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A Systematic Review of the Effectiveness of Interventions to Promote Referral; Adherence; and Uptake of Pulmonary Rehabilitation for Patients with Chronic Obstructive Pulmonary Disease

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Background: Pulmonary rehabilitation (PR) is an effective treatment for patients with chronic obstructive pulmonary disease (COPD). However, referral, uptake, and adherence remain low.

Objective: To determine effectiveness of interventions to increase patient referral, uptake, and adherence to PR programs for patients with COPD.

Methods: Randomized controlled trials (RCTs), non-randomized controlled trials, pre-post studies, and uncontrolled studies were sought from 7 databases and 3 clinical trial registries, to end August 2021. Full articles/conference abstracts were included if a coordinated set of activities was targeted to healthcare professionals (HCPs) caring for COPD patients, adults with COPD or their carers, to increase referral, uptake or adherence to any type of PR program. Two review authors independently screened titles, abstracts and full texts, extracted data and critically appraised studies using standard risk of bias tools.

Results: From 11,272 records, 30 studies (23 full-text; 7 abstracts) met inclusion criteria: study interventions and designs were varied and generally low quality, targeting patients (n=13), HCPs (n=14) or both (n=3 studies). A CCT of patient held evidence score cards increased referral by 7.3% compared to 1.3% for usual care (p-0.03). A cluster RCT involving COPD nurse home visits with individualized care plans increased uptake to 31% compared to 10% in usual care (p=0.002). For people with anxiety or depression, one RCT of cognitive behavioral therapy alongside PR increased adherence (mean sessions 14.0 (sd 1.7) compared to 12.4 (sd 2.6)).

Conclusion: Although a small number of studies, the weight of evidence suggested that interventions incorporating partnership working between patients and HCPs appeared to increase referral, uptake, and adherence with greater effectiveness than those targeting single populations. Increasing knowledge and empowering HCPs and patients may be important strategies. Concerns about study design and risk of bias suggest clear need for well-designed trials of interventions to report full pathway outcomes.

Keywords: pulmonary rehabilitation, chronic obstructive pulmonary disease, intervention, referral, uptake, adherence

Introduction

COPD is an increasingly prevalent chronic respiratory disease that presents major public health challenges worldwide.[1–3] Globally; over 300 million people have a COPD diagnosis[4] and in 2017; COPD accounted for almost 3.2 million deaths worldwide[1] making it the third leading non-communicable disease cause of mortality.[1] COPD is a debilitating disease that worsens over time; with symptoms of dyspnoa; chronic cough and fatigue associated with reduced exercise capacity.[5–7] Acute exacerbations of COPD drive disease progression which subsequently increases healthcare utilization and societal costs worldwide.[8]

Other than the treatment and prevention of exacerbations, therapy during stable COPD is aimed at reducing progression, managing symptoms, and relieving overall disease burden. Patients with more severe breathlessness (usually

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Medical Research Council (MRC) Grade 3 / modified (m)MRC 2 or worse) or worsening dyspnoa and functional limitations are eligible for pulmonary rehabilitation (PR).[9,10]

Pulmonary rehabilitation (PR) is a structured multidisciplinary program for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical performance and autonomy. Programs comprise individualized exercise programs and supportive education;[11] aiming to improve exercise capacity and health-related quality of life of people living with chronic respiratory disease. Behaviour change plays a key role in facilitating the improvement and maintenance of health-enhancing behaviours; including increased levels of physical activity.[9,12]
PR programs are commonly delivered to groups of patients in community or hospital settings; although other models of delivery; including home-based programs; are also available. Evidence that supports home-based PR (often delivered by telerehabilitation platforms) as an alternative; yet effective; PR approach for COPD patients is an emerging field.[13]

Randomized controlled trials (RCTs) show that PR is effective in improving exercise capacity, breathlessness, functional independence, and psychological well-being.[14–16] It also reduces hospital admissions. However the effect appears to be related to program comprehensiveness, which is often variable.[14,17] In order to access and enroll in PR, patients are initially referred by a healthcare professional (HCP), although in some circumstances, the patient may self-refer. Following referral is PR assessment and then program commencement. Adequate attendance of PR programs is essential in order to gain clinical and psychosocial benefits.

Despite proven effectiveness; referral to PR remains poor worldwide; regardless of availability.[18–21] Uptake (attendance of the pre-assessment or full program) and adherence is also poor. In the England and Wales audit; it was reported that of the 68,000 COPD patients referred; 47,020 (69%) attended pre-assessment; following which; 10% to 14.8% of patients did not then enroll in PR.[21,22] Hayton et al[23] reported that 71% of patients attended at least 63% of the planned eight sessions and an audit in New Zealand showed that 46% to 75% of attendees attended all 16 planned PR sessions.[18]

Patients report several factors that contribute to poor uptake, including lack of perceived benefit, too difficult to complete, fear of breathlessness and exercise.[24–27] Additional factors include the negative influence of the referring practitioner[26,28–30] and transport difficulties, including poor access and high cost of travel.[24,31] Factors associated with lower attendance include advancing age; being female; being from a minority ethnic group; being a current smoker; having greater breathlessness; living alone; experiencing financial hardship; distance from venue; long term oxygen use; having anxiety and depression; and having a reduced baseline health-related quality of life.[18,24,27,28,32–35]

Interventions designed to address each stage; to increase referral; uptake and completion are emerging. This review therefore aimed to determine the effectiveness of interventions that target healthcare workers; people living with COPD or their family; friends or caregivers which increase patient referral; uptake; and adherence to all types of PR programs for patients with COPD. This is the first systematic review that examined interventions which are likely to impact all three PR points and encompass the whole PR pathway.

Methods

The protocol for this review was published within the Cochrane Airways Group.[36]

Study Design

Systematic review of the literature to determine the effectiveness of interventions that target healthcare workers; people living with COPD or their family; friends or caregivers which increase patient referral; uptake; and adherence to PR programs for patients with COPD.

Search Strategy

We searched for randomized controlled trials in the Cochrane Airways Trials Register; which is maintained by the Information Specialist for the Group. We conducted additional searches of the following databases; using appropriate search terms to identify both randomized and non-randomized studies: Cochrane Central Register of Controlled Trials through the Cochrane Register of Studies Online (CENTRAL); MEDLINE Ovid; Embase Ovid; CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature); PEDro (Physiotherapy Evidence Database) (See Appendix 1 for search strategies). We searched all databases from their inception to 31 August 2021 with no restriction on language of publication and sought both full-text

articles and abstracts. We searched for ongoing studies from: UK Clinical Trials Gateway (ukctg.nihr.ac.uk); US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov/); World Health Organization International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch/); these authors were contacted for relevant unpublished data. Reference lists of relevant systematic reviews were also searched.

Inclusion Criteria

We anticipated a limited number of trials, therefore a broad range of study designs were included: randomized controlled trials (RCT; individual or cluster-level); non-randomized controlled trials and observational studies with concurrent comparator; pre-post studies and uncontrolled studies. We included studies in which the population was either: 1) Healthcare practitioners (of any age) who care for patients with either stable or acute COPD; in all healthcare settings; 2) adult participants (at least 18 years of age) with a primary diagnosis of COPD; with or without spirometric confirmation; had any stage of COPD; with either stable disease or post-acute exacerbation; and who may have had singular or multiple co-morbidities; or 3) partners; caregivers; family; or friends (of any age) of the COPD patient; who might influence referral; uptake; or adherence to pulmonary rehabilitation. We excluded studies in which the focus of the study was on participants receiving PR with the following primary diagnoses: asthma; bronchiectasis; lung cancer; interstitial lung disease (ILD) or congestive cardiac failure.

Interventions were eligible if they described a co-ordinated set of activities implemented in order to increase referral to; uptake of; or adherence to any type of PR program. Eligible comparators were: usual care; any concurrent control group that was not receiving an intervention. Outcomes were referral to pulmonary rehabilitation program (as measured by referral sent or received); uptake, ie, attendance of pre-pulmonary rehabilitation program assessment or one or more sessions of a pulmonary rehabilitation program; or adherence to pulmonary rehabilitation program (as specified by study reports; but usually proportion of sessions attended). We excluded interventions that were designed to target other programs; such as maintenance pulmonary rehabilitation programs.

Study Selection

Two review authors (of JW; KJ; LG and RJ) independently screened the titles and abstracts. Full-text study reports were retrieved of all potentially eligible studies; and two review authors independently screened them for inclusion; recording the reasons for exclusion of ineligible studies. Disagreement was resolved through discussion between the four reviewers; and author PA if necessary. We identified and excluded duplicates and collated multiple reports of the same study; so that each study was the unit of interest.

Data Extraction and Analysis

Two review authors independently extracted the following data from included studies using standard data extraction forms in Covidence:[37] study design; demographics and characteristics of participants; sample size; setting duration; content and target of the intervention; description of any comparator; and relevant outcome measures. We compared results; resolved disagreements by consensus; and spot-checked study characteristics for accuracy against the study report.

Assessment of Risk of Bias

Two review authors independently assessed risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions[38] for RCTs and quasi-RCTs. We assessed the risk of bias for non-randomized trials and other observational studies using the ROBINS-I tool.[39] We resolved any disagreements by discussion.

Missing Data

We contacted investigators or study sponsors to verify key study characteristics and obtain missing numerical outcome data where needed.

Presentation of Results

The considerable heterogeneity of the populations; interventions and study designs meant that there was insufficient homogeneity to enable meta-analysis to be undertaken for any of the outcome measures; so data are reported narratively with tables following SWiM guidance.[40] We have given primacy to the randomized controlled trials; which have a lower risk of bias than the non-randomized controlled trials and observational studies. Subgroup analyses were not undertaken.

Results

Study Selection

From the initial 11,272 records; 200 full-text articles were retrieved; and thirty studies were included (Figure 1); of which 23 were reported in full-text articles;[41–63] seven abstracts.[64–70] There were an additional four ongoing studies identified.[71–74]

Characteristics of Included Studies

Study Design and Setting

The 30 included studies (Table 1 for summary and Table S1 for details) were published between 2007 and 2021 and had several different study designs; including: two cluster RCTs;[61,62] four RCTs;[41,53,60,63] one quasi-randomized controlled trial;[54] two controlled clinical trials (CCTs).[47,55] Sixteen studies had a pre-post design,[43–46,48–52,57,58,64,66–69] three were uncontrolled feasibility studies,[42,59,65] and two were uncontrolled studies.[56,70]

Thirteen studies were conducted in the UK;[42,45,46,48,49,52,55,56,59,63–65,70] six in Australia;[47,53,61,62,66,68] five in Denmark;[50,51,54,57,58] four in the United States[41,44,67,69] and one each in Canada[43] and China.[60]

The included studies reported on data from 3641 individuals; quality improvement activities drew data from 48,343 patient records. Eighteen studies were conducted in secondary care settings;[41,43,46–48,51–54,56,57,60,63,64,66–69] 10 in primary care/general practice,[42,44,45,49,50,55,58,61,62,70] one in a community setting,[59] and one involving both primary and integrated care settings.[65]

Interventions and Outcomes

In fourteen studies the interventions were targeted at patients;[41,43,46,47,53–55,59–64,66] in thirteen they were targeted at health care professionals,[42,44,45,49–51,56–58,67–70] and in three at both patients and HCPs.[48,52,65] Patient-focused

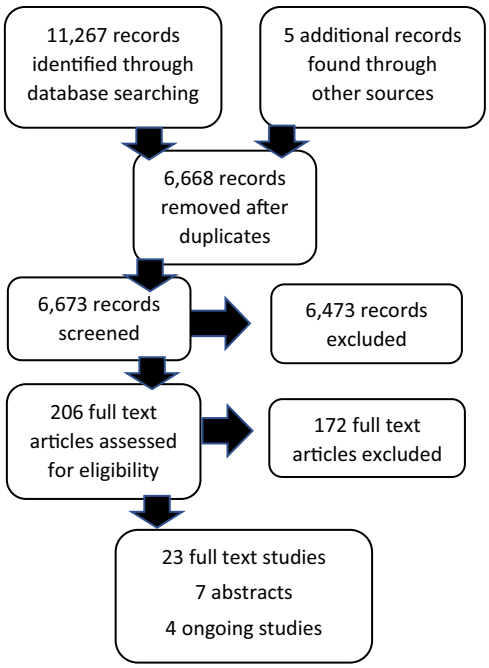

Figure 1 PRISMA.

Table 1 Characteristics of Included Studies

Author; Setting and Country	Study Design	Population/Setting	Intervention	Control	PR Pathway		
					Referral	Uptake	Adherence
Zwar 2012[61]	Cluster RCT	44 General Practices in Australia N= 451 diagnosed COPD patients	**Partnership model of care** Home visits: COPD trained nurse; working with GP and other HCPS; implement evidence based individualized care plan agreed with patients	**Usual care** COPD guidelines provided to GPs practices.		X	
Zwar 2016[62]	Cluster RCT	36 General Practices in Australia N= 254 newly diagnosed COPD patients	**Evidence-based disease management plan implemented by nurse/GP teams including**: practice staff education; computerized electronic care planning templates PLUS same case-finding/diagnosis training as control	**8 hrs case finding/ spirometry training/** interpretation for practice nurses with computer-based toolkit + copy of COPD-national guidelines.		X	
Aboumatar 2021[41]	RCT	Out-patient department in 2 hospitals in USA. N=292 diagnosed COPD patients	**Peer support + self-management support from respiratory care practitioner** Peer support via 1:1 and 8 group conversations + self-management support as control	**Self-management support from respiratory care practitioner** Written educational guide + 1-hour session and phone support		X	
Barker 2020[63]	RCT	**Secondary care; UK** n=196 COPD patients with AECOPD	**Patient co-designed education video as an adjunct to usual care**	**Usual care** COPD discharge bundle including standardized verbal information about PR + information leaflet.	X	X	X
Pumar 2019[53]	RCT	**Secondary care; Australia** N=65 undertaking PR with diagnosed COPD (75%); ILD; asthma; bronchiectasis	**CBT to treat anxiety and depression for patients attending PR** 2 x face to face 1hr CBT + 4×45 min telephone sessions. 8 weeks of PR + booklet	**Control** 8 weeks PR + booklet on COPD 4 x sham telephone calls			X

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Table 1 (Continued).

Author; Setting and Country	Study Design	Population/Setting	Intervention	Control	PR Pathway		
					Referral	Uptake	Adherence
Yao 2020[60]	RCT	**Secondary Care; China** N=128 COPD patients attending PR	**Peer support to attend PR** Patients supported to attend education lectures; community activities. Peer support by telephone/Wechat; undertook PR with patients during hospitalization. PR as described in control	**Usual care** PR including breathing exercises and 5–10 mins walking/jogging			X
Ringbaek 2016[54]	Quasi-randomized trial	**Secondary Care outpatients Demark** N=115 COPD patients attending PR	**Tablet** with instruction and training (electronic diary given to patients for home and PR use) - in addition to group PR	**Usual group PR**			X
Roberts 2015[55]	CCT	N=20 General Practices; England N=1350 Patients with COPD	**Patient held COPD scorecard** with 6 quality indicators; to discuss at COPD review. Helpline for queries.	**Usual Care** including a self-management plan; rescue pack distribution and instruction part of a regional QI intervention.	X		
Harris 2009[47]	CCT	**Secondary Care Australia** N=249 patients with moderate to severe COPD	**Patient held manual** summarizing evidence about COPD and suggested questions to ask doctor	**Usual care** Simple; single sheet pamphlet containing information about COPD	X	X	
Deprez 2009[44]	Pre-Post	**Primary care; USA** N=18 primary care practices: patients with COPD	**Adoption of evidence-based and best practice clinical guidelines** Expert support/meetings to practices; to review GOLD guidelines; plan evaluation with optional telephone; email; additional visit support	No control	X		
Wardini 2013[43]	Intervention study with historic control	**Secondary care; Canada** Moderate to severe COPD admitted to 3–4 week PR program. N=32 (intervention); n=unclear controls	**individualized virtual game system Wii workout** 3 times x week in addition to standard 5 x inpatient PR.	5 x per week inpatient PR			X
Graves 2010[46]	Intervention study with historic control	Secondary Care; England N=400 Patients referred to PR	**Pre-PR group opt-in face to face session**: 90 minutes; 8–12 weeks after referral; attend mandatory session with physio and psychologist to discuss fears; expectations and PR content.	**Usual care** No pre-PR session		X	X

Ulrik 2010[58]	Intervention study with historic control	N=124 GPs; Denmark Diagnosed COPD Survey 1: Before n=1716 Survey 2: After N=1342	**Education program for GP staff** based on the GOLD guidelines designed by a group of Danish pulmonologists and GPs with a special interest in COPD. Individual; local; and regional meetings.	**No control**	**X**		
Tottenborg 2013[57]	Retrospective cohort study	**Secondary care; Denmark** COPD Patients at any hospital outpatient clinic Year 1 (2008) n=12,111 Year 2 (2009) n=14,153 Year 3 (2010) n=15,164 Year 4 (2011) n=15,264	**Initiation of national multidisciplinary quality improvement program** in 2008 with implementation of evidence-based treatment and care.	**No control**	**X**		
Foster 2016[45]	QI study	N=8 General Practices; UK N=9 GPs n=13 practice nurses N=126 patients eligible for PR	**Range of practice-based strategies to increase referrals to PR** In-house training run by PR service (30 mins). Screen prompts at COPD review. Practice protocol re: referrer role and when to refer Memory aids-logo on coasters/mugs Pop up alerts for eligible patients	**No control**	**X**		
McCarron 2019[52]	QI study	**Secondary care; UK** Random selection of patients referred to PR who attended; attended and dropped out; did not attend. Pre n= 281; post n= 323	**Patient information** (both written and audio-visual (AV)) and **education of physicians** on the importance of PR and how to make a referral	**No control**		**X**	**X**
Hopkinson 2012[48]	Service evaluation with historic control	**Secondary care; UK** Patients discharged from hospital respiratory ward following acute exacerbation **Post-intervention**: n=94 **Pre-intervention** n=22	**COPD discharge bundle** Patient education and telephone support post discharge **Staff Education/support**: Directions to notify respiratory nurse specialist; implement discharge bundle* and prize draw incentive.	**Historic control**	**X**		

(*Continued*)

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Table 1 (Continued).

Author; Setting and Country	Study Design	Population/Setting	Intervention	Control	PR Pathway		
					Referral	Uptake	Adherence
Lange 2007[50]	Pre-post	**General Practice; Denmark** **Year 1**: n=2549 mod/severe COPD patients from n=184 GPs **Year 2**: n=2394 mod/severe COPD patients from n=156 GPs	**Educational program** to GPs and staff; and attendance of national COPD forum **to improve implementation of COPD guidelines**	**No control**	X		
Lange 2009[51]	Pre-post	**Hospital outpatients; Denmark** Patients attending COPD consultation Year 1 n=941 COPD patients Year 2 n=927 COPD patients	Staff educational program on COPD guidelines	**No control**	X		
Angus 2012[42]	Uncontrolled feasibility study	N=16 General Practices; UK N=293 patients on the COPD register; n=18 nurses	45-minute consultation using computer guided software based on NICE COPD guidelines and including PR prompts.	**No Control**	X		
White 2019[59]	Uncontrolled feasibility study	Community PR; England N=66 COPD patients newly referred to PR appointment	**Lay Health Workers support (LHW) for COPD patients referred to PR** LHW with previous experience of PR: 3 days of training; 3 phone sessions; 8 mentor meetings	**No control**		X	X
Sewell 2017[56]	Uncontrolled service evaluation	Secondary Care, England N=1170 COPD patients with suspected AECOPD	**COPD discharge bundle** delivered by specialist respiratory nurses (REDS) to inpatients pre-discharge- 5 quality outcomes plus SM manual and Breathe Easy patient group contacts.	**No control**	X		
Hull 2014[49]	Longitudinal audit	N=36 GP practices in London. Spirometry confirmed COPD patients. Year 1 population: n 259,071 COPD year 1 (n): 2798 COPD year 2 (n): 3176 COPD year 3 (n): 3391	**Locally-adapted COPD care package based on National COPD guidelines + financial incentives**. Included regular patient review and care planning; structured templates; respiratory consultant support and education at MDT meetings; network co-ordinators focused on non-attenders.	**Local and national comparators**	X		

Angus 2019[70] Abstract only	Uncontrolled service evaluation	N=741 patients on COPD registers from 54 general practices in the UK.	**Computer clinical support decision aids** incorporating GOLD 2018 guidance to support patient reviews.	**No control**	**X**		
Cox 2019[66] Abstract only	Pilot study - single arm	**Secondary care; Australia** N=29 patients with stable COPD or ILD attending outpatients	**Video patient testimonials about PR**	**No control**	**X**		
Cornwallis 2017[65] Abstract only	Prospective cohort study	**Primary /integrated care; UK** COPD diagnosis and/or FEV1 >/=50% predicted and/or on high dose inhaled corticosteroids. Primary care (n=94) or integrated respiratory care service (n=67)	**Virtual Clinic to recommend guideline-based interventions** to optimize COPD care for primary care practices and integrated respiratory service.	**No control**	**X**		
Avent 2015[64] Abstract only	Prospective cohort study	**Secondary Care; UK** N=50 Patients admitted with AECOPD; controls NR	Inpatient physiotherapy-led exercise class twice weekly during hospital admission with AECOPD.	**Usual Care**	**X**		
Nuguru 2019[67] Abstract only	Quality improvement - Pre and post no control	**Outpatient Secondary care; USA** 6 physicians and 1 registered nurse in outpatient clinic. Review of 60 charts	**Education on guidelines**	**No control**	**X**		
Tong 2017[68] Abstract only	Single centered retrospective audit	**Respiratory Ward; Secondary Care; Australia** N=70 Patients admitted for AECOPD (n=33 pre/37 post)	**Implementation of COPD pathway based on COPD guidelines. One-page check list**	**No control**	**X**		
Wexler 2019[69] Abstract only	Pre-post	**Secondary Care; USA** COPD (Gold B and above) 1 admission for AECOPD in a year N=36/39 pre/post-intervention	**Quality improvement initiative**: flyers near workstations; educational conferences; faculty reinforcement	**No control**	**X**		

Abbreviations: *RCT, randomized controlled trial; CCT, controlled clinical trial; QI, quality improvement; FEV_1, forced expiratory volume in 1 second; COPD, chronic obstructive pulmonary disease; AECOPD, acute exacerbation of COPD; ILD, interstitial lung disease; HCPs, health care professional; UK, United Kingdom; USA, United States of America; PR, pulmonary rehabilitation; GOLD, international disease classification; CBT, cognitive behavior therapy; GP, general practice; MDT, multidisciplinary team; NICE, National Institute for Health and Care Excellence.

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interventions addressed elements of the whole of the PR pathway albeit largely in individual parts; whereas HCP-focused interventions were orientated toward referral only. Only one study examined all three components of the PR pathway (referral; uptake and adherence).[63] Four studies focused on two elements: uptake and adherence[46,52,59] and referral and adherence.[64] One study described their focus as on referral but measured uptake as an outcome measure[47] rather than referral rates, and one study[62] reported PR attendance; but the mechanism was by primary care teams recommending referral. The remaining 23 targeted individual elements of the pathway.[41–45,48–51,53–58,60,61,65–70]

Interventions targeted at patients to increase uptake of the offer of PR included a pre-discharge exercise session;[64] pre-PR group opt-in session;[46] video testimonials;[66] video about PR.[63] Interventions which aimed to encourage adherence to PR included a manual with evidence about COPD and question prompts for HCPs;[47] tablet with training diary to support PR;[54] cognitive behavioral therapy for people with depressive symptoms alongside the PR program[53] and a virtual game system.[43] Three studies included interventions that adopted peer support for patients.[41,59,60] One of these highlighted the desire to include family members; but no description was offered.[59] Two studies included interventions that encouraged the patient to prompt healthcare professionals toward making a referral.[47,55]

Of the interventions targeted at staff and health care processes aimed to increase referral to PR; most were multicomponent and several were described as quality improvement initiatives.[42,44,45,49–52,57,65,67,69] Interventions included educational components,[44,50,51,58,62,67,69] computer guided consultations;[42,70] computer COPD templates;[62] prompts (electronic and paper);[45] checklists;[67,68] COPD discharge bundle[48,56] and national targets.[57]

Two studies did not report useful outcome data on referral; uptake or adherence[59,60] so were not considered further in the results.

Risk of Bias Among Included Studies

For three (50%) of the RCTs risk of bias was low in four or more of the six domains (Figure 2). All five RCTs reported the method of randomization satisfactorily; although two of the RCTs did not report concealment of allocation before entry to the study[41,62] and it was not clear in the quasi-RCT whether participants in the PR groups were aware of the allocation before consenting to take part.[54] Due to the nature of the intervention; blinding of participants and rehabilitation personnel is usually not possible; so this is a likely source of bias in the four trials that were unable to blind this aspect.[53,61–63] Two of the trials were able to provide some blinding for participants and personnel; in one study by comparing two active interventions[41] and in the quasi-RCT by delivering the intervention to all participants attending alternate PR courses.[54] Blinding of outcome assessment was adequately performed by five of the trials[41,54,61–63] although not reported in one study.[53] Four trials (67%) adequately reported outcome data[41,54,62,63] however all of the trials reported conducting intention to treat analysis. All five RCTs were pre-registered on a trials registry and reported the outcomes outlined in their methods sections; so risk of selective reporting was low;[41,53,61–63] although the quasi-RCT was unclear.[54]

Fifteen non-randomized full-text studies were assessed using the ROBINS-I tool (Figure 3).

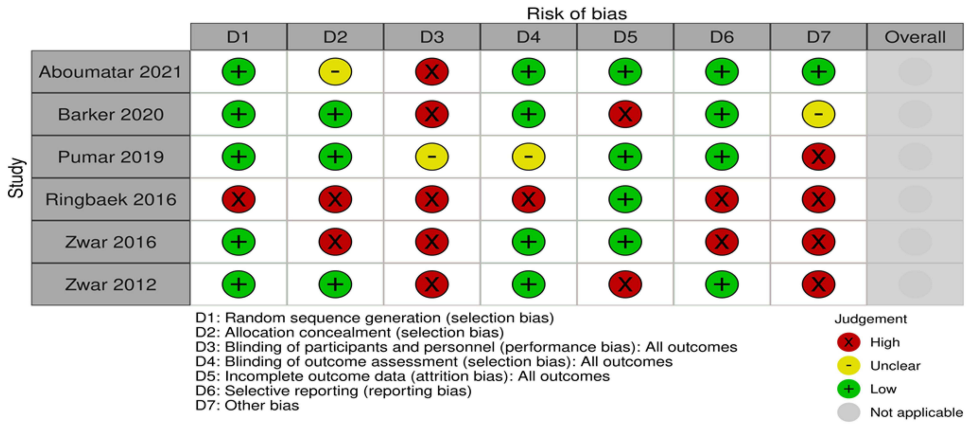

Figure 2 Risk of bias assessment: randomized studies.

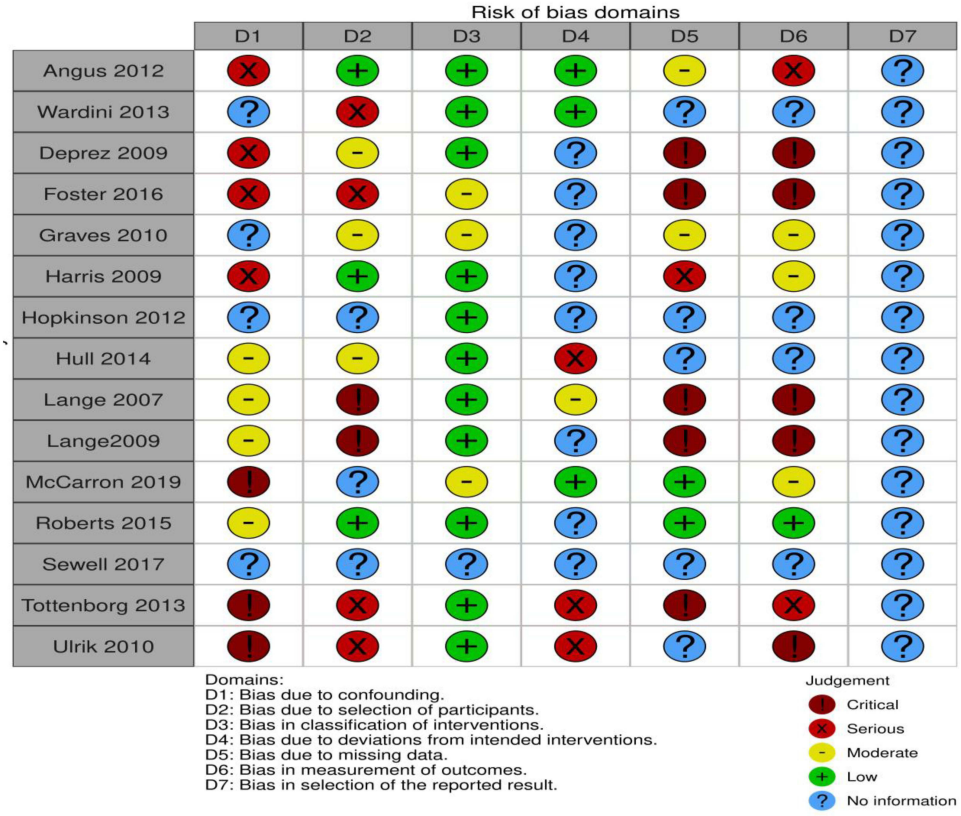

Figure 3 Risk of bias assessment: non-randomized studies.

Two CCTs were assessed as having moderate[55] and serious[47] risk of bias due to confounding. Of the remaining thirteen pre-post and non-randomized studies; seven were assessed as being at critical risk of bias[44,45,50–52,57,58] and four as serious.[42,43,48,49]

Domains most commonly assessed as critical or serious were: bias due to confounding; bias due to selection of participants; bias due to missing data and bias in the measurement of outcomes. The main omitted data for patients related to previous PR attendance; and for HCPs there were frequent omissions of number; gender; job role and post registration respiratory education. None of the non-randomized trials or observational studies had pre-registered the study or published a protocol therefore there was no information to assess selective reporting as a bias.

Seven of the non-randomized studies were only reported in abstract form and had insufficient information to adequately assess risk of bias.

Effect of Interventions on Referral to Pulmonary Rehabilitation

Twenty studies assessed interventions that sought to increase referral to PR;[42,44,45,47–51,55–58,63–70] thirteen targeted HCPs[42,44,45,49–51,56–58,67–70] and two targeted both HCPs and patients.[48,65] One study did not report referral rates as an outcome.[47]

In an RCT of 196 patients admitted to hospital with an AECOPD;[63] the intervention group received a video demonstration of PR on a tablet device in addition to usual care (COPD discharge bundles plus verbal and written information on PR). There was no statistical difference in referral rates between the intervention (71%) and control (69%) groups p= 0.75.

One controlled clinical trial sought to empower patients from primary care by increasing their COPD knowledge with patient-held score cards.[55] Patients were encouraged to share this material at their respiratory healthcare consultations and to ask for evidence-based guideline recommended care by way of prompting HCPs. There was an increase in rates of

referral to PR from baseline to 3 months; of 7.4% (adjusted for clustering); which was higher than the change in the control arm at 3 months (1.3%) (p, 0.03).

Of the uncontrolled pre-post studies; three reported significant increases in referral rates. Staff educational interventions in Denmark increased PR referral in primary care from 17% pre-intervention to 20% post-intervention (p<0.01)[50] and in secondary care from 56% to 63% (p=0.006);[51] the relatively modest increases being in the context of constraints in PR provision. A US primary care quality improvement intervention involving practice learning sessions increased referral to PR from 7% to 12% post intervention (p=0.048).[44] Additionally; a national quality improvement activity in Denmark monitored and implemented evidence-based care with hospital level performance indicators increasing the offer of a referral to PR from 55% to 91% over a three year period (RR 2.78; 95% CI 2.65; 2.90).[57]

None of the remaining studies[42,45,48,49,56,58,64,66–70] reported the statistical significance of comparisons with historical controls; although some reported large differences. A pre-post evaluation of a multi-component intervention in UK primary care consisting of care plans; feedback to practice on quality indicators and multi-disciplinary team meetings with respiratory specialists increased referral to PR from 45% to 70%.[49] A primary care intervention consisting of practice staff education and computer screen prompts increased referral rate from 10% to 49%,[45] and a primary care consultation using COPD consultation software reported a 12% increase in referrals.[70] Most interventions in secondary care focused on increasing HCP education and awareness of PR; use of checklists and discharge bundles; reporting increases in referral rates ranging from 5%-54%. Secondary care interventions with the largest reported increases in referral rates included a COPD discharge bundle and staff education[48] implementation of a COPD pathway based on national guidelines[68] and a quality improvement initiative including flyers in clinical areas; educational conferences and faculty reinforcement.[69] Caution is advised in interpreting the pre-post studies because none had concurrent control groups; therefore they were at high risk of bias.

Effect of Interventions on Uptake/Attendance of Pulmonary Rehabilitation

Seven studies provided data on the effect of interventions on attendance of the initial assessment and/or the first session of a PR program.[41,46,47,52,61–63] Two studies[47,63] were also designed to increase referral rates (see previous section).

Two were cluster RCTs;[61,62] two individually-randomized RCTs;[41,63] one CCT comparing different geographical areas[47] and two were studies with historical controls.[46,52] Of the randomized studies; three found no difference in uptake.[41,62,63] These interventions were a peer support intervention for primary and secondary care patients;[41] a patient-targeted video demonstration of PR in secondary care[63] and primary care COPD education with computerized care planning templates.[62] One cluster RCT involving 451 participants[61] reported over 20% greater uptake of PR as a result of HCPs visiting patients at home and providing a personalized care plan (31.1% v 9.6%; odds ratio (OR) 5.16 (95% CI; 2.40 to 11.10); P=0.002).

The CCT[47] (249 participants) of patient-held COPD manuals reported an attendance rate of 30% in the intervention arm compared with 6.9% in the usual care arm; which was statistically significant (p=0.05) in the socioeconomically deprived stratum.

Studies with historical control data reported contrasting results. Implementing a pre-PR session did not result in significant increases in rates of attendance of PR compared with pre-intervention (207/400 (51.8%) vs 106/200 (53%)).[46] A study which implemented education for HCP and improved audio-visual material for patients reported increases in patient attendance of PR from 58% pre-intervention to 73% and 82%; at one; and two years' post intervention (p= 0.0001).[52]

Effect of Interventions on Adherence to Pulmonary Rehabilitation

There were seven studies that sought to improve participant adherence to PR. Whilst four studies were continuations of interventions that sought to increase referral/attendance;[46,52,63,64] three additional studies directly targeted the direct engagement of PR participants.[43,53,54] Two were RCTs;[53,63] one a quasi-randomized trial;[54] three studies with historical control data[46,52,64] and one compared to "regular PR".[43] Of the four studies that undertook significance testing; two found no difference.[54,63]

An RCT of CBT for people with anxiety or depression to improve attendance and participation was reported to be more effective than usual care in enhancing PR adherence; with a mean (SD) of 14 (1.7) out of a possible 16 sessions attended in the intervention group and 12.4 (2.6) in the control group (mean difference 1.59 (95% CI 0.11 to 3.07; p= 0.03)).[53] However; a number of aspects which were not clearly reported made methodological assessment challenging; including reasons behind imbalances in group size (intervention 41; control 24); where 1:1 randomization was expected in the paper.

An RCT of an educational video for patients[63] reported no difference between intervention and control arms (completion rates 15/33 (45.5%) compared with 23/40 (57.5%); p=0.305).

A quasi-randomized controlled trial of an electronic diary to support PR adherence reported slightly greater effect than control.[54] Adherence was higher in the intervention arm (91.3% vs 82.6%; p=0.14) although not statistically significant; however; methodological quality was rated as unclear in four of the seven domains of the RoB tool.

One of the intervention studies with historic controls reported greater adherence to PR following attendance of a pre-PR session (87.9% vs 76.4%; p< 0.05).[46] However; the use of historic controls weakens conclusions. Similarly adding an individualized video fitness game to a PR program reported a 78% adherence rate (measured by participants attending 50% of sessions)[43] although only 64% mean session attendance in the intervention arm compared with 88% in the control arm.

A quality improvement study; of an intervention including education for HCPs and improved written and audio-visual material for patients reported lower adherence rates following the intervention; with 125/163 (77%) completing PR prior to the intervention; and 45/101 (57.5%) 1 year-post and 108/165 (65%) 2-years post-intervention.[52]

Ongoing Studies

Four ongoing studies were identified.[71–74] A study in India pending recruitment aims to conduct a randomized parallel group trial recruiting 110 patients with COPD admitted to hospital with an AECOPD. Admission and discharge COPD bundles will be used to assess overall care; in comparison to usual hospital care with compliance with PR as a secondary outcome.[71]

The RESTORE study; is a mixed methods feasibility study of the design and implementation of a toolkit to increase referral and uptake of PR in primary care among patients with COPD.[72] The third study; is an RCT that combines cardiac and pulmonary rehabilitation. Whilst its primary aim is to assess effectiveness; it included text support messages (five times per week) to enhance adherence and attendance compared to usual care.[73]

The fourth study is the TANDEM study; pending publication; an RCT that sought to deliver a multilevel intervention to 430 patients with COPD and mild/moderate anxiety and/or depression. The intervention includes individualized cognitive behavioral approach (CBA) sessions delivered by trained facilitators before PR commencement; with on-going telephone support; compared with usual PR referral processes. PR attendance and completion are named study outcomes.[74]

Discussion

Referral to Pulmonary Rehabilitation

We identified one RCT; one CCT and seventeen uncontrolled or historically controlled studies reporting the effects of interventions to increase referral to pulmonary rehabilitation; of which one CCT of patient empowerment using patient held score cards[55] demonstrated a significant improvement in referral to pulmonary rehabilitation and most of the uncontrolled/historically controlled studies reported increases in referral after the implementation of an intervention; but with high risk of bias. Quality improvement initiatives in primary care including staff learning activities; computer templates for COPD care; feedback on quality indicators and multidisciplinary team meetings were promising interventions within multi-component initiatives assessed by pre-post study methods.

Uptake of Pulmonary Rehabilitation

We identified four RCTs; one CCT and two non-randomized studies with historical controls (2646 participants) of interventions to improve uptake of pulmonary rehabilitation; of which one cluster RCT of primary care HCPs visiting patients at home and providing a personalized care plan found a significant increase in uptake of pulmonary rehabilitation.[61] A pre-post study of targeting both HCPs with education and patients with improved written and audio-visual material suggested increased pulmonary rehabilitation uptake.[52]

Adherence to Pulmonary Rehabilitation

We identified two RCTs; one quasi-RCT and four studies with historical/no controls. One RCT[53] found improved adherence in a group of patients with anxiety or depression who were offered cognitive behavioral therapy alongside the pulmonary rehabilitation program. An opt-in group session prior to pulmonary rehabilitation run by a physiotherapist and clinical psychologist increased adherence; albeit in a pre-post study design. None of the studies were assessed as having low risk of bias.

Timing of Pulmonary Rehabilitation Programs

Whilst they were not considered eligible for this review; three additional small trials (n=134 participants in total) were identified which explored the effect of timing of the PR program in relation to an AECOPD.[75–77] The studies hypothesized that commencing PR in hospital or soon after discharge might increase uptake. One RCT compared early PR (within 4 weeks of discharge following AECOPD) with delayed PR (at 11 weeks post discharge); however; the trial failed to recruit sufficiently and it was concluded that recruitment to PR and retention due to an early PR program was problematic.[76] Another RCT of 36 participants randomized to either early PR (commencing within 2 weeks of AECOPD in hospital) or late PR (at 6-months) demonstrated similar commencement rates (78.9% and 76.5% respectively).[75] The third study was a three arm RCT comparing PR commencement during hospital admission; 4 weeks and 8 weeks post discharge;[77] where participants randomized to the early PR program were more likely to commence PR compared to those allocated to PR at 8 weeks (OR for 8 weeks vs in-hospital 0.25 (95% CI 0.1 to 0.9; p=0.048)). Completion rates for the programs commencing at hospital admission; 4 weeks and 8 weeks were 60%; 40% and 46% respectively.

Quality of the Evidence

We have conducted a rigorous systematic review of the evidence according to predefined guidelines specified in the Cochrane Handbook.

Due to most of the studies being at high risk of bias; the overall quality of evidence was assessed as low at best. Of the 30 included studies only six were randomized controlled trials; of which one reported no relevant outcome measures and one was a quasi-RCT. Whilst all the RCTs provided sufficient data about randomization, two did not provide sufficient data to determine whether allocation was concealed and reporting of blinding of study participants and study personnel was inconsistent. One RCT was at high risk of incomplete outcome data and in one it was unclear.

Our decision to include non-randomized studies enabled us to evaluate the effectiveness of multi-component quality improvement initiatives that were assessed using routine data. The quality of reporting of these observational studies was variable. Seven studies were only reported in abstract format. The studies reported in full text had high risk of bias due to confounding; selection bias; missing data and measurement of outcomes.

The review also highlighted that despite PR being undertaken worldwide; including small provision in Africa and the Middle East (Desveaux et al 2015, Cox et al 2017); there is very little published investigation on interventions that seek to increase referral; uptake and/or adherence to PR in countries outside of the UK and Australia with thirteen and six included studies respectively.

Due to the nature of many of the studies being observational and using routinely collected data; many did not report participant characteristics; 19 (63.3%) studies reported gender and 20 (66.7%) reported age. Whilst there may be inequalities in referral to; uptake of; and adherence to PR by ethnic group or by educational level or socio-economic

status, the reporting of the participant characteristics were poor for these factors with only one study (3.3%) reporting ethnicity and three (10%) reporting socio-economic status or educational achievement. Co-morbidity burden or risk factors were rarely described (23.3%); lung function was reported in 40% and GOLD stage in 20%. Smoking status or history was reported by 56.7% of studies and previous attendance of PR by only 4 (13.3%) studies. These are major gaps; given that many of these factors could impact referral; uptake or adherence to PR. Where health care professionals were targeted; no studies adequately described where there were any selection or eligibility criteria for their participation.

The identified studies evaluated a range of different techniques to increase referral; uptake; and adherence to PR. However; most assessed only one stage of the pathway and only one RCT[63] assessed the impact of the intervention on all three relevant outcomes. Many interventions were multi-component with multiple target agents; which makes it difficult to identify effective techniques. In many cases; the description of the interventions was not clear; which would make replication difficult. No studies reported the behavioral change techniques using a taxonomy; such as that offered by Michie et al.[78]

Outcomes were also unclear and inconsistent. Some studies reported referrals made; whereas others reported referrals received by the PR service and one study reported offer of a referral. Barker et al[63] reports attendance of 50% of PR sessions (8/16); intervention mean 6/16 (37.5%) vs 10/16 (62.5%) for control. Pumar et al[53] reports session attendance rates > 61.3% and Wardini et al[43] reports PR adherence where > 50% of sessions have been attended. The remaining studies do not offer a definition for adherence. A standardized definition for adherence; perhaps based on percentage of available sessions attended; would aid comparison and interpretation of future studies.

Consistency with Previous Reviews

Previously published systematic reviews also concluded there was insufficient evidence upon which to draw recommendations on effective interventions to increase referral; uptake and adherence.[79,80] The first published systematic review on PR adherence conducted in 2017 undertaken by Jones et al;[80] reported only one study; a quasi-RCT. The review by Early et al[79] assessed interventions to increase referral and uptake. This also included non-randomized studies and included 13 primary studies; none of which included randomization. Our review demonstrates there has been an expansion of research into referral to PR; uptake and patient engagement. In terms of referral an additional ten studies were identified compared to the[79] systematic review. For uptake; this was reported as the main outcome in seven studies here; offering four additional studies[79] including three additional RCTs. Finally, of the seven studies that reported adherence outcomes in this review, only one was included in the 2017 review.[80]

Conclusion

We have conducted a rigorous systematic review of the evidence according to predefined guidelines specified in the Cochrane Handbook.

A small number of studies reported increases in PR referral; uptake and adherence from interventions that target these outcomes. However; concerns about study design and risk of bias impact conclusions about overall effectiveness and recommendations. Collaborative working; increasing knowledge and empowering HCPs and patients may be important strategies. There is a clear need for further well-designed trials of interventions to increase referral; uptake and adherence to PR and to report outcomes across the full pathway. Interventions need to be developed to promote greater PR uptake and adherence in patient populations least likely to attend. Trials which evaluate the effects of individual strategies would facilitate an understanding of which strategies are most effective.

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This systematic review formed part of Watson's PhD thesis which examined improving referral from primary care to PR for patients with COPD.[81] It was also presented at the Primary Care Respiratory Society (PCRS) conference in England in 2022.[82]

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