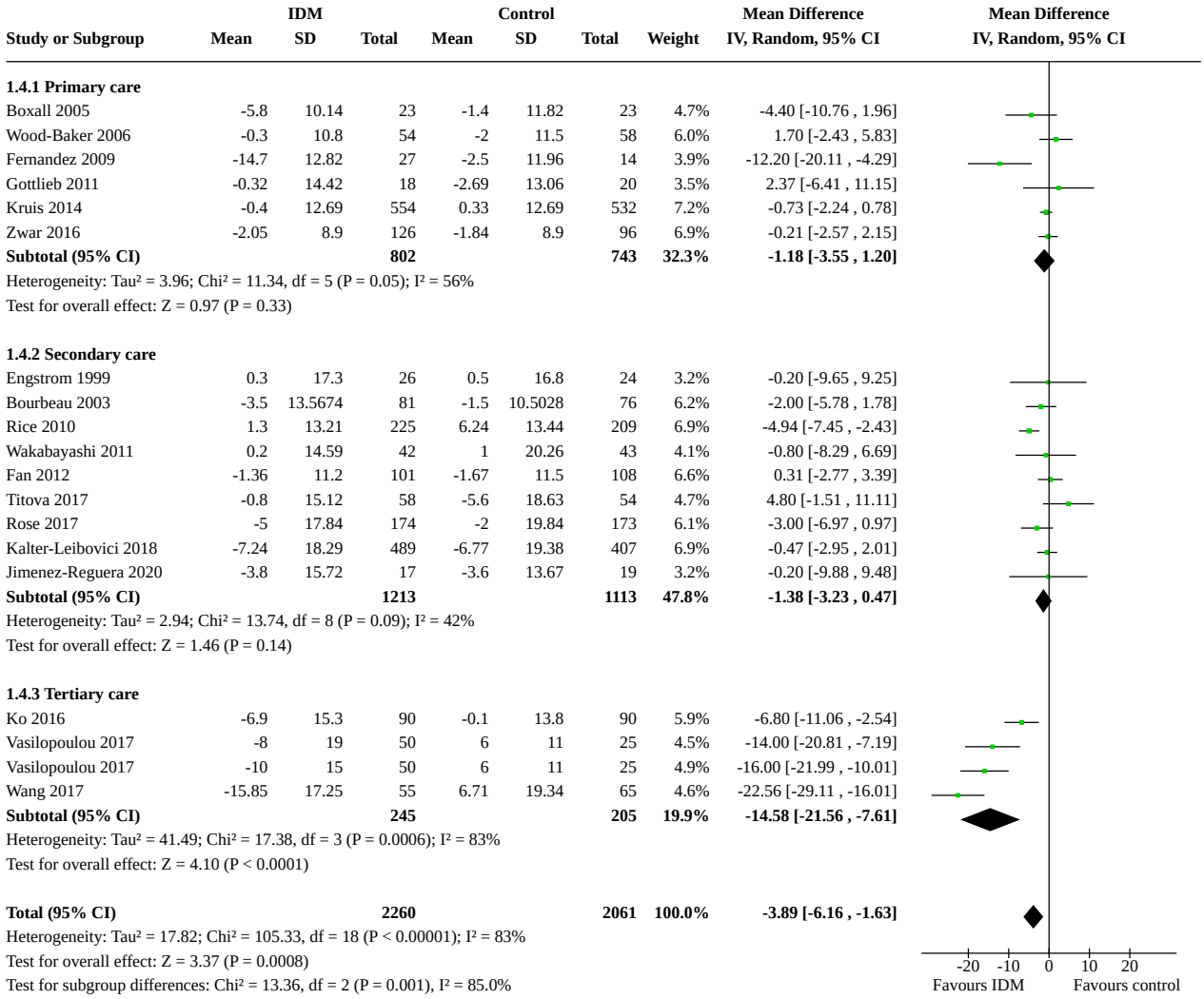


Analysis 1.3. Comparison 1: Integrated disease management versus control, update, Outcome 3: SGRQ: long-term (> 15 months)

Study or Subgroup	IDM Mean	IDM SD	IDM Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.3.1 SGRQ: total								
van Wetering 2010	-1.37	8.073	77	1.23	8.0498	80	46.5%	-2.60 [-5.12 , -0.08]
Gottlieb 2011	-0.47	17.8	15	-5.93	11	17	5.9%	5.46 [-4.96 , 15.88]
Titova 2017	-4.1	19.29	44	-2.8	22.67	44	8.0%	-1.30 [-10.10 , 7.50]
Kalter-Leibovici 2018	-6.87	21.24	457	-7.63	21.72	356	39.7%	0.76 [-2.22 , 3.74]
Subtotal (95% CI)			**593**			**497**	**100.0%**	**-0.69 [-3.31 , 1.93]**
Heterogeneity: Tau² = 2.18; Chi² = 4.37, df = 3 (P = 0.22); I² = 31%								
Test for overall effect: Z = 0.52 (P = 0.61)								
1.3.2 SGRQ: symptoms								
van Wetering 2010	-1.5	12.1095	77	-0.94	11.8959	80	49.0%	-0.56 [-4.32 , 3.20]
Gottlieb 2011	3.92	18.5	16	-10.58	19.9	18	22.1%	14.50 [1.59 , 27.41]
Titova 2017	-8	23.69	44	-6	24.37	44	29.0%	-2.00 [-12.04 , 8.04]
Subtotal (95% CI)			**137**			**142**	**100.0%**	**2.35 [-5.49 , 10.19]**
Heterogeneity: Tau² = 29.01; Chi² = 5.05, df = 2 (P = 0.08); I² = 60%								
Test for overall effect: Z = 0.59 (P = 0.56)								
1.3.3 SGRQ: activity								
van Wetering 2010	-1.29	11.4952	77	1.83	11.4487	80	84.5%	-3.12 [-6.71 , 0.47]
Gottlieb 2011	-0.61	28.4	16	-7.22	22.6	17	3.5%	6.61 [-10.97 , 24.19]
Titova 2017	-4.4	22.2	44	-0.5	23.35	44	12.0%	-3.90 [-13.42 , 5.62]
Subtotal (95% CI)			**137**			**141**	**100.0%**	**-2.87 [-6.17 , 0.43]**
Heterogeneity: Tau² = 0.00; Chi² = 1.18, df = 2 (P = 0.55); I² = 0%								
Test for overall effect: Z = 1.71 (P = 0.09)								
1.3.4 SGRQ: impact								
van Wetering 2010	-1.34	8.3666	70	1.29	8.7654	80	83.0%	-2.63 [-5.37 , 0.11]
Gottlieb 2011	-0.74	14.3	15	-3	6.4	17	10.1%	2.26 [-5.59 , 10.11]
Titova 2017	-4.2	21.66	44	-0.5	24.03	44	6.8%	-3.70 [-13.26 , 5.86]
Subtotal (95% CI)			**129**			**141**	**100.0%**	**-2.21 [-4.71 , 0.29]**
Heterogeneity: Tau² = 0.00; Chi² = 1.43, df = 2 (P = 0.49); I² = 0%								
Test for overall effect: Z = 1.73 (P = 0.08)								



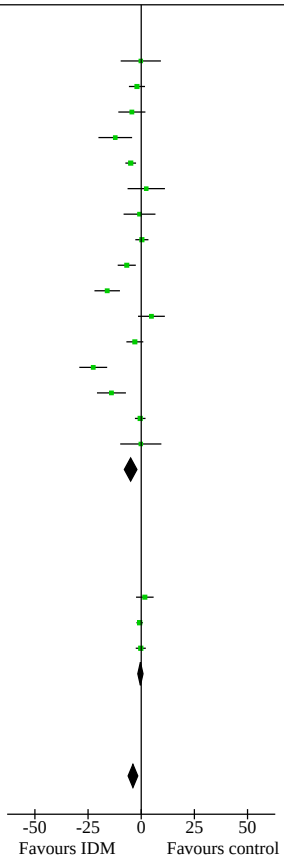
Analysis 1.4. Comparison 1: Integrated disease management versus control, update, Outcome 4: Subgroup analysis SGRQ (total score, medium-term) based on type of setting



Study or Subgroup	IDM Mean	IDM SD	IDM Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.4.1 Primary care								
Boxall 2005	-5.8	10.14	23	-1.4	11.82	23	4.7%	-4.40 [-10.76 , 1.96]
Wood-Baker 2006	-0.3	10.8	54	-2	11.5	58	6.0%	1.70 [-2.43 , 5.83]
Fernandez 2009	-14.7	12.82	27	-2.5	11.96	14	3.9%	-12.20 [-20.11 , -4.29]
Gottlieb 2011	-0.32	14.42	18	-2.69	13.06	20	3.5%	2.37 [-6.41 , 11.15]
Kruis 2014	-0.4	12.69	554	0.33	12.69	532	7.2%	-0.73 [-2.24 , 0.78]
Zwar 2016	-2.05	8.9	126	-1.84	8.9	96	6.9%	-0.21 [-2.57 , 2.15]
Subtotal (95% CI)			**802**			**743**	**32.3%**	**-1.18 [-3.55 , 1.20]**
Heterogeneity: Tau² = 3.96; Chi² = 11.34, df = 5 (P = 0.05); I² = 56%								
Test for overall effect: Z = 0.97 (P = 0.33)								
1.4.2 Secondary care								
Engstrom 1999	0.3	17.3	26	0.5	16.8	24	3.2%	-0.20 [-9.65 , 9.25]
Bourbeau 2003	-3.5	13.5674	81	-1.5	10.5028	76	6.2%	-2.00 [-5.78 , 1.78]
Rice 2010	1.3	13.21	225	6.24	13.44	209	6.9%	-4.94 [-7.45 , -2.43]
Wakabayashi 2011	0.2	14.59	42	1	20.26	43	4.1%	-0.80 [-8.29 , 6.69]
Fan 2012	-1.36	11.2	101	-1.67	11.5	108	6.6%	0.31 [-2.77 , 3.39]
Titova 2017	-0.8	15.12	58	-5.6	18.63	54	4.7%	4.80 [-1.51 , 11.11]
Rose 2017	-5	17.84	174	-2	19.84	173	6.1%	-3.00 [-6.97 , 0.97]
Kalter-Leibovici 2018	-7.24	18.29	489	-6.77	19.38	407	6.9%	-0.47 [-2.95 , 2.01]
Jimenez-Reguera 2020	-3.8	15.72	17	-3.6	13.67	19	3.2%	-0.20 [-9.88 , 9.48]
Subtotal (95% CI)			**1213**			**1113**	**47.8%**	**-1.38 [-3.23 , 0.47]**
Heterogeneity: Tau² = 2.94; Chi² = 13.74, df = 8 (P = 0.09); I² = 42%								
Test for overall effect: Z = 1.46 (P = 0.14)								
1.4.3 Tertiary care								
Ko 2016	-6.9	15.3	90	-0.1	13.8	90	5.9%	-6.80 [-11.06 , -2.54]
Vasilopoulou 2017	-8	19	50	6	11	25	4.5%	-14.00 [-20.81 , -7.19]
Vasilopoulou 2017	-10	15	50	6	11	25	4.9%	-16.00 [-21.99 , -10.01]
Wang 2017	-15.85	17.25	55	6.71	19.34	65	4.6%	-22.56 [-29.11 , -16.01]
Subtotal (95% CI)			**245**			**205**	**19.9%**	**-14.58 [-21.56 , -7.61]**
Heterogeneity: Tau² = 41.49; Chi² = 17.38, df = 3 (P = 0.0006); I² = 83%								
Test for overall effect: Z = 4.10 (P < 0.0001)								
Total (95% CI)			**2260**			**2061**	**100.0%**	**-3.89 [-6.16 , -1.63]**
Heterogeneity: Tau² = 17.82; Chi² = 105.33, df = 18 (P < 0.00001); I² = 83%								
Test for overall effect: Z = 3.37 (P = 0.0008)								
Test for subgroup differences: Chi² = 13.36, df = 2 (P = 0.001), I² = 85.0%								

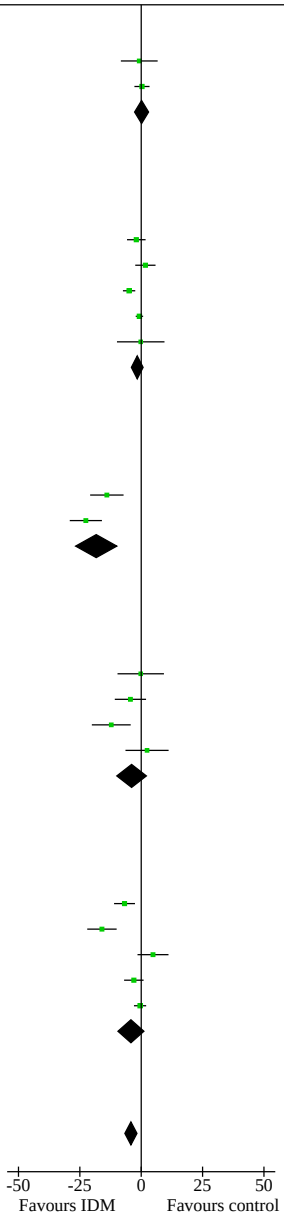
Analysis 1.5. Comparison 1: Integrated disease management versus control, update, Outcome 5: Subgroup analysis SGRQ (total score, medium-term) based on study design

Study or Subgroup	IDM Mean	IDM SD	IDM Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.5.1 RCT								
Engstrom 1999	0.3	17.3	26	0.5	16.8	24	3.2%	-0.20 [-9.65 , 9.25]
Bourbeau 2003	-3.5	13.5674	81	-1.5	10.5028	76	6.2%	-2.00 [-5.78 , 1.78]
Boxall 2005	-5.8	10.14	23	-1.4	11.82	23	4.7%	-4.40 [-10.76 , 1.96]
Fernandez 2009	-14.7	12.82	27	-2.5	11.96	14	3.9%	-12.20 [-20.11 , -4.29]
Rice 2010	1.3	13.21	225	6.24	13.44	209	6.9%	-4.94 [-7.45 , -2.43]
Gottlieb 2011	-0.32	14.42	18	-2.69	13.06	20	3.5%	2.37 [-6.41 , 11.15]
Wakabayashi 2011	0.2	14.59	42	1	20.26	43	4.1%	-0.80 [-8.29 , 6.69]
Fan 2012	-1.36	11.2	101	-1.67	11.5	108	6.6%	0.31 [-2.77 , 3.39]
Ko 2016	-6.9	15.3	90	-0.1	13.8	90	5.9%	-6.80 [-11.06 , -2.54]
Vasilopoulou 2017	-10	15	50	6	11	25	4.9%	-16.00 [-21.99 , -10.01]
Titova 2017	-0.8	15.12	58	-5.6	18.63	54	4.7%	4.80 [-1.51 , 11.11]
Rose 2017	-5	17.84	174	-2	19.84	173	6.1%	-3.00 [-6.97 , 0.97]
Wang 2017	-15.85	17.25	55	6.71	19.34	65	4.6%	-22.56 [-29.11 , -16.01]
Vasilopoulou 2017	-8	19	50	6	11	25	4.5%	-14.00 [-20.81 , -7.19]
Kalter-Leibovici 2018	-7.24	18.29	489	-6.77	19.38	407	6.9%	-0.47 [-2.95 , 2.01]
Jimenez-Reguera 2020	-3.8	15.72	17	-3.6	13.67	19	3.2%	-0.20 [-9.88 , 9.48]
Subtotal (95% CI)			**1526**			**1375**	**79.8%**	**-4.98 [-7.93 , -2.02]**
Heterogeneity: Tau² = 27.05; Chi² = 88.62, df = 15 (P < 0.00001); I² = 83%								
Test for overall effect: Z = 3.30 (P = 0.0010)								
1.5.2 Cluster-RCT								
Wood-Baker 2006	-0.3	10.8	54	-2	11.5	58	6.0%	1.70 [-2.43 , 5.83]
Kruis 2014	-0.4	12.69	554	0.33	12.69	532	7.2%	-0.73 [-2.24 , 0.78]
Zwar 2016	-2.05	8.9	126	-1.84	8.9	96	6.9%	-0.21 [-2.57 , 2.15]
Subtotal (95% CI)			**734**			**686**	**20.2%**	**-0.38 [-1.60 , 0.83]**
Heterogeneity: Tau² = 0.00; Chi² = 1.20, df = 2 (P = 0.55); I² = 0%								
Test for overall effect: Z = 0.62 (P = 0.54)								
Total (95% CI)			**2260**			**2061**	**100.0%**	**-3.89 [-6.16 , -1.63]**
Heterogeneity: Tau² = 17.82; Chi² = 105.33, df = 18 (P < 0.00001); I² = 83%								
Test for overall effect: Z = 3.37 (P = 0.0008)								
Test for subgroup differences: Chi² = 7.94, df = 1 (P = 0.005), I² = 87.4%								

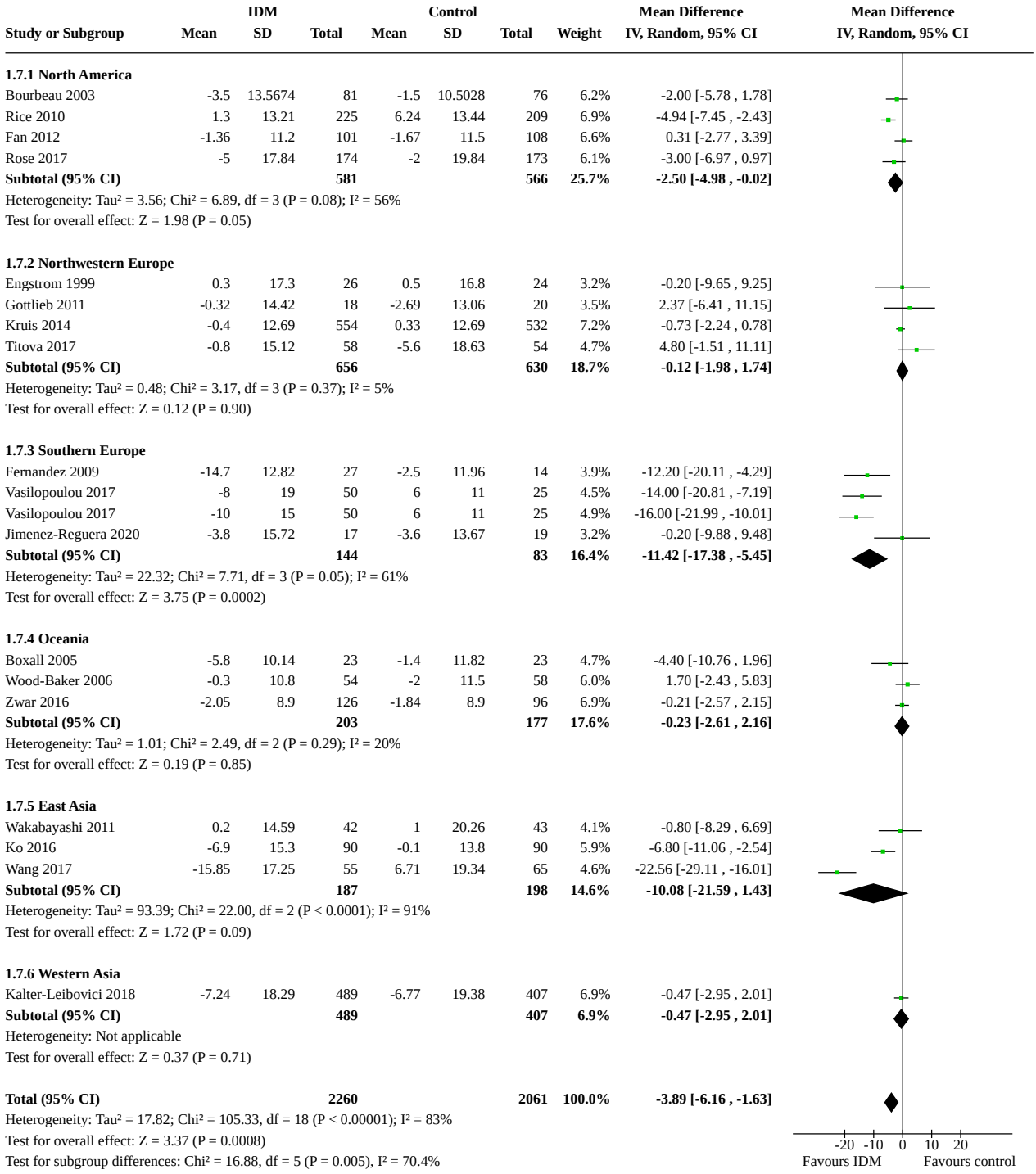


Analysis 1.6. Comparison 1: Integrated disease management versus control, update, Outcome 6: Subgroup analysis SGRQ (total score, medium-term) based on dominant component of intervention

Study or Subgroup	IDM Mean	IDM SD	IDM Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.6.1 Education								
Wakabayashi 2011	0.2	14.59	42	1	20.26	43	4.5%	-0.80 [-8.29 , 6.69]
Fan 2012	-1.36	11.2	101	-1.67	11.5	108	6.9%	0.31 [-2.77 , 3.39]
Subtotal (95% CI)			**143**			**151**	**11.5%**	**0.15 [-2.70 , 3.00]**
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.79); I² = 0%								
Test for overall effect: Z = 0.10 (P = 0.92)								
1.6.2 Self-management								
Bourbeau 2003	-3.5	13.5674	81	-1.5	10.5028	76	6.6%	-2.00 [-5.78 , 1.78]
Wood-Baker 2006	-0.3	10.8	54	-2	11.5	58	6.4%	1.70 [-2.43 , 5.83]
Rice 2010	1.3	13.21	225	6.24	13.44	209	7.2%	-4.94 [-7.45 , -2.43]
Kruis 2014	-0.4	12.69	554	0.33	12.69	532	7.6%	-0.73 [-2.24 , 0.78]
Jimenez-Reguera 2020	-3.8	15.72	17	-3.6	13.67	19	3.5%	-0.20 [-9.88 , 9.48]
Subtotal (95% CI)			**931**			**894**	**31.2%**	**-1.62 [-4.01 , 0.77]**
Heterogeneity: Tau² = 4.03; Chi² = 10.65, df = 4 (P = 0.03); I² = 62%								
Test for overall effect: Z = 1.33 (P = 0.18)								
1.6.3 Telemonitoring								
Vasilopoulou 2017	-8	19	50	6	11	25	4.9%	-14.00 [-20.81 , -7.19]
Wang 2017	-15.85	17.25	55	6.71	19.34	65	5.0%	-22.56 [-29.11 , -16.01]
Subtotal (95% CI)			**105**			**90**	**9.9%**	**-18.33 [-26.72 , -9.94]**
Heterogeneity: Tau² = 25.02; Chi² = 3.15, df = 1 (P = 0.08); I² = 68%								
Test for overall effect: Z = 4.28 (P < 0.0001)								
1.6.4 Exercise								
Engstrom 1999	0.3	17.3	26	0.5	16.8	24	3.6%	-0.20 [-9.65 , 9.25]
Boxall 2005	-5.8	10.14	23	-1.4	11.82	23	5.1%	-4.40 [-10.76 , 1.96]
Fernandez 2009	-14.7	12.82	27	-2.5	11.96	14	4.3%	-12.20 [-20.11 , -4.29]
Gottlieb 2011	-0.32	14.42	18	-2.69	13.06	20	3.9%	2.37 [-6.41 , 11.15]
Subtotal (95% CI)			**94**			**81**	**17.0%**	**-3.92 [-9.95 , 2.11]**
Heterogeneity: Tau² = 20.88; Chi² = 6.77, df = 3 (P = 0.08); I² = 56%								
Test for overall effect: Z = 1.28 (P = 0.20)								
1.6.5 Structural follow-up								
Ko 2016	-6.9	15.3	90	-0.1	13.8	90	6.3%	-6.80 [-11.06 , -2.54]
Vasilopoulou 2017	-10	15	50	6	11	25	5.3%	-16.00 [-21.99 , -10.01]
Titova 2017	-0.8	15.12	58	-5.6	18.63	54	5.1%	4.80 [-1.51 , 11.11]
Rose 2017	-5	17.84	174	-2	19.84	173	6.5%	-3.00 [-6.97 , 0.97]
Kalter-Leibovici 2018	-7.24	18.29	489	-6.77	19.38	407	7.2%	-0.47 [-2.95 , 2.01]
Subtotal (95% CI)			**861**			**749**	**30.5%**	**-4.19 [-9.48 , 1.09]**
Heterogeneity: Tau² = 30.62; Chi² = 30.99, df = 4 (P < 0.00001); I² = 87%								
Test for overall effect: Z = 1.56 (P = 0.12)								
Total (95% CI)			**2134**			**1965**	**100.0%**	**-4.20 [-6.66 , -1.73]**
Heterogeneity: Tau² = 20.32; Chi² = 102.28, df = 17 (P < 0.00001); I² = 83%								
Test for overall effect: Z = 3.34 (P = 0.0008)								
Test for subgroup differences: Chi² = 17.89, df = 4 (P = 0.001), I² = 77.6%								

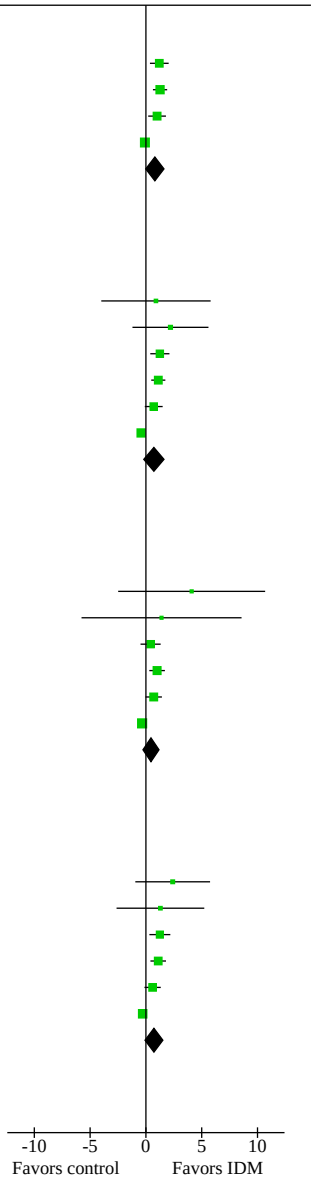


Analysis 1.7. Comparison 1: Integrated disease management versus control, update, Outcome 7: Subgroup analysis SGRQ (total score, medium-term) based on region



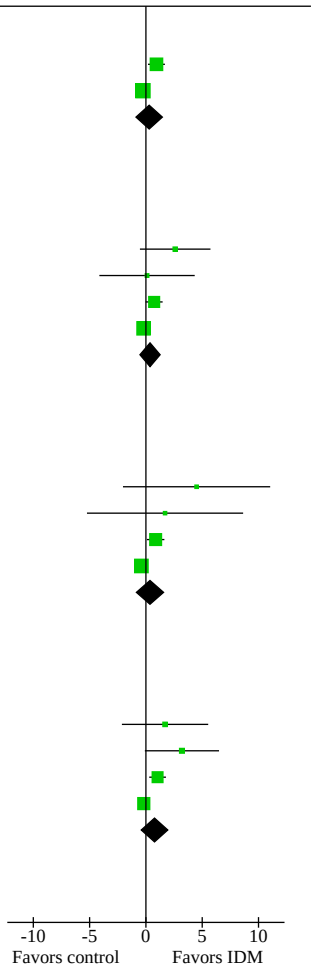
Analysis 1.8. Comparison 1: Integrated disease management versus control, update, Outcome 8: CRQ: short-term (≤ 6 months)

Study or Subgroup	IDM Mean	IDM SD	IDM Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.8.1 CRQ: dyspnoea								
Cambach 1997	1.2	1.2	14	0	0.8	8	22.8%	1.20 [0.36 , 2.04]
Güell 2000	1.18	1.41	30	-0.087	1.09	30	25.3%	1.27 [0.63 , 1.90]
Güell 2006	0.8	1.2	18	-0.2	1.2	17	23.3%	1.00 [0.20 , 1.80]
Lenferink 2019	-0.23	1.16	83	-0.14	1.01	77	28.5%	-0.09 [-0.43 , 0.25]
Subtotal (95% CI)			**145**			**132**	**100.0%**	**0.80 [-0.01 , 1.62]**
Heterogeneity: Tau² = 0.58; Chi² = 20.93, df = 3 (P = 0.0001); I² = 86%								
Test for overall effect: Z = 1.93 (P = 0.05)								
1.8.2 CRQ: fatigue								
Wijkstra 1994	2.7	6.8	11	1.8	3.5	6	3.0%	0.90 [-4.00 , 5.80]
Wijkstra 1994	4	3.9	12	1.8	3.5	7	5.5%	2.20 [-1.20 , 5.60]
Cambach 1997	1.25	1	15	0	1	8	21.2%	1.25 [0.39 , 2.11]
Güell 2000	0.79	1.15	30	-0.32	1.34	30	23.2%	1.11 [0.48 , 1.74]
Güell 2006	0.2	1.1	18	-0.5	1.3	17	21.7%	0.70 [-0.10 , 1.50]
Lenferink 2019	-0.23	0.96	83	0.2	1.05	77	25.4%	-0.43 [-0.74 , -0.12]
Subtotal (95% CI)			**169**			**145**	**100.0%**	**0.71 [-0.19 , 1.62]**
Heterogeneity: Tau² = 0.81; Chi² = 31.48, df = 5 (P < 0.00001); I² = 84%								
Test for overall effect: Z = 1.55 (P = 0.12)								
1.8.3 CRQ: emotion								
Wijkstra 1994	5	7	12	0.9	7.1	7	1.1%	4.10 [-2.48 , 10.68]
Wijkstra 1994	2.3	7.4	11	0.9	7.1	6	1.0%	1.40 [-5.77 , 8.57]
Cambach 1997	0.71	1.14	15	0.29	1	8	20.9%	0.42 [-0.48 , 1.32]
Güell 2000	0.889	1.4	30	-0.113	1.36	30	24.1%	1.00 [0.30 , 1.70]
Güell 2006	0.3	1	18	-0.4	1.2	17	23.5%	0.70 [-0.03 , 1.43]
Lenferink 2019	-0.15	0.93	83	0.19	1.12	77	29.4%	-0.34 [-0.66 , -0.02]
Subtotal (95% CI)			**169**			**145**	**100.0%**	**0.45 [-0.26 , 1.17]**
Heterogeneity: Tau² = 0.43; Chi² = 18.08, df = 5 (P = 0.003); I² = 72%								
Test for overall effect: Z = 1.24 (P = 0.21)								
1.8.4 CRQ: mastery								
Wijkstra 1994	2.9	3.9	12	0.5	3.4	7	4.7%	2.40 [-0.95 , 5.75]
Wijkstra 1994	1.8	4.8	11	0.5	3.4	6	3.6%	1.30 [-2.63 , 5.23]
Cambach 1997	1	1.25	15	-0.25	1	8	20.0%	1.25 [0.31 , 2.19]
Güell 2000	0.936	1.23	30	-0.167	1.51	30	22.8%	1.10 [0.41 , 1.80]
Güell 2006	0.6	1.1	18	0	1.1	17	22.4%	0.60 [-0.13 , 1.33]
Lenferink 2019	-0.07	0.94	83	0.22	1.02	77	26.5%	-0.29 [-0.59 , 0.01]
Subtotal (95% CI)			**169**			**145**	**100.0%**	**0.72 [-0.08 , 1.52]**
Heterogeneity: Tau² = 0.60; Chi² = 23.96, df = 5 (P = 0.0002); I² = 79%								
Test for overall effect: Z = 1.76 (P = 0.08)								



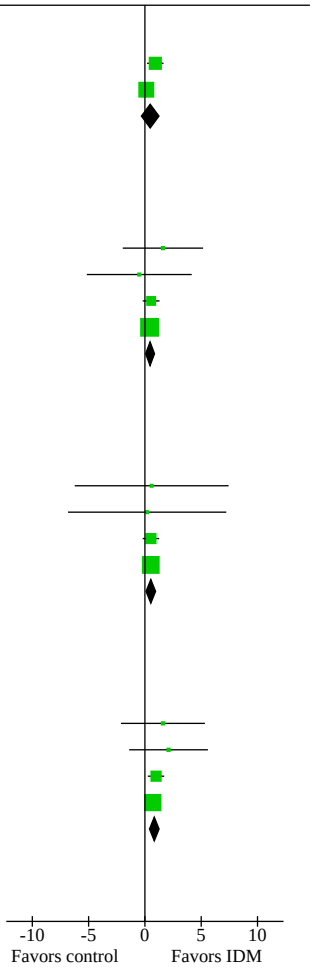
Analysis 1.9. Comparison 1: Integrated disease management versus control, update, Outcome 9: CRQ: medium-term (> 6 to 15 months)

Study or Subgroup	IDM Mean	IDM SD	IDM Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.9.1 CRQ: dyspnoea								
Güell 2000	1.167	1.446	30	0.229	1.5172	30	45.9%	0.94 [0.19 , 1.69]
Lenferink 2019	-0.29	1.15	79	-0.03	0.98	80	54.1%	-0.26 [-0.59 , 0.07]
Subtotal (95% CI)			**109**			**110**	**100.0%**	**0.29 [-0.88 , 1.46]**
Heterogeneity: Tau² = 0.63; Chi² = 8.19, df = 1 (P = 0.004); I² = 88%								
Test for overall effect: Z = 0.49 (P = 0.63)								
1.9.2 CRQ: fatigue								
Wijkstra 1994	3.9	3.9	12	1.3	3	7	7.1%	2.60 [-0.53 , 5.73]
Wijkstra 1994	1.4	5.9	11	1.3	3	6	4.1%	0.10 [-4.13 , 4.33]
Güell 2000	0.411	1.1995	30	-0.322	1.7253	30	38.6%	0.73 [-0.02 , 1.48]
Lenferink 2019	-0.09	0.81	79	0.12	1.09	80	50.2%	-0.21 [-0.51 , 0.09]
Subtotal (95% CI)			**132**			**123**	**100.0%**	**0.37 [-0.53 , 1.26]**
Heterogeneity: Tau² = 0.39; Chi² = 8.02, df = 3 (P = 0.05); I² = 63%								
Test for overall effect: Z = 0.80 (P = 0.42)								
1.9.3 CRQ: emotion								
Wijkstra 1994	4.4	7.2	12	-0.1	6.9	7	3.2%	4.50 [-2.04 , 11.04]
Wijkstra 1994	1.6	7.1	11	-0.1	6.9	6	2.9%	1.70 [-5.23 , 8.63]
Güell 2000	0.825	1.4405	30	-0.04	1.6158	30	43.1%	0.86 [0.09 , 1.64]
Lenferink 2019	-0.1	0.91	79	0.3	1.02	80	50.8%	-0.40 [-0.70 , -0.10]
Subtotal (95% CI)			**132**			**123**	**100.0%**	**0.36 [-0.84 , 1.57]**
Heterogeneity: Tau² = 0.72; Chi² = 11.21, df = 3 (P = 0.01); I² = 73%								
Test for overall effect: Z = 0.59 (P = 0.56)								
1.9.4 CRQ: mastery								
Wijkstra 1994	1.5	4.7	11	-0.2	3.3	6	7.8%	1.70 [-2.13 , 5.53]
Wijkstra 1994	3	3.9	12	-0.2	3.3	7	9.9%	3.20 [-0.09 , 6.49]
Güell 2000	1.014	1.1886	30	-0.022	1.6979	30	38.3%	1.04 [0.29 , 1.78]
Lenferink 2019	0.11	0.88	79	0.3	1.03	80	43.9%	-0.19 [-0.49 , 0.11]
Subtotal (95% CI)			**132**			**123**	**100.0%**	**0.76 [-0.41 , 1.94]**
Heterogeneity: Tau² = 0.80; Chi² = 13.44, df = 3 (P = 0.004); I² = 78%								
Test for overall effect: Z = 1.27 (P = 0.20)								



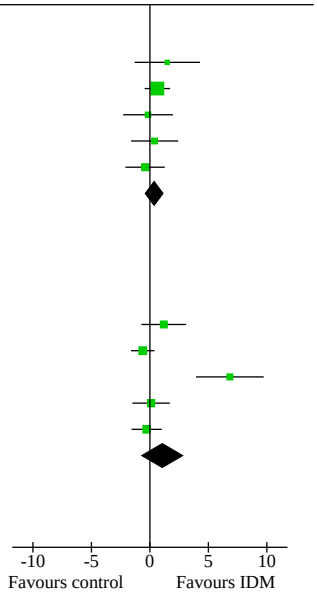
Analysis 1.10. Comparison 1: Integrated disease management versus control, update, Outcome 10: CRQ: long-term (> 15 months)

Study or Subgroup	IDM Mean	IDM SD	IDM Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.10.1 CRQ: dyspnoea								
Güell 2000	1.029	1.4011	24	0.106	1.1414	23	43.6%	0.92 [0.19 , 1.65]
Sridhar 2008	-0.72	1.2	55	-0.84	1.2	49	56.4%	0.12 [-0.34 , 0.58]
Subtotal (95% CI)			**79**			**72**	**100.0%**	**0.47 [-0.31 , 1.25]**
Heterogeneity: Tau² = 0.23; Chi² = 3.32, df = 1 (P = 0.07); I² = 70%								
Test for overall effect: Z = 1.18 (P = 0.24)								
1.10.2 CRQ: fatigue								
Wijkstra 1994	3.1	3.9	11	1.5	3.4	6	1.2%	1.60 [-1.97 , 5.17]
Wijkstra 1994	1	6.1	10	1.5	3.4	6	0.7%	-0.50 [-5.16 , 4.16]
Güell 2000	0.231	1.1562	24	-0.323	1.4387	23	28.0%	0.55 [-0.19 , 1.30]
Sridhar 2008	0.06	1.35	55	-0.35	1.11	49	70.0%	0.41 [-0.06 , 0.88]
Subtotal (95% CI)			**100**			**84**	**100.0%**	**0.46 [0.06 , 0.85]**
Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 3 (P = 0.88); I² = 0%								
Test for overall effect: Z = 2.27 (P = 0.02)								
1.10.3 CRQ: emotion								
Wijkstra 1994	2	7.8	11	1.4	6.3	6	0.4%	0.60 [-6.23 , 7.43]
Wijkstra 1994	1.6	7.9	10	1.4	6.3	6	0.4%	0.20 [-6.83 , 7.23]
Güell 2000	0.651	1.1856	24	0.115	1.3572	23	33.8%	0.54 [-0.19 , 1.27]
Sridhar 2008	0.16	1.43	55	-0.36	1.3	49	65.4%	0.52 [-0.00 , 1.04]
Subtotal (95% CI)			**100**			**84**	**100.0%**	**0.52 [0.10 , 0.95]**
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 3 (P = 1.00); I² = 0%								
Test for overall effect: Z = 2.42 (P = 0.02)								
1.10.4 CRQ: mastery								
Wijkstra 1994	1.8	4.6	10	0.2	3	6	1.3%	1.60 [-2.13 , 5.33]
Wijkstra 1994	2.3	4.3	11	0.2	3	6	1.5%	2.10 [-1.40 , 5.60]
Güell 2000	0.935	1.1415	24	-0.054	1.3812	23	34.4%	0.99 [0.26 , 1.72]
Sridhar 2008	0.43	1.33	55	-0.27	1.45	49	62.8%	0.70 [0.16 , 1.24]
Subtotal (95% CI)			**100**			**84**	**100.0%**	**0.83 [0.41 , 1.26]**
Heterogeneity: Tau² = 0.00; Chi² = 1.08, df = 3 (P = 0.78); I² = 0%								
Test for overall effect: Z = 3.83 (P = 0.0001)								



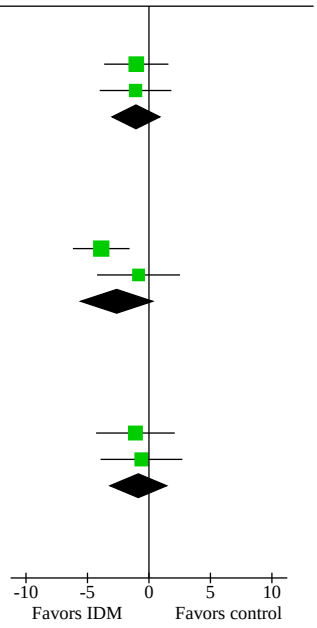
Analysis 1.11. Comparison 1: Integrated disease management versus control, update, Outcome 11: SF-36

Study or Subgroup	IDM Mean	IDM SD	IDM Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.11.1 SF-36 MCS score								
Fan 2012	1.03	9.8	101	-0.46	10.8	108	7.1%	1.49 [-1.30 , 4.28]
Kruis 2014	0.73	9.16	554	0.09	9.16	532	46.9%	0.64 [-0.45 , 1.73]
Vianello 2016	-2.07	8.89	181	-1.91	7.75	81	12.3%	-0.16 [-2.29 , 1.97]
Lilholt 2017	-4.9	17.86	578	-5.3	17.86	647	13.9%	0.40 [-1.60 , 2.40]
Kalter-Leibovici 2018	0.65	12.42	496	1.06	13.38	421	19.7%	-0.41 [-2.09 , 1.27]
Subtotal (95% CI)			**1910**			**1789**	**100.0%**	**0.36 [-0.38 , 1.11]**
Heterogeneity: Tau² = 0.00; Chi² = 1.92, df = 4 (P = 0.75); I² = 0%								
Test for overall effect: Z = 0.95 (P = 0.34)								
1.11.2 SF-36 PCS score								
Fan 2012	1.1	6.4	101	-0.09	7.7	108	19.2%	1.19 [-0.72 , 3.10]
Kruis 2014	-1.09	8.41	554	-0.48	8.41	532	23.2%	-0.61 [-1.61 , 0.39]
Vianello 2016	-1.08	11.3	181	-7.92	10.92	81	14.8%	6.84 [3.95 , 9.73]
Lilholt 2017	-2.7	14.29	578	-2.8	14.29	647	20.7%	0.10 [-1.50 , 1.70]
Kalter-Leibovici 2018	0.36	9.78	500	0.64	10.11	422	22.1%	-0.28 [-1.57 , 1.01]
Subtotal (95% CI)			**1914**			**1790**	**100.0%**	**1.06 [-0.67 , 2.79]**
Heterogeneity: Tau² = 3.10; Chi² = 24.33, df = 4 (P < 0.0001); I² = 84%								
Test for overall effect: Z = 1.20 (P = 0.23)								
Test for subgroup differences: Chi² = 0.52, df = 1 (P = 0.47), I² = 0%								



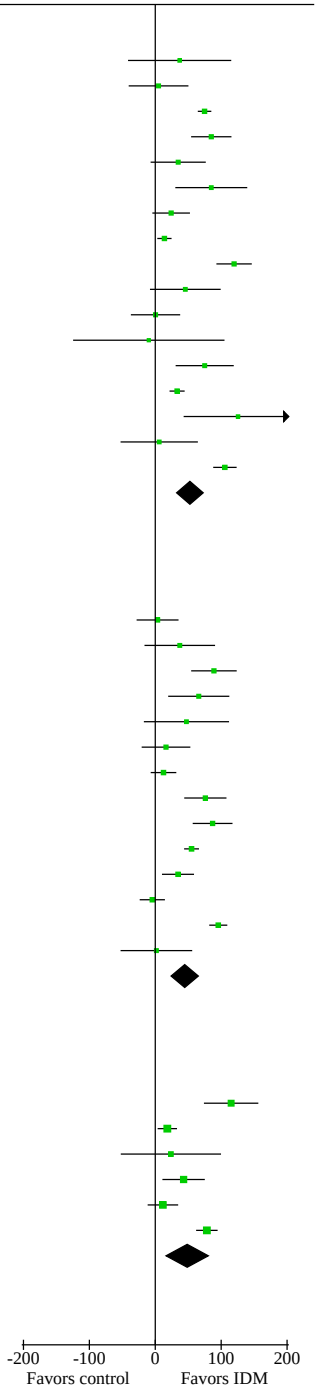
Analysis 1.12. Comparison 1: Integrated disease management versus control, update, Outcome 12: General health QoL: SIP mean difference

Study or Subgroup	IDM Mean	IDM SD	IDM Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.12.1 SIP total								
Littlejohns 1991	-0.63	9.2129	68	0.4	5.8518	65	55.5%	-1.03 [-3.64 , 1.58]
Engstrom 1999	-0.07	5.099	26	1.02	5.3889	24	44.5%	-1.09 [-4.00 , 1.82]
Subtotal (95% CI)			**94**			**89**	**100.0%**	**-1.06 [-3.00 , 0.89]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%								
Test for overall effect: Z = 1.07 (P = 0.29)								
1.12.2 SIP: physical								
Littlejohns 1991	-5.53	7.5604	68	-1.65	5.9325	65	58.6%	-3.88 [-6.18 , -1.58]
Engstrom 1999	0.28	5.099	26	1.13	6.8586	24	41.4%	-0.85 [-4.22 , 2.52]
Subtotal (95% CI)			**94**			**89**	**100.0%**	**-2.63 [-5.55 , 0.30]**
Heterogeneity: Tau² = 2.42; Chi² = 2.11, df = 1 (P = 0.15); I² = 53%								
Test for overall effect: Z = 1.76 (P = 0.08)								
1.12.3 SIP: psychosocial								
Littlejohns 1991	-2.38	11.2786	68	-1.28	7.1836	65	51.9%	-1.10 [-4.30 , 2.10]
Engstrom 1999	-0.2	6.1188	26	0.41	5.8788	24	48.1%	-0.61 [-3.94 , 2.72]
Subtotal (95% CI)			**94**			**89**	**100.0%**	**-0.86 [-3.17 , 1.44]**
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%								
Test for overall effect: Z = 0.73 (P = 0.46)								

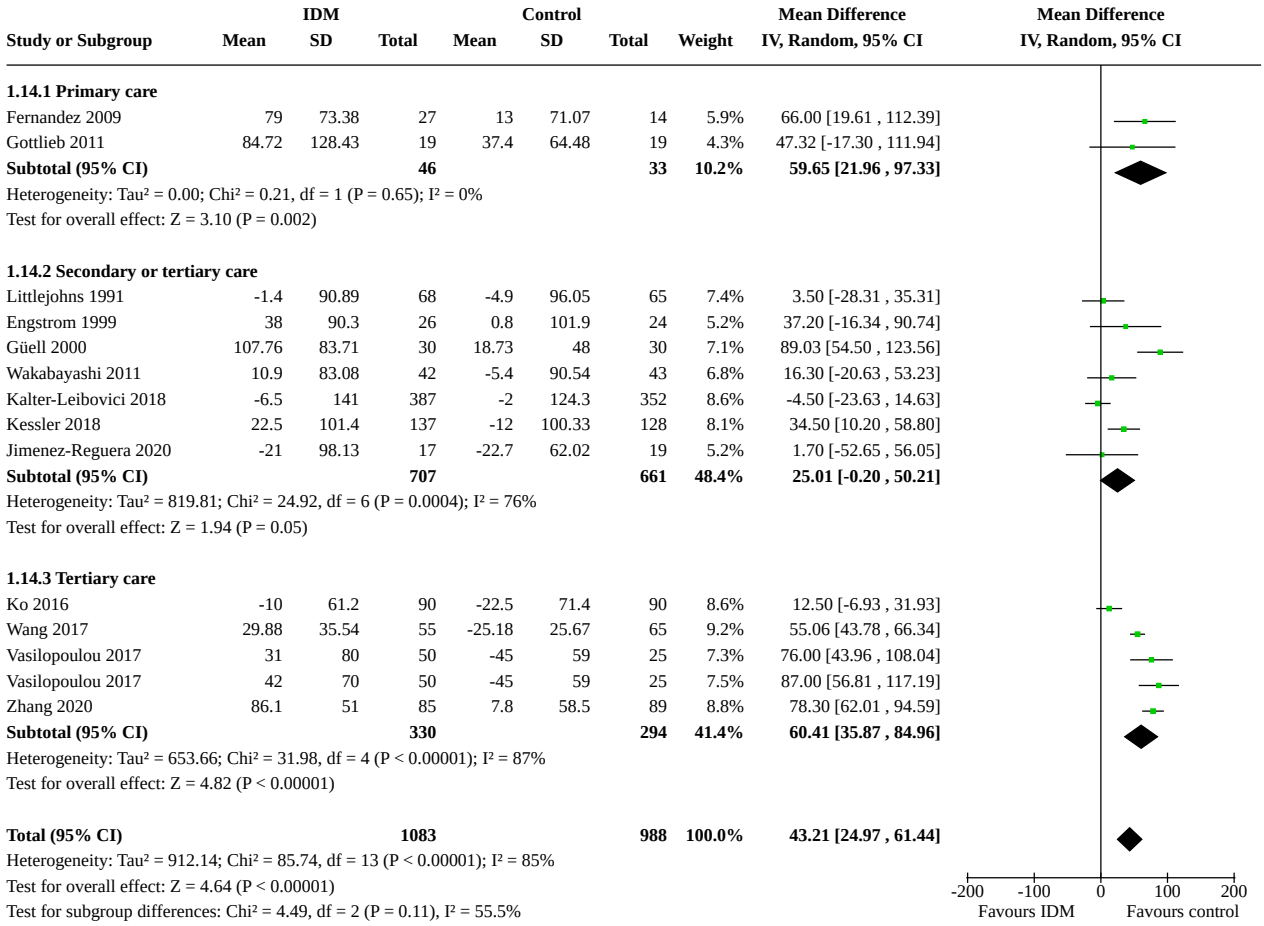


Analysis 1.13. Comparison 1: Integrated disease management versus control, update, Outcome 13: Functional exercise capacity: 6MWD

Study or Subgroup	IDM Mean	IDM SD	IDM Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.13.1 6MWD: short-term (≤ 6 months)								
Wijkstra 1994	9	87	28	-28	141	15	3.6%	37.00 [-41.29 , 115.29]
Cambach 1997	51	57	12	46	43	7	5.7%	5.00 [-40.33 , 50.33]
Bendstrup 1997	96.2	16.1	16	21.4	13.4	16	7.9%	74.80 [64.54 , 85.06]
Güell 2000	95.23	63.18	30	10.22	57.59	30	6.8%	85.01 [54.42 , 115.60]
Boxall 2005	39	69.6	23	4.2	75.1	23	6.0%	34.80 [-7.05 , 76.65]
Güell 2006	63	92	18	-22	72	17	5.1%	85.00 [30.43 , 139.57]
Theander 2009	40.6	27.2	12	16.5	45.8	14	6.9%	24.10 [-4.40 , 52.60]
van Wetering 2010	-1.4	36.38	87	-15.3	36.59	88	7.9%	13.90 [3.09 , 24.71]
Mendes 2010	81.59	59.68	56	-38.03	59.9	29	7.0%	119.62 [92.79 , 146.45]
Gottlieb 2011	49.4	94	21	3.8	81	20	5.1%	45.60 [-8.03 , 99.23]
Wakabayashi 2011	0.4	84.4	50	0	103.2	48	6.3%	0.40 [-37.01 , 37.81]
Tabak 2014	2.5	128.35	11	12.3	132	9	2.2%	-9.80 [-124.65 , 105.05]
Bernocchi 2017	60	130.51	48	-15	81.57	44	5.8%	75.00 [30.91 , 119.09]
Wang 2017	19.23	42.2	55	-13.89	10.92	65	7.8%	33.12 [21.66 , 44.58]
Khan 2019	263.88	357.29	147	138.28	357.29	141	3.4%	125.60 [43.05 , 208.15]
Jimenez-Reguera 2020	-30.2	95.1	17	-36.2	83.1	19	4.8%	6.00 [-52.65 , 64.65]
Zhang 2020	113.9	60.6	85	8.2	58.9	89	7.6%	105.70 [87.93 , 123.47]
Subtotal (95% CI)			**716**			**674**	**100.0%**	**52.56 [32.39 , 72.74]**
Heterogeneity: Tau² = 1317.49; Chi² = 165.76, df = 16 (P < 0.00001); I² = 90%								
Test for overall effect: Z = 5.11 (P < 0.00001)								
1.13.2 6MWD: medium-term (> 6 months to 15 months)								
Littlejohns 1991	-1.4	90.89	68	-4.9	96.05	65	7.4%	3.50 [-28.31 , 35.31]
Engstrom 1999	38	90.3	26	0.8	101.9	24	5.6%	37.20 [-16.34 , 90.74]
Güell 2000	107.76	83.71	30	18.73	48	30	7.1%	89.03 [54.50 , 123.56]
Fernandez 2009	79	73.38	27	13	71.07	14	6.2%	66.00 [19.61 , 112.39]
Gottlieb 2011	84.72	128.43	19	37.4	64.48	19	4.8%	47.32 [-17.30 , 111.94]
Wakabayashi 2011	10.9	83.08	42	-5.4	90.54	43	6.9%	16.30 [-20.63 , 53.23]
Ko 2016	-10	61.2	90	-22.5	71.4	90	8.3%	12.50 [-6.93 , 31.93]
Vasilopoulou 2017	31	80	50	-45	59	25	7.3%	76.00 [43.96 , 108.04]
Vasilopoulou 2017	42	70	50	-45	59	25	7.5%	87.00 [56.81 , 117.19]
Wang 2017	29.88	35.54	55	-25.18	25.67	65	8.7%	55.06 [43.78 , 66.34]
Kessler 2018	22.5	101.4	137	-12	100.33	128	7.9%	34.50 [10.20 , 58.80]
Kalter-Leibovici 2018	-6.5	141	387	-2	124.3	352	8.3%	-4.50 [-23.63 , 14.63]
Zhang 2020	102.2	45.85	85	6.6	46.36	89	8.6%	95.60 [81.90 , 109.30]
Jimenez-Reguera 2020	-21	98.13	17	-22.7	62.02	19	5.5%	1.70 [-52.65 , 56.05]
Subtotal (95% CI)			**1083**			**988**	**100.0%**	**44.69 [24.01 , 65.37]**
Heterogeneity: Tau² = 1249.22; Chi² = 118.63, df = 13 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 4.24 (P < 0.0001)								
1.13.3 6MWD: long-term (> 15 months)								
Güell 2000	116.99	62.5335	30	1.87	96.8976	30	15.4%	115.12 [73.85 , 156.39]
van Wetering 2010	-15.1	46.1376	73	-33.4	46.2186	79	19.8%	18.30 [3.61 , 32.99]
Gottlieb 2011	37.78	124	16	14.06	99	18	9.5%	23.72 [-52.33 , 99.77]
Lou 2015	16	643.86	3418	-27	643.86	2803	17.1%	43.00 [10.84 , 75.16]
Kalter-Leibovici 2018	-19.9	155.4	335	-31.5	145	312	18.6%	11.60 [-11.55 , 34.75]
Zhang 2020	86.1	51	85	7.8	58.5	89	19.6%	78.30 [62.01 , 94.59]
Subtotal (95% CI)			**3957**			**3331**	**100.0%**	**48.43 [16.37 , 80.49]**
Heterogeneity: Tau² = 1296.68; Chi² = 47.95, df = 5 (P < 0.00001); I² = 90%								
Test for overall effect: Z = 2.96 (P = 0.003)								

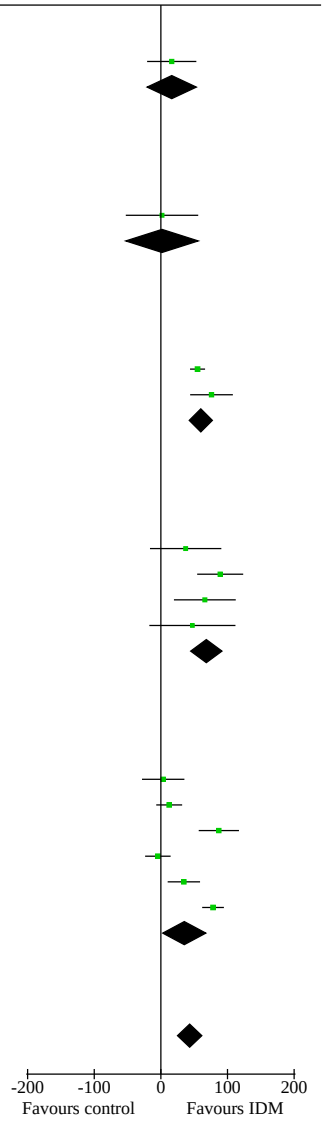


Analysis 1.14. Comparison 1: Integrated disease management versus control, update, Outcome 14: Subgroup analysis 6MWD (medium-term) based on type of setting



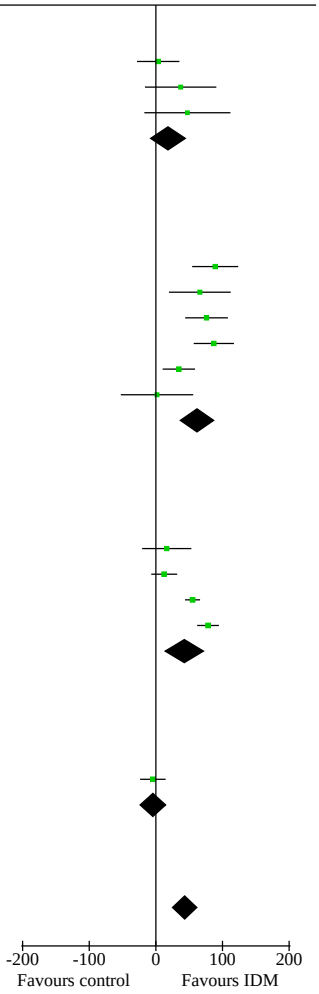
Analysis 1.15. Comparison 1: Integrated disease management versus control, update, Outcome 15: Subgroup analysis 6MWD (medium-term) based on dominant component of intervention

Study or Subgroup	IDM Mean	IDM SD	IDM Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.15.1 Education								
Wakabayashi 2011	10.9	83.08	42	-5.4	90.54	43	6.8%	16.30 [-20.63 , 53.23]
Subtotal (95% CI)			**42**			**43**	**6.8%**	**16.30 [-20.63 , 53.23]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.87 (P = 0.39)								
1.15.2 Self-management								
Jimenez-Reguera 2020	-21	98.13	17	-22.7	62.02	19	5.2%	1.70 [-52.65 , 56.05]
Subtotal (95% CI)			**17**			**19**	**5.2%**	**1.70 [-52.65 , 56.05]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.06 (P = 0.95)								
1.15.3 Telemonitoring								
Wang 2017	29.88	35.54	55	-25.18	25.67	65	9.2%	55.06 [43.78 , 66.34]
Vasilopoulou 2017	31	80	50	-45	59	25	7.3%	76.00 [43.96 , 108.04]
Subtotal (95% CI)			**105**			**90**	**16.5%**	**59.94 [42.59 , 77.29]**
Heterogeneity: Tau² = 69.07; Chi² = 1.46, df = 1 (P = 0.23); I² = 32%								
Test for overall effect: Z = 6.77 (P < 0.00001)								
1.15.4 Exercise								
Engstrom 1999	38	90.3	26	0.8	101.9	24	5.2%	37.20 [-16.34 , 90.74]
Güell 2000	107.76	83.71	30	18.73	48	30	7.1%	89.03 [54.50 , 123.56]
Fernandez 2009	79	73.38	27	13	71.07	14	5.9%	66.00 [19.61 , 112.39]
Gottlieb 2011	84.72	128.43	19	37.4	64.48	19	4.3%	47.32 [-17.30 , 111.94]
Subtotal (95% CI)			**102**			**87**	**22.5%**	**68.21 [44.75 , 91.68]**
Heterogeneity: Tau² = 18.78; Chi² = 3.09, df = 3 (P = 0.38); I² = 3%								
Test for overall effect: Z = 5.70 (P < 0.00001)								
1.15.5 Structural follow-up								
Littlejohns 1991	-1.4	90.89	68	-4.9	96.05	65	7.4%	3.50 [-28.31 , 35.31]
Ko 2016	-10	61.2	90	-22.5	71.4	90	8.6%	12.50 [-6.93 , 31.93]
Vasilopoulou 2017	42	70	50	-45	59	25	7.5%	87.00 [56.81 , 117.19]
Kalter-Leibovici 2018	-6.5	141	387	-2	124.3	352	8.6%	-4.50 [-23.63 , 14.63]
Kessler 2018	22.5	101.4	137	-12	100.33	128	8.1%	34.50 [10.20 , 58.80]
Zhang 2020	86.1	51	85	7.8	58.5	89	8.8%	78.30 [62.01 , 94.59]
Subtotal (95% CI)			**817**			**749**	**49.0%**	**35.14 [2.83 , 67.45]**
Heterogeneity: Tau² = 1481.01; Chi² = 63.72, df = 5 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 2.13 (P = 0.03)								
Total (95% CI)			**1083**			**988**	**100.0%**	**43.21 [24.97 , 61.44]**
Heterogeneity: Tau² = 912.14; Chi² = 85.74, df = 13 (P < 0.00001); I² = 85%								
Test for overall effect: Z = 4.64 (P < 0.00001)								
Test for subgroup differences: Chi² = 10.56, df = 4 (P = 0.03), I² = 62.1%								



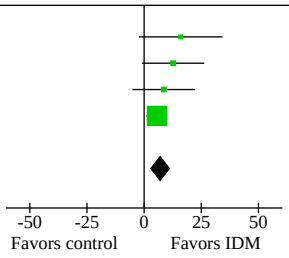
Analysis 1.16. Comparison 1: Integrated disease management versus control, update, Outcome 16: Subgroup analysis 6MWD (medium-term) based on region

Study or Subgroup	IDM Mean	IDM SD	IDM Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.16.1 Northwestern Europe								
Littlejohns 1991	-1.4	90.89	68	-4.9	96.05	65	7.4%	3.50 [-28.31 , 35.31]
Engstrom 1999	38	90.3	26	0.8	101.9	24	5.2%	37.20 [-16.34 , 90.74]
Gottlieb 2011	84.72	128.43	19	37.4	64.48	19	4.3%	47.32 [-17.30 , 111.94]
Subtotal (95% CI)			**113**			**108**	**16.9%**	**18.18 [-7.87 , 44.24]**
Heterogeneity: Tau² = 25.35; Chi² = 2.08, df = 2 (P = 0.35); I² = 4%								
Test for overall effect: Z = 1.37 (P = 0.17)								
1.16.2 Southern Europe								
Güell 2000	107.76	83.71	30	18.73	48	30	7.1%	89.03 [54.50 , 123.56]
Fernandez 2009	79	73.38	27	13	71.07	14	5.9%	66.00 [19.61 , 112.39]
Vasilopoulou 2017	31	80	50	-45	59	25	7.3%	76.00 [43.96 , 108.04]
Vasilopoulou 2017	42	70	50	-45	59	25	7.5%	87.00 [56.81 , 117.19]
Kessler 2018	22.5	101.4	137	-12	100.33	128	8.1%	34.50 [10.20 , 58.80]
Jimenez-Reguera 2020	-21	98.13	17	-22.7	62.02	19	5.2%	1.70 [-52.65 , 56.05]
Subtotal (95% CI)			**311**			**241**	**41.1%**	**61.73 [36.74 , 86.71]**
Heterogeneity: Tau² = 631.41; Chi² = 15.40, df = 5 (P = 0.009); I² = 68%								
Test for overall effect: Z = 4.84 (P < 0.00001)								
1.16.3 East Asia								
Wakabayashi 2011	10.9	83.08	42	-5.4	90.54	43	6.8%	16.30 [-20.63 , 53.23]
Ko 2016	-10	61.2	90	-22.5	71.4	90	8.6%	12.50 [-6.93 , 31.93]
Wang 2017	29.88	35.54	55	-25.18	25.67	65	9.2%	55.06 [43.78 , 66.34]
Zhang 2020	86.1	51	85	7.8	58.5	89	8.8%	78.30 [62.01 , 94.59]
Subtotal (95% CI)			**272**			**287**	**33.4%**	**42.67 [13.94 , 71.41]**
Heterogeneity: Tau² = 737.11; Chi² = 29.75, df = 3 (P < 0.00001); I² = 90%								
Test for overall effect: Z = 2.91 (P = 0.004)								
1.16.4 Western Asia								
Kalter-Leibovici 2018	-6.5	141	387	-2	124.3	352	8.6%	-4.50 [-23.63 , 14.63]
Subtotal (95% CI)			**387**			**352**	**8.6%**	**-4.50 [-23.63 , 14.63]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.46 (P = 0.64)								
Total (95% CI)			**1083**			**988**	**100.0%**	**43.21 [24.97 , 61.44]**
Heterogeneity: Tau² = 912.14; Chi² = 85.74, df = 13 (P < 0.00001); I² = 85%								
Test for overall effect: Z = 4.64 (P < 0.00001)								
Test for subgroup differences: Chi² = 19.09, df = 3 (P = 0.0003), I² = 84.3%								

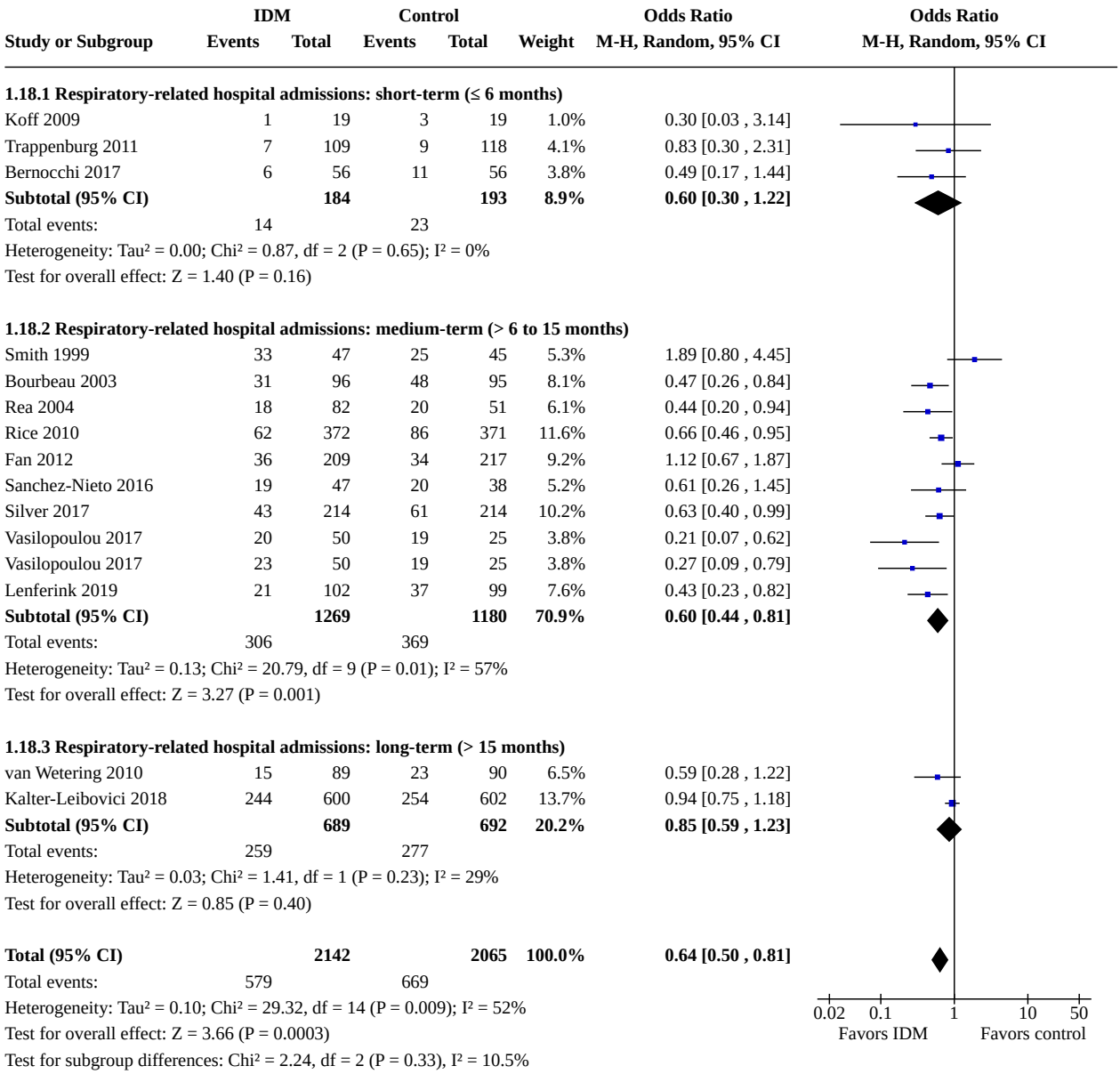


Analysis 1.17. Comparison 1: Integrated disease management versus control, update, Outcome 17: Maximal exercise capacity: cycle test (W-max)

Study or Subgroup	IDM Mean	IDM SD	IDM Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Wijkstra 1994	8	31	28	-8	28	15	4.9%	16.00 [-2.24 , 34.24]
Strijbos 1996	14	18	15	1.3	20	15	8.8%	12.70 [-0.92 , 26.32]
Engstrom 1999	9.4	25.5	26	0.8	24	24	8.6%	8.60 [-5.12 , 22.32]
van Wetering 2010	5.2	14.9238	87	-0.4	15.9474	88	77.7%	5.60 [1.02 , 10.18]
Total (95% CI)			**156**			**142**	**100.0%**	**6.99 [2.96 , 11.02]**
Heterogeneity: Tau² = 0.00; Chi² = 2.02, df = 3 (P = 0.57); I² = 0%								
Test for overall effect: Z = 3.40 (P = 0.0007)								
Test for subgroup differences: Not applicable								



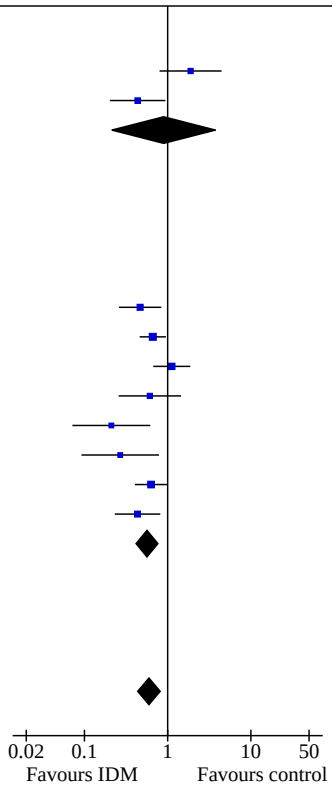
Analysis 1.18. Comparison 1: Integrated disease management versus control, update, Outcome 18: Respiratory-related hospital admissions



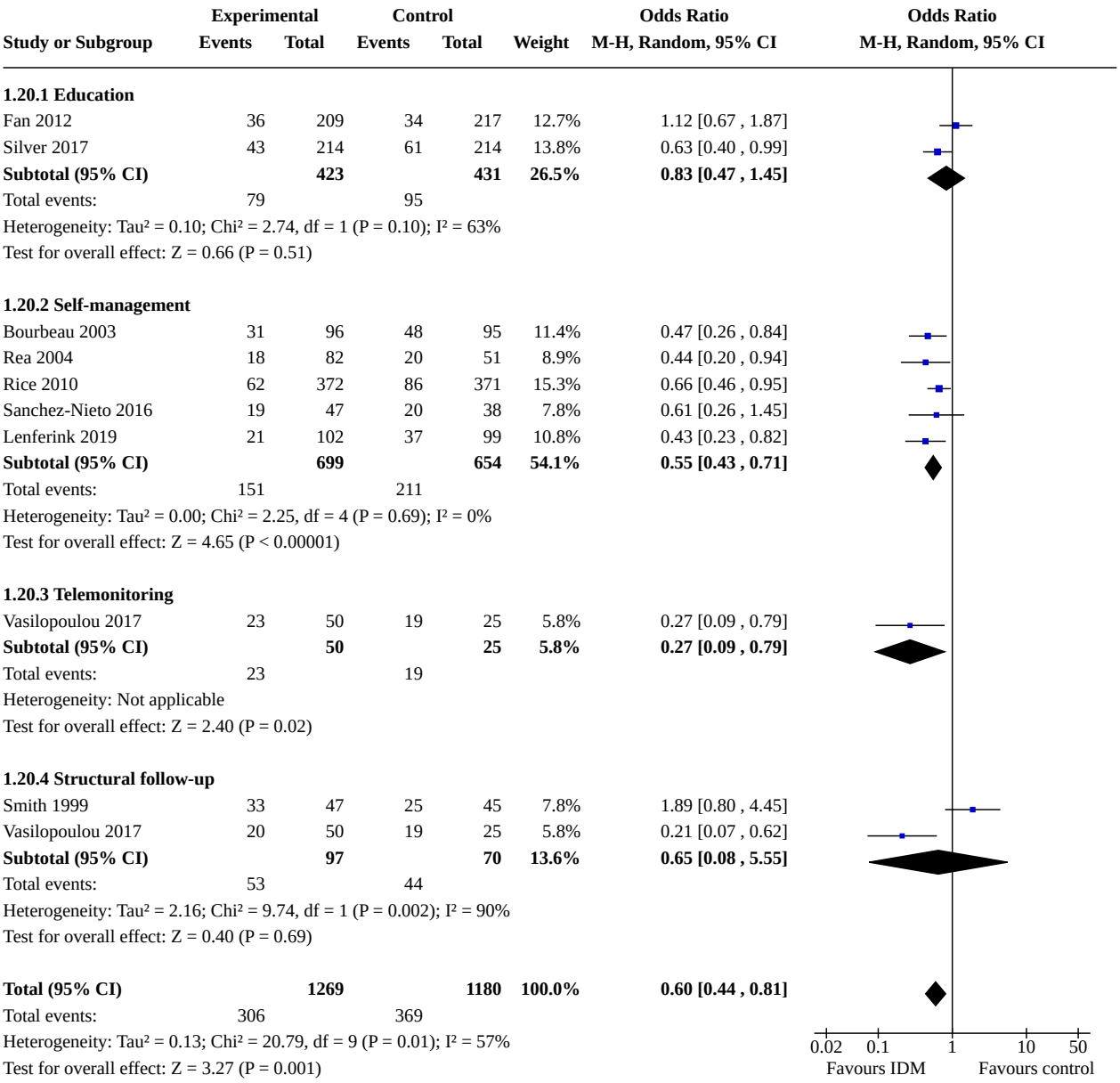
Study or Subgroup	IDM Events	IDM Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.18.1 Respiratory-related hospital admissions: short-term (≤ 6 months)						
Koff 2009	1	19	3	19	1.0%	0.30 [0.03 , 3.14]
Trappenburg 2011	7	109	9	118	4.1%	0.83 [0.30 , 2.31]
Bernocchi 2017	6	56	11	56	3.8%	0.49 [0.17 , 1.44]
Subtotal (95% CI)		**184**		**193**	**8.9%**	**0.60 [0.30 , 1.22]**
Total events:	14		23			
Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 2 (P = 0.65); I² = 0%						
Test for overall effect: Z = 1.40 (P = 0.16)						
1.18.2 Respiratory-related hospital admissions: medium-term (> 6 to 15 months)						
Smith 1999	33	47	25	45	5.3%	1.89 [0.80 , 4.45]
Bourbeau 2003	31	96	48	95	8.1%	0.47 [0.26 , 0.84]
Rea 2004	18	82	20	51	6.1%	0.44 [0.20 , 0.94]
Rice 2010	62	372	86	371	11.6%	0.66 [0.46 , 0.95]
Fan 2012	36	209	34	217	9.2%	1.12 [0.67 , 1.87]
Sanchez-Nieto 2016	19	47	20	38	5.2%	0.61 [0.26 , 1.45]
Silver 2017	43	214	61	214	10.2%	0.63 [0.40 , 0.99]
Vasilopoulou 2017	20	50	19	25	3.8%	0.21 [0.07 , 0.62]
Vasilopoulou 2017	23	50	19	25	3.8%	0.27 [0.09 , 0.79]
Lenferink 2019	21	102	37	99	7.6%	0.43 [0.23 , 0.82]
Subtotal (95% CI)		**1269**		**1180**	**70.9%**	**0.60 [0.44 , 0.81]**
Total events:	306		369			
Heterogeneity: Tau² = 0.13; Chi² = 20.79, df = 9 (P = 0.01); I² = 57%						
Test for overall effect: Z = 3.27 (P = 0.001)						
1.18.3 Respiratory-related hospital admissions: long-term (> 15 months)						
van Wetering 2010	15	89	23	90	6.5%	0.59 [0.28 , 1.22]
Kalter-Leibovici 2018	244	600	254	602	13.7%	0.94 [0.75 , 1.18]
Subtotal (95% CI)		**689**		**692**	**20.2%**	**0.85 [0.59 , 1.23]**
Total events:	259		277			
Heterogeneity: Tau² = 0.03; Chi² = 1.41, df = 1 (P = 0.23); I² = 29%						
Test for overall effect: Z = 0.85 (P = 0.40)						
Total (95% CI)		**2142**		**2065**	**100.0%**	**0.64 [0.50 , 0.81]**
Total events:	579		669			
Heterogeneity: Tau² = 0.10; Chi² = 29.32, df = 14 (P = 0.009); I² = 52%						
Test for overall effect: Z = 3.66 (P = 0.0003)						
Test for subgroup differences: Chi² = 2.24, df = 2 (P = 0.33), I² = 10.5%						

Analysis 1.19. Comparison 1: Integrated disease management versus control, update, Outcome 19: Subgroup analysis respiratory-related hospital admissions (medium-term) based on type of setting

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.19.1 Primary care						
Smith 1999	33	47	25	45	7.8%	1.89 [0.80 , 4.45]
Rea 2004	18	82	20	51	8.9%	0.44 [0.20 , 0.94]
Subtotal (95% CI)		**129**		**96**	**16.7%**	**0.89 [0.21 , 3.76]**
Total events:	51		45			
Heterogeneity: Tau² = 0.90; Chi² = 6.22, df = 1 (P = 0.01); I² = 84%						
Test for overall effect: Z = 0.15 (P = 0.88)						
1.19.2 Secondary or tertiary care						
Bourbeau 2003	31	96	48	95	11.4%	0.47 [0.26 , 0.84]
Rice 2010	62	372	86	371	15.3%	0.66 [0.46 , 0.95]
Fan 2012	36	209	34	217	12.7%	1.12 [0.67 , 1.87]
Sanchez-Nieto 2016	19	47	20	38	7.8%	0.61 [0.26 , 1.45]
Vasilopoulou 2017	20	50	19	25	5.8%	0.21 [0.07 , 0.62]
Vasilopoulou 2017	23	50	19	25	5.8%	0.27 [0.09 , 0.79]
Silver 2017	43	214	61	214	13.8%	0.63 [0.40 , 0.99]
Lenferink 2019	21	102	37	99	10.8%	0.43 [0.23 , 0.82]
Subtotal (95% CI)		**1140**		**1084**	**83.3%**	**0.56 [0.42 , 0.76]**
Total events:	255		324			
Heterogeneity: Tau² = 0.08; Chi² = 13.50, df = 7 (P = 0.06); I² = 48%						
Test for overall effect: Z = 3.72 (P = 0.0002)						
Total (95% CI)		**1269**		**1180**	**100.0%**	**0.60 [0.44 , 0.81]**
Total events:	306		369			
Heterogeneity: Tau² = 0.13; Chi² = 20.79, df = 9 (P = 0.01); I² = 57%						
Test for overall effect: Z = 3.27 (P = 0.001)						
Test for subgroup differences: Chi² = 0.38, df = 1 (P = 0.54), I² = 0%						

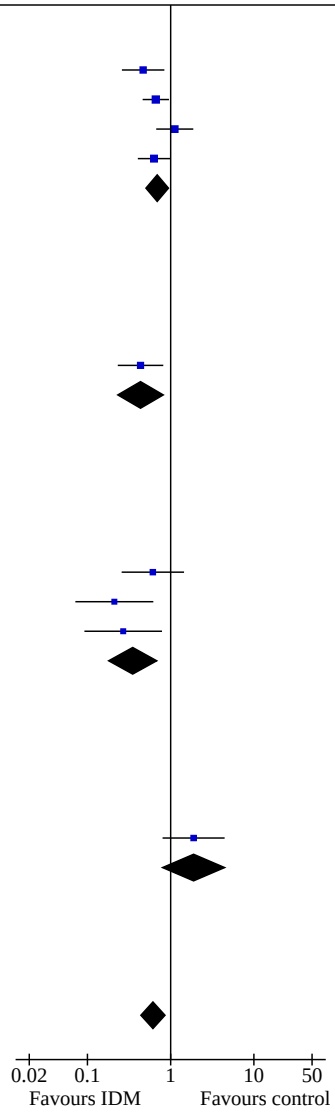


Analysis 1.20. Comparison 1: Integrated disease management versus control, update, Outcome 20: Subgroup analysis respiratory-related hospital admissions (medium-term) based on dominant component of intervention

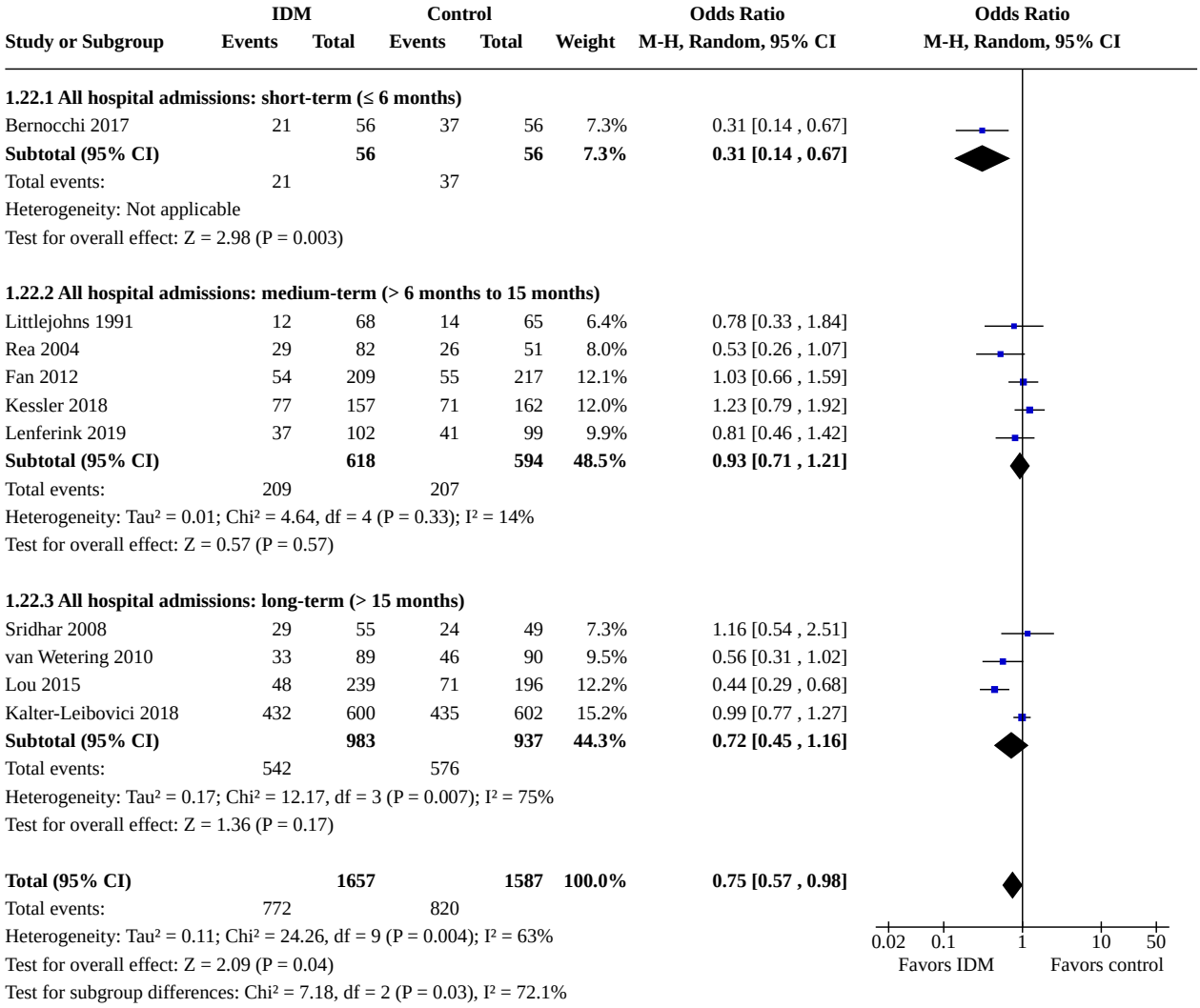


Analysis 1.21. Comparison 1: Integrated disease management versus control, update, Outcome 21: Subgroup analysis respiratory-related hospital admissions (medium-term) based on region

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.21.1 North America						
Bourbeau 2003	31	96	48	95	12.5%	0.47 [0.26 , 0.84]
Rice 2010	62	372	86	371	16.4%	0.66 [0.46 , 0.95]
Fan 2012	36	209	34	217	13.8%	1.12 [0.67 , 1.87]
Silver 2017	43	214	61	214	15.0%	0.63 [0.40 , 0.99]
Subtotal (95% CI)		**891**		**897**	**57.7%**	**0.69 [0.50 , 0.94]**
Total events:	172		229			
Heterogeneity: Tau² = 0.04; Chi² = 5.33, df = 3 (P = 0.15); I² = 44%						
Test for overall effect: Z = 2.34 (P = 0.02)						
1.21.2 Northwestern Europe						
Lenferink 2019	21	102	37	99	11.8%	0.43 [0.23 , 0.82]
Subtotal (95% CI)		**102**		**99**	**11.8%**	**0.43 [0.23 , 0.82]**
Total events:	21		37			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.60 (P = 0.009)						
1.21.3 Southern Europe						
Sanchez-Nieto 2016	19	47	20	38	8.6%	0.61 [0.26 , 1.45]
Vasilopoulou 2017	20	50	19	25	6.5%	0.21 [0.07 , 0.62]
Vasilopoulou 2017	23	50	19	25	6.6%	0.27 [0.09 , 0.79]
Subtotal (95% CI)		**147**		**88**	**21.7%**	**0.35 [0.18 , 0.68]**
Total events:	62		58			
Heterogeneity: Tau² = 0.09; Chi² = 2.68, df = 2 (P = 0.26); I² = 25%						
Test for overall effect: Z = 3.10 (P = 0.002)						
1.21.4 Oceania						
Smith 1999	33	47	25	45	8.7%	1.89 [0.80 , 4.45]
Subtotal (95% CI)		**47**		**45**	**8.7%**	**1.89 [0.80 , 4.45]**
Total events:	33		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.45 (P = 0.15)						
Total (95% CI)		**1187**		**1129**	**100.0%**	**0.61 [0.44 , 0.86]**
Total events:	288		349			
Heterogeneity: Tau² = 0.14; Chi² = 19.87, df = 8 (P = 0.01); I² = 60%						
Test for overall effect: Z = 2.88 (P = 0.004)						
Test for subgroup differences: Chi² = 10.93, df = 3 (P = 0.01), I² = 72.5%						

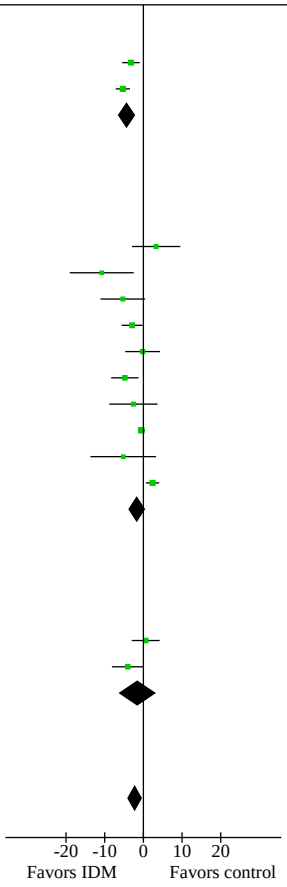


Analysis 1.22. Comparison 1: Integrated disease management versus control, update, Outcome 22: All hospital admissions



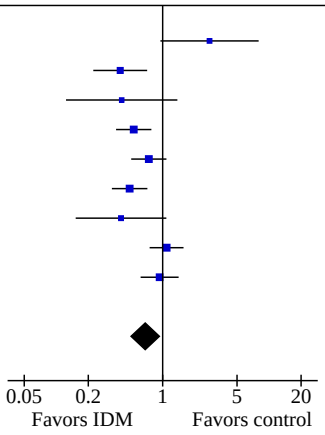
Analysis 1.23. Comparison 1: Integrated disease management versus control, update, Outcome 23: Hospital days per patient (all causes)

Study or Subgroup	IDM Mean	IDM SD	IDM Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.23.1 Hospital days per patient (all causes): short-term (≤ 6 months)								
Boxall 2005	5.6	2.96	23	8.8	4.71	23	9.7%	-3.20 [-5.47 , -0.93]
Trappenburg 2011	6.6	2.8	109	11.9	9.8	118	10.3%	-5.30 [-7.14 , -3.46]
Subtotal (95% CI)			**132**			**141**	**20.0%**	**-4.36 [-6.41 , -2.31]**
Heterogeneity: Tau² = 1.09; Chi² = 1.98, df = 1 (P = 0.16); I² = 49%								
Test for overall effect: Z = 4.17 (P < 0.0001)								
1.23.2 Hospital days per patient (all causes): medium-term (> 6 to 15 months)								
Engstrom 1999	4.9	13.77	26	1.6	8.33	24	4.6%	3.30 [-2.95 , 9.55]
Farrero 2001	7.43	15.6	46	18.2	24.55	48	3.1%	-10.77 [-19.05 , -2.49]
Bourbeau 2003	7.2	19.5	96	12.5	21.2	95	5.0%	-5.30 [-11.08 , 0.48]
Rea 2004	1.1	7.8	82	4	7.8	51	9.0%	-2.90 [-5.63 , -0.17]
Kruis 2014	10.5	37.83	554	10.7	37.83	532	6.5%	-0.20 [-4.70 , 4.30]
Ko 2016	7.41	11.29	90	12.21	12.87	90	7.8%	-4.80 [-8.34 , -1.26]
Vianello 2016	22.92	25.11	181	25.5	23.21	81	4.6%	-2.58 [-8.82 , 3.66]
Silver 2017	2	4.478	214	2.5	5.22	214	11.3%	-0.50 [-1.42 , 0.42]
Kessler 2018	17.4	35.4	157	22.6	41.8	162	3.0%	-5.20 [-13.69 , 3.29]
Lenferink 2019	9.36	7.63	102	6.99	4.34	99	10.5%	2.37 [0.66 , 4.08]
Subtotal (95% CI)			**1548**			**1396**	**65.3%**	**-1.73 [-3.71 , 0.25]**
Heterogeneity: Tau² = 5.31; Chi² = 31.08, df = 9 (P = 0.0003); I² = 71%								
Test for overall effect: Z = 1.71 (P = 0.09)								
1.23.3 Hospital days per patient (all causes): long-term (> 15 months)								
van Wetering 2010	4.9	14	87	4.3	10	88	7.7%	0.60 [-3.01 , 4.21]
Titova 2017	5.77	8.66	91	9.79	16.96	80	7.0%	-4.02 [-8.14 , 0.10]
Subtotal (95% CI)			**178**			**168**	**14.7%**	**-1.60 [-6.12 , 2.92]**
Heterogeneity: Tau² = 6.77; Chi² = 2.73, df = 1 (P = 0.10); I² = 63%								
Test for overall effect: Z = 0.69 (P = 0.49)								
Total (95% CI)			**1858**			**1705**	**100.0%**	**-2.27 [-3.98 , -0.56]**
Heterogeneity: Tau² = 6.50; Chi² = 59.31, df = 13 (P < 0.00001); I² = 78%								
Test for overall effect: Z = 2.61 (P = 0.009)								
Test for subgroup differences: Chi² = 3.62, df = 2 (P = 0.16), I² = 44.7%								



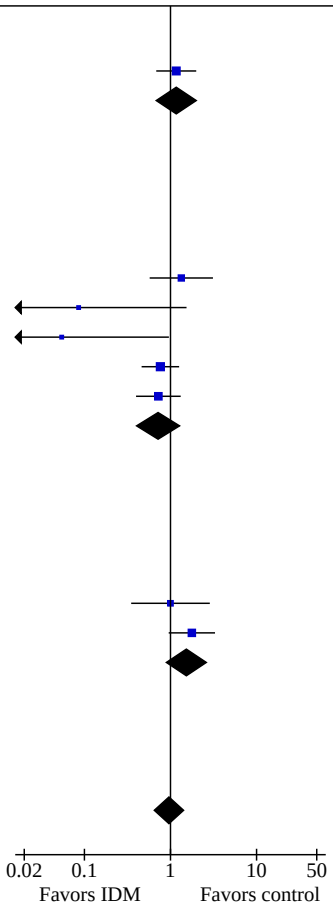
Analysis 1.24. Comparison 1: Integrated disease management versus control, update, Outcome 24: ED visits

Study or Subgroup	IDM Events	IDM Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Smith 1999	14	47	6	45	5.7%	2.76 [0.95 , 7.98]
Bourbeau 2003	39	96	60	95	11.1%	0.40 [0.22 , 0.71]
Rea 2004	5	83	7	52	4.8%	0.41 [0.12 , 1.37]
Rice 2010	51	372	85	371	14.4%	0.53 [0.36 , 0.78]
Fan 2012	99	209	119	217	14.5%	0.74 [0.51 , 1.08]
Lou 2015	92	239	110	196	14.4%	0.49 [0.33 , 0.72]
Sanchez-Nieto 2016	9	47	14	38	6.4%	0.41 [0.15 , 1.08]
Rose 2017	140	236	134	234	14.7%	1.09 [0.75 , 1.57]
Silver 2017	64	214	67	214	13.9%	0.94 [0.62 , 1.41]
Total (95% CI)		**1543**		**1462**	**100.0%**	**0.69 [0.50 , 0.93]**
Total events:	513		602			
Heterogeneity: Tau² = 0.13; Chi² = 24.70, df = 8 (P = 0.002); I² = 68%						
Test for overall effect: Z = 2.42 (P = 0.02)						
Test for subgroup differences: Not applicable						



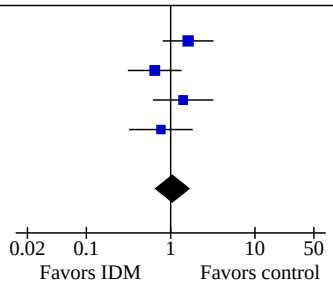
Analysis 1.25. Comparison 1: Integrated disease management versus control, update, Outcome 25: Number of patients experiencing ≥ 1 exacerbation

Study or Subgroup	IDM Events	IDM Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.25.1 Number of patients experiencing ≥ 1 exacerbation: short-term (≤ 6 months)						
Trappenburg 2011	55	103	56	113	19.3%	1.17 [0.68 , 1.99]
Subtotal (95% CI)		**103**		**113**	**19.3%**	**1.17 [0.68 , 1.99]**
Total events:	55		56			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.56 (P = 0.57)						
1.25.2 Number of patients experiencing ≥ 1 exacerbation: medium-term (> 6 months to 15 months)						
Bourbeau 2003	85	96	81	95	12.5%	1.34 [0.57 , 3.11]
Vasilopoulou 2017	41	50	25	25	1.7%	0.09 [0.00 , 1.54]
Vasilopoulou 2017	37	50	25	25	1.8%	0.05 [0.00 , 0.96]
Kessler 2018	112	157	124	162	20.2%	0.76 [0.46 , 1.26]
Lenferink 2019	66	102	71	99	17.8%	0.72 [0.40 , 1.31]
Subtotal (95% CI)		**455**		**406**	**54.0%**	**0.72 [0.40 , 1.27]**
Total events:	341		326			
Heterogeneity: Tau² = 0.17; Chi² = 7.55, df = 4 (P = 0.11); I² = 47%						
Test for overall effect: Z = 1.13 (P = 0.26)						
1.25.3 Number of patients experiencing ≥ 1 exacerbation: long-term (> 15 months)						
Sridhar 2008	53	61	53	61	9.5%	1.00 [0.35 , 2.86]
van Wetering 2010	63	89	52	90	17.2%	1.77 [0.95 , 3.29]
Subtotal (95% CI)		**150**		**151**	**26.7%**	**1.53 [0.90 , 2.61]**
Total events:	116		105			
Heterogeneity: Tau² = 0.00; Chi² = 0.84, df = 1 (P = 0.36); I² = 0%						
Test for overall effect: Z = 1.56 (P = 0.12)						
Total (95% CI)		**708**		**670**	**100.0%**	**0.96 [0.65 , 1.42]**
Total events:	512		487			
Heterogeneity: Tau² = 0.13; Chi² = 13.32, df = 7 (P = 0.06); I² = 47%						
Test for overall effect: Z = 0.21 (P = 0.83)						
Test for subgroup differences: Chi² = 3.63, df = 2 (P = 0.16), I² = 44.9%						



Analysis 1.26. Comparison 1: Integrated disease management versus control, update, Outcome 26: Number of patients using ≥ 1 course of oral steroids

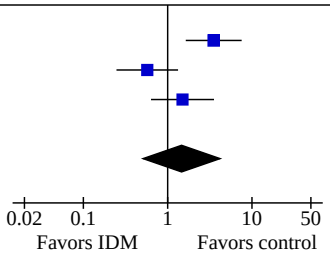
Study or Subgroup	IDM Events	IDM Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Littlejohns 1991	33	68	24	65	29.3%	1.61 [0.81 , 3.22]
Farrero 2001	20	60	27	62	27.0%	0.65 [0.31 , 1.35]
Rea 2004	31	52	21	41	22.7%	1.41 [0.62 , 3.21]
Sanchez-Nieto 2016	18	47	17	38	21.0%	0.77 [0.32 , 1.83]
Total (95% CI)		**227**		**206**	**100.0%**	**1.05 [0.66 , 1.64]**
Total events:	102		89			
Heterogeneity: Tau² = 0.06; Chi² = 4.10, df = 3 (P = 0.25); I² = 27%						
Test for overall effect: Z = 0.19 (P = 0.85)						
Test for subgroup differences: Not applicable						



Analysis 1.27. Comparison 1: Integrated disease management versus control, update, Outcome 27: Number of patients using ≥ 1 course of antibiotics

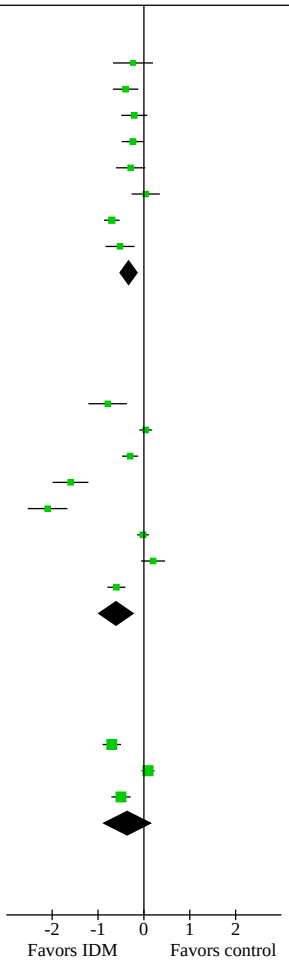
Study or Subgroup	IDM Events	IDM Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Littlejohns 1991	54	68	34	65	34.3%	3.52 [1.64 , 7.54]
Rea 2004	36	62	29	41	33.0%	0.57 [0.25 , 1.33]
Sanchez-Nieto 2016	27	47	18	38	32.7%	1.50 [0.63 , 3.55]
Total (95% CI)		**177**		**144**	**100.0%**	**1.46 [0.51 , 4.18]**
Total events:	117		81			

Heterogeneity: Tau² = 0.68; Chi² = 9.81, df = 2 (P = 0.007); I² = 80%
Test for overall effect: Z = 0.71 (P = 0.48)
Test for subgroup differences: Not applicable



Analysis 1.28. Comparison 1: Integrated disease management versus control, update, Outcome 28: MRC dyspnoea score

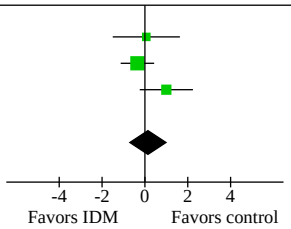
Study or Subgroup	IDM Mean	IDM SD	IDM Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.28.1 MRC dyspnoea score: short-term (≤ 6 months)								
Mendes 2010	-0.8929	0.9663	56	-0.6552	0.9738	29	9.1%	-0.24 [-0.67 , 0.20]
van Wetering 2010	-0.3	0.9327	87	0.1	0.9381	88	12.9%	-0.40 [-0.68 , -0.12]
Wakabayashi 2011	-0.2	1.0203	50	0.01	0.0778	48	12.7%	-0.21 [-0.49 , 0.07]
Bernocchi 2017	-0.17	0.495	48	0.07	0.677	44	13.8%	-0.24 [-0.48 , 0.00]
Khan 2019	-0.21	1.39	147	0.08	1.39	141	11.8%	-0.29 [-0.61 , 0.03]
Lenferink 2019	0.07	1.11	83	0.03	0.86	76	12.1%	0.04 [-0.27 , 0.35]
Zhang 2020	-0.9	0.4	85	-0.2	0.7	89	15.7%	-0.70 [-0.87 , -0.53]
Öztürk 2020	-0.32	0.7	31	0.2	0.55	30	11.9%	-0.52 [-0.84 , -0.20]
Subtotal (95% CI)			**587**			**545**	**100.0%**	**-0.33 [-0.52 , -0.15]**
Heterogeneity: Tau² = 0.05; Chi² = 24.97, df = 7 (P = 0.0008); I² = 72%								
Test for overall effect: Z = 3.52 (P = 0.0004)								
1.28.2 MRC dyspnoea score: medium-term (> 6 months to 15 months)								
Wakabayashi 2011	-0.43	0.9393	42	0.36	1.0301	43	11.5%	-0.79 [-1.21 , -0.37]
Kruis 2014	0.23	1.18	554	0.19	1.18	532	13.2%	0.04 [-0.10 , 0.18]
Ko 2016	-0.1	0.6	90	0.2	0.6	90	13.1%	-0.30 [-0.48 , -0.12]
Vasilopoulou 2017	-0.7	0.6	50	0.9	0.9	25	11.8%	-1.60 [-1.99 , -1.21]
Vasilopoulou 2017	-1.2	0.9	50	0.9	0.9	25	11.4%	-2.10 [-2.53 , -1.67]
Kalter-Leibovici 2018	0.04	0.94	496	0.06	1	424	13.3%	-0.02 [-0.15 , 0.11]
Lenferink 2019	0.28	0.94	80	0.08	0.73	78	12.7%	0.20 [-0.06 , 0.46]
Zhang 2020	-0.8	0.5	85	-0.2	0.8	89	13.0%	-0.60 [-0.80 , -0.40]
Subtotal (95% CI)			**1447**			**1306**	**100.0%**	**-0.61 [-0.98 , -0.23]**
Heterogeneity: Tau² = 0.27; Chi² = 175.53, df = 7 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 3.19 (P = 0.001)								
1.28.3 MRC dyspnoea score: long-term (> 15 months)								
Lou 2015	-0.4	4.02	3418	0.3	4.02	2803	33.1%	-0.70 [-0.90 , -0.50]
Kalter-Leibovici 2018	0.37	1.01	479	0.28	1.09	378	34.0%	0.09 [-0.05 , 0.23]
Zhang 2020	-0.6	0.6	85	-0.1	0.8	89	32.9%	-0.50 [-0.71 , -0.29]
Subtotal (95% CI)			**3982**			**3270**	**100.0%**	**-0.37 [-0.88 , 0.14]**
Heterogeneity: Tau² = 0.19; Chi² = 46.69, df = 2 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 1.41 (P = 0.16)								



Analysis 1.29. Comparison 1: Integrated disease management versus control, update, Outcome 29: Borg score

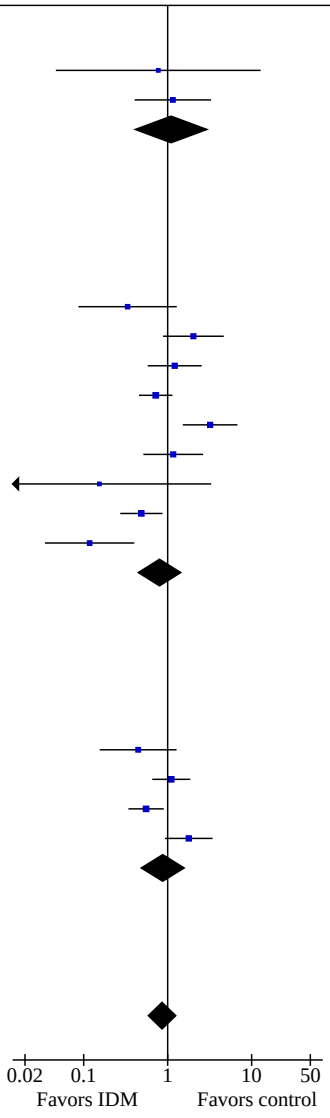
Study or Subgroup	IDM Mean	IDM SD	IDM Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Güell 2000	0.166	2.9084	30	0.1	3.2754	30	21.5%	0.07 [-1.50 , 1.63]
Boxall 2005	-0.13	1.3	23	0.22	1.4	23	48.7%	-0.35 [-1.13 , 0.43]
Gottlieb 2011	0.3	2.4	19	-0.7	1.4	20	29.7%	1.00 [-0.24 , 2.24]
Total (95% CI)			**72**			**73**	**100.0%**	**0.14 [-0.70 , 0.98]**

Heterogeneity: Tau² = 0.22; Chi² = 3.26, df = 2 (P = 0.20); I² = 39%
Test for overall effect: Z = 0.33 (P = 0.74)
Test for subgroup differences: Not applicable



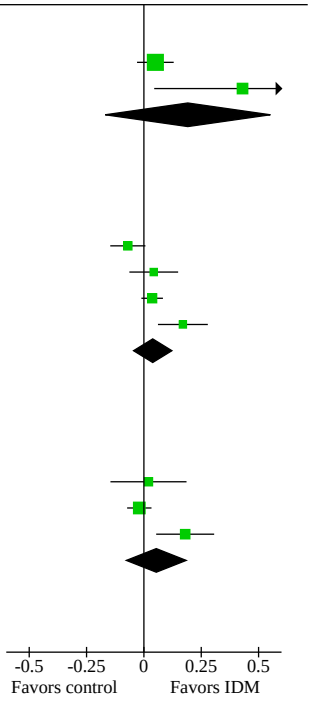
Analysis 1.30. Comparison 1: Integrated disease management versus control, update, Outcome 30: Mortality

Study or Subgroup	IDM Events	IDM Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.30.1 Mortality: short-term (≤ 6 months)						
Bernocchi 2017	1	45	1	35	1.5%	0.77 [0.05 , 12.81]
Aboumatar 2019	8	120	7	120	6.0%	1.15 [0.40 , 3.29]
Subtotal (95% CI)		**165**		**155**	**7.5%**	**1.10 [0.41 , 2.93]**
Total events:	9		8			
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.79); I² = 0%						
Test for overall effect: Z = 0.19 (P = 0.85)						
1.30.2 Mortality: medium-term (> 6 months to 15 months)						
Littlejohns 1991	3	73	9	79	4.6%	0.33 [0.09 , 1.28]
Smith 1999	33	48	25	48	7.2%	2.02 [0.88 , 4.65]
Farrero 2001	23	60	21	62	7.8%	1.21 [0.58 , 2.54]
Rice 2010	36	372	48	371	9.6%	0.72 [0.46 , 1.14]
Fan 2012	28	209	10	217	7.7%	3.20 [1.51 , 6.77]
Vianello 2016	23	181	9	81	7.3%	1.16 [0.51 , 2.64]
Sanchez-Nieto 2016	0	47	2	38	1.3%	0.15 [0.01 , 3.30]
Rose 2017	21	207	36	191	8.8%	0.49 [0.27 , 0.87]
Kessler 2018	3	157	23	162	5.1%	0.12 [0.03 , 0.40]
Subtotal (95% CI)		**1354**		**1249**	**59.5%**	**0.80 [0.45 , 1.43]**
Total events:	170		183			
Heterogeneity: Tau² = 0.54; Chi² = 34.89, df = 8 (P < 0.0001); I² = 77%						
Test for overall effect: Z = 0.75 (P = 0.45)						
1.30.3 Mortality: long-term (> 15 months)						
Sridhar 2008	6	61	12	61	6.0%	0.45 [0.16 , 1.28]
Kruis 2014	32	554	28	532	9.2%	1.10 [0.65 , 1.86]
Lou 2015	33	226	51	216	9.4%	0.55 [0.34 , 0.90]
Titova 2017	35	91	21	81	8.4%	1.79 [0.93 , 3.43]
Subtotal (95% CI)		**932**		**890**	**32.9%**	**0.87 [0.48 , 1.57]**
Total events:	106		112			
Heterogeneity: Tau² = 0.25; Chi² = 10.37, df = 3 (P = 0.02); I² = 71%						
Test for overall effect: Z = 0.45 (P = 0.65)						
Total (95% CI)		**2451**		**2294**	**100.0%**	**0.86 [0.59 , 1.25]**
Total events:	285		303			
Heterogeneity: Tau² = 0.33; Chi² = 45.51, df = 14 (P < 0.0001); I² = 69%						
Test for overall effect: Z = 0.80 (P = 0.42)						
Test for subgroup differences: Chi² = 0.30, df = 2 (P = 0.86), I² = 0%						



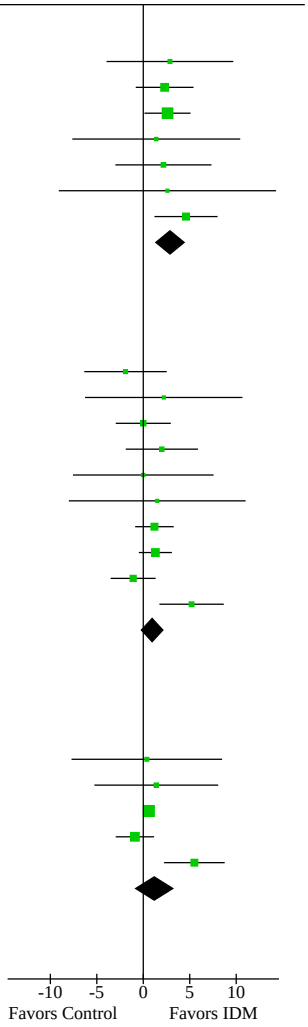
Analysis 1.31. Comparison 1: Integrated disease management versus control, update, Outcome 31: FEV_1 (litre)

Study or Subgroup	IDM Mean	IDM SD	IDM Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.31.1 FEV_1 (litre): short-term (< 6 months)								
Wood-Baker 2006	0.011	0.26	61	-0.039	0.185	62	62.8%	0.05 [-0.03 , 0.13]
Öztürk 2020	0.39	0.94	31	-0.04	0.55	30	37.2%	0.43 [0.04 , 0.82]
Subtotal (95% CI)			**92**			**92**	**100.0%**	**0.19 [-0.17 , 0.55]**
Heterogeneity: Tau² = 0.05; Chi² = 3.59, df = 1 (P = 0.06); I² = 72%								
Test for overall effect: Z = 1.04 (P = 0.30)								
1.31.2 FEV_1 (litre): medium-term (> 6 months to 15 months)								
Bourbeau 2003	-0.04	0.28	96	0.03	0.26	95	26.3%	-0.07 [-0.15 , 0.01]
Wood-Baker 2006	-0.022	0.318	54	-0.065	0.249	58	21.8%	0.04 [-0.06 , 0.15]
Kalter-Leibovici 2018	0.211	0.371	453	0.175	0.335	414	30.5%	0.04 [-0.01 , 0.08]
Zhang 2020	0.17	0.38	85	0	0.35	89	21.5%	0.17 [0.06 , 0.28]
Subtotal (95% CI)			**688**			**656**	**100.0%**	**0.04 [-0.05 , 0.12]**
Heterogeneity: Tau² = 0.01; Chi² = 13.03, df = 3 (P = 0.005); I² = 77%								
Test for overall effect: Z = 0.90 (P = 0.37)								
1.31.3 FEV_1 (litre): long-term (> 15 months)								
Sridhar 2008	-0.09	0.42	55	-0.11	0.44	49	26.1%	0.02 [-0.15 , 0.19]
Kalter-Leibovici 2018	0.158	0.362	406	0.178	0.386	363	42.1%	-0.02 [-0.07 , 0.03]
Zhang 2020	0.16	0.43	85	-0.02	0.42	89	31.8%	0.18 [0.05 , 0.31]
Subtotal (95% CI)			**546**			**501**	**100.0%**	**0.05 [-0.08 , 0.18]**
Heterogeneity: Tau² = 0.01; Chi² = 8.19, df = 2 (P = 0.02); I² = 76%								
Test for overall effect: Z = 0.81 (P = 0.42)								



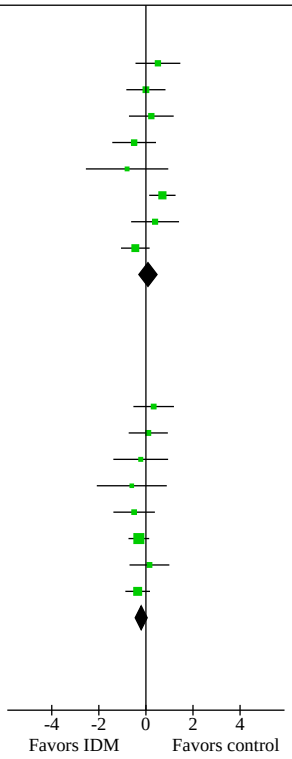
Analysis 1.32. Comparison 1: Integrated disease management versus control, update, Outcome 32: FEV_1 (% predicted)

Study or Subgroup	IDM Mean	IDM SD	IDM Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.32.1 FEV_1 (% predicted): short-term (≤ 6 months)								
Güell 2000	2.533	12.01	30	-0.337	14.8	30	5.0%	2.87 [-3.95 , 9.69]
Wood-Baker 2006	0.5	10.2	61	-1.8	7.1	62	24.0%	2.30 [-0.81 , 5.41]
van Wetering 2010	0.87	6.72	87	-1.74	9.76	88	37.7%	2.61 [0.13 , 5.09]
Wakabayashi 2011	1.6	19.9	50	0.2	25.3	48	2.8%	1.40 [-7.64 , 10.44]
Khan 2019	8.97	22.38	147	6.8	22.38	141	8.7%	2.17 [-3.00 , 7.34]
Jimenez-Reguera 2020	1.9	18.6	17	-0.7	17	19	1.7%	2.60 [-9.09 , 14.29]
Zhang 2020	3	10.3	85	-1.6	12.5	89	20.1%	4.60 [1.20 , 8.00]
Subtotal (95% CI)			**477**			**477**	**100.0%**	**2.88 [1.35 , 4.40]**
Heterogeneity: Tau² = 0.00; Chi² = 1.34, df = 6 (P = 0.97); I² = 0%								
Test for overall effect: Z = 3.70 (P = 0.0002)								
1.32.2 FEV_1 (% predicted) medium-term (> 6 to 15 months)								
Littlejohns 1991	-2.06	11.3612	68	-0.15	14.4882	65	6.0%	-1.91 [-6.35 , 2.53]
Güell 2000	3.538	16.7877	30	1.333	16.6836	30	1.8%	2.21 [-6.26 , 10.67]
Farrero 2001	-3	6.8924	46	-3	7.7423	48	11.9%	0.00 [-2.96 , 2.96]
Wood-Baker 2006	-0.3	11.4	54	-2.3	9.4	58	7.6%	2.00 [-1.89 , 5.89]
Fernandez 2009	0	13	27	0	11	14	2.2%	0.00 [-7.57 , 7.57]
Wakabayashi 2011	1.4	19.7	42	-0.1	24.8	43	1.4%	1.50 [-8.01 , 11.01]
Ko 2016	0.8	6.8	90	-0.4	7.4	90	19.8%	1.20 [-0.88 , 3.28]
Kalter-Leibovici 2018	9.6	14	453	8.3	12.7	414	23.9%	1.30 [-0.48 , 3.08]
Lenferink 2019	-1.7	7.71	81	-0.61	7.71	75	16.1%	-1.09 [-3.51 , 1.33]
Zhang 2020	3.1	10.2	85	-2.1	13	89	9.2%	5.20 [1.74 , 8.66]
Subtotal (95% CI)			**976**			**926**	**100.0%**	**0.95 [-0.20 , 2.11]**
Heterogeneity: Tau² = 0.63; Chi² = 11.14, df = 9 (P = 0.27); I² = 19%								
Test for overall effect: Z = 1.61 (P = 0.11)								
1.32.3 FEV_1 (% predicted): long-term (> 15 months)								
Güell 2000	1.875	15.8292	30	1.493	16.1962	30	5.3%	0.38 [-7.72 , 8.49]
Sridhar 2008	-1.8	17.1	55	-3.2	17.48	49	7.4%	1.40 [-5.26 , 8.06]
Lou 2015	-5.9	10.06	3418	-6.5	10.06	2803	39.6%	0.60 [0.10 , 1.10]
Kalter-Leibovici 2018	8.3	14.7	406	9.2	14.5	363	28.3%	-0.90 [-2.97 , 1.17]
Zhang 2020	1.9	10.1	85	-3.6	11.8	89	19.5%	5.50 [2.24 , 8.76]
Subtotal (95% CI)			**3994**			**3334**	**100.0%**	**1.18 [-0.82 , 3.18]**
Heterogeneity: Tau² = 2.56; Chi² = 10.75, df = 4 (P = 0.03); I² = 63%								
Test for overall effect: Z = 1.16 (P = 0.25)								



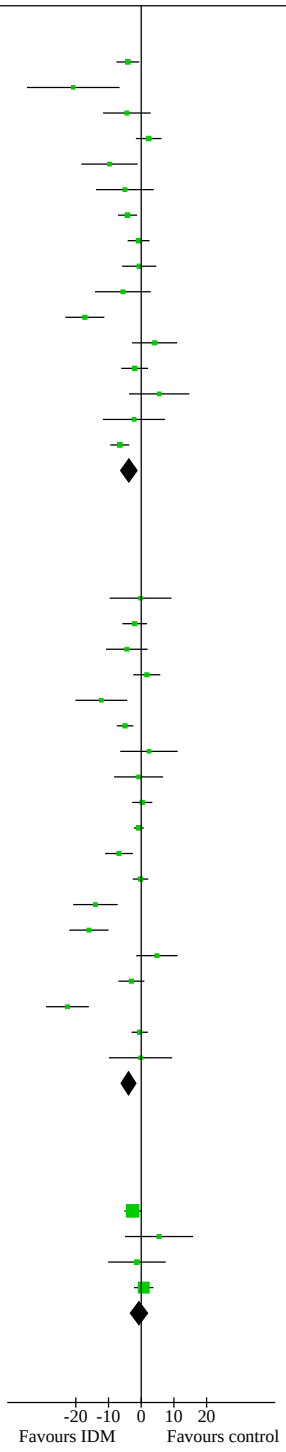
Analysis 1.33. Comparison 1: Integrated disease management versus control, update, Outcome 33: Anxiety and depression (HADS)

Study or Subgroup	IDM Mean	IDM SD	IDM Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.33.1 HADS: anxiety								
Littlejohns 1991	1.06	2.9746	68	0.55	2.6232	65	11.1%	0.51 [-0.44 , 1.46]
Trappenburg 2011	-0.4	2.7821	86	-0.4	2.9547	97	13.3%	0.00 [-0.83 , 0.83]
Vianello 2016	0.85	3.68	181	0.62	3.6	81	11.2%	0.23 [-0.72 , 1.18]
Rose 2017	-1.3	4.4	173	-0.8	4.4	172	11.5%	-0.50 [-1.43 , 0.43]
Titova 2017	-0.8	3.53	59	0	5.88	59	4.3%	-0.80 [-2.55 , 0.95]
Kessler 2018	0.2	2.5	157	-0.5	2.6	162	20.0%	0.70 [0.14 , 1.26]
Lenferink 2019	-0.76	3.53	79	-1.15	2.99	80	10.2%	0.39 [-0.63 , 1.41]
Öztürk 2020	-0.58	1.2	31	-0.13	1.22	30	18.6%	-0.45 [-1.06 , 0.16]
Subtotal (95% CI)			**834**			**746**	**100.0%**	**0.09 [-0.30 , 0.47]**
Heterogeneity: Tau² = 0.11; Chi² = 11.33, df = 7 (P = 0.12); I² = 38%								
Test for overall effect: Z = 0.44 (P = 0.66)								
1.33.2 HADS: depression								
Littlejohns 1991	0.44	2.6441	68	0.11	2.4214	65	8.7%	0.33 [-0.53 , 1.19]
Trappenburg 2011	-0.2	2.7821	86	-0.3	2.9547	97	9.3%	0.10 [-0.73 , 0.93]
Vianello 2016	0.5	4.3	181	0.72	4.5	81	4.8%	-0.22 [-1.38 , 0.94]
Titova 2017	-0.1	3.92	59	0.5	4.31	59	2.9%	-0.60 [-2.09 , 0.89]
Rose 2017	-0.6	4.2	175	-0.1	4.2	174	8.3%	-0.50 [-1.38 , 0.38]
Kessler 2018	-0.3	2.1	157	0	1.9	162	33.4%	-0.30 [-0.74 , 0.14]
Lenferink 2019	-0.34	2.78	79	-0.49	2.66	80	9.0%	0.15 [-0.70 , 1.00]
Öztürk 2020	-0.45	0.99	31	-0.1	1.09	30	23.6%	-0.35 [-0.87 , 0.17]
Subtotal (95% CI)			**836**			**748**	**100.0%**	**-0.20 [-0.45 , 0.05]**
Heterogeneity: Tau² = 0.00; Chi² = 3.85, df = 7 (P = 0.80); I² = 0%								
Test for overall effect: Z = 1.55 (P = 0.12)								



Analysis 1.34. Comparison 1: Integrated disease management versus control, update, Outcome 34: SGRQ total score

Study or Subgroup	IDM Mean	IDM SD	IDM Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.34.1 Short-term								
Bourbeau 2003	-6.4	11.8	88	-2.3	11.5	84	8.5%	-4.10 [-7.58 , -0.62]
Dheda 2004	-21	20.4	10	-0.2	12.6	15	2.4%	-20.80 [-34.96 , -6.64]
Boxall 2005	-5.8	11.8	23	-1.4	13.3	23	5.5%	-4.40 [-11.67 , 2.87]
Wood-Baker 2006	-1.1	11.2	60	-3.4	10.8	61	8.1%	2.30 [-1.62 , 6.22]
Koff 2009	-10.3	14.7	19	-0.6	12.2	19	4.6%	-9.70 [-18.29 , -1.11]
Theander 2009	-7.6	10.8	12	-2.6	12.2	14	4.5%	-5.00 [-13.84 , 3.84]
van Wetering 2010	-3.9	10.3	87	0.3	9.4	88	8.9%	-4.20 [-7.12 , -1.28]
Trappenburg 2011	0.4	10.201	86	1.2	12.8035	97	8.6%	-0.80 [-4.14 , 2.54]
Wakabayashi 2011	-2.2	13.3343	50	-1.6	13.0515	48	7.0%	-0.60 [-5.82 , 4.62]
Gottlieb 2011	-5.2	14.2	17	0.42	11.3	18	4.7%	-5.62 [-14.15 , 2.91]
Wang 2017	-12.75	15.67	55	4.48	17.64	65	6.4%	-17.23 [-23.19 , -11.27]
Titova 2017	-3.7	17.96	67	-7.8	21.16	59	5.7%	4.10 [-2.80 , 11.00]
Rose 2017	-5	19	174	-3	20	173	7.9%	-2.00 [-6.11 , 2.11]
Aboumatar 2019	2.81	30.8666	88	-2.69	31.9312	91	4.3%	5.50 [-3.70 , 14.70]
Jimenez-Reguera 2020	-2.7	13.3	17	-0.5	15.8	19	4.1%	-2.20 [-11.71 , 7.31]
Öztürk 2020	-4.03	6.03	31	2.52	5.59	30	8.9%	-6.55 [-9.47 , -3.63]
Subtotal (95% CI)			**884**			**904**	**100.0%**	**-3.78 [-6.29 , -1.28]**
Heterogeneity: Tau² = 16.21; Chi² = 54.07, df = 15 (P < 0.00001); I² = 72%								
Test for overall effect: Z = 2.96 (P = 0.003)								
1.34.2 Medium-term								
Engstrom 1999	0.3	17.3	26	0.5	16.8	24	3.2%	-0.20 [-9.65 , 9.25]
Bourbeau 2003	-3.5	13.5674	81	-1.5	10.5028	76	6.2%	-2.00 [-5.78 , 1.78]
Boxall 2005	-5.8	10.14	23	-1.4	11.82	23	4.7%	-4.40 [-10.76 , 1.96]
Wood-Baker 2006	-0.3	10.8	54	-2	11.5	58	6.0%	1.70 [-2.43 , 5.83]
Fernandez 2009	-14.7	12.82	27	-2.5	11.96	14	3.9%	-12.20 [-20.11 , -4.29]
Rice 2010	1.3	13.21	225	6.24	13.44	209	6.9%	-4.94 [-7.45 , -2.43]
Gottlieb 2011	-0.32	14.42	18	-2.69	13.06	20	3.5%	2.37 [-6.41 , 11.15]
Wakabayashi 2011	0.2	14.59	42	1	20.26	43	4.1%	-0.80 [-8.29 , 6.69]
Fan 2012	-1.36	11.2	101	-1.67	11.5	108	6.6%	0.31 [-2.77 , 3.39]
Kruis 2014	-0.4	12.69	554	0.33	12.69	532	7.2%	-0.73 [-2.24 , 0.78]
Ko 2016	-6.9	15.3	90	-0.1	13.8	90	5.9%	-6.80 [-11.06 , -2.54]
Zwar 2016	-2.05	8.9	126	-1.84	8.9	96	6.9%	-0.21 [-2.57 , 2.15]
Vasilopoulou 2017	-8	19	50	6	11	25	4.5%	-14.00 [-20.81 , -7.19]
Vasilopoulou 2017	-10	15	50	6	11	25	4.9%	-16.00 [-21.99 , -10.01]
Titova 2017	-0.8	15.12	58	-5.6	18.63	54	4.7%	4.80 [-1.51 , 11.11]
Rose 2017	-5	17.84	174	-2	19.84	173	6.1%	-3.00 [-6.97 , 0.97]
Wang 2017	-15.85	17.25	55	6.71	19.34	65	4.6%	-22.56 [-29.11 , -16.01]
Kalter-Leibovici 2018	-7.24	18.29	489	-6.77	19.38	407	6.9%	-0.47 [-2.95 , 2.01]
Jimenez-Reguera 2020	-3.8	15.72	17	-3.6	13.67	19	3.2%	-0.20 [-9.88 , 9.48]
Subtotal (95% CI)			**2260**			**2061**	**100.0%**	**-3.89 [-6.16 , -1.63]**
Heterogeneity: Tau² = 17.82; Chi² = 105.33, df = 18 (P < 0.00001); I² = 83%								
Test for overall effect: Z = 3.37 (P = 0.0008)								
1.34.3 Long-term								
van Wetering 2010	-1.37	8.073	77	1.23	8.0498	80	46.5%	-2.60 [-5.12 , -0.08]
Gottlieb 2011	-0.47	17.8	15	-5.93	11	17	5.9%	5.46 [-4.96 , 15.88]
Titova 2017	-4.1	19.29	44	-2.8	22.67	44	8.0%	-1.30 [-10.10 , 7.50]
Kalter-Leibovici 2018	-6.87	21.24	457	-7.63	21.72	356	39.7%	0.76 [-2.22 , 3.74]
Subtotal (95% CI)			**593**			**497**	**100.0%**	**-0.69 [-3.31 , 1.93]**
Heterogeneity: Tau² = 2.18; Chi² = 4.37, df = 3 (P = 0.22); I² = 31%								
Test for overall effect: Z = 0.52 (P = 0.61)								



ADDITIONAL TABLES

Table 1. Characteristics of included studies

Study	Country	Region	N (randomised)	N (completed)	Number of intervention components	Number of healthcare providers	Dominant component intervention	Duration intervention	Setting	Control group
Aboumatar 2019	USA	North America	240	187	3	2	SM	3 months	SEC	U
Aiken 2006	USA	North America	41	18	5	2	SF	6 months	PRIM	U
Bendstrup 1997	Denmark	Northwestern Europe	42	32	4	7	E	3 months	SEC	U
Bernocchi 2017	Italy	Southern Europe	112	80	5	3	TM	3 months	PRIM/SEC	
Bourbeau 2003	Canada	North America	191	165	4	4	SM	8 weeks + 10 months maintenance	SEC	U
Boxall 2005	Australia	Oceania	60	46	2	3	E	3 months	PRIM	U
Cambach 1997	Netherlands	Northwestern Europe	43	23	2	2	E	3 months	PRIM	DRUG
Dheda 2004	UK	Northwestern Europe	33	25	4	2	SF	6 months	SEC	U
Engstrom 1999	Sweden	Northwestern Europe	55	50	4	5	E	4.5 months + 7.5 months maintenance	SEC	U
Fan 2012	USA	North America	426	426	4	2	EDU	4 weeks + 11 months follow-up	SEC	U
Farrero 2001	Spain	Southern Europe	122	94	2	2	SF	12 months	SEC	U
Fernandez 2009	Spain	Southern Europe	50	41	2	2	E	11 months	PRIM	EDU
Freund 2016	Germany	Northwestern Europe	543 (COPD)	unknown	5	2	S	12 months	PRIM	U

Table 1. Characteristics of included studies *(Continued)*

Gottlieb 2011	Denmark	Northwestern Europe	61	26	4	Multi-disciplinary team, not specified	E	7 weeks + 6 months maintenance	PRIM	U
Güell 2000	Spain	Southern Europe	60	47	3	3	E	6 months + 6 months maintenance	SEC	U
Güell 2006	Spain	Southern Europe	40	25	2	4	E	4 months	TERT	DRUG
Haesum 2012	Denmark	Northwestern Europe	111	105	4	Primary and secondary caregivers, not specified	TM	4 months	PRIM/SEC	U
Jimenez-Reguera 2020	Spain	Southern Europe	44	36	6	3	SM	8 weeks + 10 months maintenance	SEC	U
Kalter-Leibovici 2018	Israel	Western Asia	1202	992	3		SF	Minimum 2 years, maximum 5 years	SEC	U
Kennedy 2013	UK	Northwestern Europe	1634	1146	2	2	SM		PRIM	U
Kessler 2018	International (Germany, France, Italy, Spain)	Northwestern Europe, Southern Europe	345	80	5	2	SF	12 months	SEC	U
Khan 2019	Pakistan	Western Asia	313	288	4	4	SF	6 months	PRIM	U
Ko 2016	China	East Asia	180	142	6	3	SF	8 weeks + 10 weeks maintenance	TERT	U
Koff 2009	USA	North America	40	38	4	2	SM	3 months	PRIM	U

Table 1. Characteristics of included studies *(Continued)*

Kruis 2014	Netherlands	Northwestern Europe	1086	810	6	5	SM	12 months	PRIM	U
Lenferink 2019	Netherlands, Australia	Northwestern Europe, Oceania	201	169	6	2	SM	9 months	SEC	U
Lilholt 2017	Denmark	Northwestern Europe	1125	574	4	2	SF	12 months	PRIM	U
Littlejohns 1991	UK	Northwestern Europe	152	133	4	3	SF	12 months	SEC	U
Lou 2015	China	East Asia	8171	6221	9	5	EDU	48 months	PRIM	U
Mendes 2010	Brazil	South America	117	85	2	2	E	3 months	PRIM/SEC	U
Öztürk 2020	Turkey	Western Asia	80	61	5	4	SM	3 months	SEC	U
Rea 2004	New Zealand	Oceania	135	117	5	4	SM/SF	12 months	PRIM/SEC	U
Rice 2010	USA	North America	743	743	3	2	SM	12 months	SEC	EDU
Rose 2017	Canada	North America	475	398	5	3	SF	9 months	SEC	U
Sanchez-Nieto 2016	Spain	Southern Europe	96	85	7	3	SM	3 months	SEC	U
Silver 2017	USA	North America	428	423	5	2	EDU	6 months	SEC	U
Smith 1999	Australia	Oceania	96	36	8	3	SF	12 months	PRIM/SEC	U
Sridhar 2008	UK	Northwestern Europe	122	104	4	3	E/SM	8 weeks + 16 months maintenance	PRIM/SEC	U
Strijbos 1996	Netherlands	Northwestern Europe	50	41	3	3	E	3 months	PRIM/SEC	U
Tabak 2014	Netherlands	Northwestern Europe	29	12	8	Primary and secondary	TM	9 months	PRIM/SEC	U

Table 1. Characteristics of included studies *(Continued)*

						caregivers, not specified				
Theander 2009	Sweden	Northwestern Europe	30	26	4	4	E	3 months	SEC	U
Titova 2017	Norway	Northwestern Europe	172	100	4	3	SF	24 months	PRIM/SEC	U
Trappenburg 2011	Netherlands	Northwestern Europe	233	193	3	3	SM	6 months	SEC	U
van Wetering 2010	Netherlands	Northwestern Europe	199	175	4	3	E	16 weeks + 20 months maintenance	SEC	U
Vasilopoulou 2017	Greece	Southern Europe	300	147	7	4	TM (A), SF (B)	8 weeks + 12 months maintenance	TERT	U
Vianello 2016	Italy	Southern Europe	334	262	5	3	TM	12 months	PRIM/SEC	U
Wakabayashi 2011	Japan	East Asia	102	85	4	2	EDU	6 months	SEC	EDU
Wang 2017	China	East Asia	130	120	4	3	TM	12 months	TERT	U
Wijkstra 1994	Netherlands	Northwestern Europe	45	43	2	3	E	3 months	PRIM	U
Wood-Baker 2006	Australia	Oceania	135	112	3	2	SM	12 months	PRIM	EDU
Zhang 2020	China	East Asia	208	174	7	5	SF	24 months	TERT	U
Zwar 2016	Australia	Oceania	254	222	3	2	EDU	6 months (flexible)	PRIM	U

Abbreviations. DRUG: optimisation of drug treatment; E: exercise; IT EDU: individual educational session; PRIM: primary care; SEC: secondary care; SF: structured follow-up; SM: self-management; TERT: tertiary care; TM: telemonitoring; U: usual care.

Table 2. Components of IDM in each included study

Author	Education	Self-management	Exacerbation/Action plan	Telemonitoring	Exercise	Psychosocial/Occupational	Smoking	Optimal medication	Nutrition	Follow-up	Case management	Multi-disciplinary
Aboumatar 2019	x	x									x	
Aiken 2006	x	x	x					x			x	
Bendstrup 1997	x				x	x	x					
Bernocchi 2017	x				x	x					x	x
Bourbeau 2003	x		x		x					x		
Boxall 2005	x				x							
Cambach 1997	x				x							
Dheda 2004	x					x		x		x		
Engstrom 1999	x				x	x			x			
Fan 2012	x		x							x	x	
Farrero 2001										x	x	
Fernandez 2009	x				x							
Freund 2016	x		x							x	x	x
Gottlieb 2011	x				x		x		x			
Güell 2000	x				x					x		
Güell 2006	x				x							
Haesum 2012		x		x						x	x	x
Jimenez-Reguera 2020	x	x		x	x			x		x		

Table 2. Components of IDM in each included study *(Continued)*

Kalter-Leibovici 2018	x			x										x		
Kennedy 2013		x													x	
Kessler 2018	x	x	x	x									x	x		
Khan 2019	x							x		x			x			
Ko 2016	x	x	x			x	x						x			
Koff 2009	x	x	x										x			
Kruis 2014	x	x	x					x					x		x	
Lenferink 2019	x	x	x							x			x		x	
Lilholt 2017		x	x										x	x		
Littlejohns 1991	x									x			x	x		
Lou 2015	x		x				x	x		x		x	x	x	x	
Mendes 2010	x					x										
Öztürk 2020	x	x	x			x	x									
Rea 2004	x		x			x							x		x	
Rice 2010	x	x	x													
Rose 2017	x	x	x											x	x	
Sanchez-Nieto 2016	x	x	x			x				x			x			
Silver 2017	x		x					x					x	x		
Smith 1999	x	x	x			x		x		x				x	x	
Sridhar 2008	x		x			x							x			
Strijbos 1996	x					x							x			

Table 2. Components of IDM in each included study *(Continued)*

Tabak 2014		x	x	x	x			x		x	x	x	
Theander 2009	x				x	x			x				
Titova 2017		x						x		x	x	x	
Trappenburg 2011	x	x	x										
van Wetering 2010	x				x		x		x				
Vasilopoulou 2017	x	x	x	x	x					x	x		
Vianello 2016		x		x				x		x	x		
Wakabayashi 2011	x	x	x				x						
Wang 2017	x		x	x								x	
Wijkstra 1994	x				x								
Wood-Baker 2006	x	x	x										
Zhang 2020	x	x			x	x	x	x		x			
Zwar 2016	x		x			x							

Abbreviations. IDM: integrated disease management.

Table 3. Table of study characteristics/outcomes: quality of life

Author	Outcome domain	Outcome measure	Time points in months (time frame)	Data reported	Pooled
Aboumatar 2019	Health-related QoL	SGRQ	4 (ST)	mean change, 95% CI, N/group	Yes
Aiken 2006	Generic QoL	SF-36	3 (ST); 6 (ST); 9 (MT); 12 (MT)	slopes of trajectories	No
Bendstrup 1997	Health-related QoL	CRQ, YGLQ	1 (ST); 3 (ST)	mean change, SEM/group/P value	Yes
Bernocchi 2017	Health-related QoL	CAT score, Barthel score	4 (ST); 6 (ST)	mean change, SD, N/group	No
Bourbeau 2003	Health-related QoL	SGRQ - total, SGRQ - subtotals	6 (ST); 9 (MT)	mean, 95% CI, N/group	Yes
Boxall 2005	Health-related QoL	SGRQ - total, SGRQ - subtotals	3 (ST); 12 (MT)	mean change, mean at follow-up with SD, N/group/time point mean difference, 95% CI, P value	Yes
Cambach 1997	Health-related QoL	CRDQ (CRQ - recalculated)	3 (ST); 6 (MT)	mean at baseline, mean change, SD, N/group	No
Dheda 2004	Health-related QoL	SGRQ - total	12 (MT)	mean change, SE. N/group, P value	Yes
Engstrom 1999	Health-related QoL	SGRQ - total, SGRQ - subtotals	12 (MT)	mean, SE, N/group/time point	Yes
Fan 2012	Health-related QoL; generic QoL	SGRQ - total, SGRQ - subtotals; SF-12 MCS; SF-12 PCS	12 (MT)	mean change, SD, N/group	Yes
Farrero 2001	Health-related QoL	CRQ	3 (ST); 12 (MT)	not reported	No
Fernandez 2009	Health-related QoL	SGRQ - total, SGRQ - subtotals	12 (MT)	mean, SD, N/group/time point	Yes
Freund 2016	n.a.	n.a.	n.a.	n.a.	n.a.
Gottlieb 2011	Health-related QoL	SGRQ - total, SGRQ - subtotals	6 (ST); 12 (MT); 18 (LT)	mean, SD, N/group/time point	Yes
Güell 2000	Health-related QoL; generic QoL	CRQ, BODE Index, VAS	3 (ST); 6 (ST); 9 (MT); 12 (MT); 18 (LT); 24 (LT)	mean, SE/group/time point	Yes
Güell 2006	Health-related QoL	CRQ	4 (ST)	mean, SD, N/group/time point	Yes
Haesum 2012	n.a.	n.a.	n.a.	n.a.	n.a.
Jimenez-Reguera 2020	Health-related QoL; generic QoL	SGRQ, CAT, EQ-5D, VAS	6 (ST); 12 (MT)	mean, SD, N/group/time point	Yes

Table 3. Table of study characteristics/outcomes: quality of life *(Continued)*

Kalter-Leibovici 2018	Health-related QoL; generic QoL	SGRQ-total, SF-12 MCS, SF-12 PCS	12 (MT); 24 (LT)	mean change, SD, N/group	Yes
Kennedy 2013	Generic QoL	EQ-5D	6 (ST); 12 (MT)	mean change, SD, N/group	No
Kessler 2018	Health-related QoL	SGRQ - COPD specific, BODE Index	12 (MT)	mean, SD, N/group (at 12 months) adjusted MD, 95% CI, N, P value	No
Khan 2019	Health-related QoL	BODE Index	6 (ST)	MD, 95% CI, P value, N	No
Ko 2016	Health-related QoL	SGRQ - total, SGRQ - subtotals	12 hs (MT)	mean change, SD, N/group	Yes
Koff 2009	Health-related QoL	SGRQ - total, SGRQ - subtotals	3 (ST)	mean change, 95% CI, N/group	Yes
Kruis 2014	Health-related QoL; generic QoL	SGRQ - total, SGRQ - subscores, CCQ, SF-36 PCS, SF-36 MCS	12 (MT)	mean change, 95% CI, N/group	Yes
Lenferink 2019	Health-related QoL	CRQ, CAT	6 (ST); 12 (MT)	mean change, SD, N/group (additional data)	Yes
Lilholt 2017	Generic QoL	SF-36 MCS, SF-36 PCS	12 (MT)	MD, 95% CI, P value, N	Yes
Littlejohns 1991	n.a.	n.a.	n.a.	n.a.	n.a
Lou 2015	Health-related QoL	BODE Index	48 (LT)	mean change, SD, N/group adjusted median D, 95% CI, P value	No
Mendes 2010	Health-related QoL	BODE Index	3 (ST)	mean, SD, N/group/time point - box and whisker plots	No
Öztürk 2020	Health-related QoL; generic QoL	SGRQ, CAT, SF-36 subdomains	3 (ST)	mean, SD, N/group/time point	Yes
Rea 2004	Health-related QoL; generic QoL	CRQ, SF-36 subdomains	12 (MT)	mean, N/group/time point, P value difference	Yes
Rice 2010	Health-related QoL	SGRQ - total	12 (MT)	mean change/group mean difference (95% CI)	Yes
Rose 2017	Health-related QoL	SGRQ - total, BODE Index	6 (ST); 12 (MT)	mean, SD/group	Yes
Sanchez-Nieto 2016	n.a.	n.a.	n.a.	n.a.	n.a
Silver 2017	n.a.	n.a.	n.a.	n.a.	n.a
Smith 1999	Health-related QoL	COOP	12 (MT)	mean, SE, N/group/follow-up	No

Table 3. Table of study characteristics/outcomes: quality of life *(Continued)*

Sridhar 2008	Health-related QoL	CRQ	24 (LT)	mean, SD, N/group/time point	Yes
Strijbos 1996	n.a.	n.a.	n.a.	n.a.	n.a
Tabak 2014	Health-related QoL; generic QoL	CCQ, EQ-5D Index, EQ-5D VAS score	1 (ST); 3 (MT)	mean, SD, N/group/time point	No
Theander 2009	Health-related QoL	SGRQ - total, SGRQ - subtotals	3 (ST)	mean baseline, SD mean, SD/group	Yes
Titova 2017	Health-related QoL	SGRQ - total, SGRQ - subtotals	6 (ST); 12 (MT); 4 (LT)	mean, 95% CI/group/time point MD, 95% CI, N, P value	Yes
Trappenburg 2011	Health-related QoL	SGRQ - total, SGRQ - subtotals, CCQ	6 (ST)	mean change, SE, N/group	Yes
van Wetering 2010	Health-related QoL	SGRQ - total, SGRQ - subtotals	4 (ST); 12 (MT); 24 (LT)	mean, SE, N/group MD, MD adjusted, SE, P value	Yes
Vasilopoulou 2017	Health-related QoL	SGRQ - total, CAT score	2 (ST); 14 (MT)	mean, SD, N/group/time point	Yes
Vianello 2016	Generic QoL	SF-36 PCS, SF-36 MCS	12 (MT)	mean, SD, N/group	Yes
Wakabayashi 2011	Health-related QoL	SGRQ - total	6 (ST); 12 (MT)	mean, SD, N/group/time point	Yes
Wang 2017	Health-related QoL	SGRQ - total, SGRQ - subtotals	1 (ST); 3 (ST); 6 (ST); 12 (MT)	mean, SD, N/group/time point	Yes
Wijkstra 1994	Health-related QoL	CRQ	3 (ST); 6 (ST); 12 (MT); 18 (LT)	mean change, SD, N/group	Yes
Wood-Baker 2006	Health-related QoL	SGRQ - total, SGRQ - subtotals	6 (ST); 12 (MT)	mean, SD, N/group/time point	Yes
Zhang 2020	Health-related QoL	CAT score	3 (ST); 6 (ST); 12 (MT); 24 (LT)	mean, SD, N/group/time point	No
Zwar 2016	Health-related QoL	SGRQ - total, CAT score	12 (MT)	mean, SD, N, P value, t test statistic/group/time point	Yes

Abbreviations. CAT: COPD Assessment Test; CCQ: Chronic COPD Questionnaire; CI: confidence interval; COOP: Dartmouth Primary Care Co-operative Quality of Life Questionnaire; CRQ: Chronic Respiratory Questionnaire; EQ-5D: EuroQol Quality of Life - 5 domains; LT: long-term follow-up; MCS: Mental Component Score; MD: mean difference; MT: medium-term follow-up; QoL: quality of life; PCS: Physical Component Score; SD: standard deviation; SE: standard error; SGRQ: St. George's Respiratory Questionnaire; SF-12: Short Form-12; SF-36: Short Form-36; SIP: Sickness Impact Profile; ST: short-term follow-up; VAS: visual analogue scale; YGLQ: York Quality of Life Questionnaire.

Table 4. Table of study characteristics outcomes: functional and maximum exercise capacity

Author	Outcome domain	Outcome measure	Time points in months (time frame)	Data presented	Pooled

Table 4. Table of study characteristics outcomes: functional and maximum exercise capacity *(Continued)*

Bendstrup 1997	functional exercise capacity	6MWD	1 (ST); 3 (ST); 6 (ST)	mean change, SEM, group/P value	Yes
Bernocchi 2017	functional exercise capacity	6MWD	4 (ST);	mean change, 95% CI, N/group	Yes
Bourbeau 2003	functional exercise capacity	6MWD	4 (ST); 12 (MT)	not reported	No
Boxall 2005	functional exercise capacity	6MWD	3 (ST)	mean, mean change, SD mean/group, P value	Yes
Cambach 1997	functional and maximum exercise capacity	6MWD, W-max	3 (ST); 6 (ST)	mean change, SD, N/group	Yes
Engstrom 1999	functional exercise capacity	6MWD	12 (MT)	mean, SE, N/group/time point	Yes
Fernandez 2009	functional exercise capacity	6MWD, leg fatigue score	12 (MT)	mean, SD, N/group/time point	Yes
Gottlieb 2011	functional and maximum exercise capacity	6MWD	6 (ST); 12 (MT); 18 (LT)	mean, SD, N/group/time point	Yes
Güell 2000	functional and maximum exercise capacity	6MWD, W-max	3 (ST); 6 (ST); 9 (MT); 12 (MT); 18 (LT); 24 (LT)	mean, SE, group/time point	Yes
Güell 2006	functional exercise capacity	6MWD	4 (ST)	mean, SD, N/group/time point	Yes
Jimenez-Reguera 2020	functional exercise capacity	6MWD	6 (ST); 12 (MT)	mean, SD, N/group/time point	Yes
Kalter-Leibovici 2018	functional exercise capacity	6MWD	12 (MT); 24 (LT)	mean change, SD, N/group	Yes
Kessler 2018	functional exercise capacity	6MWD	12 (MT)	mean, SD, N/group (at 12 months) adjusted MD, 95% CI, N, P value	Yes
Khan 2019	functional exercise capacity	6MWD	6 (ST)	mean change, SD, N/group, MD, 95% CI	Yes
Ko 2016	functional exercise capacity	6MWD	12 (MT)	mean change, SD, N/group, P value	Yes
Littlejohns 1991	functional exercise capacity	6MWD	12 (MT)	mean change, 95% CI, N/group	Yes
Lou 2015	functional exercise capacity	6MWD	48 (LT)	mean change, SD, N/group adjusted median D, 95% CI, P value	Yes
Mendes 2010	functional exercise capacity	6MWD	3 (ST)	mean, SD, N/group/time point - box and whisker plots	Yes

Table 4. Table of study characteristics outcomes: functional and maximum exercise capacity *(Continued)*

Rea 2004	functional and maximum exercise capacity	Shuttle walk test	12 (MT)	mean, N/group/time point, P value difference	No
Strijbos 1996	functional and maximum exercise capacity	W-max, 4MWT, Borg scores during cycle test	6 (ST); 12 (MT); 18 (LT)	mean, SD, N/group/time point	Yes
Tabak 2014	functional exercise capacity	6MWD	1 (ST); 3 (MT)	mean, SD, N/group/time point	Yes
Theander 2009	functional and maximum exercise capacity	6MWD, grip strength	3 (ST)	mean change, SD, N/group	Yes
van Wetering 2010	functional and maximum exercise capacity	6MWD, W-max	4 (ST); 12 (MT); 24 (LT)	mean change, SE, N/group	Yes
Vasilopoulou 2017	functional and maximum exercise capacity	6MWD, W-max	2 (ST); 14 (MT)	mean, SD, N/group/time point	Yes
Wakabayashi 2011	functional exercise capacity	6MWD	6 (ST); 12 (MT)	mean change, SD, N/group/ time point, P value	Yes
Wang 2017	functional exercise capacity	6MWD	1 (ST); 3 (ST); 6 (ST); 12 (MT)	mean change, SD, N/group	Yes
Zhang 2020	functional exercise capacity	6MWD	3 (ST); 6 (ST); 12 (MT); 24 (LT)	mean, SD, N/group/time point	Yes
Wijkstra 1994	functional exercise capacity	6MWD	3 (ST); 6 (ST); 12 (MT); 18 (LT)	mean change, SD, N/group	Yes (3 months only)

Abbreviations. 4MWT: 4-minute walk test; 6MWD: 6-minute walking distance; CI: confidence interval; LT: long-term follow-up; MD: mean difference; MT: medium-term follow-up; SD: standard deviation; SE: standard error; ST: short-term follow-up; W-max: maximum exercise capacity (in watts).

Table 5. Table of study characteristics outcomes: exacerbation outcomes

Author	Outcome domain	Outcome measure	Time points, months (time frame)	Data reported	Pooled
Aboumatar 2019	hospitalisations; ED visit	respiratory-related hospital admissions; hospital admissions (all causes); ED visits	6 (ST)	Incidence rate, 95% CI, N/group	Yes
Bernocchi 2017	hospitalisations	respiratory-related hospital admissions; hospital admissions (all causes)	6 (ST)	n, N/group	Yes
Bourbeau 2003	hospitalisations; ED visit; exacerbation	respiratory-related hospital admissions; hospital days per patient; ED visits; number of patients experiencing ≥ 1 exacerbation	6 (ST); 9 (MT)	n, N/group, mean, SD/group	Yes

Table 5. Table of study characteristics outcomes: exacerbation outcomes *(Continued)*

Boxall 2005	hospitalisations	respiratory-related hospital admissions; hospital days per patient	3 (ST); 12 (MT)	n, N/group, mean, SD/ group	Yes
Engstrom 1999	hospitalisations	hospital days per patient	12 (MT)	mean, SD/ group	Yes
Fan 2012	hospitalisations; ED visit; exacerbation	respiratory-related hospital admissions; hospital days per patient; ED visits; patients using ≥ 1 course of oral steroids; patients using ≥ 1 course of antibiotics	12 (MT)	n, N/group, rate per person-year, mean, SD, N/group	Yes
Farrero 2001	hospitalisations	hospital days per patient	12 (MT)	mean, SD/ group	Yes
Freund 2016	hospitalisations	hospital days per patient	12 (MT)	mean difference, 95% CI, N, P value	No
Güell 2000	exacerbation	mean exacerbation rate	24 (LT)	n as count data, mean, SD/ group	Yes
Kalter-Leibovici 2018	hospitalisations	respiratory-related hospital admissions; hospital admissions (all causes)	36 (LT)	n, N/group	Yes
Kessler 2018	hospitalisations, exacerbation	total hospital admissions (all causes); percentage of hospital days	12 (MT)	n, N/group	Yes
		total respiratory-related hospital admissions	12 (MT)	n, N/group	No
		hospital days per patient; number of patients experiencing ≥ 1 exacerbation	12 (MT)	n, N/group; mean, SD/ group	Yes
Ko 2016	hospitalisations	hospital days per patient	12 (MT)	mean, SD/ group	Yes
Koff 2009	hospitalisations	respiratory-related hospital admissions	3 (ST)	n, N/group	Yes
Kruis 2014	hospitalisations	hospital days per patient; mean exacerbation rate	12 (MT)	mean, 95% CI/ group, incidence rate ratio, 95% CI, N (for mild and severe exacerbations)	Yes
Lenferink 2019	hospitalisations; exacerbation	respiratory-related hospital admissions; hospital admissions (all causes); hospital days per patient; number of patients experiencing ≥ 1 exacerbation	12 (MT)	n, N/group, mean, 95% CI, N/group	Yes
Littlejohns 1991	hospitalisations; exacerbation	hospital admissions (all causes); patients using ≥ 1 course of oral steroids; patients using ≥ 1 course of antibiotics	12 (MT)	n, N/group	Yes

Table 5. Table of study characteristics outcomes: exacerbation outcomes *(Continued)*

Lou 2015	hospitalisations; ED visit	hospital admissions (all causes); ED visits	48 (LT)	%, N/group	Yes
Rea 2004	hospitalisations; ED visit; exacerbation	respiratory-related hospital admissions; hospital admissions (all causes); hospital days per patient; ED visits; patients using ≥ 1 course of oral steroids; patients using ≥ 1 course of antibiotics	12 (MT)	n, N/group, mean/group	Yes
Rice 2010	hospitalisations; ED visit	respiratory-related hospital admissions; ED visits	12 (MT)	n, N/group	Yes
Rose 2017	hospitalisations; ED visit	hospital days per patient; ED visits	12 (MT)	n, N/group, median, IQR/group	Yes
Sanchez-Nieto 2016	hospitalisations; ED visit; exacerbation	respiratory-related hospital admissions; ED visits; patients using ≥ 1 course of oral steroids; patients using ≥ 1 course of antibiotics	12 (MT)	n, N/group	Yes
Silver 2017	hospitalisations; ED visit	hospital days per patient; ED visits	12 (MT)	n, N/group, median, IQR/group	Yes
Smith 1999	hospitalisations; ED visit	respiratory-related hospital admissions; ED visits	12 (MT)	n, N/group	Yes
Sridhar 2008	hospitalisations; exacerbation	hospital admissions (all causes); number of patients experiencing ≥ 1 exacerbation	24 (LT)	n, N/group	Yes
Tabak 2014	ED visit	ED visits	3 (MT)	median, IQR/group	No
Titova 2017	hospitalisations	Total number of hospitalisations; categories of patients "HA category 1 (≤ 1 HA per year) and HA category 2 (≥ 2 HA per year)"	12 (MT); 24 (LT)	n, N (count data)	No
Trappenburg 2011	hospitalisations; exacerbation	respiratory-related hospital admissions; hospital days per patient; number of patients experiencing ≥ 1 exacerbation	6 (ST)	n, N; mean, SD, N/group/time point mean difference, 95% CI, P value	Yes
van Wetering 2010	hospitalisations; exacerbation	hospital days per patient; number of patients experiencing ≥ 1 exacerbation	24 (LT)	mean, SD/group, n, N/group	Yes
Vasilopoulou 2017	hospitalisations; exacerbation	respiratory-related hospital admissions; hospital admissions (all causes); hospital days per patient; number of patients experiencing ≥ 1 exacerbation; mean exacerbation rate	14 (MT); 24 (LT)	n, N/ group/ time point, mean, SD/ group	Yes
Vianello 2016	hospitalisations; ED visit	hospital days per patient (all causes); hospital days per patient (respiratory related); ED visits	12 (MT)	mean, SD, N/ group, rate per person-year	Yes

Table 5. Table of study characteristics outcomes: exacerbation outcomes *(Continued)*

Wakabayashi 2011	ED visit	ED visits	12 (MT)	mean, SD, N/group/time point	Yes
Zhang 2020	hospitalisations; ED visit	admission rates; length of stay; ED visits (all outcomes for entire study population)	3 (ST);6 (ST); 12 (MT); 24 (LT)	n, N (count data), median, IQR/group	No

Abbreviations. CI: confidence interval; ED: emergency department; IQR: interquartile range; T: long-term follow-up; MD: mean difference; MT: medium-term follow-up; SD: standard deviation; SE: standard error; ST: short-term follow-up.

Table 6. Table of study characteristics outcomes: secondary outcomes

Author	Outcome domain	Outcome measure	Time points, months (time frame)	Data reported	Pooled
Aboumatar 2019	Mortality	Mortality	4 (ST)	n, N	Yes
Bernocchi 2017	Dyspnoea	mMRC	4 (ST)	mean change, SD, N/group	Yes
	Mortality	Mortality	4 (MT)	n, N	Yes
Bourbeau 2003	Lung function	FEV_1, FEV_1% predicted	12 (MT)	mean, SD, N/group/time point	Yes
Boxall 2005	Dyspnoea	Borg score	3 (ST); 12 (MT)	mean change, mean at follow-up with SD, N/group/time point mean difference, 95% CI, P value	Yes
Engstrom 1999	Depression	MACL	12 (MT)	mean, SE, N/group/time point	No
Fan 2012	Mortality	Mortality	12 (MT) - mean 250 days' follow-up	n, N	Yes
Farrero 2001	Lung function	FEV_1% predicted	12 (MT)	mean, SD, N/group/time point, P value	Yes
	Mortality	Mortality	12 (MT)	n, N	Yes
Fernandez 2009	Lung function	FEV_1% predicted	12 (MT)	mean, SD, N/group/time point	Yes
Gottlieb 2011	Dyspnoea	Borg score	6 (ST); 12 (MT); 18 (LT)	mean, SD, N/group/time point	Yes
Güell 2000	Lung function	FEV_1% predicted	3 (ST); 6 (ST); 9 (MT); 12 (MT); 18 (LT); 24 (LT)	mean, SE, group/time point	Yes
		Borg score	3 (ST); 6 (ST); 9 (MT); 12 (MT); 18 (LT); 24 (LT)	mean, SE, group/time point	Yes

Table 6. Table of study characteristics outcomes: secondary outcomes *(Continued)*

Güell 2006	Depression	Revised Symptom Checklist (SCL-90-R)	4 (ST)	mean, SD, N/group/time point	No
Jimenez-Reguera 2020	Lung function	FEV_1% predicted (reported as FEV_1 in litres)	6 (ST)	mean, SD, N/group/time point	Yes
Kalter-Leibovici 2018	Lung function	FEV_1% predicted	12 (MT); 24 (LT)	mean change, SD, N/group	Yes
	Dyspnoea	mMRC	12 (MT); 24 (LT)	mean change, SD, N/group	Yes
Kessler 2018	Depression	HADS depression, HADS anxiety	12 (MT)	mean, SD, N/group (at 12 months) adjusted MD, 95% CI, N, P value	Yes
	Mortality	Mortality	12 (MT)	n, N	Yes
Khan 2019	Lung function	FEV_1% predicted	6 (ST)	mean change, SD, N/group, MD, 95% CI	Yes
	Dyspnoea	mMRC	6 (ST)	mean change, SD, N/group, MD, 95% CI	Yes
Ko 2016	Lung function	FEV_1% predicted	12 (MT)	mean change, SD, N/group	Yes
	Dyspnoea	mMRC	12 (MT)	mean change, SD, N/group	Yes
Koff 2009			3 (ST)	mean change, 95% CI, N/group	Yes
Kruis 2014	Dyspnoea	mMRC	12 (MT)	mean change, 95% CI, N/group	Yes
	Mortality	Mortality	12 (MT)	n, N	Yes
Lenferink 2019	Lung function	FEV_1% predicted	12 (MT)	mean change, SD, N/group (additional data)	Yes
	Dyspnoea	mMRC	6 (ST); 12 (MT)	mean change, SD, N/group (additional data)	Yes
	Depression	HADS total score	6 (ST); 12 (MT)	mean change, SD, N/group	Yes
Littlejohns 1991	Lung function	FEV_1% predicted	12 (MT)	mean change, 95% CI, N/group	Yes
	Depression	HADS depression, HADS anxiety	12 (MT)	mean change, 95% CI, N/group	Yes
	Mortality	Mortality	12 (MT)	n, N	Yes
Lou 2015	Lung function	FEV_1% predicted	48 (LT)	mean change, SD, N/group adjusted median D, 95% CI, P value	No
	Dyspnoea	mMRC	48 (LT)	mean change, SD, N/group adjusted median D, 95% CI, P value	Yes
	Mortality	Mortality	48 (MT)	n, N	Yes

Table 6. Table of study characteristics outcomes: secondary outcomes *(Continued)*

Mendes 2010	Dyspnoea	mMRC	3 (ST)	mean, SD, N/group/time point - box and whisker plots	No
Öztürk 2020	Lung function	FEV_1	3 (ST)	mean, SD, N/group/time	Yes
	Dyspnoea	mMRC	3 (ST)	mean, SD, N/group/time	Yes
	Depression	HADS depression, HADS anxiety	3 (ST)	mean, SD, N/group/time	Yes
Rice 2010	Mortality	Mortality	12 (MT)	n, N	Yes
Rose 2017	Depression	HADS depression, HADS anxiety	6 (ST); 12 (MT)	mean, SD/group	Yes
	Mortality	Mortality	12 (MT)	n, N	Yes
Sanchez-Nieto 2016	Mortality	Mortality	12 (MT)	n, N	Yes
Smith 1999	Lung function	FEV_1, FEV_1% predicted	12 (MT)	mean, SE/group	No
	Mortality	Mortality	12 (MT)	n, N	Yes
Sridhar 2008	Lung function	FEV_1, FEV_1% predicted	48 (LT)	mean, SD, N/group/time point	Yes
	Mortality	Mortality	48 (MT)	n, N	Yes
Titova 2017	Depression	HADS depression, HADS anxiety	6 (ST); 12 (MT); 24 (LT)	mean, 95% CI/group/time point MD, 95% CI, N, P value	Yes
	Mortality	Mortality	24 (MT)	n, N	Yes
Trappenburg 2011	Depression	HADS depression, HADS anxiety	6 (ST)	mean change, SE, N/group	Yes
van Wetering 2010	Lung function	FEV_1% predicted	4 (ST)	mean, SE, N/group	Yes
	Dyspnoea	MRC	4 (ST); 12 (MT); 24 (LT)	mean, SE, N/group	Yes
Vasilopoulou 2017	Dyspnoea	mMRC	2 (ST); 14 (MT)	mean, SD, N/group/time point	Yes
Vianello 2016	Depression	HADS depression, HADS anxiety	12 (MT)	mean, SD, N/group	Yes
	Mortality	Mortality	12 (MT)	n, N	Yes
Wakabayashi 2011	Lung function	FEV_1% predicted	6 (ST); 12 (MT)	mean, SD, N/group/time point	Yes
	Dyspnoea	mMRC	6 (ST); 12 (MT)	mean, SD, N/group/time point	Yes
Wang 2017	Lung function	FEV_1	3 (ST); 6 (ST); 12 (MT)	mean, SD, N/group/time point	No (reporting error)

Table 6. Table of study characteristics outcomes: secondary outcomes *(Continued)*

	Dyspnoea	mMRC	3 (ST); 6 (ST); 12 (MT)	mean, SD, N / group / time point	No (reporting error)
Wijkstra 1994	Lung function	FEV_1	3 (ST); 6 (ST); 12 (MT); 18 (LT)	mean change, SD, N/group (only for 3 months' follow-up)	Yes
Wood-Baker 2006	Lung function	FEV_1, FEV_1% predicted	6 (ST); 12 (MT)	mean, SD, N/group	Yes
Zhang 2020	Lung function	FEV_1, FEV_1% predicted	3 (ST); 6 (ST); 12 (MT); 24 (LT)	mean, SD, N/group/time point	Yes
	Dyspnoea	mMRC	3 (ST); 6 (ST); 12 (MT); 24 (LT)	mean, SD, N/group/time point	
Zwar 2016	Lung function	FEV_1% predicted	12 (MT)	mean, SD, N/group/time point MD, 95% CI, P value, N	Yes

Abbreviations. CI: confidence interval; FEV_1: forced expiratory volume in one second; HADS: Hospital Anxiety and Depression Scale; LT: long-term follow-up; MD: mean difference; mMRC: modified Medical Research Council Dyspnoea Scale; MT: medium-term follow-up; SD: standard deviation; SE: standard error; ST: short-term follow-up.

Table 7. Sensitivity analysis primary outcomes

Outcome	No. of studies	No. of participants	Studies omitted	Effect	Effect size	95% CI	I^2	P value
1.1 SGRQ: short-term (≤ 6 months)								
1.1.1 SGRQ: total	12	1386	Gottlieb 2011, Titova 2017, Wang 2017, Wood-Baker 2006	MD	-3.65	-5.66, -1.64	0.04	46
	16	1788		MD	-3.78	-6.29, -1.28	<0.00001	72
1.1.2 SGRQ: symptoms	9	919	Gottlieb 2011, Titova 2017, Wang 2017, Wood-Baker 2006	MD	-1.94	-5.26, 1.38	0.09	41
	13	1327		MD	-1.56	-5.66, 2.53	<0.00001	71
1.1.3 SGRQ: activity	9	916	Gottlieb 2011, Titova 2017, Wang 2017, Wood-Baker 2006	MD	-3.63	-5.66, -1.61	0.49	0
	0	1320		MD	-3.04	-5.80, -0.28	0.02	50
1.1.4 SGRQ: impact	9	917	Gottlieb 2011, Titova 2017, Wang 2017, Wood-Baker 2006	MD	-4.1	-6.30, -1.90	0.17	31
		1322		MD	-3.76	-5.94,-1.57	0.04	46
1.2 SGRQ: medium-term (> 6 to 15 months)								
1.2.1 SGRQ: total	13	3889	Engstrom 1999, Gottlieb 2011, Titova 2017, Wang 2017, Wood-Baker 2006	MD	-3.95	-6.06, -1.84	<0.00001	78
	18	4321		MD	-3.89	-6.16, -1.63	<0.00001	83
1.2.2 SGRQ: symptoms	7	2195	Engstrom 1999, Gottlieb 2011, Titova 2017, Wang 2017, Wood-Baker 2006	MD	-3.11	-6.00, -0.21	0.04	55
	12	2628		MD	-3.88	-7.75, -0.02	<0.00001	79

Table 7. Sensitivity analysis primary outcomes *(Continued)*

1.2.3 SGRQ: activity	7	2175	Engstrom 1999, Gottlieb 2011, Titova 2017, Wang 2017, Wood-Baker 2006	MD	-3.09	-5.98, -0.20	0.008	65
	12	2608		MD	-2.57	-5.53,0.38	< 0.0001	71
1.2.4 SGRQ: impact	7	2178	Engstrom 1999, Gottlieb 2011, Titova 2017, Wang 2017, Wood-Baker 2006	MD	-3.2	-6.19, -0.21	0.95	0
	12	2610		MD	-3.34	-6.26, -0.41	<0.00001	77
1.3 SGRQ: long-term (> 15 months)								
1.3.1 SGRQ: total	2	970	Gottlieb 2011, Titova 2017	MD	-1.02	-4.30, 2.27	0.09	65
	4	1090		MD	-0.69	-3.31, 1.93	0.22	31
1.3.2 SGRQ: symptoms	1	157	Gottlieb 2011, Titova 2017	MD	n.a.	n.a.	n.a	n.a
	3	279		MD	2.35	-5.49, 10.19	0.08	60
1.3.3 SGRQ: activity	1	157	Gottlieb 2011, Titova 2017	MD	n.a.	n.a.	n.a.	n.a.
	3	278		MD	-2.87	-6.17, 0.43	0.55	0
1.3.4 SGRQ: impact	1	150	Gottlieb 2011, Titova 2017	MD	n.a.	n.a.	n.a.	n.a.
	3	270		MD	-2.21	-4.71, 0.29	0.49	0
1.8 CRQ: short-term (≤ 6 months)								
1.8.1 CRQ: dyspnoea	1	160	Cambach 1997, Güell 2000, Güell 2006	MD	n.a.	n.a.	n.a.	n.a.
	4	277		MD	0.8	-0.01, 1.62	0.0001	86
1.8.2 CRQ: fatigue	3	196	Cambach 1997, Güell 2000, Güell 2006	MD	0.01	-1.34, 1.35	0.28	21
	6	314		MD	0.71	-0.19, 1.62	<0.00001	84

Table 7. Sensitivity analysis primary outcomes *(Continued)*

1.8.3 CRQ: emotion	3	196	Cambach 1997, Güell 2000, Güell 2006	MD	-0.33	-0.65, -0.01	0.37	0
	6	314		MD	0.45	-0.26, 1.17	0.003	72
1.8.4 CRQ: mastery	3	196	Cambach 1997, Güell 2000, Güell 2006	MD	0.38	-1.20, 1.96	0.22	35
	6	314		MD	0.72	-0.08, 1.52	0.0002	79
1.9 CRQ: medium-term (> 6 to 15 months)								
1.9.1 CRQ: dyspnoea	1	159	Güell 2000	MD	n.a.	n.a.	n.a.	n.a.
	2	219		MD	0.29	-0.88, 1.46	0.004	88
1.9.2 CRQ: fatigue	3	195	Güell 2000	MD	0.35	-1.22, 1.93	0.21	35
	4	255		MD	0.37	-0.53, 1.26	0.05	63
1.9.3 CRQ: emotion	3	195	Güell 2000	MD	0.26	-1.91, 2.43	0.9	20
	4	255		MD	0.36	-0.84, 1.57	0.01	73
1.9.4 CRQ: mastery	3	195	Güell 2000	MD	1.06	-1.19, 3.30	0.08	60
	4	255		MD	0.76	-0.41, 1.94	0.004	78
1.10 CRQ: long-term (> 15 months)								
1.10.1 CRQ: dyspnoea	1	104	Güell 2000	MD	n.a.	n.a.		
	2	151		MD	0.47	-0.31, 1.25	0.07	70
1.10.2 CRQ: fatigue	3	137	Güell 2000	MD	0.42	-0.05, 0.89	0.75	0
	4	184		MD	0.46	0.06, 0.85	0.88	0
1.10.3 CRQ: emotion	3	137	Güell 2000	MD	0.52	0.00, 1.04	1	0
	4	184		MD	0.52	0.10, 0.95	1	0

Table 7. Sensitivity analysis primary outcomes *(Continued)*

1.10.4 CRQ: mastery	3	137	Güell 2000	MD	0.75	0.22, 1.28	0.67	0
	4	184		MD	0.83	0.41, 1.26	0.78	0
1.11 SF-36								
1.11.1 SF-36 MCS score	3	2212	Lilholt 2017, Vianello 2016	MD	0.44	-0.43, 1.31	0.44	0
	5	3699		MD	0.36	-0.38,1.11	0.75	0
1.11.2 SF-36 PCS score	3	2217	Lilholt 2017, Vianello 2016	MD	-0.17	-1.05, 0.71	0.33	0
	5	3704			1.06	-0.67, 2.79	< 0.0001	84
1.13 Functional exercise capacity: 6MWD								
1.13.1 6MWD: short-term (≤ 6 months)	8	886	Bendstrup 1997, Bernocchi 2017 Cambach 1997, Gottlieb 2011, Güell 2000, Güell 2006, Mendes 2010, Tabak 2014, Wang 2017	MD	41	4.40, 77.60	< .00001	92
	17	1390		MD	52.56	32.39,72.74	< 0.0001	90
1.13.2 6MWD: medium-term (> 6 months to 15 months)	9	1576	Engstrom 1999, Güell 2000, Kessler 2018, Wang 2017	MD	40.49	9.71, 71.27	<0.00001	92
	13	2071		MD	44.69	24.01, 65.37	<0.00001	90
1.13.3 6MWD: long-term (> 15 months)	3	973	Gottlieb 2011, Güell 2000, Lou 2015	MD	36.4	-6.43, 79,24	<0.00001	94
	6	7288		MD	48.43	16.37, 80.49	<0.00001	90
1.18 Respiratory-related hospital admissions								
1.18.1 Respiratory-related hospital admissions: short-term (≤ 6 months)	2	265	Bernocchi 2017	OR	0.71	0.28, 1.81	0.43	0
		377		OR	0.6	0.30, 1.22	0.65	0
1.18.2 Respiratory-related hospital	8	2224	Rea 2004, Smith 1999	OR	0.56	0.42, 0.76	0.06	48

Table 7. Sensitivity analysis primary outcomes *(Continued)*

admissions: medium-term (> 6 to 15 months)		2449		OR	0.6	0.44, 0.81	0.01	57
1.18.3 Respiratory-related hospital admissions: long-term (> 15 months)	2	0	n.a.	OR	n.a.	n.a.	n.a.	
	2	1381		OR	0.85	0.59, 1.23	0.23	29
1.22 All hospital admissions								
1.22.2 All hospital admissions: medium-term (> 6 months to 15 months)	3	760	Rea 2004, Kessler 2018	OR	0.91	0.66, 1.26	0.74	0
	5	1212		OR	0.93	0.71, 1.21	0.33	14
1.22.3 All hospital admissions: long-term (> 15 months)	3	1485	Lou 2015	OR	0.88	0.61, 1.27	0.2	38
	4	1920		OR	0.72	0.45, 1.04	0.007	55
1.23 Hospital days per patient (all causes)								
1.23.1 Hospital days per patient (all causes): short-term (≤ 6 months)	2	0	n.a.	MD	n.a.	n.a.	n.a.	
	2	273		MD	-4.36	-6.41, -2.31	0.16	49
1.23.2 Hospital days per patient (all causes): medium-term (> 6 to 15 months)	5	2086	Engstrom 1999, Farrero 2001, Kessler 2018, Rea 2004, Vianello 2016	MD	-1.01	-3.41, 1.38	0.001	78
	10	2944		MD	-1.73	-3.71, 0.25	0.0003	71
1.23.3 Hospital days per patient (all causes): long-term (> 15 months)	1	175	Titova 2017	MD	n.a.	n.a.	n.a.	n.a.
	2	346		MD	-1.6	-6.12, 2.92	0.1	63
1.24 ED visits	6	2343	Lou 2015, Rea 2004, Smith 1999,	OR	0.69	0.50, 0.94	0.02	64
	9	3005		OR	0.69	0.50, 0.93	0.02	68

Table 7. Sensitivity analysis primary outcomes *(Continued)*

1.26 Number of patients using ≥ 1 course of oral steroids	2	218	Farrero 2001, Rea 2004	OR	1.17	0.57, 2.40	0.19	42
	4	433		OR	1.05	0.66, 1.64	0.25	27
1.27 Number of patients using ≥ 1 course of antibiotics	2	218	Rea 2004	OR	2.35	1.02, 5.42	0.15	53
	3	321		OR	1.46	0.51, 4.18	0.007	80

Abbreviations. 6MWD: 6-minute walking distance; CI: confidence interval; CRQ: Chronic Respiratory Questionnaire; ED: emergency department; MD: mean difference; OR: odds ratio; SF-36: Short Form-36; SGRQ: St. George's Respiratory Questionnaire.

APPENDICES

Appendix 1. MEDLINE (Ovid) search strategy

1. exp Pulmonary Disease, Chronic Obstructive/
2. Chronic Obstructive Pulmonary Disease.tw.
3. Chronic Obstructive Airway Disease.tw.
4. Chronic Obstructive Lung Disease.tw.
5. pulmonary emphysema.tw.
6. chronic bronchitis.tw.
7. (COPD or COAD or COBD or AECOPD).tw.
8. Chronic Airflow Obstruction.tw.
9. or/1-8
10. disease management/
11. Disease management.tw.
12. exp Managed Care Programs/
13. managed care.tw.
14. insurance.tw.
15. case management.tw.
16. exp Patient Care Planning/
17. "patient care plan$".tw.
18. "nursing care plan$".tw.
19. "goals of care".tw.
20. "care goal".tw.
21. exp "Delivery of Health Care, Integrated"/
22. (integrated adj3 (health$ or care$ or delivery or system$)).tw.
23. disease state management.tw.
24. Comprehensive Health Care/
25. "comprehensive health care".tw.
26. ((interdisciplin$ or multidisciplin$) adj3 (care or health$ or delivery or system$)).tw.
27. Primary Nursing/
28. "primary nursing".tw.
29. "community based".tw.
30. exp Patient-Centered Care/
31. Patient Care Management/
32. (patient adj3 (care or management)).tw.
33. practice guideline/
34. education, medical, continuing/ or education, nursing, continuing/
35. exp community health services/
36. Primary Health Care/
37. "patient care team".tw.
38. "critical pathways".tw.
39. Self Care/
40. (continuity adj3 care).tw.
41. guideline$.tw.
42. "clinical protocol".tw.
43. "patient education".tw.
44. (self-care or "self care").tw.
45. reminder system$.tw. or Reminder Systems/
46. Health Education/
47. Health Promotion/
48. (health adj3 (education or promotion)).tw.
49. Community Health Planning/
50. ambulatory care.tw.
51. feedback.tw.
52. or/10-51
53. (clinical trial or controlled clinical trial or randomized controlled trial).pt.
54. (randomized or randomised).ab,ti.
55. placebo.ab,ti.
56. dt.fs.
57. randomly.ab,ti.

58. trial.ab,ti.
59. groups.ab,ti.
60. or/53-59
61. Animals/
62. Humans/
63. 61 not (61 and 62)
64. 60 not 63
65. 9 and 52 and 64

Appendix 2. Embase (Ovid) search strategy

1. chronic obstructive lung disease/
2. Chronic Obstructive Pulmonary Disease.tw.
3. Chronic Obstructive Airway Disease.tw.
4. Chronic Obstructive Lung Disease.tw.
5. pulmonary emphysema.tw.
6. chronic bronchitis.tw.
7. (COPD or COAD or COBD or AECOPD).tw.
8. Chronic Airflow Obstruction.tw.
9. or/1-8
10. disease management/
11. Disease management.tw.
12. managed care/
13. managed care.tw.
14. (insurance and "case management").tw.
15. patient care planning/
16. "patient care plan$".tw.
17. "nursing care plan$".tw.
18. "goals of care".mp.
19. "care goal".tw.
20. integrated health care system/
21. (integrated adj3 (health$ or care$ or delivery or system$)).tw.
22. disease state management.tw.
23. health care/
24. "comprehensive health care".tw.
25. ((interdisciplin$ or multidisciplin$) adj3 (care or health$ or delivery or system$)).tw.
26. primary nursing/
27. "primary nursing".tw.
28. "community based".tw.
29. patient care/
30. (patient adj3 (care or management)).tw.
31. practice guideline/
32. medical education/
33. exp community care/
34. primary health care/
35. "patient care team".tw.
36. "critical pathways".tw.
37. "case management".tw.
38. self care/
39. (continuity adj3 "patient care").tw.
40. guideline$.tw.
41. "clinical protocol".tw.
42. "patient education".tw.
43. (self-care or "self care").tw.
44. reminder system/
45. reminder systems.tw.
46. health education/
47. health promotion/
48. (health adj3 (education or promotion)).tw.
49. health care planning/
50. ambulatory care.tw.
51. feedback.tw.

52. or/10-51
53. Randomized Controlled Trial/
54. randomization/
55. controlled clinical trial/
56. Double Blind Procedure/
57. Single Blind Procedure/
58. Crossover Procedure/
59. (clinica$ adj3 trial$).tw.
60. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (mask$ or blind$ or method$)).tw.
61. exp Placebo/
62. placebo$.ti,ab.
63. random$.ti,ab.
64. ((control$ or prospectiv$) adj3 (trial$ or method$ or stud$)).tw.
65. (crossover$ or cross-over$).ti,ab.
66. or/53-65
67. exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
68. human/ or normal human/ or human cell/
69. 67 and 68
70. 67 not 69
71. 66 not 70
72. 9 and 52 and 71

Appendix 3. CINAHL (EBSCO) search strategy

S1 (MH "Pulmonary Disease, Chronic Obstructive+")

S2 COPD

S3 "chronic Obstructive Pulmonary Disease"

S4 "Chronic Obstructive Airway Disease"

S5 "Chronic Obstructive Lung Disease"

S6 "pulmonary emphysema"

S7 "chronic bronchitis"

S8 COAD

S9 "Chronic Airflow Obstruction"

S10 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9

S11 (MH "Disease Management")

S12 "Disease management"

S13 (MH "Managed Care Programs+")

S14 "managed care"

S15 insurance and "case management"

S16 (MH "Patient Care Plans+")

S17 "patient care plan*"

S18 "nursing care plan*"

S19 "goals of care"

S20 "care goal"

S21 (MH "Health Care Delivery, Integrated")

S22 (integrated and (health* or care* or delivery or system*))

S23 "disease state management"

S24 "Comprehensive Health Care"

S25 ((interdisciplin* or multidisciplin*) and (care or health* or delivery or system*))

S26 (MH "Primary Nursing")

S27 "primary nursing"

S28 "community based"

S29 (MH "Patient Centered Care")

S30 "patient care"

S31 "patient management"

S32 (MH "Education, Medical, Continuing")

S33 Education, Nursing, Continuing

S34 (MH "Community Health Services+")

S35 (MH "Primary Health Care")

S36 "patient care team"

S37 (MH "Critical Path")

S38 "case management"

S39 (MH "Self Care")

S40 (MH "Continuity of Patient Care")

S41 guideline*

S42 "clinical protocol"

S43 "patient education"

S44 self-care or "self care"

S45 (MH "Reminder Systems")

S46 "reminder system*"

S47 (MH "Health Education")

S48 (MH "Health Promotion+")

S49 (health N3 educat*) or (health N3 promot*)

S50 "Community Health Planning"

S51 "ambulatory care"

S52 feedback

S53 S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52

S54 S10 and S53

S55 (DE "RANDOMIZED CONTROLLED TRIALS")

S56 (MH "Double-Blind Studies")

S57 (MH "Random Assignment")

S58 (MH "Placebos")

S59 placebo*

S60 random*

S61 crossover* or cross-over*

S62 clinical* and (trial* or study or studies)

S63 (single* or double* or triple*) and blind*

S64 S55 or S56 or S57 or S58 or S59 or S60 or S61 or S62 or S63

S65 S54 and S64 [Limiters - Exclude MEDLINE records; Published Date from: 19900101-20111231]

Appendix 4. CENTRAL search strategy

S1 (MH "Pulmonary Disease, Chronic Obstructive+")
S2 COPD
S3 "chronic Obstructive Pulmonary Disease"
S4 "Chronic Obstructive Airway Disease"
S5 "Chronic Obstructive Lung Disease"
S6 "pulmonary emphysema"
S7 "chronic bronchitis"
S8 COAD
S9 "Chronic Airflow Obstruction"
S10 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9
S11 (MH "Disease Management")
S12 "Disease management"
S13 (MH "Managed Care Programs+")
S14 "managed care"
S15 insurance OR "case management"
S16 (MH "Patient Care Plans+")
S17 "patient care plan*"
S18 "nursing care plan*"
S19 "goals of care"
S20 "care goal"
S21 (MH "Health Care Delivery, Integrated")
S22 (integrated and (health* or care* or delivery or system*))
S23 "disease state management"
S24 "Comprehensive Health Care"
S25 ((interdisciplin* or multidisciplin*) and (care or health* or delivery or system*))
S26 (MH "Primary Nursing")
S27 "primary nursing"
S28 "community based"
S29 (MH "Patient Centered Care")
S30 "patient care"
S31 "patient management"
S32 (MH "Education, Medical, Continuing")
S33 Education, Nursing, Continuing
S34 (MH "Community Health Services+")
S35 (MH "Primary Health Care")
S36 "patient care team"
S37 (MH "Critical Path")
S38 "case management"
S39 (MH "Self Care")
S40 (MH "Continuity of Patient Care")
S41 guideline*
S42 "clinical protocol"
S43 "patient education"
S44 self-care or "self care"

S45 (MH "Reminder Systems")
S46 "reminder system*"
S47 (MH "Health Education")
S48 (MH "Health Promotion+")
S49 (health N3 educat*) or (health N3 promot*)
S50 "Community Health Planning"
S51 "ambulatory care"
S52 feedback
S53 S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52
S54 S10 and S53
S55 (DE "RANDOMIZED CONTROLLED TRIALS")
S56 (MH "Double-Blind Studies")
S57 (MH "Random Assignment")
S58 (MH "Placebos")
S59 placebo*
S60 random*
S61 crossover* or cross-over*
S62 clinical* and (trial* or study or studies)
S63 (single* or double* or triple*) and blind*
S64 S55 or S56 or S57 or S58 or S59 or S60 or S61 or S62 or S63
S65 S54 and S64

Appendix 5. Cochrane Airways Group Register search strategy

#1 MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All AND INSEGMENT
#2 MeSH DESCRIPTOR Bronchitis, Chronic AND INSEGMENT
#3 (obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*) AND INSEGMENT
#4 COPD:MISC1 AND INSEGMENT
#5 (COPD OR COAD OR COBD OR AECOPD):TI,AB,KW AND INSEGMENT
#6 #1 OR #2 OR #3 OR #4 OR #5 AND INSEGMENT
#7 MeSH DESCRIPTOR Disease Management AND INSEGMENT
#8 disease management AND INSEGMENT
#9 MeSH DESCRIPTOR Managed Care Programs Explode All AND INSEGMENT
#10 managed care AND INSEGMENT
#11 insurance AND INSEGMENT
#12 case management AND INSEGMENT
#13 MeSH DESCRIPTOR Patient Care Planning Explode All AND INSEGMENT
#14 patient care plan* AND INSEGMENT
#15 nursing care plan* AND INSEGMENT
#16 goals of care AND INSEGMENT
#17 care goal AND INSEGMENT
#18 MeSH DESCRIPTOR Delivery of Health Care, Integrated Explode All AND INSEGMENT
#19 (integrated) NEAR3 (health* or care* or delivery or system*) AND INSEGMENT
#20 disease state management AND INSEGMENT
#21 MeSH DESCRIPTOR Comprehensive Health Care AND INSEGMENT
#22 comprehensive health care AND INSEGMENT
#23 ((interdisciplin* or multidisciplin*) NEAR3 (care or health* or delivery or system*)) AND INSEGMENT
#24 MeSH DESCRIPTOR Primary Nursing AND INSEGMENT
#25 primary nursing AND INSEGMENT
#26 community based AND INSEGMENT
#27 MeSH DESCRIPTOR Patient-Centered Care AND INSEGMENT
#28 MeSH DESCRIPTOR Patient Care Management AND INSEGMENT
#29 patient care AND INSEGMENT
#30 patient management AND INSEGMENT
#31 MeSH DESCRIPTOR Education, Medical, Continuing AND INSEGMENT
#32 MeSH DESCRIPTOR Education, Nursing, Continuing AND INSEGMENT
#33 MeSH DESCRIPTOR Community Health Services Explode All AND INSEGMENT
#34 MeSH DESCRIPTOR Primary Health Care AND INSEGMENT
#35 patient care team AND INSEGMENT
#36 critical pathway* AND INSEGMENT

#37 MeSH DESCRIPTOR Self Care AND INSEGMENT
#38 continuity NEAR3 care AND INSEGMENT
#39 guideline* AND INSEGMENT
#40 clinical protocol AND INSEGMENT
#41 patient education AND INSEGMENT
#42 self-care or "self care" AND INSEGMENT
#43 MeSH DESCRIPTOR Reminder Systems AND INSEGMENT
#44 reminder system* AND INSEGMENT
#45 MeSH DESCRIPTOR Health Education AND INSEGMENT
#46 MeSH DESCRIPTOR Health Promotion AND INSEGMENT
#47 (health) NEAR3 (educat* or promot*) AND INSEGMENT
#48 MeSH DESCRIPTOR Community Health Planning AND INSEGMENT
#49 ambulatory care AND INSEGMENT
#50f eedback AND INSEGMENT
#51 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 AND INSEGMENT
#52 (#6 AND #51) AND (INREGISTER)

Appendix 6. ClinicalTrials.gov search strategy

Field	Search term
Study type	interventional
Condition	COPD
Intervention	disease management OR integrated OR comprehensive

WHAT'S NEW

Date	Event	Description
21 September 2020	New citation required and conclusions have changed	Abstract, plain language summary, results, discussion, and conclusions redrafted. Background and methods brought up-to-date, including use of current Cochrane risk of bias tool and dealing with missing data. Subgroup analyses revised. Summary of findings table updated Conclusions strengthened through the addition of 26 new studies. Conclusions based on short-term (up to 6 months), medium-term (6 to 15 months), and long-term (longer than 15 months) effects
21 September 2020	New search has been performed	New literature search run

HISTORY

Protocol first published: Issue 11, 2011
Review first published: Issue 10, 2013

CONTRIBUTIONS OF AUTHORS

AK, NC, and NS wrote the protocol.

AK and NS wrote the previous version of this review.

CP, EM, and PH selected trials.

CP, EM, and PH extracted data and assessed risk of bias.

CP was responsible for data management and data analysis in RevMan.

CP and PH completed the clinical interpretation of results

All review authors contributed to and approved the final version of the review.

Contributions of editorial team

Chris Cates (Coordinating Editor and Contact Editor) checked data entry for the review update; edited the review update ; advised on methods, interpretation, and content; and approved the review update prior to publication.

Emma Dennett (Managing Editor) co-ordinated the editorial process; advised on interpretation and content; and edited the review.

Emma Jackson (Assistant Managing Editor) conducted peer review and edited sections of the review.

Elizabeth Stovold (Information Specialist) designed the search strategy; ran the searches; and edited the search methods section.

DECLARATIONS OF INTEREST

NC is a senior researcher in the field of integrated disease management programmes who is involved in several initiatives promoting education, developing software applications, and providing e-health solutions, which may be considered as a potential conflict of interest.

CP: none known.

EM: none known.

AK: was a PhD student on the RECODE trial, which investigates the effectiveness of integrated care for primary care COPD patients in a cluster-randomised controlled trial in primary care. The Leiden University Medical Centre received a grant from ZonMW (Dutch governmental agency) and additional financial support from Achmea (Dutch Healthcare Insurer) for the RECODE trial. In the future, our RCT will be included in the Cochrane Review.

NS: none known.

PH: has received payment from E-wise for development of a continuous medical education programme for general practitioners and pharmacists on severe asthma. E-wise does not provide any type of disease management programme.

SOURCES OF SUPPORT

Internal sources

- LUMC, Leiden, Netherlands

  Leiden University Medical Centre

External sources

- All, Other

  The authors declare that no funding such was received for this systematic review

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added Borg score next to MRC Dyspnea Score as an instrument to measure dyspnoea under secondary outcomes.

We did not search the DARE database for non-Cochrane Reviews.

Update of 2020 allowed a more detailed evaluation of endpoints. We evaluated outcomes at the endpoints (1) short term (up to 6 months); (2) medium term (6 to 15 months), and (3) long term (more than 15 months), instead of at short- (12 months or less) and long-term (longer than 12 months) follow-up.

We presented results for continuous outcomes in the 'Summary of findings' table for medium-term follow-up only, instead of for short-, medium-, and long-term follow-up.

We included telemonitoring as a separate intervention component.

We included a definition of 'high-quality' studies following our RoB judgement and performed sensitivity analysis on high-quality studies only.

INDEX TERMS

Medical Subject Headings (MeSH)

Disease Management; Dyspnea; Exercise Tolerance; *Pulmonary Disease, Chronic Obstructive [therapy]; Quality of Life

MeSH check words

Aged; Humans; Male