Efficacy of supervised maintenance exercise following pulmonary rehabilitation on health care use: a systematic review and meta-analysis

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Introduction: The clinical benefit of continued supervised maintenance exercise programs following pulmonary rehabilitation in COPD remains unclear. This systematic review aimed to synthesize the available evidence on the efficacy of supervised maintenance exercise programs compared to usual care following pulmonary rehabilitation completion on health care use and mortality.

Methods: Electronic databases (MEDLINE, Embase, CINAHL, Cochrane Central Register of Controlled Trials, Web of Science, and PEDro) and trial registers (ClinicalTrials.gov and Current Controlled Trials) were searched for randomized trials comparing supervised maintenance exercise programs with usual care following pulmonary rehabilitation completion. Primary outcomes were respiratory-cause hospital admissions, exacerbations requiring treatment with antibiotics and/or systemic corticosteroids, and mortality.

Results: Eight trials (790 COPD patients) met the inclusion criteria, six providing data for meta-analysis. Continued supervised maintenance exercise compared to usual care following pulmonary rehabilitation completion significantly reduced the risk of experiencing at least one respiratory-cause hospital admission (risk ratio 0.62, 95% confidence interval [CI] 0.47–0.81, P<0.001). Meta-analyses also suggested that supervised maintenance exercise leads to a clinically important reduction in the rate of respiratory-cause hospital admissions (rate ratio 0.72, 95% CI 0.50–1.05, P=0.09), overall risk of an exacerbation (risk ratio 0.79, 95% CI 0.52–1.19, P=0.25), and mortality (risk ratio 0.57, 95% CI 0.17–1.92, P=0.37).

Conclusion: In the first systematic review of the area, current evidence demonstrates that continued supervised maintenance exercise compared to usual care following pulmonary rehabilitation reduces health care use in COPD. The variance in the quality of the evidence included in this review highlights the need for this evidence to be followed up with further high-quality randomized trials.

Keywords: pulmonary rehabilitation, health outcomes, supervised maintenance programs, hospitalization, exacerbations

Introduction

Pulmonary rehabilitation is defined as “a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors.” Pulmonary rehabilitation has well-established benefits in improving exercise capacity, health-related quality life, and psychological well-being in chronic lung conditions such as COPD. However, the clinical benefit of continued supervised maintenance exercise programs following pulmonary rehabilitation in COPD remains unclear. This systematic review aimed to synthesize the available evidence on the efficacy of supervised maintenance exercise programs compared to usual care following pulmonary rehabilitation completion on health care use and mortality.

Methods

Electronic databases (MEDLINE, Embase, CINAHL, Cochrane Central Register of Controlled Trials, Web of Science, and PEDro) and trial registers (ClinicalTrials.gov and Current Controlled Trials) were searched for randomized trials comparing supervised maintenance exercise programs with usual care following pulmonary rehabilitation completion. Primary outcomes were respiratory-cause hospital admissions, exacerbations requiring treatment with antibiotics and/or systemic corticosteroids, and mortality.

Results

Eight trials (790 COPD patients) met the inclusion criteria, six providing data for meta-analysis. Continued supervised maintenance exercise compared to usual care following pulmonary rehabilitation completion significantly reduced the risk of experiencing at least one respiratory-cause hospital admission (risk ratio 0.62, 95% confidence interval [CI] 0.47–0.81, P<0.001). Meta-analyses also suggested that supervised maintenance exercise leads to a clinically important reduction in the rate of respiratory-cause hospital admissions (rate ratio 0.72, 95% CI 0.50–1.05, P=0.09), overall risk of an exacerbation (risk ratio 0.79, 95% CI 0.52–1.19, P=0.25), and mortality (risk ratio 0.57, 95% CI 0.17–1.92, P=0.37).

Conclusion

In the first systematic review of the area, current evidence demonstrates that continued supervised maintenance exercise compared to usual care following pulmonary rehabilitation reduces health care use in COPD. The variance in the quality of the evidence included in this review highlights the need for this evidence to be followed up with further high-quality randomized trials.
as COPD.\textsuperscript{1,2} The strength of the evidence for these benefits in COPD has led to calls for an end to randomized controlled trials comparing pulmonary rehabilitation with usual care.\textsuperscript{3} However, the benefits of pulmonary rehabilitation have been shown to be short term\textsuperscript{2} with the condition of most patients returning to baseline at 12 months.\textsuperscript{4} Consequently, there is interest in exercise programs that may maintain the initial benefits of pulmonary rehabilitation.\textsuperscript{5,6}

Supervised maintenance exercise programs after pulmonary rehabilitation in COPD appear to be more effective in preserving the improvements in exercise capacity up to 6 months but show no effects with respect to health-related quality of life postrehabilitation.\textsuperscript{5,7} Exacerbations and hospital admissions are the key events in the management of COPD, but the effects of exercise, particularly supervised maintenance programs following pulmonary rehabilitation, on these outcomes have received little attention. A recent systematic review has highlighted the role of pulmonary rehabilitation in reducing hospitalizations due to COPD exacerbations.\textsuperscript{8} This supported a previous systematic review that showed a reduction in the risk of hospital readmission when completing pulmonary rehabilitation following exacerbation,\textsuperscript{9} albeit the quality of this evidence has recently been downgraded due to inconsistencies in the estimates of effect.\textsuperscript{9} There is increasing interest in assessing these outcomes in response to exercise interventions following pulmonary rehabilitation to identify if the duration of benefits from a pulmonary rehabilitation program alone can be prolonged or rather enhanced during the postrehabilitation period.\textsuperscript{8} A previous systematic review of supervised maintenance exercise programs following pulmonary rehabilitation in COPD had included studies that reported health care use; however, data were not statistically combined to quantify effect size.\textsuperscript{5} Despite the availability of new evidence in the area since this review, there remains no systematic review that has synthesized the evidence of the effects of supervised maintenance exercise training programs compared to usual care following pulmonary rehabilitation on outcomes related to health care use. Therefore, the aim of this systematic review was to collate and synthesize all of the available evidence from randomized controlled trials in order to estimate the size of the effect of supervised maintenance exercise programs following pulmonary rehabilitation on health care use.

**Methods**

The protocol for this study (CRD42016035509) was registered in advance on PROSPERO (International Prospective Register of Systematic Reviews; www.crd.york.ac.uk/PROSPERO/).

**Selection criteria**

**Participants**

Adults with a confirmed diagnosis of COPD (in line with national or international criteria, eg, British Thoracic Society, American Thoracic Society/European Respiratory Society, and Global Initiative for Chronic Obstructive Lung Disease) who had completed a pulmonary rehabilitation program.\textsuperscript{11-13}

**Intervention**

Studies were included if patients were randomized to a supervised maintenance exercise training program following pulmonary rehabilitation.

**Comparison**

The comparator was any concurrent control group who had completed pulmonary rehabilitation and returned to “usual care.”

**Outcomes**

Primary outcomes were hospital admissions (respiratory cause), exacerbations requiring treatment with antibiotics and/or systemic corticosteroids, and all-cause mortality.

Secondary outcome measures were hospital admissions (all-cause), outpatient visits, length of hospital stay (respiratory or all-cause), and general practitioner (GP) visits.

**Study design**

Studies included in this review had to have adhered to the following study designs: parallel-group randomized controlled trials (allocation at individual or cluster level or using quasi-random method) or crossover randomized controlled trials (data up to point of crossover only).

**Search strategy**

Searches were conducted to identify any relevant completed or ongoing systematic reviews using the following sources: Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and PROSPERO. Published trials were identified through searches on the following bibliographic databases: MEDLINE, Embase, CINAHL, Cochrane Central Register of Controlled Trials, Web of Science, and PEDro. Searches of ongoing trial registers, such as ClinicalTrials.gov and Current Controlled Trials, were also undertaken. Gray literature was also searched via EThOS (British Library) and Conference Proceedings Index (Web of Science Core Collection). Searches were conducted from database inception to August 2017. No limits were set on language or publication status. Search terms were structured...
around the population (eg, “Lung Diseases, Obstructive”, “COPD”), intervention (eg, “Exercise Therapy”, “exercise* N3 supervi* OR training OR maintenance OR program*”), and study type (eg, “randomised”, “randomized”, “controlled”). An example of a full search strategy for CINAHL is presented in Table S1. Database searching was supplemented by contact with study authors and research groups, forward and backward citation tracking from included studies or previous relevant reviews, with further Internet searching via Google Scholar until August 2017.

Search results were collated using EndNote (Clarivate Analytics, Philadelphia, PA, USA). Duplicate citations were removed prior to independent screening of title and abstracts according to inclusion criteria by two reviewers. Full-text articles were obtained for all studies that were unable to be excluded based on title and abstract, before further independent screening to decide on final eligibility. Discrepancies in study eligibility were resolved through discussion between reviewers.

Data extraction and quality appraisal
Data extraction took place using a modified Cochrane Data Extraction Template including elements adapted from a taxonomy form previously used in randomized controlled trials.14 Data were extracted by one reviewer and checked for accuracy by a second reviewer. List of characteristics extracted from studies is available in the Supplementary materials.

Two reviewers independently assessed the risk of bias for included studies using the Cochrane Risk of Bias Tool with the following domains: random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias.15 Each domain was classified as low, unclear, or high with the risk of bias for each study classified using the following criteria: 1) low risk of bias (all criteria were deemed low), 2) medium risk of bias (one criterion graded as high or two criteria graded as unclear), and 3) high risk of bias (more than one criterion was deemed high or more than two criteria graded unclear). Disagreements between reviewers were resolved through further discussion.

Data analysis
All analyses were performed using Review Manager Version 5.3. The primary measures of effect were treated as dichotomous data (defined as the total number of participants in each group who had been hospitalized for respiratory cause, treated for an exacerbation, or died [all-cause]) and interpreted as risk ratios. Rate ratio of hospital admissions (respiratory-cause) and exacerbations was also calculated using the incidence rate in the intervention groups divided by the incidence rate in the control groups. Secondary outcomes of hospital admissions (all-cause), GP visits (all-cause), and outpatient visits were treated as dichotomous outcomes only and were interpreted as risk ratios. Length of hospital admissions (respiratory and all-cause) were analyzed as a continuous outcome and expressed as the between-groups difference in means. All primary and secondary outcomes were analyzed using raw data provided by authors rather than mean values presented in publications. If studies reported the same outcome measures, data were combined statistically using a random-effects meta-analysis. We contacted study authors to obtain missing numerical outcome data, and in cases where studies only reported certain outcomes of health care use, we verified that no additional data were available. The generic inverse-variance random-effects model for rates of hospitalization (respiratory) and exacerbation included the (natural) logarithms of the rate ratios and the standard error of the rate ratio.15 Statistical heterogeneity was assessed by the $I^2$ value. Data were not pooled if heterogeneity was found to be moderate ($I^2>30\%$). If heterogeneity was identified, potential sources were explored. Prespecified subgroup analyses included the setting, frequency, and delivery (training level of supervisor, combined with education) of supervised maintenance exercise programs. To test the robustness of findings in primary outcome measures, planned prespecified sensitivity analyses involved the removal of studies categorized as medium or high risk of bias within the Cochrane Risk of Bias Tool.

Results
After the removal of duplicates, searches identified 3,730 records to be screened, of which 3,688 records were excluded based on title and abstract (Figure 1). Full texts were obtained for the remaining 42 records. Information on excluded texts and reasons for these can be found in Table S2. Ten records (eight studies) met the inclusion criteria (Table 1), of which six studies had data available for meta-analysis. Two studies were excluded from the meta-analysis due to data not being available in the appropriate format16 and outcome definitions (eg, exacerbation) not meeting review eligibility criteria.17

Characteristics of included studies
The eight included studies were published between 2002 and 2017 (Table 1). The eight studies, in total, randomized 790 COPD patients (64% males), with study sample sizes ranging between 40 and 164. All stages of COPD severity (airflow limitation) were represented across included studies. All studies, except Moullec et al,23,24 randomized patients to
either a control group (usual care) or a supervised maintenance exercise program following pulmonary rehabilitation. Moullec et al\textsuperscript{23,24} used a quasi-random method, whereby patients were consecutively assigned following pulmonary rehabilitation discharge. All supervised maintenance exercise interventions lasted between 9 and 12 months except for Guell et al\textsuperscript{25} who provided a program for 36 months. Ringbaek et al\textsuperscript{19} and Ries et al\textsuperscript{16} had 6- and 12-month observation periods, respectively, following the completion of supervised maintenance exercise, data for which were not relevant for analysis in this review. Intervention procedures varied considerably between studies with one study providing an intense program of 3.5 h of supervised maintenance exercise a week,\textsuperscript{23,24} whereas another study provided one supervised maintenance session every 3 months.\textsuperscript{20,21} More details on interventions for all of the studies are given in Table 1.

Primary and secondary outcomes of this review were determined by either self-reporting of events by patients\textsuperscript{16,17} or self-report validated through examination of health records.\textsuperscript{18–25} Health care use was reported as a secondary outcome in the majority of studies\textsuperscript{16–24} with the publication of one study not reporting relevant outcomes.\textsuperscript{25} Contact with authors of this study provided unpublished data relevant to this review. None of the studies had outcome data for all planned meta-analyses.

The risk of bias assessment was hindered by poor study reporting. Some studies presented with several unclear risks of bias domains, leading to overall high risk of bias. Due to high attrition rates, the risk of bias in four of the included studies in the meta-analyses was classified as high (Table 2). The only study with a low risk of bias was unable to be included in meta-analyses due to the lack of availability of data.\textsuperscript{16}

Primary outcomes

Hospital admissions (respiratory cause)

Meta-analysis of five trials\textsuperscript{18,20,22–25} demonstrated a statistically significant reduction in the risk of experiencing at least one respiratory-cause hospital admission with continued supervised maintenance exercise following pulmonary rehabilitation (risk ratio 0.62, 95% confidence interval (CI) 0.47–0.81, \(P<0.001\)) (Figure 2A). There were no indications of heterogeneity in the findings (\(I^2=0\%\)).

Three trials provided data on incidence rates,\textsuperscript{18,20,25} whereby the overall estimate of the average effect suggested a reduction in the rate of respiratory-cause hospital admissions with supervised maintenance exercise (rate ratio 0.72, 95% CI 0.50–1.05, \(P=0.09\), \(I^2=0\%\)) (Figure 2B).

Exacerbations requiring treatment with antibiotics and/or systemic corticosteroids

Meta-analysis of two trials\textsuperscript{18,22} suggested a reduction in the risk of experiencing at least one exacerbation with supervised maintenance exercise (risk ratio 0.79, 95% CI 0.52–1.19,
### Table 1 Characteristics of included studies

| Study (country) | Sample size, gender, age | FEV\(_1\) % predicted (spirometry), smoking history | Inclusion/exclusion criteria | Study aim, design, unit of allocation | Pulmonary rehabilitation program (setting, components, duration, frequency) | Maintenance program (setting, components, duration, frequency) | Primary outcome (1) and other outcomes and follow-up (2) |
|-----------------|--------------------------|----------------------------------------------------|-------------------------------|--------------------------------------|---------------------------------------------------------------|----------------------------------------------------------------|---------------------------------------------------------------|
| Ries et al (2003)\(^{16}\) (USA) | 164 participants | FEV\(_1\) %pred, mean ± SD All: 45% Con: n/a | Inclusion: clinical diagnosis of chronic lung disease; chronic symptoms and perceived disability from disease; stable state; no other significant medical or psychiatric conditions that would interfere with program participation; commitment to abstain from smoking | Assess a telephone-based maintenance intervention for retaining benefits following pulmonary rehabilitation | Exercise and education combined with psychosocial support Twelve 2 h sessions over 8 weeks | Weekly semistructured phone calls and monthly supervised reinforcement sessions (1.5 h supervised exercise, 0.5 h topic review, 0.5 h social time) for 12 months | (1) Pulmonary function, exercise tolerance, dyspnea, depression (2) QoL, health status, health care use |
| Brooks et al (2002)\(^{17}\) (Canada) | 85 participants | FEV\(_1\) %pred, mean ± SD All: 45% Con: n/a | Inclusion: severe stable COPD (FEV\(_1\) <40% predicted, FEV\(_1\)/FVC <0.7); completion of inpatient or outpatient rehabilitation; nonsmoker for a minimum of 6 months; aged 49–85 years | Compare the effects of two postrehabilitation programs on functional exercise capacity and health-related QoL in patients with COPD RCT, cluster | Exercises – breathing, treadmill or cycle exercises, interval and upper extremity training, leisure walking Patient education and psychosocial support included (relaxation and occupational therapies) Inpatient – five times a week for 6 weeks Outpatient – three times a week at the center and at home for 8 weeks | Monthly 2 h group sessions supervised by a physical therapist for 12 months. First hour for discussion around home rehabilitation program, second hour for performing components of the home exercise program under supervision. Phone calls made between visits with standardized questions regarding adherence to home exercises | (1) 6MWT, CRQ (2) Medical outcomes survey: short-form 36, SGRQ, subject compliance, pulmonary function |
| Spencer et al (2010)\(^{18}\) (Australia) | 48 participants | FEV\(_1\) %pred, mean ± SD All: 45% Con: n/a | Inclusion: COPD diagnosis; completed an 8 week pulmonary rehabilitation program; FEV\(_1\)/FVC <70% and FEV\(_1\) <80% predicted | Determine if weekly supervised exercise following pulmonary rehabilitation would maintain functional exercise capacity and QoL RCT, individual | Exercises – 20 min walking, 20 min cycling, 10 min arm cycling, upper and lower limb strength training 8 weeks in a pulmonary rehabilitation gym | Pulmonary rehabilitation gym for 12 months. Supervised exercise 1 day/week with unsupervised exercise 4 days/week. Exercises prescribed in line with exercise undertaken during pulmonary rehabilitation | (1) 6MWT, SGRQ (2) Lung function tests, ISWT, ESWT, HADS, hospital admissions, length of stay and exacerbations |
| Ringbaek et al (2010)\(^{19}\) (Denmark) | 96 participants | FEV\(_1\) %pred, mean ± SD All: 45% Con: n/a | Inclusion: stable COPD (FEV\(_1\) <80%, FEV\(_1\)/FVC <70%); motivation for pulmonary rehabilitation; completion of 7 weeks of pulmonary rehabilitation | Examine whether maintenance training improved long-term effect of pulmonary rehabilitation RCT, individual | Supervised walking and cycling both at 85% of predicted VO\(_2\) peak and unsupervised exercise at home Twice a week for 7 weeks with supplementary education once a week | Weekly supervised exercise for the first 6 months, every second week for the next 6 months, and no supervised exercise for the last 6 months. Unsupervised exercise at home encouraged | (1) ESWT, SGRQ (2) Hospitalization (time to first admission, admission rates, days in hospital), exercise adherence, attendance at evaluation visits |

(Continued)
| Study (country) | Sample size, gender, age | FEV\(_1\), % predicted (spirometry), smoking history | Inclusion/exclusion criteria | Study aim, design, unit of allocation | Pulmonary rehabilitation program (setting, components, duration, frequency) | Maintenance program (setting, components, duration, frequency) | Primary outcome (1) and other outcomes and follow-up (2) |
|-----------------|--------------------------|--------------------------------------------------|-----------------------------|--------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| Wilson et al (2015)\(^9\) and Burns et al (2016)\(^1\) (UK) | 148 participants (country) | FEV\(_1\), %pred, mean ± SD | Inclusion: >35 years of age; COPD diagnosis (FEV\(_1\), <80%); >20 pack-year smoking history; completed at least 60% of pulmonary rehabilitation sessions Exclusion: cardiac or pulmonary disease (other than COPD); myocardial infarction within 6 months or unstable angina; respiratory infection within last 4 weeks; uncontrolled or severe comorbidities; cognitive complications | Evaluate long-term effect of maintenance exercise on health-related QoL Assess the cost-effectiveness of maintenance exercise following pulmonary rehabilitation on health-related QoL RCT, individual | Exercises – walking, cycling, sit to stand, step-ups, arm exercises with dumbbells. High intensity (85% of maximum capacity) Once a week for 8 weeks (1 h for exercise and 1 h for education). Endurance exercise everyday and strength exercise two more times a week at home | Individually tailored strength and endurance exercises including walking, cycling, sit-to-stand, step-ups, and arm exercises with dumbbells One 2 h (1 h exercise and 1 h education) session every 3 months for 12 months. Same group of patients from original pulmonary rehabilitation. Home exercise program review | (1) CRQ (dyspnea) (2) CRQ (other domains), ESWT, BMI, body fat, HADS, EQ5D |
| Roman et al (2013)\(^2\) (Spain) | 71 participants (country) | FEV\(_1\), %pred, mean ± SD (95% CI) | Inclusion: 35–74 years old; moderate COPD diagnosis; smokers or nonsmokers Exclusion: musculoskeletal conditions affecting ability to exercise; terminal illness/other severe disease | Use maintenance postpulmonary rehabilitation to improve QoL in COPD RCT, individual | Exercises – low intensity peripheral muscle training. One session a week for 9 months | Low intensity peripheral muscle training. One session a week for 9 months | |
| Moullec et al (2008)\(^3\) and Moullec and Ninot (2010)\(^4\) (France) | 40 participants (country) | FEV\(_1\), %pred, mean ± SD | Inclusion: FEV\(_1\)/FVC <0.7, FEV\(_1\), 30%–79% predicted; no indication for home oxygen therapy; stable state for the previous 2 months; no change in medication and symptoms for the previous 4 weeks; >40 years of age; no previous pulmonary rehabilitation experience Exclusion: medical or psychiatric disturbances that would hinder program participation; diagnosis of asthma; congestive left heart failure; terminal disease | Determine changes in the emotional and functional dimensions of QoL in COPD 1 year after a pulmonary rehabilitation program with or without a follow-up intervention Quasi-RCT, individual | Twenty inpatient sessions over 4 weeks | Community gymnasium Individualized strength, interval, breathing, and endurance training with nature walking at ventilatory threshold 96 sessions across 12 months. Exercise training (3.5 h/week; 72 sessions); health education (2 h/month; 12 sessions); psychosocial support (with discussion group 1 h/month; 12 sessions) | (1) 6MWT, QoL (SGRQ and WHOQoL-Brief) (2) Six-item questionnaire with a VAS, maximal exercise capacity, physical activity, health care utilization, attendance, pulmonary function |
Guell et al (2017) (Spain)

138 participants
Int: n=68
Con: n=70
Males: n=122
Females: n=15
Age, mean ± SD
Int: 64±9
Con: 64±8
FEV₁%pred, mean ± SD
Int: 34±11%
Con: 34±9%
No data available on smoking status

Inclusion: COPD diagnosis (grade II–IV severity); clinically stable during previous 4 weeks; 18–75 years old; exsmokers or with intention to quit; BODE index value between 3 and 10
Exclusion: bronchodilator response (FEV₁ increment >15% of the baseline value after 200 µg of inhaled bronchodilator); other respiratory diagnoses; severe coronary artery disease; orthopedic diseases limiting mobility; life expectancy <2 years; inability to cooperate

Assess the efficacy of a supervised maintenance program after pulmonary rehabilitation on improving symptoms, exercise capacity, and health-related QoL compared to just pulmonary rehabilitation on its own

Three hospital-based 2 h sessions a week for 8 weeks. Supplemented with four education sessions and chest physiotherapy

30 min weight-lifting (0.5 kg in each hand, increased by 1 kg a week until peak tolerance), 30 min leg cycling (start at 50% maximum load achieved during initial exercise test, load increased by 10 W if heart rate and oxygen saturation are stable and exercise is tolerated)

Secondary outcomes

Hospital admissions (all-cause)

Length of stay (respiratory cause and all-cause)

One trial provided data for length of hospital stay due to respiratory cause, mean difference 0.69, 95% CI 0.18 to 1.21, P=0.038, I²=0% (Figure S2). The overall estimate of effect suggested a nonsignificant reduction in the risk of experiencing at least one outpatient visit with supervised maintenance exercise (risk ratio 0.78, 95% CI 0.55–1.14, P=0.20).

Outpatient visits

Only one trial provided data for outpatient visits. The meta-analysis of three trials suggested a minimal reduction in the number of patients making at least one GP visit with supervised maintenance exercise (risk ratio 0.92, 95% CI 0.77–1.11, P=0.38, I²=0%) (Figure S1).

Mortality

Meta-analysis of two trials suggested a reduction in the risk of all-cause mortality with supervised maintenance exercise, but this was not statistically significant (risk ratio 0.57, 95% CI 0.17–1.92, P=0.37, I²=0%) (Figure 4). The trial by Roman et al. was omitted from this analysis due to no events occurring in either group during the trial.

Supervised exercise on alternate weeks at hospital for 36 months. Unsupervised home exercise program (3 days a week) similar to hospital program (15 min chest physiotherapy, 30 min arm training, 30 min leg training). Supplemented by structured phone calls from physiotherapists every 15 days

Exercise similar to pulmonary rehabilitation. Exercises, if well tolerated, were progressed at hospital visits

Meta-analysis of three trials suggested a nonsignificant reduction in the risk of experiencing at least one outpatient visit with supervised maintenance exercise (rate ratio 0.95, 95% CI 0.53–1.60, P=0.38, I²=0%) (Figure S1). The overall estimate of effect suggested no significant difference in the risk of experiencing at least one outpatient visit with supervised maintenance exercise compared to hospital stay due to all-cause, mean difference −0.20, 95% CI −1.61 to 1.21, P=0.88, I²=0% (Figure S2).

Sensitivity analyses

As all studies included in the meta-analyses were assessed to have a medium or high risk of bias, we were unable to perform our prespecified sensitivity analyses. However, we performed an additional sensitivity analysis and could not confirm that a sensitivity analysis was excluded on the outcomes of supervised maintenance exercise compared to hospital stay due to all-cause, mean difference −0.20, 95% CI −1.61 to 1.21, P=0.88, I²=0% (Figure S2).
Assessing the number of patients suffering one or more exacerbation between groups (ie, risk ratio) will show the direction of the intervention effect, but it is heavily influenced by the duration of the trial.\textsuperscript{26} Pooled analyses excluding Guell et al\textsuperscript{25} led to the loss of statistical significance and reduction in the overall effect of supervised maintenance exercise on the overall risk of experiencing at least one respiratory-cause hospital admission (risk ratio 0.77, 95% CI 0.47–1.25, \textit{P}=0.29) (Figure 6). Due to limited number of completed trials, it was not possible to perform meaningful synthesis of prespecified subgroups on our primary outcomes.

## Discussion

To our knowledge, this is the first systematic review to identify eight completed randomized trials that compared the efficacy of supervised maintenance exercise following pulmonary rehabilitation with usual care on health care use in COPD, six of which had relevant data to be synthesized using meta-analysis.
Summary of main findings

Data synthesis of five trials\(^ {18,20,22-25}\) suggests that, on average, supervised maintenance exercise following pulmonary rehabilitation significantly reduces the risk of experiencing at least one respiratory-cause hospital admission by 38%. The current available evidence is heavily weighted by one trial,\(^ {25}\) whereby the magnitude of the point estimate is sensitive to the inclusion of this trial (due to length of follow-up). Synthesized data from three trials\(^ {18,20,25}\) suggest that, on average, supervised maintenance exercise may also have an effect on multiple admissions by reducing the rate of respiratory-cause admissions by 28%. While pooling of studies for other primary measures in this review (relative risk reduction in exacerbations requiring treatment with medication and all-cause mortality of 21% and 43%, respectively) did not translate to statistically significant changes, the point estimates of effect do surpass proposed thresholds of clinical significance.\(^ {26,27}\) There is currently no evidence that supervised maintenance exercise following pulmonary rehabilitation has an effect on the risk of all-cause hospital admission or GP visits. Furthermore, there are insufficient data to synthesize the effect of supervised maintenance exercise on outpatient visits or duration of hospital stay following respiratory-cause and all-cause admission.

Strengths and limitations of the review

A strength of this review is that it is the first to conduct comprehensive searches and synthesis of published and unpublished data on health care use during supervised maintenance exercise programs compared to usual care following pulmonary rehabilitation. This review followed a preset, publicly available protocol detailing specific methodology. When the protocol for this review was written however, we did not anticipate the inclusion of trials with substantial differences in study follow-up. The recent study of Guell et al.\(^ {25}\) has received plaudits for conducting such a long follow-up period of postpulmonary rehabilitation maintenance. We feel that this deviation from our protocol in performing sensitivity analysis was strongly justified on the basis that studies with a longer observation period are likely to impact the robustness of our findings.

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**Figure 3** Trial-level data, effect estimates, and forest plot of comparison for the overall risk (of experiencing at least one event) (A) and incidence rates (B) of exacerbation requiring treatment with medication.

**Abbreviations:** CI, confidence interval; IV, inverse variance; SE, standard error.

**Figure 4** Trial-level data, effect estimates, and forest plot of comparison for the risk of mortality.

**Abbreviations:** CI, confidence interval; IV, inverse variance.
Extensive efforts were made to contact all trial authors to obtain additional data when outcomes did not appear in the available reports. The retrieval of additional data (beyond the published literature) reflects a key strength of our review. We, however, recognize that two studies\(^{16,17}\) that met review eligibility criteria were not included in our meta-analyses; hence, this must be noted as a limitation. We identified inconsistencies in how our review outcomes were reported. The majority of the studies were limited by expressing hospitalizations/exacerbations as mean number of events per study group only and simply interpreted as a difference in means. However, a small minority of patients who experience multiple events can heavily influence this measure of effect, and the interpretation of such estimates is not as informative as when discrete (count) data are analyzed as ratios. From a statistical point of view, a strength of our review is that our measures of effect make full use of the data that have been collected in the included studies. Clinically, we allow health care practitioners and other relevant stakeholders to be able to interpret the effect of supervised maintenance exercise on hospitalization rates (ie, severe exacerbation) or risk of an exacerbation treated with antibiotics and/or systemic corticosteroids does not exceed the threshold of clinical usefulness, we cannot exclude the possibility that the reduction is of a magnitude not considered clinically worthwhile. Hence, the available evidence can be considered consistent with either an increase or a decrease in hospitalization rates (ie, severe exacerbation) or risk of an exacerbation as a result of the intervention.

The proportion of missing outcome data compared to observed outcome data in some of the trials\(^{20–25}\) is enough to induce a clinically relevant bias in the observed intervention effects. There is no consensus on how to handle participants in a meta-analysis for whom data are not available.\(^{15}\) We opted for an available case analysis as opposed to intention to treat analysis using imputation. Although our findings do provide an analysis of efficacy, the lack of intention to treat approach precludes an effectiveness analysis of the supervised maintenance exercise.\(^{29}\)

Effects estimated from published studies only may be inflated due to bias toward the nonpublication of studies with nonsignificant effects. The fact that all of the included published studies did not report significant effects of supervised
maintenance exercise on health care use mitigates concerns about publication bias. All of the trials included in the meta-analyses were classified as having an overall medium or high risk of bias. Therefore, the quality of the overall evidence presented in this review is low. There were many individual domains where the risk of bias was unclear, primarily due to incomplete reporting. It is important to consider that this may not be poor reporting per se, and rather limitations in study design. Also, as commonly found in COPD trials, especially those >6 months in duration, many studies were classified as having high attrition bias.

Comparison with other reviews
No previous systematic review has synthesized data from randomized controlled trials assessing the effects of supervised maintenance exercise following pulmonary rehabilitation on health care use. There were three previous systematic reviews in COPD that had synthesized the available evidence on supervised maintenance programs following pulmonary rehabilitation, but meta-analyses were limited to exercise capacity and quality of life outcomes. Similarities, with regard to the benefits of exercise in our review, can be seen with Moore et al where data from randomized controlled trials on health care use following pulmonary rehabilitation alone were synthesized. However, this review did not focus on interventions aiming to maintain exercise regimens following pulmonary rehabilitation but instead evaluated the short- and long-term benefits of initial pulmonary rehabilitation programs on exacerbations compared to no treatment. It was concluded that the delivery of pulmonary rehabilitation to stable COPD patients or patients following acute exacerbations results in reduced rates of hospitalizations compared to usual care. Our findings suggest that continuing maintenance exercise in a supervised manner following pulmonary rehabilitation may further enhance the benefit on certain health care use outcomes.

Implications for clinical practice
Based on the evidence presented in this review, it would currently be unwise to make specific recommendations on clinical care within this area. Due to the low precision (wide confidence intervals) in our effect estimates, only one of our meta-analyses translated to a statistically significant difference in health care use as a result of supervised maintenance exercise. However, early indications are promising, whereby the current point estimates of effect in some of the outcomes (eg, exacerbation rate) would be large enough to be classified as clinically significant. These clinically significant findings could have large implications for future postrehabilitation care. While there are proposals that “one size does not fit all” with pulmonary rehabilitation maintenance, supervised maintenance exercise will likely play an important part in future practice recommendations. Arguably, the funding and reimbursement of supervised maintenance programs following pulmonary rehabilitation may not be cost-effective in the short term due to the initial outlay of setting up a program; however, the potential reductions in health care use in the medium to long term seen within this review may be large enough to produce a favorable cost–benefit ratio to health care budgets. This review highlights the importance of this active area of research and upon completion of further studies, its influence on future clinical practice.

Implications for future research
The findings of our meta-analyses must be interpreted in relation to quality and quantity of available evidence. The low precision of the individual study estimates (as a result of small sample sizes and hence low number of events) widens the confidence intervals for the point estimates of effect, highlighting the important impact that further research could have.

Further randomized trials addressing the current uncertainty about the effects of supervised maintenance exercise versus usual care on outcomes such as mortality and risk of exacerbation would need to be large (in sample size and/or a duration of follow-up ≥12 months). None of the included studies reported an a priori sample size calculation to determine the effect of supervised maintenance exercise on outcomes related to health care use. Future studies should include an appropriately powered sample size calculation based on proposed minimal clinically important differences. These studies should also adopt proper statistical analysis of outcomes (particularly exacerbations). Typical distribution of COPD exacerbations data and recommended statistical approaches have been discussed elsewhere. To facilitate critical appraisal and interpretation, future randomized trials would also benefit from adhering to Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Our findings have general applicability to all stable COPD patients referred to pulmonary rehabilitation. As none of the included trials stratified randomization by COPD severity, it is unclear whether our findings are equally applicable to all stages of COPD severity or exacerbation status. Further research is required to ascertain the effects of supervised exercise following pulmonary rehabilitation.
maintenance exercise programs following early rehabilitation programs where patients are inherently considered to have a greater baseline risk of health care use. Similarly, our review was limited to patients with a diagnosis of COPD; efficacy of exercise maintenance options for other chronic respiratory conditions requires attention.

During our searches, we identified two protocols of randomized trials (based in the USA and Canada) that meet our eligibility criteria (Table S3). Compared to usual care following pulmonary rehabilitation, one study is randomizing patients to Tai Chi classes, or a walking group for a 6-month period, while another study is randomizing patients to a 12-month community exercise program. An update on the synthesis of the available evidence would be encouraged upon completion of the trials. For the design and delivery of new trials, research teams should note recent recommendations from the Australian and New Zealand Pulmonary Rehabilitation Guidelines that maintenance programs of monthly or three monthly supervised exercises (or less frequently) are insufficient to maintain exercise capacity or quality of life. It is reasonable to suggest that this frequency of supervised maintenance exercise compared with usual care is also unlikely to benefit outcomes related to health care use. However, we recognize that there is growing interest in different approaches to maintain the benefits of pulmonary rehabilitation, for example, telehealth (telecoaching and pedometer feedback).

**Conclusion**

This systematic review and meta-analysis suggests that supervised maintenance exercise programs compared to usual care following pulmonary rehabilitation may be beneficial in reducing health care use. However, the quality of the available evidence was variable. This outlines the requirement for methodologically sound and large studies to provide more precise estimates for the effects of postpulmonary rehabilitation maintenance.

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**Disclosure**

The authors report no conflicts of interest in this work.

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Supplementary materials

Methods

Data extraction

The following study characteristics were extracted: methods of the study (date/title of the study, aim of study, study design, unit of allocation, duration of study, duration of intervention, primary outcome, secondary outcomes, and funding source), participants (population description, demographics, inclusion criteria, exclusion criteria, method of recruitment of participants, total number randomized, clusters, baseline imbalances, withdrawal and exclusions, and subgroups reported), intervention and where relevant comparator (group name, number randomized to group-sample size, description, venue numbers/locations, duration and frequency of maintenance exercise training period, delivery, providers, co-interventions, compliance/adherence, and defined parameters of usual care), and outcomes (outcome name, outcome type, outcome definition, person measuring/reporting, unit of measurement, scales [upper and lower limits], outcome tool validation, imputation of missing data, assumed risk estimate, and level of power).

Table S1 Example search strategy of a bibliographic database (CINAHL)

| Number | Search term                                                                 | Field        |
|--------|----------------------------------------------------------------------------|--------------|
| 1      | Lung diseases, obstructive                                                | MH (explode)|
| 2      | Lung diseases, interstitial                                                | MH (explode)|
| 3      | Pulmonary fibrosis                                                         | TX           |
| 4      | COPD                                                                       | TX           |
| 5      | Chronic obstructive pulmonary disease                                      | TX           |
| 6      | COAD                                                                       | TX           |
| 7      | COBD                                                                       | TX           |
| 8      | Emphysem<sup>a</sup>                                                      | TX           |
| 9      | Chronic bronchitis                                                        | TX           |
| 10     | Cystic fibrosis                                                           | TX           |
| 11     | Pneumoconiosis                                                            | TX           |
| 12     | Sarcoidosis                                                                | TX           |
| 13     | Asthma                                                                    | TX           |
| 14     | Bronchiectasis                                                            | TX           |
| 15     | Alveolitis                                                                 | TX           |
| 16     | Histiocytosis                                                             | TX           |
| 17     | Granulomatosis                                                             | TX           |
| 18     | Bagassosis                                                                | TX           |
| 19     | Asbestosis OR byssiosis OR siderosis OR silicosis OR berylliosis OR anthracosilicosis | TX           |
| 20     | Scleroderma                                                               | TX           |
| 21     | 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 | MH (explode) |
| 22     | Exercise therapy                                                          | MH (explode) |
| 23     | Activities of daily living                                                | MH           |
| 24     | Rehabilitation research                                                   | MH (explode) |
| 25     | Physical and rehabilitation medicine                                       | MH           |
| 26     | Physical fitness                                                          | MH           |
| 27     | Exercise movement techniques                                              | MH (explode) |
| 28     | Telerehabilitation                                                        | MH           |
| 29     | Rehabilitation N2 pulmonary OR respiratory OR physical OR early           | TI, AB       |
| 30     | Exercis<sup>b</sup> N3 supervi<sup>b</sup> OR training OR maintenance OR program<sup>b</sup> | TI, AB       |
| 31     | Physical activit<sup>b</sup>                                              | TI, AB       |
| 32     | Maintenance N2 intervention OR group OR exercise OR program<sup>b</sup> OR training | TI, AB       |
| 33     | 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32            | TI, AB       |
| 34     | Randomised                                                                | TI, AB       |
| 35     | Randomized                                                                | TI, AB       |
| 36     | Randomly                                                                  | TI, AB       |
| 37     | Trial                                                                     | TI, AB       |
| 38     | Controlled                                                                | TI, AB       |
| 39     | 34 OR 35 OR 36 OR 37 OR 38                                                | TI, AB       |
| 40     | 21 AND 33 AND 39                                                         |              |

Notes: Searches encompassed other chronic lung conditions as part of a wider review. <sup>a</sup>Truncation operator.
Table S2 Characteristics of excluded studies

| Study                          | Reason(s) for exclusion                                      |
|-------------------------------|-------------------------------------------------------------|
| Andrews et al (2015)          | Not a randomized trial                                      |
| Bernocchi et al (2016)        | Intervention not relevant (unsupervised)                    |
| Berry et al (2003)            | Outcomes not applicable                                     |
| Bertolini et al (2016)        | Not randomized; outcomes not applicable; intervention not relevant (unsupervised) |
| Brooks et al (2002)           | Outcomes not applicable                                     |
| Browne et al (2013)           | Conference abstract – full text included                    |
| Carriero-Kohlman et al (2005) | Intervention not relevant (did not include pulmonary rehabilitation) |
| Cejudo et al (2014)           | Conference abstract – full text included; outcomes not applicable |
| Cejudo et al (2014)           | Conference abstract – full text included; outcomes not applicable |
| Cruz et al (2016)             | Intervention not relevant (behavioral feedback intervention-unsupervised) |
| Desveaux et al (2016)         | Ongoing trial – data not available                          |
| du Moulin et al (2009)        | Intervention not relevant (unsupervised); outcomes not applicable |
| Eisner and van Straten (2003) | Conference title only                                       |
| Elliott et al (2004)          | Outcomes not applicable                                     |
| Fu et al (2016)               | Intervention not relevant (no exercise intervention post-pulmonary rehabilitation) |
| Gomez et al (2006)            | Conference abstract – full text included                    |
| Guell et al (2000)            | Intervention not relevant (control group did not receive pulmonary rehabilitation) |
| Heppner et al (2006)          | Not a randomized trial                                      |
| Hill and McDonald (2004)      | Outcomes not applicable                                     |
| Kottsch et al (2016)          | Intervention not relevant (unsupervised)                    |
| Linneberg et al (2012)        | Outcomes not applicable                                     |
| Martinez et al (2008)         | Conference abstract – full text included                    |
| Moy et al (2015)              | Ongoing trial – data not available                          |
| Perumal et al (2010)          | Not a randomized trial                                      |
| Pleguezuelos et al (2013)     | Intervention not relevant (unsupervised); outcomes not applicable |
| Ries et al (2008)             | Intervention not relevant (unsupervised and control group received additional care); outcomes not applicable |
| Ringbaek et al (2009)         | Conference abstract – full text included                    |
| Rodriguez-Trigo et al (2011)  | Conference abstract – full text included                    |
| Scalvini et al (2016)         | Intervention not relevant (unsupervised)                    |
| Spencer et al (2007)          | Conference abstract – full text included                    |
| Spencer et al (2009)          | Conference abstract – full text included                    |
| Swerts et al (1990)           | Outcomes not applicable                                     |
| van Wetering et al (2010)     | Intervention not relevant (control group did not receive pulmonary rehabilitation); outcomes not applicable |
| Vasilopoulou et al (2017)     | Intervention not relevant (control group did not receive pulmonary rehabilitation) |

Notes: Abstract and full text were nonretrievable. Study excluded due to presentation as a conference title only in search results.

Figure S1 Trial-level data, effect estimates, and forest plot of comparison for the risk of all-cause hospital admission.

Abbreviations: CI, confidence interval; IV, inverse variance.
Figure S2 Trial-level data, effect estimates, and forest plot of comparison for the risk of GP visits.

Abbreviations: CI, confidence interval; GP, general practitioner; IV, inverse variance.

Table S3 Ongoing studies

| Study name or title | Study period (start and end dates) (country) | Study design | Participants | Intervention and comparison | Relevant outcomes |
|---------------------|---------------------------------------------|--------------|--------------|-----------------------------|-------------------|
| LEAP: design and rationale of a randomized controlled trial of Tai Chi | August 2012 to September 2017 (USA) | Randomized controlled trial (2:2:1 ratio) | 90 COPD patients who have just been discharged from pulmonary rehabilitation | 1. Tai Chi (1 h, twice a week for 3 months, then once a week for 3 months. A total of 36 classes) | Hospital admissions (respiratory) and acute exacerbations (use of corticosteroids and/or antibiotics verified by medical records) |
| Effects of a community-based, postrehabilitation exercise program in COPD: protocol for a randomized controlled trial with embedded process evaluation | November 2012 to August 2018 (Canada) | Randomized controlled trial | 100 COPD patients who have completed pulmonary rehabilitation within the last 2 weeks | 1. Usual care (standard home exercise instructions postpulmonary rehabilitation) | 2. Community-based exercise program (1 h, minimum of two sessions per week (option to do more) for 1 year) |

Abbreviation: LEAP, long-term exercise after pulmonary rehabilitation.

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