

## Review Article

# Pre-operative optimisation for chronic obstructive pulmonary disease: a narrative review

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## Summary

Chronic obstructive pulmonary disease is a condition commonly present in older people undergoing surgery and confers an increased risk of postoperative complications and mortality. Although predominantly a respiratory disease, it frequently has extra-pulmonary manifestations and typically occurs in the context of other long-term conditions. Patients experience a range of symptoms that affect their quality of life, functional ability and clinical outcomes. In this review, we discuss the evidence for techniques to optimise the care of people with chronic obstructive pulmonary disease in the peri-operative period, and address potential new interventions to improve outcomes. The article centres on pulmonary rehabilitation, widely available for the treatment of stable chronic obstructive pulmonary disease, but less often used in a peri-operative setting. Current evidence is largely at high risk of bias, however. Before surgery it is important to ensure that what have been called the 'five fundamentals' of chronic obstructive pulmonary disease treatment are achieved: smoking cessation; pulmonary rehabilitation; vaccination; self-management; and identification and optimisation of co-morbidities. Pharmacological treatment should also be optimised, and some patients may benefit from lung volume reduction surgery. Psychological and behavioural factors are important, but are currently poorly understood in the peri-operative period. Considerations of the risk and benefits of delaying surgery to ensure the recommended measures are delivered depends on patient characteristics and the nature and urgency of the planned intervention.

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## Introduction

*When I saw the doctor [about having surgery] ... he told me there was the likelihood that there would be complications because of the severity of the chronic obstructive pulmonary disease, but that worried me. [1]*

Around 4.5% of the UK population aged over 40 years are affected by chronic obstructive pulmonary disease [2], of whom 40% or more remain undiagnosed [3]. It is a condition associated with ageing, a history of smoking, and socio-economic disadvantage. As a consequence, the prevalence of chronic obstructive pulmonary disease in

peri-operative patients is higher than in age-matched population groups (e.g. 40% in thoracic surgery, 5–10% in general surgery, 10–12% in cardiac surgery) [4–7]. The anaesthetist is therefore likely to encounter peri-operative patients with varying severities of chronic obstructive pulmonary disease, who may be anywhere in the range from being undiagnosed and untreated to receiving maximal medical support from respiratory specialists.

Chronic obstructive pulmonary disease is an independent risk factor for complications and death after surgery, with odds ratios (95%CI) of 1.35 (1.3–1.4),  $p < 0.0001$  and 1.29 (1.19–1.39),  $p < 0.0001$ , respectively [6, 8]. The risk is particularly high for surgery involving the heart and chest [6, 8], but extends to all operations. The OR (95%CI) of potential complications include: the risk of unanticipated early re-intubation, 1.6 (1.4–1.8),  $p < 0.001$  [9]; postoperative pneumonia and respiratory failure, 1.71 (1.59–1.83),  $p < 0.0001$ ; myocardial infarction, 1.25 (1.02–1.54),  $p = 0.03$ ; cardiac arrest, 1.29 (1.13–1.47),  $p = 0.0002$ ; sepsis, 1.13 (1.05–1.22),  $p = 0.001$ ; and renal insufficiency requiring dialysis, 1.28 (1.13–1.46),  $p = 0.0001$  [7].

For most people with chronic obstructive pulmonary disease, surgery is a frightening prospect, as their risk of morbidity and death from most major operations is increased [7, 10]. Many people with chronic obstructive pulmonary disease or other chronic diseases refuse treatment due to fear of side-effects [11]. For those who proceed, there remains significant pre-operative anxiety, which in itself has been shown to exacerbate postoperative pain [1], wound complications [12] and recovery times [13].

This review aims to present methods for the pre-operative optimisation of chronic obstructive pulmonary disease, focusing on interventions used in patients with stable chronic obstructive pulmonary disease that could potentially be incorporated into peri-operative medicine.

## Methods

We performed an initial scoping search to identify peri-operative optimisation techniques for chronic obstructive pulmonary disease to include in this review, and a second, more detailed search to identify papers investigating the efficacy of pre-operative pulmonary rehabilitation in patients with chronic obstructive pulmonary disease. The search period was up to 25 April 2020, and we performed searches in the following electronic databases: MEDLINE, EMBASE and the Cochrane Central Register of Controlled trials (CENTRAL). The search terms are listed in Tables S1 and S2 in the online Supporting Information.

One author screened all titles and abstracts of papers to identify relevant studies for inclusion. We aimed to include studies performed on patients with chronic obstructive pulmonary disease in the peri-operative period. We did not limit the search for a specific outcome measure or type of study (other than excluding review articles) as we were aware that there were few randomised controlled trials in this field.

Our exclusion criteria were studies not written in the English language; studies not performed on adult humans; studies not performed during the pre-operative period; studies not performed on patients with chronic obstructive pulmonary disease; and those not using pulmonary rehabilitation as the primary intervention.

We deliberately did not include search terms for other types of respiratory training, nor for exercise that was not specifically called 'pulmonary rehabilitation', to increase the specificity of the search. We used the PubMed 'related articles' function and searched through reference lists for relevant papers to identify any additional studies for inclusion.

## Results

Eleven reviews were identified using the scoping search, of which five were excluded for various reasons (Figure S1 in online Supporting Information). Six full text reviews were qualitatively analysed to find optimisation techniques that could be covered in this article, and the following categories were chosen for this review: pulmonary rehabilitation; smoking cessation; pharmacological therapy; symptom optimisation; nutritional optimisation; and lung volume reduction interventions.

Two hundred and fifty-four records were identified using the second search, of which 240 were excluded (Fig. 1). Twelve papers were included in a qualitative analysis for pulmonary rehabilitation [14–25]. Of these, four described pulmonary rehabilitation data from randomised controlled trials [14, 16, 20, 25]. One study compared pulmonary rehabilitation with usual care [14]. The primary intervention was not pulmonary rehabilitation for two studies [16, 20]; and the third compared pre-operative with postoperative pulmonary rehabilitation and both [25]. There was variability in study design (Table 1) and in the components of a 'pulmonary rehabilitation' programme (Table 2). We performed a risk of bias assessment for randomised studies using the revised Cochrane risk-of-bias tool for randomised trials (RoB2) [26] (Table 3) and the risk of bias in non-randomised studies of interventions (ROBINS-1) [27] (Table 4) for observational studies.

### **Approach to the patient with chronic obstructive pulmonary disease in the peri-operative clinic**

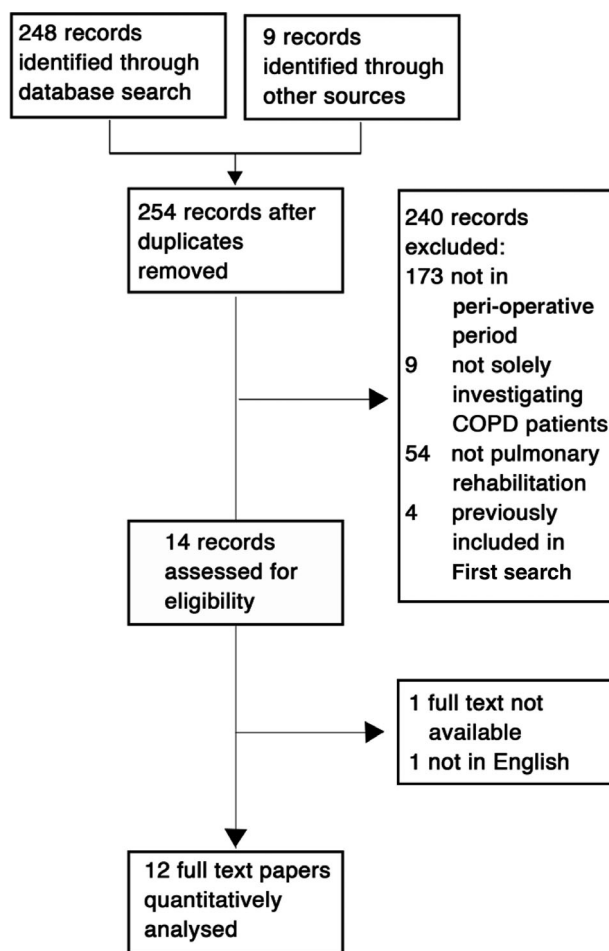
The peri-operative period is a unique opportunity to improve patients' ability to handle operative stress and recovery by making personalised modifications to their risk profile. If clinicians maintain a low threshold for suspicion of the diagnosis of chronic obstructive pulmonary disease in patients who smoke, these patients may be optimised early to improve outcomes and reduce complications.

There are a number of considerations related to chronic obstructive pulmonary disease around the time of surgery. These include: identifying the respiratory condition and ensuring that it is appropriately characterised (e.g. exacerbation frequency, degree of hyperinflation and emphysema, hypoxia/pulmonary hypertension, respiratory failure); ensuring that general care for the condition has been optimised, including multimorbidity; balancing the risks and benefits of surgery and considering whether a delay to optimise the condition is justified; specific concerns

related to the severity of the respiratory disease and the type of operation; and whether established interventions can still produce the same level of clinical benefit if they are shortened or simplified to avoid delaying surgery.

A useful approach in any person with long-term breathlessness or a condition where breathlessness can be a feature is the 'Breathing SPACE' approach developed by the London Respiratory Network [28]. This acronym prompts clinicians to consider smoking (cessation), pulmonary disease (is it present and has care been optimised?), anxiety (or other psychological issues), cardiovascular disease (is it present and has care been optimised?); and exercise (is fitness/obesity an issue, has pulmonary rehabilitation been considered?).

For the care of chronic obstructive pulmonary disease, the recent update of National Institute of Health and Care Excellence (NICE) guidance [29] emphasises 'five fundamentals' of chronic obstructive pulmonary disease care summarised here [30]: offer treatment and support to



**Figure 1** Flow diagram for second literature search (pulmonary rehabilitation). COPD, chronic obstructive pulmonary disease.

**Table 1** Summary of characteristics of pulmonary rehabilitation studies.

Study	Type of study	Intervention group (n)	Comparator group(s) (n)	Number of sessions	Duration of sessions	Main outcomes reported
Benzo et al. [14]	Prospective randomised controlled trial	1st study: Pulmonary rehabilitation (?) 2nd study: Pulmonary rehabilitation (10)	1st study: Usual care (?) 2nd study: Usual care (9)	2nd study: 10	Unclear	Length of stay in hospital and ICU Postoperative pulmonary complications Chest tube duration
Bobbio et al. [15]	Prospective observational study	Pulmonary rehabilitation (12)	No comparator	20	1.5 h	VO <sub>2</sub> max Lung function tests
Criner et al. [16]	Prospective randomised controlled trial	Medical management + pulmonary rehabilitation (18)	Bilateral lung volume reduction surgery + medical management + pulmonary rehabilitation (19)	Unclear	Unclear	Functional status Gas exchange Symptom limited maximal exercise performance 6MWD
Divisi et al. [17]	Prospective observational study	Pulmonary rehabilitation (27)	No comparator	24	1.5 h	Lung function tests Cardiopulmonary exercise testing 6MWD Clinical parameters
Mujovic et al. [18]	Prospective interventional study	Pulmonary rehabilitation (83)	No comparator	30–60	45 min	Lung function tests 6MWD Symptom status
Mujovic et al. [19]	Prospective observational study	Pulmonary rehabilitation (56)	No pulmonary rehabilitation (47)	30–60	45 min	Lung function tests 6MWD Symptom status
Ries et al. [20]	Analysis of randomised controlled trial data	Pulmonary rehabilitation (1218)	No comparator	12–16	Unclear	Maximal work rate Quality of life Level of dyspnoea
Saito et al. [21]	Retrospective cohort study	Pulmonary rehabilitation (51)	No pulmonary rehabilitation (65)	Unclear	Unclear	Lung function tests Length of stay Postoperative complications
Sekine et al. [22]	Prospective observational study	Pulmonary rehabilitation (22)	No pulmonary rehabilitation (60)	Unclear	Unclear	Lung function tests Surgical outcomes
Stefanelli et al. [23]	Prospective randomised study	Pulmonary rehabilitation (Unclear n)	No pulmonary rehabilitation (unclear n)	15	3 h	Lung function tests VO <sub>2</sub> max
Vagvolgyi et al. [24]	Prospective interventional study	Pulmonary rehabilitation pre-operatively (68)	Pulmonary rehabilitation postoperatively (72) Pulmonary rehabilitation pre- and postoperatively (68)	Unclear	30 min	Lung function tests Quality of life Level of dyspnoea Length of stay in intensive care Smoking cessation rate
Vagvolgyi et al. [25]	Prospective randomised controlled trial	Pulmonary rehabilitation pre-operatively (72)	Pulmonary rehabilitation postoperatively (86). Pulmonary rehabilitation pre and post operatively (80)	Unclear	30 min	6MWD Lung function tests Level of dyspnoea Quality of life

6MWD, 6-min walking distance; VO<sub>2</sub> max, maximal oxygen uptake measured during cardiopulmonary exercise testing; ICU, intensive care unit.

**Table 2** Components of pulmonary rehabilitation for each study.

Study	Pre-treatment	Breathing exercises	Aerobic exercises	Smoking cessation	Pharmacological optimisation	Nutritional input	Psychological input	Setting	Supervision
Benzo et al. [14]	×	✓	✓	×	×	×	×	Unclear	Supervised
Bobbio et al. [15]	✓	✓	✓	✓	✓	×	×	Hospital outpatients	Partial
Criner et al. [16]	?	?	?	?	?	?	?	Unclear	Unclear
Divisi et al. [17]	✓	✓	✓	✓	×	✓	×	Unclear	Supervised
Mujovic et al. [18]	✓	✓	×	×	✓	×	×	Unclear	Supervised
Mujovic et al. [19]	✓	✓	×	×	✓	×	×	Unclear	Supervised
Ries et al. [20]	×	✓	✓	×	×	✓	✓	Hospital outpatients	Supervised
Saito et al. [21]	✓	✓	✓	✓	✓	×	×	Unclear	Partial
Sekine et al. [22]	✓	✓	✓	✓	×	×	×	Hospital inpatient	Supervised
Stefanelli et al. [23]	✓	✓	✓	×	×	×	×	Hospital outpatients	Supervised
Vagvolgyi et al. [24]	×	✓	✓	✓	×	×	✓	Unclear	Supervised
Vagvolgyi et al. [25]	×	✓	✓	✓	×	×	✓	Unclear	Supervised

stop smoking; offer pneumococcal and influenza vaccinations; offer pulmonary rehabilitation for people with chronic obstructive pulmonary disease (if indicated); co-develop a personalised self-management plan; and optimise treatment of comorbidities.

The National Chronic Obstructive Pulmonary Disease Audit Programme's 2014–2015 report of practice across Wales [31] demonstrated inadequate uptake and delivery of many of these 'five fundamentals' based on primary care records: for example, one in five patients did not receive the influenza vaccine; and 22% of patients did not have smoking cessation advice despite being current smokers. This is echoed by patient reports of inadequate delivery of aspects of care [32, 33]. Pre-operative assessment clinics offer an opportunity to ensure that these fundamentals have been addressed. If not, surgery may be usefully delayed if the delay offers more benefit than risk to the patient.

### Targets for peri-operative optimisation

While chronic obstructive pulmonary disease is primarily a respiratory condition, it is widely considered to be a multi-system disease [34], with patients also experiencing a range of symptoms [35, 36], including breathlessness, cough, fatigue and mood disturbances, which affect their functional abilities to varying degrees [36]. Lung function only

determines part of this picture and spirometry only captures one, albeit important, part of lung function [37]. Evidence is emerging that patient-reported outcome measures and functional ability tests are better than lung function testing at predicting respiratory disease severity and clinical outcomes such as the rate of peri-operative complications [38–40].

Examples of patient-reported outcomes include health-related quality of life measurements, which include physical and mental health categories [41, 42], and perceived disability scales such as the Medical Research Council breathlessness scale [43]. The chronic obstructive pulmonary disease assessment test is a simple patient-reported outcome measure that uses plain language terms and can be used in most clinical contexts [44]. Functional ability tests include 6-minute walking distance [45], incremental shuttle walk tests and generic tests for frailty such as the short physical performance battery [46].

It is important to appreciate the limitations of changes in patient-reported outcome measures as peri-operative targets; for example, the Medical Research Council Breathlessness Scale is insensitive to small changes in clinical status. The ideal patient-reported outcome measures are those that are well validated, have no

**Table 3** Risk of bias for included randomised controlled trials using revised Cochrane risk-of-bias tool (RoB 2)[26]

Study	Randomisation	Deviation from intended intervention	Missing data	Measurement of outcomes	Reported result	Overall
Benzo et al. [14] (Study 2 used for the risk of bias assessment)	●	●	●	●	●	●
Criner et al. [16]	●	●	●	●	●	●
Vagvolgyi et al. [25]	●	●	●	●	●	●

Green circle ● = Low risk of bias; yellow circle ● = raises some concerns in at least one domain for this result; red circle ● = high risk of bias in at least one domain for this result; or some concerns for multiple domains in a way that substantially lowers confidence in the result.

Overall risk of bias is equal to the most severe level of bias found in any domain. For studies with some concerns for multiple domains (>3 out of 5) in a way that substantially lowers confidence in the result, the overall risk of bias is judged to be high.

significant ceiling or floor effects, and relate to relevant metrics such as the minimal clinically important difference.

### Pulmonary rehabilitation

Pulmonary rehabilitation is a supervised programme of exercise training and health education for people with chronic lung conditions. There is a wealth of robust evidence supporting the use of pulmonary rehabilitation in stable chronic obstructive pulmonary disease in improving clinical outcomes, breathlessness and health-related quality of life [31, 47]. Pulmonary rehabilitation is widely available across the UK and is free of charge for patients under the National Health Service.

A typical programme in the UK is of at least 6 weeks' duration and includes a minimum of twice-weekly supervised sessions. These feature supervised, individually tailored and prescribed progressive exercise training, including both aerobic and resistance training [48]. It should be noted that pulmonary rehabilitation is distinct from pre-operative exercise training programmes, which are not specific to chronic obstructive pulmonary disease, and vary widely in content and methods of delivery.

Pulmonary rehabilitation also includes a defined, structured education programme on smoking cessation, understanding the symptoms and self-management options for chronic obstructive pulmonary disease. After the programmes, participants are provided with an individualised plan for ongoing exercise maintenance and their outcomes are assessed using measures of exercise capacity, breathlessness and health status [48].

The minimal clinically important difference is 0.5 for the Chronic Respiratory Questionnaire [49, 50],  $\pm 4$  for the St George's Respiratory Questionnaire [49], and  $-2$  to  $-3$  for the Chronic Obstructive Pulmonary Disease Assessment Test (CAT) [44]. Higher scores for the St George's Respiratory Questionnaire and Chronic Obstructive

Pulmonary Disease Assessment Tests indicate worsening limitations on activity.

Cochrane review evidence from a number of high-quality randomised controlled trials demonstrated that pulmonary rehabilitation confers improvements greater than the minimal clinically important differences for the four quality of life domains (breathlessness, fatigue, emotional function and mastery) measured by the Chronic Respiratory Questionnaire (mean difference (95%CI) 0.68 (0.45–0.92)) [47]. There were demonstrable improvements in health status measured by St George's Respiratory Questionnaire (mean difference (95%CI)  $-6.89$  ( $-9.21$  to  $-3.32$ )), and the Chronic Obstructive Pulmonary Disease Assessment Test (mean difference (95% CI)  $-3$  ( $-1$  to  $-7$ )). [44, 51–54]. Exercise tolerance is also improved [48, 55, 56].

Following pulmonary rehabilitation, participants often report feeling a sense of improved 'ownership' and control over their illness. Qualitative studies of pulmonary rehabilitation participants have demonstrated that the programmes also provide an important source of social support and belonging in a community [57] as the courses are run as group sessions in which participants meet others with similar conditions.

Trial data have shown reductions in the number of chronic obstructive pulmonary disease exacerbations requiring general practice or hospital interventions, the length of stay in hospital and risk of readmission after an exacerbation [58, 59]. The number needed to treat to improve any Chronic Respiratory Questionnaire domain above the minimal clinically important difference with pulmonary rehabilitation is between 2 and 4 [60, 61].

There is randomised controlled trial evidence that the improvements in health-related quality of life and exercise capacity seen in pulmonary rehabilitation studies for stable chronic obstructive pulmonary disease are also seen in patients who undergo pulmonary rehabilitation after an

**Table 4** Risk of bias for non-trial papers using Risk of Bias in Non-randomised Studies of Interventions (ROBINS-1)[27]

Study	Confounding	Selection	Classification of intervention	Deviation from intended intervention	Missing data	Measurement of outcomes	Reported result	Overall
Bobbio et al. [15]	●	●	●	●	?	●	●	●
Divisi et al. [17]	●	●	●	●	?	●	●	●
Mujovic et al. [18]	●	●	●	●	?	●	●	●
Ries et al. [20]	?	?	●	●	?	●	●	●
Mujovic et al. [19]	●	●	●	●	?	●	●	●
Saito et al. [21]	●	●	●	●	?	●	●	●
Sekine et al. [22]	●	●	●	●	?	●	●	●
Stefanelli et al. [23]	●	●	●	?	?	●	●	●
Vagvolgyi et al. [24]	●	●	●	?	?	●	●	●

Green circle ● = low risk of bias: comparable to a well performed randomised trial with regard to this domain; yellow circle ● = moderate risk of bias: sound for a non-randomised study with regard to this domain but not comparable to a well-performed randomised trial; orange circle ● = serious risk of bias: presence of some important problems; red circle ● = critical risk of bias: too problematic to provide any useful evidence on the effects of intervention; question mark ? = no information, insufficient information provided to determine any risk of bias. Overall risk of bias is equal to the highest level of bias found in any domain.

acute exacerbation of chronic obstructive pulmonary disease [62].

Pulmonary rehabilitation programmes are cost effective. The total cost for a typical programme is estimated to be £725 (£862/\$954) per patient [63], and the cost for a 'maintenance' session after the initial course is estimated to be £14 (£17/\$18) [64, 65]. Although there is growing interest in pulmonary rehabilitation in the peri-operative period, the evidence base is limited [14–25]. Here we appraise that evidence to justify the need for definitive studies.

Marlow et al. (Marlow et al., unpublished observations, <https://www.medrxiv.org/content/10.1101/19007914v1>) performed a study (NIHR study reference: PB-PG-1215-20040) testing feasibility of a randomised controlled trial of pre-operative pulmonary rehabilitation in patients with chronic obstructive pulmonary disease scheduled for major surgery. Unfortunately, the study was closed early due to difficulties in identifying and recruiting participants. A major challenge was that eligible patients tended to be identified too late in the surgical pathway [Marlow et al., unpublished observations, <https://www.medrxiv.org/content/10.1101/19007914v1>].

The strongest evidence that pulmonary rehabilitation confers benefit to surgical patients with chronic obstructive pulmonary disease comes from the National Emphysema Treatment Trial, in which 1218 participants received pulmonary rehabilitation before random allocation to lung volume reduction surgery or conventional medical therapy [20, 66]. This study demonstrated that pulmonary rehabilitation in the pre-operative period is an achievable

intervention with no reported negative effects, and that the benefits of pulmonary rehabilitation were equivalent to what would be expected for the treatment of stable chronic obstructive pulmonary disease. The main limitation to the trial was that pulmonary rehabilitation was an entry criterion to randomisation, so it is impossible to ascertain the effect of pulmonary rehabilitation on surgical outcome.

In the 12 studies found in our second literature search on pulmonary rehabilitation in the peri-operative period [14–25], only seven rehabilitation programmes met the criteria for 'pulmonary rehabilitation' defined earlier based on the national chronic obstructive pulmonary disease pulmonary rehabilitation audit [48], and there was widespread variation in duration, setting, exercise component, measured outcomes and educational components of each programme (Table 2). Outcome measures studied varied considerably, with four studies reporting postoperative clinical outcomes and three studies reporting quality of life measures (Table 1). The risk of bias is high in almost all the analysed studies (Tables 3 and 4). For example, pre-operative pulmonary rehabilitation decreased the length of stay in hospital by up to 9 days in one cohort study of 22 participants in the intervention group [22]. One small randomised controlled trial of 19 participants reported fewer days requiring a chest drain postoperatively in the pulmonary rehabilitation arm [14]. No statistically significant differences were found for other clinical postoperative outcomes such as tracheal re-intubation and the incidence of postoperative pneumonia in the three studies that reported these measures [14, 21–

22], but the first was an underpowered randomised controlled trial with only 19 patients [14]; the second was a retrospective cohort study which had unclear definitions of 'postoperative complications' [21]; and the third was a prospective study of 22 patients where the pulmonary rehabilitation intervention was adjusted by the physiotherapist or surgeon in charge with no reporting of what each patient eventually received [22].

Overall, none of the studies reviewed reported harm from pulmonary rehabilitation, but the reported improvements in forced expiratory volume in 1 second (FEV1), 6-minute walking distance, maximal oxygen consumption and other parameters must be interpreted with caution based on the relatively small sample sizes (range 12 to 238 excluding the paper describing the National Emphysema Treatment Trial results), biases in methodology (Tables 1, 3 and 4) and heterogeneity in the pulmonary rehabilitation programmes (Table 2).

Patients on lung transplant waiting lists with chronic obstructive pulmonary disease form a specific subgroup, often with severe disease but with limited management options and an unpredictable waiting time to surgery once the decision to operate has been made. It may be possible to use this time as an opportunity for pulmonary rehabilitation to improve quality of life and functional ability [67]. Some lung transplant programmes have made pulmonary rehabilitation a pre-requisite before patients are listed for surgery; there have been suggestions that the extent of improvement in exercise capacity after pre-operative pulmonary rehabilitation may predict postoperative recovery [67].

Patients with chronic obstructive pulmonary disease presenting to pre-operative assessment clinics for elective surgery should be treated following the National Institute of Care and Clinical Excellence (NICE) guidelines for stable chronic obstructive pulmonary disease [29]. These include a referral to pulmonary rehabilitation. Patients who are scheduled for more urgent operations, such as those for cancer, present a different challenge.

Participants need to commit time, energy and effort to pulmonary rehabilitation programmes. While there are strong beneficial effects for participants with stable chronic obstructive pulmonary disease who complete the programme, approximately 25% of participants do not complete the programme [48]. The main barriers to uptake and completion of pulmonary rehabilitation are: other comorbidities; lack of perceived benefit; transport issues; depression; exacerbation and hospitalisation during the programme; and other calls on participant's time [48, 68].

In the peri-operative setting, one randomised controlled trial experienced difficulty recruiting participants

because patients were not willing to delay their surgery by 4 weeks in order to take part in pulmonary rehabilitation [14]. Patients may have other concurrent investigations and treatment such as chemotherapy before their operations, which may also create a potential barrier to their ability to participate. Thus, further work is required to find ways to overcome the various barriers to pulmonary rehabilitation in the peri-operative setting.

Despite strong evidence supporting the beneficial effects of pulmonary rehabilitation in the treatment of stable chronic obstructive pulmonary disease [31, 47], currently available evidence supporting specific effects on peri-operative outcomes is of low quality. If the benefits in stable chronic obstructive pulmonary disease were found to be transferable to the peri-operative period, then pulmonary rehabilitation for surgical patients could potentially be implemented into existing programmes, as the framework is already well established within the National Health Service.

### **Nutrition**

Chronic obstructive pulmonary disease is a disease requiring high metabolic energy expenditure, often causing severe weight loss [69]. A retrospective cohort study of 400 people with the condition found that a low body mass index was a significant independent predictor for increased mortality [70]. Failure to gain weight with nutritional supplementation is a poor prognostic sign in chronic obstructive pulmonary disease.

The 2012 update of the Cochrane review on nutritional supplements for patients with chronic obstructive pulmonary disease differed from previous versions, showing that nutritional supplementation promotes significant weight gain among patients with chronic obstructive pulmonary disease; particularly if patients are malnourished [71]. Weight gain of as little as 2 kg can improve patients' functional states in stable disease, as well as in exacerbations [70, 72]. A post-hoc analysis of randomised controlled trial data for 203 patients with chronic obstructive pulmonary disease found that weight gain of more than 2 kg every 8 weeks was possible with nutritional supplementation [70]. Forli et al. conducted a prospective randomised study of 46 chronic obstructive pulmonary disease patients on the lung transplant waiting list who were randomised to receive nutritional supplements or no intervention [73]. They found that an energy intake of 180% of resting energy expenditure could induce weight gain of 2 kg [73]. They noted that inpatient interventions to improve nutritional state before surgery appear more effective than outpatient interventions; in contrast to the findings of the Cochrane review, they found that patients receiving their ordinary diet were more likely to



gain weight than those receiving nutritional supplements [73]. However, the study was prone to bias, as participants recorded their food intake themselves throughout the study (as outpatients for 7 days before their hospital stay and for 3 days during their hospital stay)[73].

### **Smoking cessation**

A report by the Royal College of Anaesthetists states that patients with chronic obstructive pulmonary disease undergoing surgery, smoking cessation is associated with: reduced symptom burden; improved postoperative wound healing and surgical outcomes; and reduced length of stay in critical care [74]. The Royal College of Physicians published a report on tobacco dependency in the NHS [75] which estimated that the additional cost of care for a smoker who develops a surgical site infection due to smoking ranged between £814 (€968/\$1071) to £6626 (€7882/\$8719), and in 2015/16, the smoking-attributable cost of wound infection following surgery was more than £2.5 million (€2.9 million/\$3.3 million)[75].

A joint briefing by the Royal College of Anaesthetists and Royal College of Surgeons with the Faculty of Public Health and Action on Smoking and Health has emphasised the importance of quitting smoking in the peri-operative period and has suggested methods to encourage smoking cessation [74]. These methods include a combination of pharmacotherapy and behavioural support to help smokers stop smoking. There is also a growing use of technological support for smoking cessation, such as smartphone applications, and growing use of financial incentives to help motivate smokers to stop smoking [75]. Drugs available include dual nicotine replacement, varenicline, bupropion, nortriptyline and cytosine. A Cochrane review showed that intensive 4- to 8-week interventions such as nicotine replacement therapy and counselling in a group of peri-operative smokers could also increase the likelihood of long-term smoking cessation postoperatively [76].

Smoking cessation is a standard component of pulmonary rehabilitation. Thus an effective peri-operative pulmonary rehabilitation programme would have an additional benefit of contributing to the NHS Trust's activities in the tobacco and alcohol commissioning for quality and innovation (CQUIN) scheme, which was updated in March 2019 [77].

### **Symptom optimisation**

We are just beginning to understand the subtleties of the connection between objective disease markers of disease severity (e.g. lung function tests), psychological functioning, and breathlessness [78]. It is becoming clearer that the

connections between physical and mental health may have a strong influence on physical health outcomes, patient choice and behaviour [79, 80].

In the current literature, mood (anxiety and depression) is the most commonly measured psychological factor in studies of chronic obstructive pulmonary disease. Mood disturbances occur in one in four people with chronic obstructive pulmonary disease [81]. Importantly, psychological functioning is considerably more complex and nuanced than simply 'mood', yet few studies delve any more deeply than this.

Patients with psychological distress (including mood disturbances) have worse physical health outcomes. One example is a higher risk of mortality, HR (95%CI) 1.93 (1.04–3.58);  $p < 0.1$ , after admission for an exacerbation even after adjusting for duration and severity of chronic obstructive pulmonary disease [82]. The experience and severity of clinical symptoms such as breathlessness is higher among patients with chronic obstructive pulmonary disease who have depression and anxiety than those without these psychological disorders (unstandardised regression coefficient,  $B = 0.75$ ,  $p = 0.028$ ) [83], and one study demonstrated that breathlessness is a stronger predictor of survival in chronic obstructive pulmonary disease than spirometry [84].

Meta-analysis of a number of randomised controlled trials reported that mind-body interventions such as tai chi, yoga, relaxation and mindfulness were associated with significant improvements in physical outcomes (measured using the chronic respiratory questionnaire dyspnoea scale and 6-minute walking distance) and mood (anxiety and depression) [85–88].

There are no studies investigating mental health interventions in patients with chronic obstructive pulmonary disease in the peri-operative period, but neuroimaging research has suggested that part of the benefit of pulmonary rehabilitation may relate to alterations in brain functioning relating to the processing of breathlessness and anxiety sensations [79]. Pulmonary rehabilitation could also be an ideal opportunity for appropriately selected patients to participate in mind-body interventions [89].

### **Lung volume reduction procedures**

Lung volume reduction surgery involves surgical removal of emphysematous lung tissue from the most diseased parts of the lung. It was originally developed as a palliative procedure. The previously mentioned National Emphysema Treatment Trial was a multicentre randomised controlled crossover trial studying the effects of lung volume reduction surgery on mortality and maximal work-load [66]. The trial

demonstrated that lung volume reduction surgery reduced mortality among patients with predominantly upper lobe emphysema and low exercise capacity (risk ratio for death 0.47,  $p = 0.005$ ). A Cochrane review of 11 studies showed that lung volume reduction surgery is effective for selected patients with diffuse emphysema but is associated with risks of early mortality and adverse events [90].

Results in modern practice with unilateral video-assisted thoracic surgery (as opposed to bilateral surgery) are good and the procedure is generally well tolerated in appropriately selected patients managed through a multi-disciplinary team [91, 92]. Most of these patients would have received a full course of pulmonary rehabilitation before lung volume reduction surgery. The 6-week period used for pulmonary rehabilitation would increase the time available for other optimisation techniques such as smoking cessation and nutritional interventions.

Systematic review evidence from observational studies has shown that lung volume reduction surgery could be used as an optimisation measure to delay patients from requiring lung transplant surgery, or to offer temporary improvement while patients await their transplant surgery [93].

There has been extensive interest in bronchoscopically placed valves in the lung in patients with severe emphysema, [94–99] with guidance from the National Institute for Health and Clinical Excellence (NICE) on its use [100]. These are only effective in people who have intact interlobar fissures, as collateral ventilation between the target lobe and adjacent lung prevents target lobe atelectasis from occurring. The results of direct comparison trials in patients who are eligible for both lung volume reduction surgery and endobronchial valve treatment are awaited [101].

### **Pharmacological optimisation**

The main pharmacological interventions for stable chronic obstructive pulmonary disease are well described in the NICE guidelines [29]. Few studies have been carried out on alternative or additional specific pharmacological agents in peri-operative chronic obstructive pulmonary disease management. A double-blinded randomised study of 40 patients found that pre-treatment with 20 mg oral prednisolone reduces the rates of tracheal re-intubation, and duration of hospital stay compared with placebo for cardiopulmonary bypass surgery [102]. A retrospective study of 104 patients showed that pre-treatment with inhaled bronchodilator and steroids for 10 days before the day of surgery improved extubation times and length of stay in hospital postoperatively, but the study was at risk of bias

from missing data at time of selection and comparison with a historical cohort [103].

### **Implications for research**

There is an unmet need to work out ways to deliver pulmonary rehabilitation within a surgical pathway, both locally and nationally. The pathways for respiratory evaluation are best established in cardiothoracic surgery, and a peri-operative trial comparing 3 weeks of pre-operative home pulmonary rehabilitation versus control has recently been approved [104]. For other types of major surgery however, the short time frame between anaesthetic pre-assessment and the day of surgery, and multiple steps and teams involved in the patients' journeys needs consideration when designing a randomised controlled trial [Marlow et al, unpublished observations, <https://www.medrxiv.org/content/10.1101/19007914v1>]. Alternative research methods may be required to build the evidence base.

Observational studies to scope out local patient pathways and time between each point (e.g. average duration between decision to operate and day of operation) could be useful to help identify time points in the pathways where modifications can occur. Quality improvement projects incorporating 'plan, do, study and act' cycles could be conducted to improve adherence to NICE guidelines and local peri-operative guidelines for chronic obstructive pulmonary disease. Qualitative studies interviewing stakeholders and knowledge into action frameworks such as the SHIFT-Evidence framework [105] for bringing evidence into practice can help change practice at a policy-making level that could lead to better systems and outcomes alongside stakeholder engagement and infrastructure changes.

The importance of patient and public involvement in pulmonary rehabilitation studies cannot be overstated. Patients and their advocates could be consulted on the pragmatic aspects of achieving a higher completion rate for patients who are enrolled in pulmonary rehabilitation programmes. Local focus groups may also be helpful in determining barriers to completing pulmonary rehabilitation programme and possible solutions. Community services and 'lay health worker' involvement may improve patient participation in pulmonary rehabilitation [106, 107].

In terms of peri-operative pulmonary rehabilitation, unanswered questions include the health economics of a peri-operative pulmonary rehabilitation programme, as well as the extent of the clinically important difference that peri-operative pulmonary rehabilitation can confer on chronic

obstructive pulmonary disease patients undergoing surgery. While the ideal components of a pulmonary rehabilitation programme have been extensively studied, it is unclear if an 'abbreviated' peri-operative programme with fewer sessions or components would still confer the same benefits as a standard programme for people with stable disease.

A better understanding of a person's mental health needs may influence the peri-operative outcomes for chronic obstructive pulmonary disease. This may have wide-ranging applications including helping with our understanding of other chronic diseases or diseases linked to addictive substances. Future work on this subject needs to take a broader approach rather than continue to perpetuate the conflation of mood with a broader psychological functioning.

### Implications for clinical practice

The first step to improving the peri-operative outcomes for chronic obstructive pulmonary disease patients is to make the diagnosis: consider using simple methods such as spirometry for any patient presenting to peri-operative services with a smoking history or using the 'Breathing SPACE' approach to evaluate patients with long-term breathlessness [28].

Once the diagnosis of chronic obstructive pulmonary disease is made, all patients should be managed in accordance with the five fundamental principles described in the NICE guidelines [29], which includes a referral to pulmonary rehabilitation in all eligible patients. The local routes of referral and criteria for eligibility for pulmonary rehabilitation services should be clarified.

Peri-operative medicine units could form networks with respiratory medicine to help improve access and increase the time available before surgery to institute interventions such as pharmacological management, or conduct further investigations. Collaboration with mental health services can be key to improving cross-specialty understanding of patients' mental health needs and providing high-quality holistic care for patients with chronic obstructive pulmonary disease as well as patients with other mental health conditions.

Implementing a 'chronic obstructive pulmonary disease pathway' for peri-operative medicine may be a method to best prepare people with COPD for surgery.

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## Supporting Information

Additional supporting information may be found online via the journal website.

**Table S1.** Search terms used for first search.

**Table S2.** Search terms used for second search.

**Figure S1.** Search 1 study flow diagram.

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