# Interventions to improve quality of care in patients with chronic obstructive pulmonary disease in primary health care settings: rapid review

***This document is a supplement to the rapid policy brief on the issue.***

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## Contributions of authors

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## Competing interests

The authors do not have any relevant competing interests.


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## List of abbreviations

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| GOLD | Global Initiative for Chronic Obstructive Lung Disease |
| ICS | Indian Chest Society |
| LMICs | Low- and middle-income countries |
| NCCP | National College of Chest Physicians |
| NCD | Non Communicable Disease |
| PHC | Primary Health Care |
| PICO | Population, interventions, comparisons and outcomes |
| WHO | World Health Organization |

# Executive Summary

**Background**: Chronic obstructive pulmonary disease (COPD) is a highly prevalent disease, with an increasing burden worldwide, particularly in low- and middle-income countries. Majority of the patients with COPD are treated in the primary health care settings.

**Objective**: To provide a comprehensive synthesis of evidence on interventions to improve quality of care among patients with COPD within a primary healthcare context.

**Methods**: A comprehensive systematic search was conducted in four electronic databases including PubMed, Embase, Cochrane Library and Health Systems Evidence to identify systematic reviews and primary studies published in the past five years. Reviews and studies that examined both nonpharmacological and pharmacological interventions of interest to improve quality of care in terms of quality of life, and other relevant clinical and health outcomes were included.

**Results**: The report included 11 systematic reviews and five primary studies of interest. Almost all the systematic reviews and primary studies were conducted in high-income countries, mainly Australia, some countries in Europe including UK, and USA. Overall, there was limited and mixed, and in some cases inconclusive evidence on the effectiveness of some interventions targeted at improving quality of care for patients with COPD in primary care. There is some evidence of effectiveness for self-management support and education, pulmonary rehabilitation, integrated care and pharmacotherapy. Self-management education and support may include interventions focussed on techniques to help patients monitor and control their symptoms and to tailor treatment, as necessary.

**Conclusion**: The findings from this review highlight the gaps in evidence on quality of care for patients with COPD in primary health care settings, particularly in low- and middle-income countries. It is necessary that these gaps are addressed to generate contextualised evidence that ensures relevance, with a focus on feasibility of high-impact interventions at the primary health care level.

**Key words**: chronic obstructive pulmonary disease, COPD, quality of care, primary healthcare, evidence synthesis

# 1. Background

Chronic obstructive pulmonary disease (COPD) is a common non-communicable and treatable disease, which is characterised by airflow obstruction. Airways obstruction is generally due to decreased forced expiratory volume in one second (FEV1) relative to the forced vital capacity (FVC).(1) The disease is generally classified into four different stages based on the severity of airflow obstruction: mild, moderate, severe and very severe disease. There are other factors such as exercise capacity and the degree of dyspnoea that may play a role in determining the severity of the disease. Data suggests that there is an increasing burden of COPD worldwide, more so in low- and middle-income countries (LMICs).(2) The number of cases of COPD in India increased from an average of 28·1 million in 1990 to an average of 55·3 million in 2016.(2)

Primary health care (PHC), as defined by the World Health Organization (WHO) is “essential health care based on scientifically sound and socially acceptable methods and technology, which make universal health care accessible to all individuals and families in a community. It is through their full participation and at a cost that the community and the country can afford to maintain at every stage of their development in the spirit of self-reliance and self-determination".(3) Quality of care (QoC) is defined as the degree to which health care services improve desired health outcomes that are consistent with current professional knowledge.(4, 5) However, to achieve QoC, the health care that is provided should be safe, effective, timely, efficient, equitable and people-centred. (3)

Nonpharmacological interventions such as self-management, education, smoking cessation, and exercise are used to treat and manage COPD in terms of preventing the progression of the disease.(6-11) These interventions could improve health-related quality of life in many patients. Pharmacological therapy can help relieve patients’ symptoms, reduce the frequency of exacerbations, improve exercise tolerance and improve quality of life.(12-14)

The State Health Resource Centre (SHRC) in Raipur, Chhattisgarh identified that there is a high burden of chronic obstructive pulmonary disease (COPD) in the State, and that there is a knowledge gap in relation to the evidence-based strategies for improving QoC among patients with COPD in PHC settings. This is also necessitated by an increased need for good quality care. The Centre requested for a rapid overview of evidence-based interventions or strategies to improve QoC for patients with COPD in PHC settings to help inform decision-making. Rapid evidence synthesis (RES) is a form of evidence synthesis that provides timely and practical information to guide decision-making needs of policy-makers.

This is a comprehensive overview of published research evidence that highlights evidence-based strategies targeted at improving QoC in patients with COPD within the PHC context. This approach provides an overview of existing systematic reviews

(SRs) and primary studies, and is particularly helpful where multiple SRs on a similar topic of interest or interventions have been conducted. Also, the review identifies knowledge gaps in the QoC domain for COPD from a PHC perspective.

**Review question**

- What is the best available evidence on the effectiveness of interventions to improve quality of care among patients with COPD in primary healthcare settings?

# 2. Methods

This section describes the methods used in the development of the rapid review.

## Inclusion Criteria (PICO)

Systematic reviews and/or primary studies that met the following criteria were included.

### Population

Patients irrespective of age with a diagnosis of COPD.

### Intervention

Reviews that examined interventions designed to improve the QoC in the treatment of COPD in PHC settings were considered for inclusion. The following interventions were considered:

- Pulmonary rehabilitation (e.g. physical activity including exercise, education, breathing techniques, nutrition counselling)
- Self-management (encouraging smoking cessation and healthy lifestyle behaviours)
- Pharmacotherapy for symptomatic management (oxygen therapy, inhaled bronchodilators, inhaled corticosteroids, influenza vaccination)
- Integrated care (joint participation of generalist and specialist care physicians in the planned delivery of care)
- Peer support
- Telehealth or mHealth
- Financial incentives

Reviews that examined the effectiveness of COPD medications (comparative effectiveness), medical procedures, complementary and alternative medicine, psychological interventions, school-based therapy, and of nutrients were excluded.

### Outcome/s

Quality of care was defined as patient reported outcome measures, clinical and physiological measures (as defined by systematic review and primary study authors).

### Study designs

Systematic reviews/meta-analyses of randomised controlled trials (RCTs) or non-RCTs, controlled before after studies or interrupted time series (ITS) studies published in the last 5 years were included. In the absence of SRs for interventions of interest, primary studies of interest (RCTs, non-RCTs, before-and-after studies and ITS studies) were searched for. Qualitative SRs and primary studies, observational and descriptive studies, case reports, case series, commentaries, and expert opinions were not considered.

### Setting

Systematic reviews and/or primary studies that were specifically conducted in primary health care or general practice context were included.

## Search methods

A comprehensive search for SRs was conducted in four electronic databases such as PubMed, Cochrane Library, EMBASE, and Health Systems Evidence. The search strategies are provided in Appendix 1. An additional search for primary studies of interest was conducted in the same databases, for all the interventions except for self-management interventions. Search strategies are provided in Appendix 2. The search was restricted to reviews and primary studies published in the English language in the past 5 years for recency and relevancy.

## Data collection, and reporting

Quantitative data was extracted from included SRs and primary studies using separate semi-structured data collection forms. The data extracted included details about the review/study (study designs, setting, country) and sample characteristics (sample size, participants' age, gender), interventions, outcome measures, and results of significance (estimated effect size with corresponding 95% confidence interval if quantitative statistical analysis was conducted).

## Data synthesis and reporting

A narrative summary of the included SRs and primary studies aided by tables, where appropriate is presented.

# 3. Results

The results section presents detailed findings from the systematic reviews and primary studies (where appppropriate), based on the type of intervention.

# Description of characteristics of included systematic reviews

## Search results and study selection

The PRISMA diagrams (Figure 1 and 2) report on the number of SRs and primary studies identified, the screening process and the final list of included reviews and primary studies. All titles and abstracts of the reviews were screened by one reviewer (SM). The full texts of the potentially eligible SRs were examined by a single reviewer (SM), with two other reviewers (JT and MK) conducting a secondary examination. Any disagreements were resolved by discussion. Reviews and studies that did not clearly meet the inclusion criteria were excluded. The full texts of the remaining reviews were retrieved and assessed for methodological quality. Critical appraisal of primary studies was not conducted.

Overall, 11 SRs were included in the review, and the key characteristics of the included SRs are summarised in Appendix 3. Almost all the studies included in the SRs were conducted in high-income countries such as the United States, United Kingdom, Australia, Canada, and in some countries in Europe. The included reviews were published between 2016 and 2019. Fifty-five SRs were excluded following full text examination in detail. A list of the excluded SRs is provided in Appendix 4. The SRs were excluded mainly due to not being relevant to primary health care settings.

The search for primary studies identified a total of 66 studies from four databases. The titles and abstracts of 66 studies were screened. Nine studies were identified as potentially eligible for full text examination, and on detailed review, five studies were included in the review. Figure 2 presents the PRISMA flow chart with the study selection process. The key characteristics of the included primary studies are provided in Appendix 5.

## Methodological quality of included SRs

The critical appraisal results of included SRs are provided in Appendix 6, which were appraised using the AMSTAR-2 checklist (Appendix 7), a 16-item questionnaire. Most of the SRs were of moderate to high methodological quality. However, a majority of the SRs did not refer to an apriori protocol and did not assess or report on publication bias.

**Figure 1 PRISMA Study selection flow chart for systematic reviews**

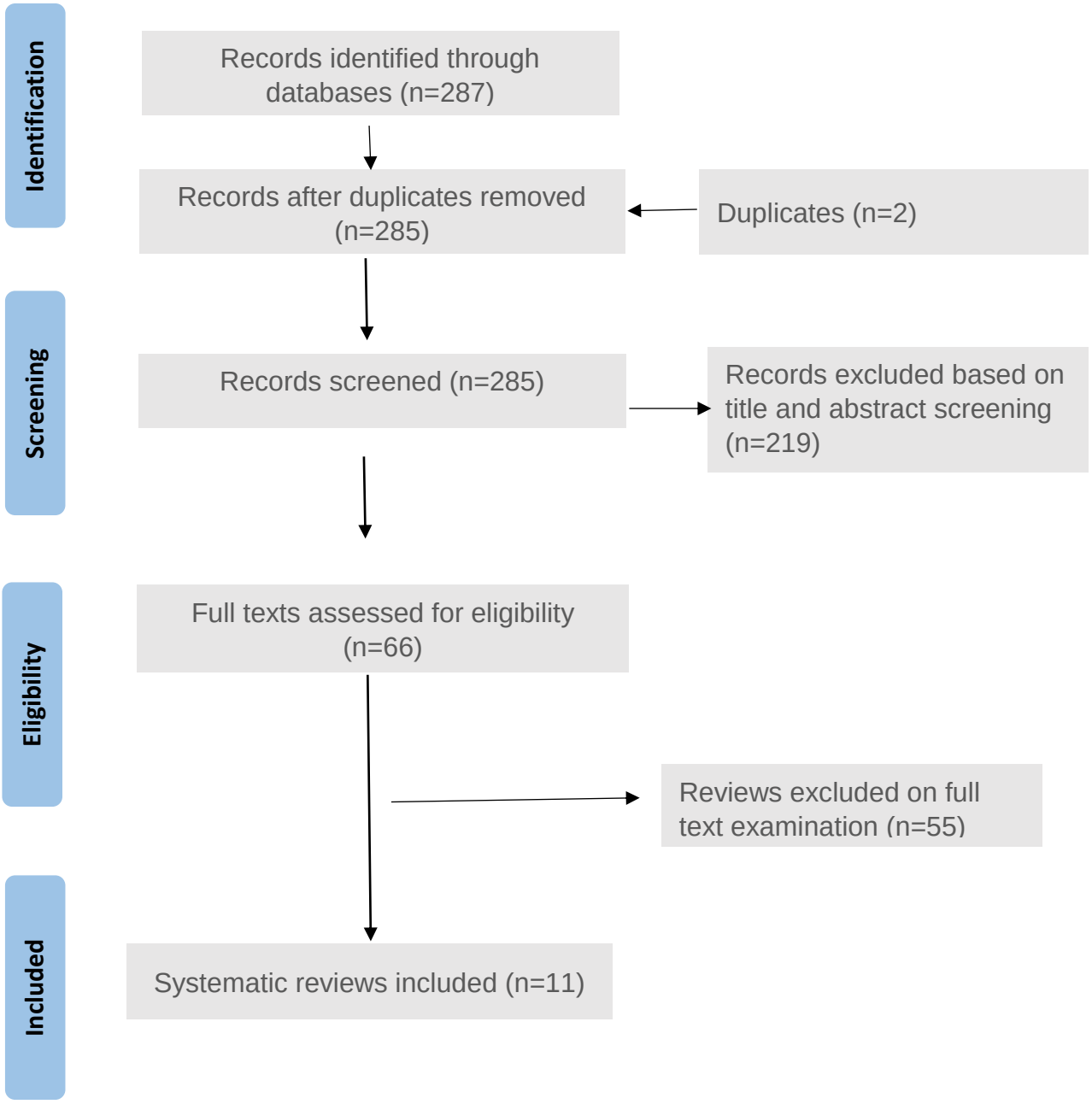
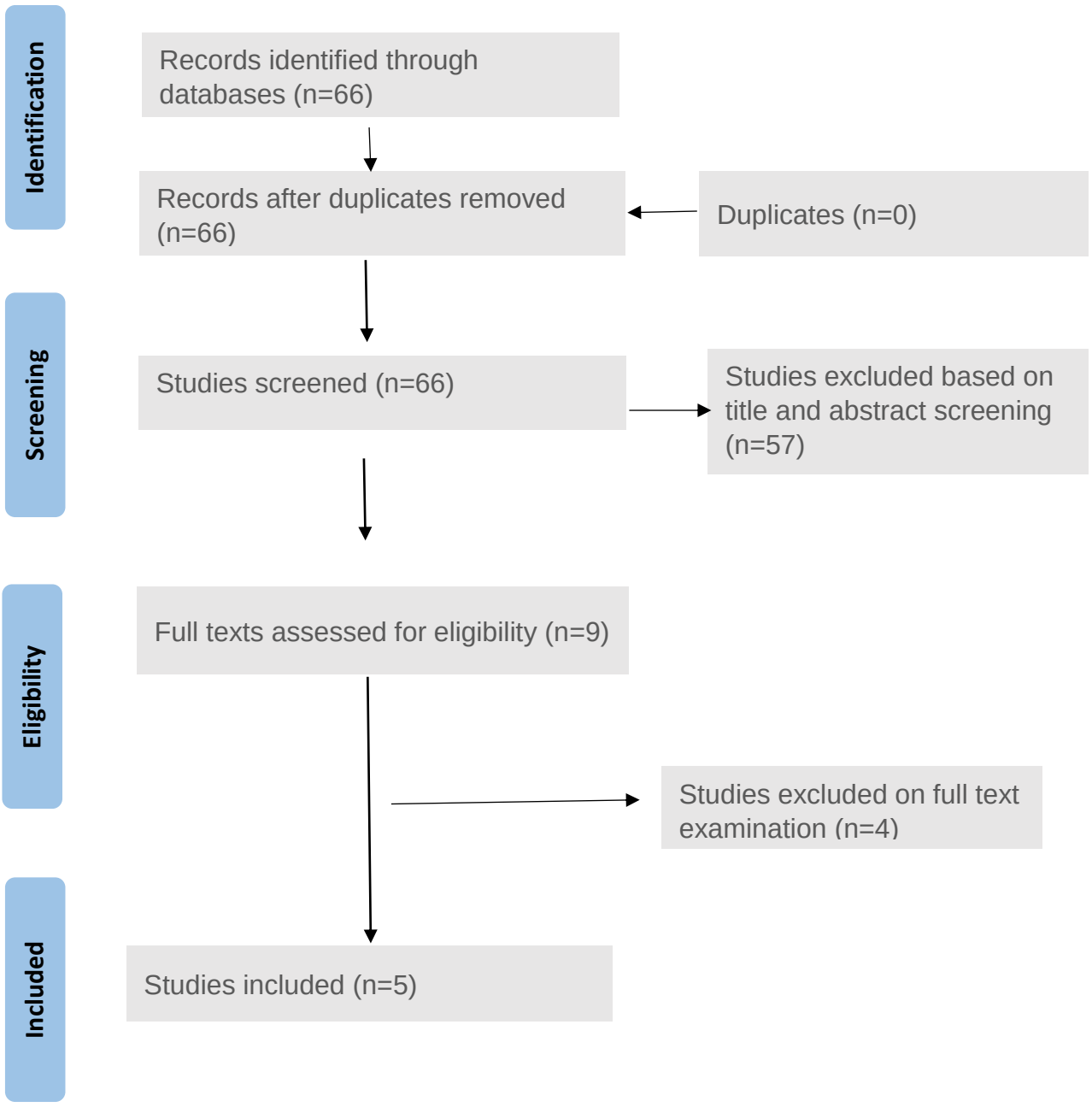


**Figure 2 PRISMA study selection flow chart for primary studies**



# Summary of evidence from included systematic reviews

This section presents the key findings from the included SRs based on the different types of interventions of interest. The findings for each intervention are summarised based on the sub-categories of interventions, where appropriate. Main outcomes measured included health-related qualty of life (HRQoL), and hospital admissions.

## Self-management

Self-management refers to the ability of a patient to deal with the symptoms, treatment, physical consequences and lifestyle changes related to COPD. Self-management enables patients with COPD to manage and control the disease, including adhering to medications appropriately with good inhaler technique, early recognition of exacerbations of symptoms, regular exercise to maintain lung function and exercise capacity, and smoking cessation. Four SRs evaluated self-management interventions, which looked at different components and/or were delivered by different professionals in the PHC settings.(6-9) Another SR on self-management was identified; however, was not included due to poor reporting and lack of adequate details and data.(15) Further, the trials included in this SR(15) were included in other four SRs.(6-9)

### Nurse-led self-management(6)

The clinical and cost-effectiveness of self-management interventions delivered by nurses in the community for patients with COPD was examined in a SR that included 20 RCTs (total 3384 participants). The trials were conducted mostly in high-income countries (HICs), in 14 different countries in Europe, North America, Australasia and East Asia. The sample size in the RCTs ranged from 52 to 464 Participants, with the mean age of participants ranging between 58–73 years. The studies' duration ranged from 3 to 24 months.

Majority of the studies in the SR included specialist respiratory nurses, with only one study including community health nurse. Four other studies included nurses trained in the intervention. The self-management components examined included information about COPD, symptom management, lifestyle, management of psychological consequences, professional support and communication. Self-management interventions were delivered with at least one face-to-face contact with a nurse in most studies, and in a few studies entirely via telephone contact.

There was mixed evidence on improvement in health related quality of life (HRQoL). Five studies demonstrated statistically significant and clinically relevant HRQoL improvements in the self-management intervention group when compared to usual care group at follow up. However, nine other studies reported no effect. Similar results were found in the rate of hospital admissions. Seven studies reported on COPD-specific hospital admissions, wherein three trials reporting a statistically significant reduction in the rate of all-cause hospitalisations at 12 months follow up in the intervention group compared to usual care group. However, three other studies found no significant differences in the admission rates. Only one out of eight studies reported

a statistically significant reduction in COPD related hospital admission rate at 12 months follow up among intervention group patients. Also, three out of six studies reported significantly lower numbers of all-cause emergency department visits in the intervention group (follow up ranging from 3 months to 24 months).

Three out of five studies reported on the frequency of unscheduled all-cause physician visits. Significant differences were found in physician visits between the intervention and the usual care groups in favour of the self-management group. Six out of 10 studies reported significant improvements in self-efficacy in the intervention group. No significant differences in satisfaction and frequency of exacerbation were reported between the two groups.

Four studies analysed the cost-effectiveness of nurse-led self-management programmes. In one study, it was found that nurse-led patient education improved patient outcomes and reduced costs compared to usual care. Two other studies reported that compared to usual care, the cost of the self-management programme exceeded savings in healthcare utilisation (from a third-party healthcare payer and health service perspective). In one other study that undertook cost-utility analysis, it was found that the cost of the self-management programme was twice that of usual care. Further, it was reported that the intervention had no measurable beneficial effects on health related QoL or quality adjusted life years (QALYs).

### Self-management support strategies(7)

A SR of 58 RCTs evaluated the effectiveness of self-management support interventions delivered face-to-face in primary care practice on COPD-specific outcomes. Only 12 RCTs included patients with COPD, which were predominantly from the United Kingdom (UK) and the United States (US). Studies were conducted in general practices, primary care clinics and community pharmacies. Other participants characteristics were not reported clearly. Interventions were delivered by general practitioners or nurses specialised in respiratory health. The various self-management intervention components examined included support, education, training, and provision of written action plans. Results showed that there were no significant changes in clinical outcomes, including the frequency of use of antibiotic courses and oral corticosteroids over 12 months. The disease knowledge score (Bristol COPD Knowledge Questionnaire) significantly increased from 27.6 ± 8.7 to 36.5 ± 7.7 points in the intervention group, compared to the unchanged score in the control group (29.6 ± 7.9 to 30.2 ± 7.2), compared to baseline data. None of the studies reported statistically significant changes in self-efficacy (COPD self-efficacy scale (CSES)) scores at 24 months follow up.

### Community-based self-management interventions in primary care(8)

A SR of 12 RCTs evaluated the effectiveness of community-based self-management interventions in COPD patients on HRQoL, and reduced health care utilisation. Almost all the studies were conducted in HICs such as the UK, Australia, The Netherlands, Sweden, Germany, US, China and New Zealand. Sample size in the trials ranged from 5214 to 82179 participants, with the mean age of participants ranging from 61 to 73 years. Interventions were delivered by general practitioners, nurse practitioners,

medical assistants, respiratory physician nurses, health psychologists and trained peers. The content of the interventions focussed on management of exacerbations and responding to participants' self-management queries, information about educational materials, physical activity advice, smoking cessation, breathing and medication management. Meta-analyses demonstrated that there was no difference in HRQoL (measured by the St George's Respiratory Questionnaire (SGRQ)) at the final follow-up (SGRQ total score −0.29, 95% CI −2.09, 1.51). The meta-analysis results for the Chronic Respiratory Disease Questionnaire (CRQ) domains of dyspnoea, emotions, fatigue and mastery were in favour of the self-management interventions; however, these were statistically non-significant. There were no statistically significant differences at follow-up in emergency department visits and hospital admissions, as reported in seven trials.

### Self-management interventions including action plans for exacerbations(9)

The efficacy of COPD-specific self-management interventions that include written action plans for exacerbations of COPD was evaluated in one SR. The review included only five RCTs that were relevant to PHC setting, and were conducted in general practices, and primary health care clinics. The mean age of the participants ranged between 57-74 years, with the majority being older adults and male. Various self-management intervention examined included: iterative process, self-recognition of COPD exacerbations, education regarding COPD and smoking cessation, and exercise or physical activity component.

Self-management with written action plans in one study showed significant and clinically relevant lower total SGRQ total scores in the intervention group (HRQoL improved by 8.2 points) when compared with no change in the usual care group. However, another study reported no significant difference in SGRQ total score after 12 months of follow-up. Three studies measured COPD-specific HRQoL using the CRQ. In one study, two of the four CRQ domains, fatigue and mastery, showed statistically significant higher scores (indicating better HRQoL), in the self-management intervention group (17.7 and 21.4, respectively) compared to the usual care group (15.7 and 20.7, respectively). In another study, CRQ dyspnoea domain was found to improve in both groups over time; however, only the self-management group sustained the within-group changes that exceeded the minimal clinically important difference (MCID) of 0.5. The third study reported no statistically significant mean treatment difference between the two groups for the CRQ total score at 24 months of follow-up; however, more participants in the intervention group showed a clinically important improvement compared to those in the usual care group.

Self-management interventions that included written action plans in consultation with patients showed a significant reduction in odds of respiratory-related hospitalisations when compared to the usual care group in two trials (OR 0.44, 95% CI: 0.21 to 0.95, and OR 0.41, 95% CI 0.08 to 2.19). However, in a third trial, more respiratory-related hospitalisations were reported in the intervention group (1.1 per participant per year) compared to the usual care group (0.7 per participant per year). In two other trials, it was reported that there was no statistically significant difference in all-cause hospital

admissions between the two groups (OR 0.54, 95% CI 0.26 to 1.09; OR 0.63, 95% CI 0.31 to 1.26).

A statistically non-significant lower number of all-cause hospitalisation days was reported in the intervention group compared to the usual care group (3.2 versus 6.8), in one trial. However, the same trial reported significantly fewer respiratory-related hospitalisation days per participant per year in the intervention group (from 2.8 to 1.1) compared to a significant increase for the usual care group (from 3.5 to 4.0 days). No statistically significant difference in emergency department (ED) visits was reported between the intervention group (five visits (6%)) and usual care group (seven (13.5%) visits) in one other trial, after 12 months of follow-up.

One trial reported no statistically significant difference in healthcare utilisation (GP visits) between the intervention and usual care groups (Mean Difference (MD) 2.60, 95% CI -0.63 to 5.83). The mean number of COPD exacerbations per participant reported in one trial were found to be non-statistically significant (MD 0.28, 95% CI -0.45 to 1.01, n = 53) between the intervention and control groups. One trial reported almost a similar number of participants who started prednisolone, antibiotics or both to manage exacerbations in the self-management group (n = 16, 11%) compared to the usual care group (n = 13, 10%), at one year follow-up. A higher number of exacerbations in the self-management group were managed by starting prednisolone antibiotics or both (OR 3.98, 95% CI 1.10 to 15.58), in the second year of follow-up. No statistically significant differences in mortality were found between the intervention and control group participants (RD 0.1229, 95% CI --0.0188 to 0.2646; RD -0.0528, 95% CI -0.1324 to 0.0268; RD -0.0105, 95% CI -0.0397 to 0.0187) in three RCTs. In one RCT, no statistically significant changes or difference in participants' self-efficacy was reported between the intervention and control groups according to the CSES total score (MD -0.17, 95% CI -0.64 to 0.30) and domain scores, at 24 months of follow up.

### Smoking cessation(16)

A SR of eight relevant RCTs evaluated the effectiveness of behavioural or pharmacological smoking cessation interventions, or both, in smokers with COPD.(16) One trial demonstrated that high-intensity behavioural treatment increased abstinence rates when compared with usual care (RR 1.09, 95% CI 0.59 to 2.04). Pharmacotherapy plus high-intensity behavioural treatment was effective in increasing quit rates (RR 2.53, 95% CI 1.83 to 3.50) compared with placebo plus high-intensity behavioural treatment. Individually, nicotine sublingual tablet and varenicline significantly increased the quit rate, whereas, nortriptyline did not. Pooled analysis of two studies on bupropion showed a positive effect of bupropion compared with placebo. When comparing different kinds of pharmacological treatments, bupropion did not seem to be more effective than nortriptyline, or nicotine patch. In one trial, high-intensity behavioural treatment plus nicotine gum was found to increase abstinence rates compared with usual care. In another trial, high-intensity behavioural treatment with hospitalisation plus any NRT was found to increase the chance of quitting compared with usual care. Pooled results from five studies showed that the prolonged

abstinence rate at 12 months' follow-up was significantly more in the intervention group (34%) compared to 9% in the usual care group (RR 3.80, 95% CI 3.28 to 4.4).

### Inhaler Technique Education(10)

A SR assessed the effectiveness of inhaler technique education in older adults with COPD to improve clinical control and reduce disease exacerbations. However, only one study was relevant to PHC setting, and it was conducted in South Korea. Inhalation technique education was provided by health professionals using oral instructions and video education, and an action plan. The frequency of the intervention included three educational visits conducted with follow-up visits held every two weeks. Quality of life was measured using COPD Assessment Test (CAT), which showed that there was a significant improvement by 51.2% (n = 65/127) after education in the intervention group. The usage of inhaler showed statistically significant changes, particularly for enough breathing out before inhalation (71.4%) and holding their breath after inhalation (70.7%), which were the two most improved items.

## Pulmonary rehabilitation(11, 17, 18)

One SR,(11) one RCT,(17) and one quasi-experimental study(18) assessed the effectiveness of pulmonary rehabilitation (PR) in improving outcomes for COPD patients.

A SR evaluated the efficacy of PR in patients with COPD.(11) The review included 17 RCTs; however, only two RCTs were relevant to PHC setting, and these were conducted in Hong Kong and Ireland. Follow up duration in the two studies was 6 weeks and 24 months respectively. Intervention was community-based, structured, nurse-pulmonary rehabilitation that included aerobic exercise, upper limb exercise (ULE), and lower limb exercise (LLE). In one RCT conducted in Hong Kong, statistically significant differences were reported in QoL in terms of fatigue (MD 0.00, 95% CI −0.26 to 0.26, but not in the other RCT conducted in Ireland (MD 0.10, 95% CI −0.91 to 1.11). However, clinically important changes were reported in both RCTs. Similar results were reported for QoL in terms of mastery, with one RCT (MD 0.18, 95% CI −0.11 to 0.47) showing significant differences, and the other RCT showing no significant differences (MD 0.00, 95% CI −0.77 to 0.77). Statistically and clinically non-significant differences were reported for both RCTs for QoL in terms of emotion (MD 0.00, 95% CI −0.26 to 0.26, and MD 0.10, 95% CI −0.91 to 1.11).(11)

One RCT compared the effectiveness and feasibility of an interactive web-based PR programme to conventional PR.(17) The trial was conducted in the UK, wherein the participants were recruited from primary care and community rehabilitation services. Participants in the intervention group received a web-based programme to work through the website, exercising and recording their progress as well as reading educational material. A statistically significant improvement was reported within each group in the Endurance shuttle walk test (ESWT) (intervention group: mean change 189±211.1; conventional PR: mean change 184.5 ±247.4) and CRQ-D (intervention

group: mean change 0.7±1.2; conventional PR: mean change 0.8±1.0). No significant differences were reported between the two groups for clinical outcomes.(17)

A quasi-experimental study assessed the effectiveness of a nurse-led multidisciplinary PR programme among moderate to severe COPD patients, over a 3-year period.(18) The study included 103 participants recruited from PHC centres and was conducted in Sweden. The mean age of the participants in the intervention group was 67±3 years and in the control group 68±1 years. The intervention included a nurse-led PR programme, conducted over a six-week period, with two hours per week sessions. One hour was devoted to theory and the other to physical activity, and education around smoking cessation. The (6MWT) improved after one year for patients (IRR 33.16, 95% CI 19.66 to 46.65), but the improvement was not sustained at three-year follow up (IRR -13.68, 95% CI -33.22 to 5.86), when the distance became shorter than at baseline. However, participants in the intervention group were generally able to walk for a greater distance compared with the controls. There was no difference in the CCQ score between the intervention and the control group (IRR 0.03, 95% CI -0.33 to 0.39). No significant increase in the risk of exacerbation was reported after one year compared with baseline measure (IRR 0.93, 95% CI 0.65 to 1.34); however, the risk increased after three years.(18)

### Behavioural lifestyle intervention to enhance physical activity(19)

A trial assessed the effectiveness of a behavioral intervention to increase daily physical activity and improve HRQoL and functional performance.(19) The trial was conducted in USA that included 305 participants with COPD recruited from primary care and pulmonary clinics. Participants above 45 years of age were eligible for PR. All patients in the study received self-management education during a 6-week period, with the intervention group subsequently, receiving behavioural intervention delivered over 20 weeks. Overall, for CRQ-D (-0.03) and 6-minute-walk distance (6MWD) (-13.6) at 18 months follow up, there were no statistical or clinically significant differences between the intervention and the usual care groups. Further, there was little change for CRQ-D at 18 months compared with baseline measures for either the usual care group (20.09) or the intervention group (20.03), with no significant difference between the two groups. There were statistically but not clinically significant declines in 6MWD over the 18 months among both groups. The average declines were 213.6 meters for the intervention group and 222.6 meters for the usual care group, with no statistical difference reported between the groups. Hospitalisations for COPD exacerbations were the most common adverse event in both groups; however, there were nearly twice as frequent among those in the usual care group compared with the intervention group (49.47% vs. 28.28%), which was significant.(19)

## Integrated care/Disease management programme(20, 21)

A cluster-RCT conducted in The Netherlands assessed the cost-effectiveness of a COPD-disease management (COPD-DM, RECODE) programme in primary care.(20)

The trial included 40 clusters of primary care teams and a total of 10,086 participants. Majority of the participants were male, with more than half of the total participants being former smokers. The COPD-DM programme included education on proper diagnosis, optimising medication adherence, motivational interviewing, smoking cessation counselling, applying self-management plans including early recognition and treatment of exacerbations, physical (re)activation and nutritional support. The number of QALYs was significantly lower (0.04) in the intervention group compared to the usual care group, with no significant difference in the percentage of patients with a MCID on the CCQ, over a 2-year period. The costs per patient were significantly higher in the intervention group compared to the usual care group by €408 (as of year 2015) from the healthcare perspective, over a 12-month period.(20)

Another cluster-RCT assessed the effectiveness of integrated care for COPD delivered at 30 public healthcare facilities (23 primary and 7 secondary) across three districts of Punjab, Pakistan.(21) The trial included 288 participants in the final analysis. The mean age in the intervention group was 48.11±13.89 years, and in the control group 48.47±12.86 years, with the majority of the participants being male (>70%) in both the groups. The intervention group health facilities received contextualised care protocols and tools, a 2-day training of doctors and allied staff on full set of care tasks, and materials including inhalers and mobile phones. The Body mass index, airway Obstruction, Dyspnoea, Exercise capacity (BODE) score improved (i.e. score reduced) in both the groups, but there was a statistically and clinically significantly greater reduction in the intervention group compared with the control group (difference -1, 95% CI = -1.5 to -0.4), from baseline and at five month follow-up visits. A statistically and clinically significantly greater percentage of COPD control (difference 29 percentage points, 95% CI = 12.4 to 45.6), significantly higher quit rate among smokers (difference 32 percentage points, 95% CI = 15.4 to 48.5), and treatment adherence (difference 40.4 percentage points, 95% CI = 24.2 to 56.7) were reported in the intervention group compared with the control group, at 6-month follow-up.(21)

## Pharmacotherapy(12-14, 22)

Four SRs included some studies that assessed the effectiveness of various combinations of long acting muscarinic antagonists (LAMA)/long acting beta agonists (LABA) in improving various clinical outcomes among patients with COPD in PHC settings.

### Single-inhaler LABA/LAMA combinations versus placebo

*Tiotropium (LAMA) 5 µg once daily, tiotropium + olodaterol (LABA) 5/5 µg once daily, and tiotropium + olodaterol 5/5 µg once daily(13)*

A SR assessed the effects of single-inhaler LABA/LAMA combinations versus placebo on clinically meaningful outcomes in patients with stable COPD.(13) The review included 23 RCTs; however, only one multicentre RCT was relevant to PHC setting,

with sites across Australia, New Zealand and USA. The trial included 303 patients (200 men), aged over 60 years. Interventions included tiotropium (LAMA) 5 µg once daily, tiotropium + olodaterol (LABA) 5/5 µg once daily, and tiotropium + olodaterol 5/5 µg once daily with (exercise training) for 12 weeks, with or without self-management behavior-modification. Self-management behavior-modification (SMBM) plus tiotropium/olodaterol, with or without exercise training, significantly improved exercise endurance test (EET) at Week 8 versus SMBM plus placebo (treatment ratio vs. placebo: with exercise training, 1.46, 95% CI 1.20 to 1.78; without exercise training, 1.29, 95% CI 1.06 to 1.57). No significant increases in steps per day from baseline were reported for SMBM plus placebo at week 12 (increase of 1,098) when other therapies were added.(13)

*Tiotropium (LAMA) + salmeterol (LABA) vs placebo and formoterol + tiotropium versus tiotropium(14)*

The efficacy and safety of available formulations from four different groups of inhalers (i.e. LABA/LAMA combination, LABA/ICS combination, LAMA and LABA) in people with moderate to severe COPD was assessed in a SR of 99 RCTs.(14) However, only two RCTs were relevant to PHC, which were conducted in Canada and the US. Studies were conducted in community primary care clinics and primary care centres. Total number of participants in the two RCTs were 304 and 255, with a mean age of 64 and 68 years respectively. Interventions included tiotropium (LAMA) + salmeterol (LABA): tiotropium 18 Sg once daily using a HandiHaler + salmeterol 25 µg/puff, 2 puffs twice daily using a pressurised metered-dose inhaler using a spacer device; and tiotropium + placebo: tiotropium, 18 µg once daily, + placebo inhaler, 2 puffs twice daily. Formoterol (LABA) 12 µg twice daily and tiotropium (HandiHaler) 18 µg once daily in the morning delivered via two separate inhalers; and formoterol-matched placebo twice daily and tiotropium 18 µg once daily delivered via two separate inhalers.(14)

Patients who received tiotropium plus placebo experienced 1.61 exacerbations per patient-year of follow-up, compared with 1.75 exacerbations per patient-year in the tiotropium plus salmeterol group and 1.37 exacerbations per patient-year in the tiotropium plus fluticasone–salmeterol group. Patients treated with tiotropium plus fluticasone–salmeterol reported lower rates of severe exacerbations of COPD requiring hospitalisation compared to patients treated with tiotropium plus placebo (incidence rate ratio (IRR) 0.53, 95% CI 0.33 to 0.86).(14) All-cause hospitalisations significantly reduced in patients treated with tiotropium plus fluticasone–salmeterol compared with patients treated with tiotropium plus placebo. Tiotropium plus salmeterol or tiotropium plus fluticasone–salmeterol (one year therapy) significantly improved HRQoL compared to therapy with tiotropium plus placebo. The 1-year change in total score on the SGRQ was −4.5 points in the tiotropium plus placebo group, −6.3 points in the tiotropium plus salmeterol group, and −8.6 points in the tiotropium plus fluticasone–salmeterol group.

Significantly greater improvements were reported in the forced expiratory volume (FEV 1) with the combination of formoterol + tiotropium compared to tiotropium alone at all time points of the study. The increase in FEV1, 5 minutes after the first dose was 180 mL with the combination versus 40 mL with tiotropium alone. At the endpoint, FEV1 increased 340 mL with combination versus 170 mL with tiotropium.(14)

### Single inhaler triple therapy (extrafine) versus single inhaler dual therapy and/or separate triple therapy(22)

Single inhaler triple therapy (inhaled corticosteroids/LABAs/LAMAs) was compared with single inhaler dual therapy (LABA/LAMA) and/or separate triple therapy for the management of COPD in a SR.(22) The review included seven RCTs; however, only two RCTs were conducted in PHC settings. Both the trials included patients with symptomatic COPD, with an FEV1 of less than 50%, and had at least one moderate or severe COPD exacerbation in the previous 12 months. One trial compared extrafine (beclomethasone dipropionate, formoterol fumarate, and glycopyrronium (BDP/FF/G)) inhaled triple therapy versus dual bronchodilator therapy (indacaterol plus glycopyrronium (IND/GLY)). The rates of moderate-to-severe COPD exacerbations were 0·50 per patient per year (95% CI 0·45 to 0·57) for patients receiving BDP/FF/G and 0·59 (0·53 to 0·67) per patient per year for those receiving IND/GLY. The rate of moderate-to-severe COPD exacerbations was significantly lower with BDP/FF/G than with IND/GLY (rate ratio of 0·848, 95% CI 0·723–0·995), which indicated a 15% reduction in the exacerbation rate. The proportion of patients who had adverse events was found to be similar between the two groups. Pneumonia was reported in 28 (4%) patients receiving BDP/FF/G and in 27 (4%) patients receiving IND/GLY.(22)

Another trial compared single inhaler extrafine fixed triple therapy (beclometasone dipropionate, formoterol fumarate, and glycopyrronium bromide with tiotropium) versus open triple LAMA therapy (beclometasone dipropionate, formoterol fumarate plus tiotropium). The results showed that the rates of moderate-to-severe COPD exacerbations were 0·46 per patient per year for fixed triple compared to 0·57 for tiotropium, and 0·45 for open triple therapy. Extrafine fixed triple was found to be superior to tiotropium (rate ratio 0·80, 95% CI 0·69 to 0·92); however, the rates of moderate-to-severe exacerbations were similar with fixed triple and open triple therapies. The time to first moderate-to-severe exacerbation was significantly extended with fixed triple versus tiotropium. The time to first severe exacerbation was prolonged with fixed triple compared with tiotropium (hazard ratio (HR) 0·70, 95% CI 0·52 to 0·95); however, was similar for fixed triple and open triple therapies (HR 1·05, 95% CI 0·70 to 1·56). Fixed triple therapy was associated with a greater improvement in HRQoL (SGRQ total score) than tiotropium at all time points except week 26, and a similar improvement with open triple at most timepoints, with the exception of weeks 26 and 52. A similar proportion of patients had adverse events in the three groups, with most being mild or moderate. The incidence of pneumonia was reported in a small percentage of patients, and was similar in the three treatment groups (fixed triple (28 (3%)), tiotropium (19 (2%)), and open triple (12 (2%))). (22)

### Inhalation delivery devices (Tiotropium Respimat versus tiotropium HandiHaler)

A SR evaluated the efficacy and safety of once-daily licensed doses tiotropium Respimat® (5 µg, (an aqueous solution delivered Soft Mist™ inhaler) and tiotropium HandiHaler® inhalation device (18 µg, (dry powder formulation delivered by means of an inhalation device) in patients with COPD.(12) Only two out of 22 RCTs were relevant to PHC setting that reported on data from a Dutch integrated primary care database. A total of 11,287 patients, aged ≥40 years, and including 24,522 episodes of tiotropium use were included, with ≥1 year of follow-up. The use of tiotropium Respimat® (Hazard Ratio (HR) 1.27, 95% CI 1.03–1.57) was associated with a 30% increased risk of mortality compared with tiotropium HandiHaler®, with the highest risk for cardiovascular and/or cerebrovascular deaths (HR 1.56, 95% CI 1.08–2.25).(12)

# 4. Conclusion

Whilst most patients are managed in primary care, the majority of the trials included in the identified systematic reviews recruited participants with more severe disease, and from secondary care or teriary care.

The included reviews found that although several self-management intervention components were described in the studies, there was no evidence to suggest that one component was more effective than the others. Self-management support interventions are multicomponent, and should be tailored to the patients' needs. Core components included provision of COPD education; strategies to support adjustment to life with COPD, and to support treatment adherence; tailored support to encourage physical activities; written action plans for acute exacerbations; and disease-specific training to monitor and control COPD. Community-based interventions to support self-management for COPD in primary care were not found to be effective in improving HRQol or in reducing anxiety or depression. There is some evidence to suggest that nurse-led self-management support interventions improved self-efficacy, anxiety and unscheduled physician visits. However, evidence was lacking on the effectiveness of nurse-led self-management interventions in improving HRQoL and reducing costs.

Supportive interventions including self-management support and advice on smoking-cessation from primary healthcare professionals may help smokers to quit, and enhance the success of smoking cessation attempts. There was sufficient evidence that smokers with COPD who received a combination of behavioural support and medication (e.g. nicotine replacement therapy, bupropion, and varenicline) were more likely to quit compared to those who only received behavioural support. Nicotine sublingual tablet and varenicline were found to significantly improve quit rates

compared to nortiptyline. Further, buproprion was found to be more effective than placebo in improving quit rates.

Self-management interventions should be based on individualised assessment of COPD to improve HRQoL, reduce the risk of exacerbations, mortality and costs. Self-management interventions that include written action plans for acute exacerbations of COPD symptoms significantly improved HRQoL and reduced respiratory-related hospital admissions. Written action plans that included a smoking cessation programme were found to be effective in further improving HRQoL. However, no statistically significant difference in the number of all-cause hospitalisation days, emergency department visits, general practitioner visits, and dyspnoea scores were reported with self-management interventions.

Inhalation technique education significantly improved HRQoL among patients with COPD, particularly for enough breathing out before inhalation and holding their breath after inhalation. Outcomes such as number of exacerbations were not reported. The results were based on a single small study conducted in South Korea. There is limited evidence to suggest that pulmonary rehabilitation including exercise programmes in primary care are effective in improving patient outcomes. Majority of the patients with COPD in primary care present with mild or moderate forms of the disease, and may therefore not have access to secondary care pulmonary rehabilitation programmes. In resource-scarce settings, it may not be feasible to arrange for physical exercise programmes in primary care, and therefore integrated care may be an option. Once patients with COPD achieve an increased level of physical activity, support from a primary health care professional may be required to maintain the levels. Very limited evidence from a single trial in Pakistan suggested that a multicomponent integrated care package significantly improved outcomes related to lung function, mortality, treatment adherence, COPD control, and smoking cessation rates. However, the cost of the programme was not examined in this study. Another trial from the Netherlands reported that an integrated care programme was not cost-effective in primary care, when compared to usual care.

Pharmacological management for COPD patients is used to control symptoms, reduce frequency and severity of exacerbations, improve HRQoL and exercise tolerance. Inhaled bronchodilators (β2 agonists) can be beneficial in the symptomatic management of COPD in primary care. A combination of tiotropium (LAMA)/olodaterol (LABA), with or without exercise training, significantly improved exercise endurance test at 8 weeks compared to placebo. Salmeterol (LABA) plus tiotropium (LAMA) therapy did not significantly improve rates of COPD exacerbations but was found to improve lung function, HRQoL, and hospitalisation rates in patients with moderate to severe COPD. A combination treatment with formoterol (LABA) plus tiotropium (LAMA) was found to provide greater therapeutic benefits than tiotropium alone, particularly in relation to lung function.

Treatment with extrafine fixed triple therapy was more effective compared with LAMA monotherapy and tiotropium on the number of moderate-to-severe exacerbations (20% reduction), FEV1, and HRQoL. Similarly, treatment with extrafine inhaled corticosteroid-containing triple therapy regimen of BDP/FF/G was more effective in reducing the rate of moderate-to-severe COPD exacerbations than the dual bronchodilator combination of IND/GLY. Overall, single inhaler triple therapy for COPD patients can significantly reduce the rates of moderate or severe exacerbations of COPD, as well as improve lung function and HRQoL compared with LABA/LAMA or ICS/LABA dual therapy.

The use of tiotropium Respimat® is associated with an increased risk of mortality compared with tiotropium HandiHaler®. Physicians have to consider the efficacy and safety of inhaler devices with long-term tiotropium maintenance therapy.

# 5. Recommendations for future research

- Further studies should include cost analyses for definitive conclusions on the effects of various strategies in primary health care settings.
- Trials with a larger sample size, longer follow ups, and tailored intervention content and delivery methods would be beneficial to address the knowledge gaps relevant to primary health care settings.

# 6. Strengths and limitations of the review

***Strengths***

- A comprehensive search strategy was used to identify SRs and primary studies of interest.
- A valid tool (AMSTAR-2 checklist) was used to assess the methodological quality of the included SRs.

***Limitations***

- The SRs were identified based on searches in only four databases. It is possible that this approach may have resulted in not identifying some other eligible SRs. However, to address this limitation, an additional search for primary studies was conducted, where reviews were lacking for interventions of interest.
- The search was restricted to the last five years and non-English language SRs were excluded; which may have resulted in exclusion of some relevant reviews and studies.

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# 8. Appendices

## Appendix 1: Search Strategies

**PubMed**

| No. | Search terms | Number of hits |
|---|---|---|
| #1 | Pulmonary Disease, Chronic Obstructive[MeSH] OR "chronic obstructive pulmonary disease"[tw] OR "chronic obstructive airway disease"[tw] OR "COPD"[tw] OR "COAD"[tw] OR "chronic obstructive lung disease"[tw] OR "chronic airflow obstruction*"[tw] OR "chronic airway obstruction"[tw] OR "chronic obstructive bronchitis"[tw] OR "chronic obstructive bronchopulmonary disease"[tw] OR "chronic obstructive lung disorder"[tw] OR "chronic obstructive pulmonary disorder"[tw] OR "chronic obstructive respiratory disease"[tw] | 86144 |
| #2 | "self-management"[MeSH] OR "self-management"[tw] OR "self management"[tw] OR "self care"[tw] OR "self-care"[tw] OR "pulmonary rehabilitation"[tw] OR "physical activity"[tw] OR exercise[MeSH] OR exercise[tw] OR education[MeSH] OR education[tw] OR "breathing techniques"[tw] OR "nutrition counselling"[tw] OR "drug therapy"[MeSH] OR "drug therapy"[tw] OR pharmacotherapy[tw] OR pharmacotherapies[tw] OR "drug treatment"[tw] OR "pharmacological therapy"[tw] OR "pharmacological treatment"[tw] OR "oxygen therapy"[tw] OR "inhaler techniques"[tw] OR ((inhaled[tw] OR inhaler[tw]) AND ("bronchodilator agents"[MeSH] OR "bronchodilator agents"[tw] OR bronchodilators[tw] OR "bronchial dilating agents"[tw] OR "broncholytic agents"[tw] OR "bronchodilating agent*"[tw] OR bronchodilatant[tw] OR "bronchospasmolytic agent"[tw] OR corticosteroids[tw] OR "adrenal cortex hormones"[MeSH] OR "adrenal cortex hormones"[tw] OR corticoids[tw] "adrenal steroid hormone"[tw])) OR "influenza vaccination"[tw] OR "integrated care"[tw] OR "peer support"[tw] OR "peer group" OR telemedicine[MeSH] OR telemedicine[tw] OR telehealth[tw] OR mhealth[tw] OR eHealth[tw] OR e-Health[tw] OR "financial incentives"[tw] OR "financial rewards"[tw] | 4530789 |
| #3 | "quality of health care"[MeSH] OR "quality of health care"[tw] OR "quality of healthcare"[tw] OR "health care quality"[tw] OR "healthcare quality"[tw] OR "quality of care"[tw] OR "health care evaluation"[tw] | 6847265 |
| #4 | "systematic review*"[tw] OR "meta-analysis as topic"[MeSH] OR "meta analy*"[tw] OR "metaanaly*"[tw] OR "systematic overview*"[tw] OR "review literature as topic"[MeSH] | 197095 |
| #5 | #1 AND #2 AND #3 AND #4 AND Filters: Published in the last 5 years; Humans; English | **256** |

**Cochrane Library**

| No. | Search terms | Number of hits |
|---|---|---|
| #1 | "chronic obstructive lung disease" OR "chronic obstructive lung disease" OR "chronic obstructive pulmonary disease" OR "chronic obstructive airway disease" OR "COPD" OR "COAD" OR "chronic airflow obstruction*" OR "chronic airway obstruction" OR "chronic obstructive bronchitis" OR "chronic obstructive bronchopulmonary disease" OR "chronic obstructive lung disorder" OR "chronic obstructive pulmonary disorder" OR "chronic obstructive respiratory disease" | 19981 |
| #2 | "self-management" OR "pulmonary rehabilitation" OR "physical activity" OR exercise OR education OR "breathing techniques" OR "nutrition counselling" OR "drug therapy" OR pharmacotherapy OR pharmacotherapies OR "drug treatment" OR "pharmacological therapy" OR "pharmacological treatment" OR "oxygen therapy" OR "inhaler techniques" OR ((inhaled OR inhaler) AND ("bronchodilating agent*" OR "bronchodilator agents" OR bronchodilators OR bronchodilators OR "bronchial dilating agents" OR "broncholytic agents" OR bronchodilatant OR "bronchospasmolytic agent" OR "adrenal cortex hormones" OR corticoids OR corticosteroids OR "adrenal steroid hormone")) OR "influenza vaccination" OR "integrated care" OR "peer support" OR "peer group" OR telehealth OR telemedicine OR eHealth OR e-Health OR mhealth OR "financial incentives" OR "financial rewards" | 535662 |
| #3 | "health care quality" OR "health care quality" OR "healthcare quality" OR "quality of care" OR "quality of healthcare" OR "quality of healthcare" OR "health care evaluation" | 7884 |
| #4 | #1 AND #2 AND #3 AND Filters: Systematic reviews; Published in the last 5 years | **21** |

**EMBASE**

| No. | Search terms | Number of hits |
|---|---|---|
| #1 | "chronic obstructive lung disease"/de OR "chronic obstructive lung disease" OR "chronic obstructive pulmonary disease" OR "chronic obstructive airway disease" OR "COPD" OR "COAD" OR "chronic airflow obstruction*" OR "chronic airway obstruction" OR "chronic obstructive bronchitis" OR "chronic obstructive bronchopulmonary disease" OR "chronic obstructive lung disorder" OR "chronic obstructive pulmonary disorder" OR "chronic obstructive respiratory disease" | 158687 |
| #2 | "self-management" OR "pulmonary rehabilitation" OR "physical activity"/de OR "physical activity" OR exercise OR education/de OR education OR "breathing techniques" OR "nutrition counselling" OR "drug therapy"/de OR "drug therapy" OR pharmacotherapy OR pharmacotherapies OR "drug treatment" OR "pharmacological therapy" OR "pharmacological treatment" OR "oxygen therapy" OR "inhaler techniques" OR ((inhaled OR inhaler) AND ("bronchodilating agent"/de OR "bronchodilating agent*" OR "bronchodilator agents" OR bronchodilators OR "inhaled bronchodilators" OR "bronchial dilating agents" OR "broncholytic agents" OR bronchodilatant OR "bronchospasmolytic agent" OR "adrenal cortex hormones" OR | 6871190 |

| | | |
|---|---|---|
| | corticoids OR corticosteroids/de OR corticosteroids OR "adrenal steroid hormone")) OR "influenza vaccination" OR "integrated care" OR "peer support" OR "peer group"/de OR "peer group" OR telehealth/de OR telehealth OR telemedicine OR eHealth OR e-Health OR mhealth OR "financial incentives" OR "financial rewards" | |
| #3 | "health care quality"/de OR "health care quality" OR "healthcare quality" OR "quality of care" OR "quality of healthcare" OR "quality of healthcare" OR "health care evaluation" | 279792 |
| #4 | "systematic review"/de OR "systematic review*" OR "meta analy*" OR metaanaly* OR "meta-analysis" OR "systematic overview*" | 469662 |
| #5 | #1 AND #2 AND #3 AND #4 AND [embase]/lim NOT [medline]/lim AND [humans]/lim AND [2015-2020]/py AND [english]/lim | **10** |

Total number of hits (SRs) from three databases = **287**

**Health Systems Evidence**

| No. | Search terms | Number of hits |
|---|---|---|
| #1 | (("chronic obstructive lung disease" OR "chronic obstructive lung disease" OR "chronic obstructive pulmonary disease" OR "chronic obstructive airway disease" OR "COPD" OR "COAD" OR "chronic airflow obstruction*" OR "chronic airway obstruction" OR "chronic obstructive bronchitis" OR "chronic obstructive bronchopulmonary disease" OR "chronic obstructive lung disorder" OR "chronic obstructive pulmonary disorder" OR "chronic obstructive respiratory disease") AND ("health care quality" OR "health care quality" OR "healthcare quality" OR "quality of care" OR "quality of healthcare" OR "quality of healthcare" OR "health care evaluation")) | **0** |

## Appendix 2: Search Strategies for primary studies

**PubMed**

| No. | Search terms | Number of hits |
|---|---|---|
| #1 | Pulmonary Disease, Chronic Obstructive[MeSH] OR "chronic obstructive pulmonary disease"[tw] OR "chronic obstructive airway disease"[tw] OR "COPD"[tw] OR "COAD"[tw] OR "chronic obstructive lung disease"[tw] OR "chronic airflow obstruction*"[tw] OR "chronic airway obstruction"[tw] OR "chronic obstructive bronchitis"[tw] OR "chronic obstructive bronchopulmonary disease"[tw] OR "chronic obstructive lung disorder"[tw] OR "chronic obstructive pulmonary disorder"[tw] OR "chronic obstructive respiratory disease"[tw] | 87024 |

| | | |
|---|---|---|
| #2 | "pulmonary rehabilitation"[tw] OR "physical activity"[tw] OR exercise[MeSH] OR exercise[tw] OR education[MeSH] OR education[tw] OR "breathing techniques"[tw] OR "nutrition counselling"[tw] OR "drug therapy"[MeSH] OR "drug therapy"[tw] OR pharmacotherapy[tw] OR pharmacotherapies[tw] OR "drug treatment"[tw] OR "pharmacological therapy"[tw] OR "pharmacological treatment"[tw] OR "oxygen therapy"[tw] OR "inhaler techniques"[tw] OR ((inhaled[tw] OR inhaler[tw]) AND ("bronchodilator agents"[MeSH] OR "bronchodilator agents"[tw] OR bronchodilators[tw] OR "bronchial dilating agents"[tw] OR "broncholytic agents"[tw] OR "bronchodilating agent*"[tw] OR bronchodilatant[tw] OR "bronchospasmolytic agent"[tw] OR corticosteroids[tw] OR "adrenal cortex hormones"[MeSH] OR "adrenal cortex hormones"[tw] OR corticoids[tw] "adrenal steroid hormone"[tw])) OR "influenza vaccination"[tw] OR "integrated care"[tw] OR "peer support"[tw] OR "peer group" OR telemedicine[MeSH] OR telemedicine[tw] OR telehealth[tw] OR mhealth[tw] OR eHealth[tw] OR e-Health[tw] OR "financial incentives"[tw] OR "financial rewards"[tw] | 876345 |
| #3 | "quality of health care"[MeSH] OR "quality of health care"[tw] OR "quality of healthcare"[tw] OR "health care quality"[tw] OR "healthcare quality"[tw] OR "quality of care"[tw] OR "health care evaluation"[tw] | 1462472 |
| #4 | "randomized controlled trial*"[tw] OR "randomized controlled trials as topic"[MeSH] OR "clinical trial*"[tw] OR "randomised controlled stud*"[tw] OR "randomized controlled stud*"[tw] OR "randomised controlled trial*"[tw] OR "non-randomized controlled trials as topic"[MeSH] OR "quasi-experimental stud*"[tw] OR "evaluation stud*"[tw] OR "program evaluation"[tw] OR "pretest-posttest"[tw] OR "non-randomized"[tw] OR "non-randomised"[tw] OR nonrandomized[tw] OR nonrandomised[tw] OR "controlled before-after studies"[tw] OR "interrupted time series studies"[tw] OR "repeated measures studies"[tw] | 377657 |
| #5 | "primary health care"[tw] OR "primary health care"[tw] OR "primary healthcare"[tw] OR "primary care"[tw] OR "first line care"[tw] OR "general practice"[tw] | 200039 |
| #6 | #1 AND #2 AND #3 AND #4 AND #5 AND Filters: Published in the last 5 years; Humans; English | **58** |

**Cochrane Library**

| No. | Search terms | Number of hits |
|---|---|---|
| #1 | "chronic obstructive lung disease" OR "chronic obstructive lung disease" OR "chronic obstructive pulmonary disease" OR "chronic obstructive airway disease" OR "COPD" OR "COAD" OR "chronic airflow obstruction*" OR "chronic airway obstruction" OR "chronic obstructive bronchitis" OR "chronic obstructive bronchopulmonary disease" OR "chronic obstructive lung disorder" OR "chronic obstructive pulmonary disorder" OR "chronic obstructive respiratory disease" | 19688 |
| #2 | "pulmonary rehabilitation" OR "physical activity" OR exercise OR education OR "breathing techniques" OR "nutrition counselling" OR "drug therapy" OR pharmacotherapy OR pharmacotherapies OR "drug treatment" OR | 537300 |

| | | |
|---|---|---|
| | "pharmacological therapy" OR "pharmacological treatment" OR "oxygen therapy" OR "inhaler techniques" OR ((inhaled OR inhaler) AND ("bronchodilating agent*" OR "bronchodilator agents" OR bronchodilators OR bronchodilators OR "bronchial dilating agents" OR "broncholytic agents" OR bronchodilatant OR "bronchospasmolytic agent" OR "adrenal cortex hormones" OR corticoids OR corticosteroids OR "adrenal steroid hormone")) OR "influenza vaccination" OR "integrated care" OR "peer support" OR "peer group" OR telehealth OR telemedicine OR eHealth OR e-Health OR mhealth OR "financial incentives" OR "financial rewards" | |
| #3 | "health care quality" OR "health care quality" OR "healthcare quality" OR "quality of care" OR "quality of healthcare" OR "quality of healthcare" OR "health care evaluation" | 7917 |
| #4 | "primary health care" OR "primary healthcare" OR "primary care" OR "first line care" OR "general practice" | 27624 |
| #4 | #1 AND #2 AND #3 AND #4 AND Filters: RCTs; Published in the last 5 years | **10** |

**EMBASE**

| No. | Search terms | Number of hits |
|---|---|---|
| #1 | "chronic obstructive lung disease"/de OR "chronic obstructive lung disease" OR "chronic obstructive pulmonary disease" OR "chronic obstructive airway disease" OR "COPD" OR "COAD" OR "chronic airflow obstruction*" OR "chronic airway obstruction" OR "chronic obstructive bronchitis" OR "chronic obstructive bronchopulmonary disease" OR "chronic obstructive lung disorder" OR "chronic obstructive pulmonary disorder" OR "chronic obstructive respiratory disease" | 160506 |
| #2 | "pulmonary rehabilitation" OR "physical activity"/de OR "physical activity" OR exercise OR education/de OR education OR "breathing techniques" OR "nutrition counselling" OR "drug therapy"/de OR "drug therapy" OR pharmacotherapy OR pharmacotherapies OR "drug treatment" OR "pharmacological therapy" OR "pharmacological treatment" OR "oxygen therapy" OR "inhaler techniques" OR ((inhaled OR inhaler) AND ("bronchodilating agent"/de OR "bronchodilating agent*" OR "bronchodilator agents" OR bronchodilators OR "inhaled bronchodilators" OR "bronchial dilating agents" OR "broncholytic agents" OR bronchodilatant OR "bronchospasmolytic agent" OR "adrenal cortex hormones" OR corticoids OR corticosteroids/de OR corticosteroids OR "adrenal steroid hormone")) OR "influenza vaccination" OR "integrated care" OR "peer support" OR "peer group"/de OR "peer group" OR telehealth/de OR telehealth OR telemedicine OR eHealth OR e-Health OR mhealth OR "financial incentives" OR "financial rewards" | 6925832 |
| #3 | "health care quality"/de OR "health care quality" OR "healthcare quality" OR "quality of care" OR "quality of healthcare" OR "quality of healthcare" OR "health care evaluation" | 281704 |
| #4 | "randomized controlled trial"/de OR "randomized controlled trial*" OR "randomised controlled trial*" OR "randomised controlled stud*" OR "randomized controlled stud*" OR "controlled clinical trial" OR "quasi- | 1288259 |

| | | |
|---|---|---|
| | experimental study"/de OR "quasi experimental stud*" OR "evaluation stud*" OR "program evaluation" OR "pretest-posttest" OR "non-randomized" OR "non-randomised" OR nonrandomized OR nonrandomised OR "controlled before-after studies" OR "interrupted time series studies" OR "repeated measures studies" | |
| #5 | "primary health care"/de OR "primary health care" OR "primary healthcare" OR "primary care" OR "first line care" OR "general practice" | 383956 |
| #6 | #1 AND #2 AND #3 AND #4 AND #5 AND [embase]/lim NOT [medline]/lim AND [humans]/lim AND [2015-2020]/py AND [english]/lim | **4** |

Total number of hits (SRs) from three databases =

**Health Systems Evidence**

| No. | Search terms | Number of hits |
|---|---|---|
| #1 | (("chronic obstructive lung disease" OR "chronic obstructive lung disease" OR "chronic obstructive pulmonary disease" OR "chronic obstructive airway disease" OR "COPD" OR "COAD" OR "chronic airflow obstruction*" OR "chronic airway obstruction" OR "chronic obstructive bronchitis" OR "chronic obstructive bronchopulmonary disease" OR "chronic obstructive lung disorder" OR "chronic obstructive pulmonary disorder" OR "chronic obstructive respiratory disease") AND ("health care quality" OR "health care quality" OR "healthcare quality" OR "quality of care" OR "quality of healthcare" OR "quality of healthcare" OR "health care evaluation")) | **0** |

## Appendix 3: Description of included systematic reviews

| Review citation details | Objective/focus of the review | Review and participants' characteristics | Interventions & outcome measure(s) | Brief findings |
|---|---|---|---|---|
| Baker and Fatoye 2017 | To synthesise the evidence for the clinical effectiveness of self-management interventions delivered by nurses in the community for patients with COPD.<br>To assess the cost-effectiveness of nurse-led, community based self-management programmes for patients with COPD in terms of reduction in health service use in the long-term. | 20 RCTs from 26 studies, which were conducted in 14 different countries in Europe, North America, Australasia and East Asia. The sample size in the RCTs ranged from 52 to 464 Participants, with a total of 3384 patients included in the 20 studies.<br>Mean age of participants was across the RCTs was 58–73 years. Gender distribution was variable across studies (18 to 97% males). Follow-up length varied among studies, ranging from three to 24 months. | Majority of the studies included specialist respiratory nurses, and only one study included community health nurse. Four other studies included nurses trained in the intervention. The self-management components examined in various studies included information about COPD, symptom management, lifestyle, management of psychological consequences, professional support and communication. Level of support through planned contacts varied between two 20-min telephone calls. The delivery modes of self-management interventions varied; mostly including at least one face-to-face contact with a nurse, and in a few studies entirely via telephone contact. | Five studies reported statistically significant and clinically relevant improvements in health related QoL in the self-management group when compared to usual care during follow up. However, nine other studies reported no effect.<br>Seven studies reported on COPD-specific admissions, with three trials reporting a statistically significant reduction in the rate of all-cause hospitalisations in the 12 months post-intervention in the self-management group when compared to usual care. Three other studies found no significant differences in the admission rates. Only one out of eight studies reporting on COPD related hospital admissions found a statistically significant reduction in hospitalisation rate in 12 months among intervention group patients. Three out of six studies reported significantly lower numbers of all-cause emergency department visits in the intervention group.<br>Three out of five studies reported significant differences between groups with results favouring the self- |

| Review citation details | Objective/focus of the review | Review and participants' characteristics | Interventions & outcome measure(s) | Brief findings |
|---|---|---|---|---|
| | | | Outcomes measured: HRQoL, use of health care resources, self-efficacy, satisfaction, and economic outcomes | management group on the frequency of unscheduled all-cause physician visits.<br>Six out of 10 studies reported significant improvements in self-efficacy in the intervention group.<br>No significant between differences in satisfaction and frequency of exacerbations were reported in five and six studies respectively.<br>Two out of four studies reported that compared to usual care, the cost of the self-management programme exceeded savings in healthcare utilisation. |
| Dahl and Kaplan 2016 | To summarise and evaluate the efficacy and safety of tiotropium Respimat® and tiotropium HandiHaler® in patients with COPD | 22 RCTs included in the review, but only two RCTs reported on data from a Dutch integrated primary care database were relevant to PHC.<br>Total population of 11,287, including 24,522 episodes of tiotropium use. Patients aged ⩾40 years were included, with ⩾1 year of follow-up. | Tiotropium Respimat® and tiotropium HandiHaler®, once-daily licensed doses of 5 and 18 µg, respectively.<br><br>Outcomes measured: safety in terms of mortality, both all-cause and cardiovascular-related. | Use of tiotropium Respimat® (HR 1.27, 95% CI 1.03–1.57) was associated with an almost 30% increased risk of mortality compared with tiotropium HandiHaler®, with the highest risk for cardiovascular and/or cerebrovascular death (HR 1.56, 95% CI 1.08–2.25). |
| Dineen-Griffin et al 2019 | To summarise the evidence of effectiveness for self-management support interventions | 58 RCTs predominantly from the United Kingdom (UK) and USA. 12 RCTs included patients with COPD. Settings | Interventions were delivered mostly by general practitioners or nurses specialised in respiratory | No significant changes reported in clinical outcomes, including the frequency of use of antibiotic courses and oral corticosteroids over 12 months. |

| Review citation details | Objective/focus of the review | Review and participants' characteristics | Interventions & outcome measure(s) | Brief findings |
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| | delivered face-to-face in primary care practice | included general practice, primary care clinics and community pharmacies. Other participants' characteristics not reported clearly. | health. Self-management intervention components included support, education, training, and provision of written action plans.<br><br>Outcomes measured: clinical (changes in PEF, courses of antibiotics, oral corticosteroids and frequency of exacerbations), physical, social and psychological functioning and changes in HRQoL, and self-efficacy. | Compared with baseline measures, disease knowledge score (Bristol COPD Knowledge Questionnaire) significantly increased from 27.6 ± 8.7 to 36.5 ± 7.7 points in the intervention group, compared to the unchanged score in the control group (29.6 ± 7.9 to 30.2 ± 7.2). Use of disease specific measures showed positive changes in HRQoL (CCQ). No statistically significant changes in self-efficacy (CSES) scores were reported at 24 months. |
| Jolly et al 2018 | To evaluate whether self-management interventions in COPD patients recruited from primary care lead to improved health-related quality of life, improved health outcomes and reduced health care utilisation | 12 RCTs, with four trials carried out in the UK, two in Australia and one each in The Netherlands, Sweden, Germany, US, China and New Zealand. Sample size in the trials ranged from 5214 to 82179 participants, including a total of 10,647 participants.<br>The mean age of participants ranged from 61 to 73 years and 48.1% of the participants were male. | Interventions' duration ranged from one month to at least 2 years across different studies. Interventions were delivered by various health care professionals (GPs, nurse practitioners, medical assistants, respiratory physician nurses, health psychologists and trained peers). The content of the interventions focussed mainly on exacerbation management and responding to participants self-management queries, | Meta-analyses showed that there was no difference in HRQoL measured by the SGRQ at final follow-up (SGRQ total score −0.29, 95% CI −2.09, 1.51).<br>The meta-analysis results for the CRQ domains of dyspnoea, emotions, fatigue and mastery favoured the self-management interventions; however, were not statistically significant.<br>Seven of the trials reported health care utilisation outcomes with most reporting no statistically significant differences at follow-up in emergency department visits and hospital admissions. |

| Review citation details | Objective/focus of the review | Review and participants' characteristics | Interventions & outcome measure(s) | Brief findings |
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| | | | information about educational materials, physical activity advice, smoking cessation, breathing and medication management.<br><br>Outcomes measured: HRQoL; anxiety and depression, exercise capacity, lung function, dyspnoea and health care utilisation. | Similarly, meta-analyses results showed that HADS anxiety and depression were not significantly different between the intervention and control groups. |
| Lai et al 2019 | To compare the effects of single inhaler triple therapy comprised of inhaled corticosteroids (ICSs), LABAs, and LAMAs with dual therapies comprised of either LABA/LAMA, ICS/LABA or separate ICS/LABA plus LAMA triple therapy | 7 RCTs included, but only two trials were relevant to PHC setting. Both trials were large, multicentred and conducted mainly across countries in Europe (Argentina, Belarus, Bulgaria, Croatia, Germany, Hungary, Italy, Mexico, Poland, Romania, Russia, Slovakia, Turkey, the UK, and Ukraine). A mixture of settings mainly including secondary care, followed by primary care. Total number of participants included in the two trials was 4223. | Extrafine (beclomethasone dipropionate, formoterol fumarate, and glycopyrronium (BDP/FF/G)) inhaled triple therapy versus dual bronchodilator therapy (indacaterol plus glycopyrronium (IND/GLY)). Single inhaler extrafine fixed triple therapy (beclomethasone dipropionate, formoterol fumarate, and glycopyrronium bromide with tiotropium) versus open triple LAMA therapy (beclomethasone dipropionate, formoterol fumarate plus tiotropium). | The rate of moderate-to-severe COPD exacerbations was significantly lower with BDP/FF/G than with IND/GLY (rate ratio of 0·848, 95% CI 0·723–0·995). The rates of moderate-to-severe COPD exacerbations were 0·50 per patient per year (95% CI 0·45 to 0·57) for patients receiving BDP/FF/G and 0·59 (0·53 to 0·67) per patient per year for those receiving IND/GLY.<br><br>The rates of moderate-to-severe COPD exacerbations were 0·46 per patient per year for fixed triple compared to 0·57 for tiotropium, and 0·45 for open triple therapy. The time to first severe exacerbation was prolonged with fixed triple compared with tiotropium (HR |

| Review citation details | Objective/focus of the review | Review and participants' characteristics | Interventions & outcome measure(s) | Brief findings |
|---|---|---|---|---|
| | | Majority of the participants were aged 55 years and above, predominantly male and were current or ex-smokers. | Outcomes measured: number of exacerbations and adverse effects | 0·70, 95% CI 0·52 to 0·95); and similar for fixed triple and open triple therapies (HR 1·05, 95% CI 0·70 to 1·56).<br>The mean changes from baseline in pre-dose FEV1 at week 52 were 0·082 L (95% CI 0·065 to 0·100) for fixed triple, 0·021 L (0·003 to 0·039) for tiotropium and 0·085 L (0·061 to 0·110) for open triple. Fixed triple was associated with a greater improvement in mean SGRQ total score than tiotropium at all time points except week 26, and a similar mean change from baseline in SGRQ total score to open triple at most timepoints, with the exception of weeks 26 and 52. |
| Lenferink et al 2017 | To evaluate the efficacy of COPD-specific self-management interventions that include an action plan for exacerbations of COPD compared with usual care in terms of health-related quality of life, respiratory-related hospital admissions and other health outcomes | 22 RCTs; however, only 5 RCTs were conducted in general practices, and primary health care clinics.<br>Total number of participants included in 5 RCTs 574. The study follow up duration ranged between 3 to 24 months.<br>The mean age of the participants ranged between 57-74 years, with majority being older adults and male. | Self-management interventions included: Iterative process, self-recognition of COPD exacerbations, education regarding COPD and smoking cessation, and exercise or physical activity component.<br><br>Outcomes measured: HRQoL (SGRQ), hospitalisations, health utilisation, medication | Self-management with written action plans in one RCT showed significant and clinically relevant lower total SGRQ total scores in the self-management intervention group (HRQoL was improved by 8.2 points) when compared with the usual care group (no change). However, another RCT found no significant difference in SGRQ total score after 12 months of follow-up.<br><br>Three studies (n=394) measured |

| Review citation details | Objective/focus of the review | Review and participants' characteristics | Interventions & outcome measure(s) | Brief findings |
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| | | | use, smoking cessation plans, and exacerbations. | COPD-specific HRQoL using the CRQ. In one RCT, two of the four CRQ domains, fatigue and mastery, showed statistically significant higher scores, indicating better HRQoL, for the self-management intervention group (17.7 and 21.4, respectively) compared to usual care (15.7 and 20.7, respectively). In another RCT, CRQ dyspnoea was found to improve in both groups over time; however, only the self-management group sustained the within-group changes that exceeded the MCID of 0.5. The third RCT reported no statistically significant mean treatment difference between the self-management intervention and usual care group for the CRQ total score at 24 months of follow-up; however, more participants in the intervention group showed a clinically important improvement compared to the usual care group. Self-management interventions that included written action plans in consultation with patients showed a reduction in odds of respiratory-related hospitalisations when compared to the usual care group in two RCTs (OR 0.44, 95% CI: 0.21 to 0.95, and OR 0.41, 95% |

| Review citation details | Objective/focus of the review | Review and participants' characteristics | Interventions & outcome measure(s) | Brief findings |
|---|---|---|---|---|
| | | | | CI 0.08 to 2.19). However, in a third RCT, more respiratory-related hospitalisations were reported in the intervention group (1.1 per participant per year) compared to usual care (0.7 per participant per year).<br>No statistically significant difference in all-cause hospital admissions was reported in 2 RCTs (OR 0.54, 95% CI 0.26 to 1.09; OR 0.63, 95% CI 0.31 to 1.26).<br>In one RCT, a lower number of all-cause hospitalisation days was reported in the intervention group compared to the usual care group (3.2 versus 6.8), which was statistically non-significant.<br>However, significantly fewer respiratory-related hospitalisation days per participant per year were reported in the intervention group (from 2.8 to 1.1) compared to a significant increase for the usual care group (from 3.5 to 4.0 days).<br>No statistically significant difference in ED visits was reported between the intervention and usual care groups in one RCT. Five (6%) all-cause ED visits in the intervention group and seven (13.5%) visits in the usual care group after 12 months of follow-up. |

| Review citation details | Objective/focus of the review | Review and participants' characteristics | Interventions & outcome measure(s) | Brief findings |
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| | | | | One RCT reported no statistically significant difference in healthcare utilisation (GP visits) between the intervention and usual care (MD 2.60, 95% CI -0.63 to 5.83).<br>The mean number of COPD exacerbations per participant were not statistically significant (MD 0.28, 95% CI -0.45 to 1.01, n = 53), as reported in one RCT.<br>One RCT reported almost a similar number of participants who started prednisolone, antibiotics or both to manage exacerbations in the self-management group (n = 16, 11%) compared to the usual care group (n = 13, 10%) in the first year of follow-up. A higher number of exacerbations in the self-management group were managed by starting prednisolone antibiotics or both (OR 3.98, 95% CI 1.10 to 15.58), in the second year of follow-up.<br>No statistically significant differences in mortality were found between intervention and control group participants (RD 0.1229, 95% CI --0.0188 to 0.2646; RD -0.0528, 95% CI -0.1324 to 0.0268; RD -0.0105, 95% CI -0.0397 to 0.0187) in three RCTs. |

| Review citation details | Objective/focus of the review | Review and participants' characteristics | Interventions & outcome measure(s) | Brief findings |
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| | | | | In one RCT, no statistically significant changes or difference in participants' self-efficacy was reported between the intervention and control groups according to the CSES total (MD -0.17, 95% CI -0.64 to 0.30) and domain scores after 24 months of follow up. |
| Maricoto et al 2019 | To assess the effectiveness of inhaler technique education in older adults with COPD to improve clinical control and reduce disease exacerbations | Eight studies were included; however, only one study (quasi-experimental) was relevant to PHC, which was conducted in South Korea. 127 participants with COPD were included, 89% (n = 113) were men and the mean age was 67.8 ± 10.1 years. | Inhalation technique education, provided by health professionals, using (e.g., oral instructions and video education, and an action plan). Three educational visits conducted with follow-up visits held every two weeks.<br><br>Outcomes measured: Knowledge about their disease, quality of life, inhaler use technique, patients and physicians satisfaction with the education program. | QoL measured using CAT in COPD patients was significantly improved by 51.2% (n = 65/127) after education. The usage of inhaler showed statistically significant changes, particularly enough breathing out before inhalation (71.4%) and holding their breath after inhalation (70.7%) were the first two higher improving items. |
| Maqsood et al 2019 | To assess the effects of single-inhaler LABA/LAMA combinations versus placebo on clinically meaningful outcomes in | 23 RCTs included in the review; however, only one multicentre RCT relevant to PHC, with sites across Australia, New Zealand and USA. | Tiotropium (LAMA) 5 µg once daily, tiotropium + olodaterol (LABA) 5/5 µg once daily, and tiotropium + olodaterol 5/5 µg once daily with (exercise training) for 12 weeks, with or | Self-management behavior-modification (SMBM) plus tiotropium/olodaterol, with or without exercise training, significantly improved EET at Week 8 versus SMBM plus placebo (treatment ratio vs. placebo: with exercise training, 1.46; 95% confidence interval, 1.20-1.78; |

| Review citation details | Objective/focus of the review | Review and participants' characteristics | Interventions & outcome measure(s) | Brief findings |
|---|---|---|---|---|
| | patients with stable COPD. | 303 patients (200 men), aged over 60 years. | without self-management behavior-modification.<br><br>Outcomes measured: exercise endurance time and symptom limitation | without exercise training, 1.29; 95% confidence interval, 1.06-1.57). No significant increases in steps per day from baseline were observed over SMBM plus placebo at week 12 (increase of 1,098) when other therapies were added. |
| Oba et al 2018 | To compare the efficacy and safety of available formulations from four different groups of inhalers (i.e. LABA/LAMA combination, LABA/ICS combination, LAMA and LABA) in people with moderate to severe COPD. | 99 RCTs included in the review but only two RCTs were relevant to PHC, conducted in Canada and the USA. Studies were conducted in community primary care clinics and primary care centres. Total participants in two RCTs 304 and 255, with a mean age of 64 and 68 years respectively. | Tiotropium (LAMA) + salmeterol (LABA): tiotropium 18 Sg once daily using a HandiHaler + salmeterol 25 µg/puff, 2 puffs twice daily using a pressurised metered-dose inhaler using a spacer device; and tiotropium + placebo: tiotropium, 18 µg once daily, + placebo inhaler, 2 puffs twice daily.<br>Formoterol (LABA) 12 µg twice daily and tiotropium (HandiHaler) 18 µg once daily in the morning delivered via 2 separate inhalers; and Formoterol-matched placebo twice daily and tiotropium 18 µg once daily delivered via 2 separate inhalers. | The absolute risk reduction for exacerbations was −2.0 percentage points (95% CI −12.8 to 8.8 percentage points) for tiotropium plus salmeterol (LABA) compared to tiotropium plus placebo and 2.8 percentage points (95% CI −8.2 to 13.8 percentage points) for tiotropium plus fluticasone–salmeterol versus tiotropium plus placebo. Patients who received tiotropium plus placebo experienced 1.61 exacerbations per patient-year of follow-up, compared with 1.75 exacerbations per patient-year in the tiotropium plus salmeterol group and 1.37 exacerbations per patient-year in the tiotropium plus fluticasone–salmeterol group. Patients treated with tiotropium plus fluticasone–salmeterol had lower rates of severe exacerbations of COPD requiring hospitalisation compared to patients treated with tiotropium plus placebo (incidence rate |

| Review citation details | Objective/focus of the review | Review and participants' characteristics | Interventions & outcome measure(s) | Brief findings |
|---|---|---|---|---|
| | | | Outcomes measured: exacerbations, HRQoL, hospitalisations, and lung function. | ratio 0.53, 95% CI 0.33 to 0.86). All-cause hospitalisations significantly reduced in patients treated with tiotropium plus fluticasone–salmeterol compared with patients treated with tiotropium plus placebo. One year of therapy with tiotropium plus salmeterol or tiotropium plus fluticasone–salmeterol significantly improved HRQoL compared to therapy with tiotropium plus placebo. The 1-year change in total score on the SGRQ was −4.5 points in the tiotropium plus placebo group, −6.3 points in the tiotropium plus salmeterol group, and −8.6 points in the tiotropium plus fluticasone–salmeterol group.<br><br>Significantly greater improvements in the FEV(1) were reported with the combination of formoterol + tiotropium compared to tiotropium alone at all time points. The increase in FEV(1) 5 minutes after the first dose was 180 mL with the combination versus 40 mL with tiotropium alone. At the endpoint, FEV(1) increased 340 mL with combination versus 170 mL with tiotropium. Significantly greater reductions from baseline in symptom |

| Review citation details | Objective/focus of the review | Review and participants' characteristics | Interventions & outcome measure(s) | Brief findings |
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| | | | | scores and daytime albuterol use were reported at endpoint with the combination dual therapy compared to tiotropium monotherapy. |
| Van Eerd et al 2016 | To evaluate the effectiveness of behavioural or pharmacological smoking cessation interventions, or both, in smokers with COPD | 16 trials (involving 13,123 participants, who were smokers) included in the review. Eight of the trials were conducted in primary care clinics and/or general practices.<br>Half of the studies included an equal number of male and female participants; and majority participants in the rest of the studies were male. The age range of the participants was from 48 to 66 years. | Behavioural treatments including individual counselling, combined with some form of group counselling, telephone counselling, and/or self-help/written material.<br>Pharmacological treatments (accompanied by behavioural treatments) included nicotine replacement therapy (NRT) sublingual tablet , bupropion, nortriptyline, and varenicline.<br><br>Primary outcome was continuous or prolonged abstinence over a period of ≥6 months. Secondary outcome included point prevalence abstinence rate. | In one study, the prolonged abstinence rate at six months was 4.4% (79/1814) in the behavioural-treatment group, compared to 0.2% (3/1748) in the usual-care group. The RR was 5.38 (95% CI 8.03 to 80.22) and the RD was 0.04 (95% CI 0.03 to 0.05). The point prevalence abstinence rates showed a positive effect of the behavioural-treatment group on abstinence rates from 12 to 48 months follow up.<br>In another study the participants in one behavioural-treatment group received high-intensity individual counselling and proactive telephone counselling. This group was compared with less intensive individual counselling and proactive telephone counselling. The prolonged abstinence rate at 12 months' follow-up in the group with high-intensity counselling was 10% (19/187) compared with 9% (17/183) in the group receiving less high-intensive counselling. The RR was 1.09 (95% CI 0.59 to 2.04) and the RD was 0.01 (95% CI -0.05 to 0.07). |

| Review citation details | Objective/focus of the review | Review and participants' characteristics | Interventions & outcome measure(s) | Brief findings |
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| | | | | NRT sublingual tablet, bupropion, and varenicline were found to increase the chance of quitting compared with placebo. The prolonged abstinence rates in the intervention groups ranged from 14% to 27%, compared to 5% to 9% in the placebo group. The pooled RR was 2.53 (95% CI 1.83 to 3.50) and the RD 0.10 (95% CI 0.07 to 0.14).<br>Bupropion was compared with NRT patch in one study. Prolonged abstinence rates at 12 months were 16% (5/32) in the bupropion group and 21% (8/38) in the NRT patch group with a RR of 0.74 (95% CI 0.27 to 2.05) and a RD of -0.05 (95% CI -0.23 to 0.13).<br>One study compared NRT with NRT plus bupropion. Prolonged abstinence data were not available, and 12 months' point prevalence rates were 15% (39/252) in the NRT group and 6% (18/291) in the NRT plus bupropion group (RR 2.50, 95% CI 1.47 to 4.26; RD 0.09, 95% CI 0.04 to 0.15).<br>Bupropion was compared with nortriptyline in a study. In the group using bupropion, 27% (12/44) were prolonged abstinent at six months versus 21% (11/52) in the group using |

| Review citation details | Objective/focus of the review | Review and participants' characteristics | Interventions & outcome measure(s) | Brief findings |
|---|---|---|---|---|
| | | | | nortriptyline. The RR was 1.29 (95% CI 0.63 to 2.63) and the RD was 0.06 (95% CI -0.11 to 0.23).<br>Five studies compared a combination of behavioural treatment and pharmacotherapy with usual care. The prolonged abstinence rate at 12 months' follow-up in the intervention group was 34% (1345/3923) compared to 9% in the usual care group (177/1964) (RR 3.80, 95% CI 3.28 to 4.41; and RD 0.25, 95% CI 0.23 to 0.27). The prolonged abstinence at five years' follow-up was 21% (835/3923) and in the usual-care group 5% (102/1964) (RR 4.10, 95% CI 3.36 to 5.00; and RD 0.16, 95% CI 0.14 to 0.18). |
| Yang et al 2019 | To evaluate the efficacy of pulmonary rehabilitation in patients with COPD | 17 RCTs included in the review; however, only two RCTs were relevant to PHC, which were conducted in Hong Kong and Ireland. Follow up duration in both the studies was 6 weeks and 24 months. | Community-based, structured, nurse-pulmonary rehabilitation that included aerobic exercise, ULE, and LLE.<br><br>Outcomes measured: QoL | Statistically significant differences were reported in QoL in terms of fatigue in one RCT conducted in Hong Kong (MD 0.00, 95% CI −0.26 to 0.26, but not in the other RCT conducted in Ireland (MD 0.10, 95% CI −0.91 to 1.11). However, clinically significant changes were reported in both RCTs. Similar results were reported for QoL in terms of mastery, with one RCT (MD 0.18, 95% CI −0.11 to 0.47) showing significant differences, and the other RCT showing |

| Review citation details | Objective/focus of the review | Review and participants' characteristics | Interventions & outcome measure(s) | Brief findings |
|---|---|---|---|---|
| | | | | no significant differences (MD 0.00, 95% CI −0.77 to 0.77).<br>Statistically and clinically non-significant differences were reported for both RCTs for QoL in terms of emotion (MD 0.00, 95% CI −0.26 to 0.26, and MD 0.10, 95% CI −0.91 to 1.11). |

6MWD/T - 6-minute-walk distance/test; BODE - Body mass index, airway Obstruction, Dyspnoea, Exercise capacity; C – Control group; CAT – COPD Assessment Test; CRQ - Chronic Respiratory Disease Questionnaire; CSES - COPD self-efficacy scale; CI – Confidence Interval; ED – Emergency Department; EET – Exercise endurance time; ESWT - Endurance shuttle walk test; FU – Follow Up; GP - General Practitioner; HADS - Hospital Anxiety and Depression Scale; HR – Hazard ratio; HRQoL – Health-related quality of life; HR – Hazard Ratio; I = Intervention group; IQR – InterQuartile Range; LABA - Long-acting Beta2-agonists; LAMA - Long-acting Anti-muscarinic Agents; LLE – Lower Limb Exercise; MCID - Minimal clinical important difference; OR – Odds Ratio; PEF - Peak Expiratory Flow; PHC – Primary Health Care; PR - Pulmonary rehabilitation; RCT – Randomised Controlled Trial; SD - Standard Deviation; SMD – Standardised Mean Difference; SME – Self-management Education; SGRQ - St George's Respiratory Questionnaire; QALY – Quality adjusted life years; QoL – Quality of Life; ULE – Upper Limb Exercise

## Appendix 4: List of excluded systematic reviews

1. Adolfo JR, Dhein W, Sbruzzi G. Intensity of physical exercise and its effect on functional capacity in COPD: systematic review and meta-analysis. J Bras Pneumol. 2019;45(6):e20180011.
2. Baxter DA, Shergis JL, Fazalbhoy A, Coyle ME. Muscle energy technique for chronic obstructive pulmonary disease: a systematic review. Chiropr Man Therap. 2019;27:37.
3. Bekkat-Berkani R, Wilkinson T, Buchy P, Dos Santos G, Stefanidis D, Devaster JM, et al. Seasonal influenza vaccination in patients with COPD: a systematic literature review. BMC Pulm Med. 2017;17(1):79.
4. Calzetta L, Ora J, Cavalli F, Rogliani P, O'Donnell DE, Cazzola M. Impact of LABA/LAMA combination on exercise endurance and lung hyperinflation in COPD: A pair-wise and network meta-analysis. Respir Med. 2017;129:189-98.
5. Calzetta L, Rogliani P, Matera MG, Cazzola M. A Systematic Review With Meta-Analysis of Dual Bronchodilation With LAMA/LABA for the Treatment of Stable COPD. Chest. 2016;149(5):1181-96.
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## Appendix 5: Description of included primary studies

| Review citation details | Objective/focus of the study | Study and participants' characteristics | Interventions & outcome measure(s) | Brief findings |
|---|---|---|---|---|
| Boland et al 2015 | To assess the cost-effectiveness of a COPD-disease management (COPD-DM) programme in primary care, called RECODE | A cluster-RCT conducted in The Netherlands, including 40 clusters of primary care teams randomised to the COPD-DM programme or usual care and including a total of 10,086 participants.<br>The mean age of participants in the intervention group was 68.2±11.3 years, and in the usual care group was 68.4±11.1 years. Majority of the participants were male, with more than half of the total participants being former smokers. | The COPD-DM programme included education on proper diagnosis, optimising medication adherence, motivational interviewing, smoking cessation counselling, applying self-management plans including early recognition and treatment of exacerbations, physical (re)activation and nutritional support.<br><br>Outcomes measured: Costs related to costs per QALYs, costs per additional patient with an MCID on the CCQ; costs per additional patient with an MCID on the SGRQ and costs per exacerbation prevented. | The number of QALYs was significantly lower (0.04) in the intervention group compared to the usual care group while there was no significant difference in the percentage of patients with a MCID on the CCQ, over a 2-year period.<br>The costs per patient were significantly higher in the intervention group compared to the usual care group by €408 from the healthcare perspective, over a 12-month period. |

| Review citation details | Objective/focus of the study | Study and participants' characteristics | Interventions & outcome measure(s) | Brief findings |
|---|---|---|---|---|
| Chaplin et al 2017 | To assess the effectiveness and feasibility of an interactive web-based PR programme compared to conventional PR | The RCT was conducted in the UK, with participants recruited from primary care and community rehabilitation services. Total number of participants 103. Mean age of the participants in the intervention group 66.4±10.1 years, and in the conventional PR group was 66.1±8.1 years. Majority of the participants were male (more than 60%). | Participants in the intervention group were given a web-based programme to work through the website, exercising and recording their progress as well as reading educational material. Conventional PR included twice weekly, 2 hourly sessions (an hour for exercise training and an hour for education).<br><br>Outcomes measured: measures of exercise capacity; QoL; recruitment rates; and patient preference. | A statistically significant improvement was reported within each group in the ESWT (intervention group: mean change 189±211.1; conventional PR: mean change 184.5 ±247.4) and CRQ-D (intervention group: mean change 0.7±1.2; conventional PR: mean change 0.8±1.0). No significant differences reported between the groups in any clinical outcome. All outcome measures used were found to be feasible to administer. |
| Coultas et al 2016 | To assess the effectiveness of a behavioral intervention to increase daily physical activity and improve health-related quality of life and functional performance | RCT conducted in USA including 305 participants with COPD in primary care and pulmonary clinics. Participants aged 45 years and above were eligible for pulmonary rehabilitation. | All patients received self-management education during a 6-week period, with the intervention group subsequently, receiving behavioural intervention delivered over 20 weeks. | Overall, for CRQ-D (-0.03) and 6MWD (-13.6) at 18 months, there were no statistical or clinically significant differences between the usual care and intervention groups. Further, there was little change for CRQ-D at 18 months compared with baseline for either the usual care group (20.09) or the intervention group (20.03), with no difference between groups. |

| Review citation details | Objective/focus of the study | Study and participants' characteristics | Interventions & outcome measure(s) | Brief findings |
|---|---|---|---|---|
| | | | Outcome measures: change from baseline to 18 months for the dyspnoea domain of the self-administered CRQ and the 6MWD; self-efficacy; and hospitalisations. | There were statistically but not clinically significant declines in 6MWD over the 18 months among both groups. The average declines were 222.6 meters for the usual care group and 213.6 meters for the intervention group; however, no statistical difference between the groups. Hospitalisations for COPD exacerbations were the most common adverse event in both groups; however, there were nearly twice as frequent among those in the usual care group compared with the intervention group (49.47% vs. 28.28%), which was significant. |
| Khan et al 2019 | To assess the effectiveness of integrated care for COPD delivered at public healthcare facilities | Cluster RCT undertaken in 30 public health facilities (23 primary and 7 secondary), across three districts of Punjab, Pakistan. 303 participants recruited, with 288 participants included in the final analysis. Mean age in the intervention group was 48.11 ± 13.89 years, and in the control group 48.47 ± 12.86 years. Majority of the participants were male (more than 70%). | The intervention group facilities received contextualised care protocols and tools, 2-day training of doctors and allied staff on full set of care tasks, and materials including inhalers and mobile phones. In addition, the facility staff were enabled to enhance COPD treatment and follow-up care.<br><br>Outcomes measured: Mean change in patient | The BODE Index improved (i.e. score reduced) in both the groups, but there was a statistically and clinically significantly greater reduction in the intervention group compared with the control group (difference -1, 95% CI = -1.5 to -0.4), from baseline and at five month follow-up visits.<br>A statistically and clinically significantly greater percentage of COPD control (difference 29 percentage points, 95% CI = 12.4 to 45.6), significantly higher quit rate among smokers (difference 32 percentage points, 95% CI = 15.4 to 48.5), and adherence (difference 40.4 percentage points, 95% CI = 24.2 to 56.7) was reported in the intervention |

| Review citation details | Objective/focus of the study | Study and participants' characteristics | Interventions & outcome measure(s) | Brief findings |
|---|---|---|---|---|
| | | | BODE index score from baseline to 6-month follow-up; COPD control; smoking status and treatment adherence. | group compared with the control group, at 6-month follow-up.<br><br>BODE index score: MD -1.67 (95% CI -2.18 to -1.16), intervention group, and MD -0.66 (95% CI -1.09 to -0.22) in the control group.<br>COPD control: 66.88% (95% CI 54.99 to 78.77), intervention group, and 38.20% (95% CI 22.35 to 54.06) in the control group.<br>Quit rate among smokers: 53.90% (34.98 to 72.82) in the intervention group, and 17.52% (7.36 to 27.69) in the control group.<br>Follow up adherence: 65.54% (52.64 to 78.44) in the intervention group, and 25.17% (14.86 to 35.47) in the control group. |
| Zakrisson et al 2016 | To assess the effectiveness of a nurse-led multidisciplinary PR programme among moderate to severe COPD patients, over a 3-year period | Quasi-experimental study design including 103 participants recruited from PHC centres and conducted in Sweden. Mean age of participants in the intervention group 67±3 years and in the control group 68±1 years. Almost equal number of male and female participants in both the groups, with comparatively less females in the control group than male participants. | Nurse-led PR programme, two hours per week over a six-week period, one hour of which was devoted to theory and the other to physical activity, and education around smoking cessation.<br><br>Outcomes measured: functional capacity (6MWT), QoL (CCQ) and exacerbation frequency. | The 6MWT improved after one year for patients (IRR 33.16, 95% CI 19.66 to 46.65), but the improvement was not sustained for three years (IRR -13.68, 95% CI -33.22 to 5.86), when the distance became shorter than at baseline. However, intervention group were generally able to walk for a greater distance compared with the controls. There was no difference in the CCQ score between the intervention and the control group (IRR 0.03, 95% CI -0.33 to 0.39). After adjustment for baseline factors, the patients exhibited an improvement of 0.24 in the CCQ score after one year (IRR -0.23, 95% CI -0.39 |

| Review citation details | Objective/focus of the study | Study and participants' characteristics | Interventions & outcome measure(s) | Brief findings |
|---|---|---|---|---|
| | | | | to -0.07]*; however, not sustained over a 3-year period (IRR -0.08, 95% CI -0.28 to 0.12). There was no significant increase in the risk of exacerbation after one year compared with baseline (IRR 0.93, 95% CI 0.65 to 1.34); however, the risk increased after three years. |

6MWD/T - 6-minute-walk distance/test; BODE - Body mass index, airway Obstruction, Dyspnoea, Exercise capacity; C – Control group; CAT – COPD Assessment Test; CRQ - Chronic Respiratory Disease Questionnaire; CSES - COPD self-efficacy scale; CI – Confidence Interval; ED – Emergency Department; EET – Exercise endurance time; ESWT - Endurance shuttle walk test; FU – Follow Up; GP - General Practitioner; HADS - Hospital Anxiety and Depression Scale; HR – Hazard ratio; HRQoL – Health-related quality of life; HR – Hazard Ratio; I = Intervention group; IQR – InterQuartile Range; LABA - Long-acting Beta2-agonists; LAMA - Long-acting Anti-muscarinic Agents; LLE – Lower Limb Exercise; MCID - Minimal clinical important difference; OR – Odds Ratio; PEF - Peak Expiratory Flow; PHC – Primary Health Care; PR - Pulmonary rehabilitation; RCT – Randomised Controlled Trial; SD - Standard Deviation; SMD – Standardised Mean Difference; SME – Self-management Education; SGRQ - St George's Respiratory Questionnaire; QALY – Quality adjusted life years; QoL – Quality of Life; ULE – Upper Limb Exercise

## Appendix 6: Critical appraisal results of included systematic reviews assessed using the AMSTAR-2 checklist (see Appendix 7)

| Citation | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q9 | Q10 | Q11 | Q12 | Q13 | Q14 | Q15 | Q16 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baker and Fatoye 2017 | Y | PY | Y | PY | Y | Y | Y | Y | Y | N | NMC | NMC | Y | N | NMC | Y |
| Dahl and Kaplan 2016 | N | N | N | PY | N | N | Y | Y | N | N | Y | N | N | Y | N | Y |
| Dineen-Griffin et al 2019 | Y | PY | Y | PY | Y | N | N | PY | Y | N | NMC | NMC | Y | Y | NMC | N |
| Jolly et al 2018 | Y | PY | Y | PY | Y | Y | N | PY | PY | N | N | N | Y | Y | Y | Y |
| Lai et al 2019 | Y | N | Y | PY | Y | Y | N | PY | Y | N | NMC | NMC | Y | Y | NMC | Y |
| Lenferink et al 2017 | Y | PY | Y | PY | Y | Y | Y | Y | Y | N | Y | Y | Y | Y | Y | Y |
| Maricoto et al 2019 | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | Y | Y | Y | N | Y |
| Maqsood et al 2019 | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Oba et al 2018 | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |

| Citation | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q9 | Q10 | Q11 | Q12 | Q13 | Q14 | Q15 | Q16 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Van Eerd et al 2016 | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Yang et al 2019 | Y | N | Y | PY | Y | Y | N | PY | Y | N | Y | Y | Y | Y | N | N |

Y- Yes; N - No; PY – Partial Yes; NMC – No Meta-analysis Conducted

## Appendix 7. AMSTAR-2 Appraisal Checklist

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non- randomised studies of healthcare interventions, or both.

**1. Did the research questions and inclusion criteria for the review include the components of PICO?**

For Yes:
- ☐ Population
- ☐ Intervention
- ☐ Comparator group
- ☐ Outcome

Optional (recommended)
- ☐ Timeframe for follow-up

☐ Yes
☐ No

**2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?**

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:
- ☐ review question(s)
- ☐ a search strategy
- ☐ inclusion/exclusion criteria
- ☐ a risk of bias assessment

For Yes:
As for partial yes, plus the protocol should be registered and should also have specified:
- ☐ a meta-analysis/synthesis plan, if appropriate, *and*
- ☐ a plan for investigating causes of heterogeneity
- ☐ justification for any deviations from the protocol

☐ Yes
☐ Partial Yes
☐ No

**3. Did the review authors explain their selection of the study designs for inclusion in the review?**

For Yes, the review should satisfy ONE of the following:
- ☐ *Explanation for* including only RCTs
- ☐ OR *Explanation for* including only NRSI
- ☐ OR *Explanation for* including both RCTs and NRSI

☐ Yes
☐ No

**4. Did the review authors use a comprehensive literature search strategy?**

For Partial Yes (all the following):
- ☐ searched at least 2 databases (relevant to research question)
- ☐ provided key word and/or search strategy
- ☐ justified publication restrictions (e.g. language)

For Yes, should also have (all the following):
- ☐ searched the reference lists / bibliographies of included studies
- ☐ searched trial/study registries
- ☐ included/consulted content experts in the field
- ☐ where relevant, searched for grey literature
- ☐ conducted search within 24 months of completion of the review

☐ Yes
☐ Partial Yes
☐ No

**5. Did the review authors perform study selection in duplicate?**

For Yes, either ONE of the following:
- ☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

☐ Yes
☐ No

**6. Did the review authors perform data extraction in duplicate?**

For Yes, either ONE of the following:
- ☐ at least two reviewers achieved consensus on which data to extract from included studies
- ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

☐ Yes
☐ No

**7. Did the review authors provide a list of excluded studies and justify the exclusions?**

For Partial Yes:
- ☐ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:
- ☐ Justified the exclusion from the review of each potentially relevant study

☐ Yes
☐ Partial Yes
☐ No

**8. Did the review authors describe the included studies in adequate detail?**

For Partial Yes (ALL the following):
- ☐ described populations
- ☐ described interventions
- ☐ described comparators
- ☐ described outcomes
- ☐ described research designs

For Yes, should also have ALL the following:
- ☐ described population in detail
- ☐ described intervention in detail (including doses where relevant)
- ☐ described comparator in detail (including doses where relevant)
- ☐ described study's setting
- ☐ timeframe for follow-up

☐ Yes
☐ Partial Yes
☐ No

**9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?**

RCTs

For Partial Yes, must have assessed RoB from
- ☐ unconcealed allocation, *and*
- ☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)

For Yes, must also have assessed RoB from:
- ☐ allocation sequence that was not truly random, *and*
- ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome

☐ Yes
☐ Partial Yes
☐ No
☐ Includes only NRSI

NRSI

For Partial Yes, must have assessed RoB:
- ☐ from confounding, *and*
- ☐ from selection bias

For Yes, must also have assessed RoB:
- ☐ methods used to ascertain exposures and outcomes, *and*
- ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome

☐ Yes
☐ Partial Yes
☐ No
☐ Includes only RCTs

**10. Did the review authors report on the sources of funding for the studies included in the review?**

For Yes
- ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies

☐ Yes
☐ No

**11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?**

**RCTs**
For Yes:

- ☐ The authors justified combining the data in a meta-analysis
  - ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.
  - ☐ AND investigated the causes of any heterogeneity

☐ Yes
☐ No
☐ No meta-analysis conducted

**For NRSI**
For Yes:

- ☐ The authors justified combining the data in a meta-analysis
  - ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present
  - ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available
  - ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review

☐ Yes
☐ No
☐ No meta-analysis conducted

**12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?**

For Yes:

- ☐ included only low risk of bias RCTs
- ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.

☐ Yes
☐ No
☐ No meta-analysis conducted

**13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?**

For Yes:

- ☐ included only low risk of bias RCTs
- ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results

☐ Yes
☐ No

**14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?**

For Yes:

- ☐ There was no significant heterogeneity in the results
- ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review

☐ Yes
☐ No

**15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?**

For Yes:

- ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias

☐ Yes
☐ No
☐ No meta-analysis conducted

**16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?**

For Yes:

- ☐ The authors reported no competing interests OR
- ☐ The authors described their funding sources and how they managed potential conflicts of interest

☐ Yes
☐ No