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Early View

Task force report

European Respiratory Society Clinical Practice Guideline on symptom management for adults with serious respiratory illness

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European Respiratory Society Clinical Practice Guideline on symptom management for adults with serious respiratory illness

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Take home message [253 characters]: This ERS taskforce provides recommendations on symptom management in adults with serious respiratory illness including multicomponent services, graded exercise therapy, fan therapy, breathing techniques, supplemental oxygen, opioids, and needs assessment.

ABSTRACT

Respiratory symptoms are ubiquitous and impair health-related quality of life in people with respiratory disease. This European Respiratory Society (ERS) task force aimed to provide recommendations for symptomatic treatment in people with serious respiratory illness.

The ERS task force comprised 16 members, including representatives of people with serious respiratory illness and informal caregivers. Seven questions were formulated, six in the 'Population, Intervention, Comparison, Outcome' (PICO) format, which were addressed with full systematic reviews and evidence assessed using Grading of Recommendations Assessment, Development and Evaluation (GRADE). One question was addressed narratively. An 'evidence-to-decision' framework was used to formulate recommendations.

To treat symptoms in people with serious respiratory illness, the task force suggests the use of graded exercise therapy (conditional recommendation, low certainty of evidence); and suggests the use of a multicomponent services, handheld fan and breathing techniques (conditional recommendations, very low certainty of evidence). The task force suggests not to use opioids (conditional recommendation, very low certainty of evidence); and suggests either administering or not administering supplemental oxygen therapy (conditional recommendation, low certainty of evidence). The task force suggests that needs assessment tools may be used as part of a comprehensive needs assessment, but do not replace patient centred care and shared decision making (conditional recommendation, low certainty of evidence). The low certainty of evidence, modest impact of interventions on patient-centred outcomes, and absence of effective strategies to ameliorate cough highlight the need for new approaches to reduce symptoms and enhance wellbeing for individuals who live with serious respiratory illness.

INTRODUCTION

Chronic lung diseases, such as chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD), are among the leading causes of disability and premature death worldwide [1]. Respiratory symptoms, predominantly breathlessness and cough, are widely reported by people with serious respiratory illness and adversely impact health-related quality of life (HrQoL) [2, 3]. Breathlessness may be insufficiently recognised [4] and under-treated [5]. A European Respiratory Society (ERS) Guideline recently recommended that palliative care, including symptomatic treatment, is provided when physical, psychological, social or existential needs are identified through holistic needs assessment, and that palliative treatment is integrated into routine respiratory care [6]. The need for evidence-based symptomatic treatment is immense.

A range of interventions that aim to alleviate respiratory symptoms are used in clinical practice, including non-pharmacological approaches such as multicomponent breathlessness services, graded exercise therapy, increased airflow, breathing techniques, and supplemental oxygen; and pharmacological treatments such as opioids. However, there is no clinical practice guideline to inform evidence-based decision making for effective symptom management in people with serious respiratory illness. The aim of this European Respiratory Society (ERS) task force was to provide recommendations for symptomatic treatment in people with serious respiratory illness.

METHODS

We used ERS methodology for clinical practice guideline development [7, 8]. The task force (co-chaired by AEH, ME and NS) consisted of 16 members, including four representatives of people living with COPD or ILD and informal caregivers, and specialists in nursing, respiratory medicine, palliative care, physiotherapy, pharmacy, and methodology. Seven early career members were included (NS, AR, AS, CR, AB, AP, ZA). Conflicts of interest were declared and managed according to ERS policies. A methodologist (TT) ensured that ERS methodological requirements were met. An information specialist (LR) provided search expertise, and four postdoctoral researchers (ZA, AB, AP, AG) assisted with systematic reviews, but did not participate in formulation of questions or recommendations.

Six PICO questions and one narrative question were selected by ranking and consensus (see online supplement), with input from task force members and patient representatives. Outcomes were also selected by ranking and consensus, with the highest ranked outcome designated as 'critical' and others as 'important'. Subgroups of task force members worked on each question via teleconference, with two in-person meetings in September 2022 and September 2023. The evidence synthesis and evidence profile for PICO question four were prepared by external methodologists.

We defined serious illness related to respiratory disease (hereafter referred to as 'serious respiratory illness') as a respiratory condition that carries a high risk of mortality, negatively impacts quality of life and daily function, and/or is burdensome in symptoms, treatments, or caregiver stress [9]. All underlying diagnoses of lung disease were included except lung cancer, as symptom management guidelines for this group are available elsewhere [10, 11].

For each included question, a search strategy was designed and executed by the information specialist (LR) (see online supplement). Randomised controlled trials (RCTs) were used as the main body of evidence. Relevant RCTs were identified from previous systematic reviews where available, followed

by additional searches to identify RCTs published more recently. For each question, a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram documented the identification of studies [12]. Two task force members or external methodologists independently extracted data and assessed risk of bias using the Cochrane Risk of Bias 1 tool [13]. Where data were clinically homogeneous, meta-analysis using a random effects model was conducted using Revman software [14].

GRADE evidence profiles were created for each PICO question [15, 16]. Certainty of evidence for each outcome was rated as high, moderate, low, or very low. For the non-PICO question, the evidence was summarized narratively and certainty was assessed for the body of evidence, using the GRADE domains. For all questions the evidence-to-decision framework was used to structure discussions and to document the factors considered for the recommendations [17, 18]. Draft recommendations were discussed at meetings of the task force, including patient representatives, until consensus was reached. Task force chairs (AH and ME) held an additional meeting with representatives of people with COPD or ILD to discuss the recommendations. The strength of the recommendations was rated as either strong (phrased with "We recommend") or conditional (phrased with "We suggest") [19, 20].

RESULTS

Recommendations for clinical practice are in Table 1, with recommendations for research in Table 2. The PRISMA diagrams, complete list of included studies, GRADE evidence profiles and evidence-to-decision tables are in the online supplement.

Question 1: Should a multicomponent service be used to reduce symptoms in people with serious respiratory illness?

Recommendation: We suggest that multicomponent services should be used to reduce symptoms in people with serious respiratory illness (conditional recommendation, very low certainty of evidence).

Summary of evidence: A multicomponent service is a model of care that offers more than one intervention, including at least one non-pharmacological intervention. Patients are enrolled due to symptoms, not diagnosis; pulmonary rehabilitation and disease-specific services were considered outside the scope of this review.

The search identified one relevant systematic review [21] with four eligible RCTs. The search for additional RCTs identified 1393 records, of which 14 were screened in full text, identifying one additional RCT. Five RCTs (439 participants) were included. Two recruited only people with non-malignant lung disease, predominantly COPD [22, 23]. Three studies involved mixed populations [24-26]; authors provided data for participants with non-malignant lung disease for two of these. Three studies evaluated similar multicomponent interventions, involving individualized self-management support from a multidisciplinary team at home or as an outpatient, using predominantly non-pharmacological approaches such as breathing and relaxation techniques [22, 24, 26]. Another study published as abstract involved a similar intervention delivered by nurses [23]. One study not included in meta-analyses (n=13 participants) tested the feasibility of a brief paramedic intervention at emergency call-out [25]. The four studies included in meta-analyses measured primary end points at 4-8 weeks.

Our critical outcome of breathlessness was evaluated using the Chronic Respiratory Questionnaire (CRQ) and four different breathlessness numerical rating scale (NRS) scores. Multicomponent services improved breathlessness mastery (CRQ mastery) compared to usual care (mean difference (MD) 0.43 points, 95% confidence interval [95% CI] 0.20 to 0.67, 3 RCTs, 327 participants) [22, 24, 26]. The mean effect did not exceed the minimum important difference (MID) of 0.5 points [27]. Multicomponent

services improved average breathlessness measured using the 0-10 NRS over 24 hours (MD -0.50 points, 95% CI -1.00 to 0.00, 2 RCTs, 238 participants); the lower limit of the CI included the MID of 1 point [28]. Three other breathlessness NRS measures improved with intervention compared to control, but were not statistically significant (NRS distress from breathlessness MD -0.24 points, 95% CI -1.30 to 0.82, 1 RCT 87 participants [24]; NRS worst breathlessness in last 24 hours MD -0.58 points, 95% CI-2.09 to 0.94, 1 RCT, 65 participants [24]; NRS severity of breathlessness on exertion in last 24 hours MD -0.84 points, 95% CI -1.92 to 0.25, 1 RCT, 65 participants [24]). The lower end of the CI included the MID (1 point) and clinically relevant effects could not be excluded.

Multicomponent services improved the important outcome of HrQoL compared to usual care (CRQ total score, MD 0.24 points, 95% CI 0.04 to 0.40, 2 RCTs, 237 participants), although the upper end of the CI did not include the MID (0.5 points) [24, 26]. The CRQ dyspnoea domain improved with multicomponent services (MD 0.13 points,95% CI -0.10 to 0.36, 3 RCTs, 259 participants), however the CI did not include the MID of 0.5 points [23, 24, 26]. The important outcome of fatigue did not improve with multicomponent services (CRQ fatigue, MD 0.10 points, 95% CI -0.16 to 0.37, 3 RCTs, 261 participants) [23, 24, 26]. Cough was not evaluated in any study.

One study reported adverse events [26]. In the intervention arm, 44/71 participants (62%) experienced 65 events (two were considered related to the intervention: a skin reaction following an allergy test, and a side effect from morphine) and 48/80 participants in the control arm (60%) experienced 79 events. Survival from randomisation to six months was better in the breathlessness support service group (intervention) than the control group (50 of 53 [94%] vs 39 of 52 [75%]); survival differences were significant for both COPD and ILD [24].

Direct costs to deliver multicomponent services were low. One study reported average costs of €357 (SD €132) per patient, with specialist respiratory physiotherapy (€157, SD €59; 44% of costs) and visits

to palliative medicine specialists (€128, SD €47; 36% of costs) as major components [26]. Another study reported average cost of the intervention was £156 (SD £80) per patient [22, 26]. Cost-effectiveness was reported in three studies, with inconsistent findings, which may reflect variation across healthcare systems [22, 24, 26]; one study reported that total care costs varied substantially between individuals [22].

The overall certainty of evidence was very low. Certainty of evidence was affected by risk of bias, mainly detection and reporting bias, imprecision, and baseline variation in outcomes between groups.

***Justification**:* This recommendation places a high value on consistent improvements in breathlessness mastery and HrQoL with multicomponent services, with minimal risk and low direct costs. Although mean effects did not always reach the MID, the confidence interval included the MID for our critical outcome of breathlessness. The accepted MIDs for breathlessness were not generated in people with serious respiratory illness, so it is possible that smaller improvements in breathlessness could be clinically important. Multicomponent services are valued by patients, as they address gaps in current health care and deliver meaningful improvements in daily life and at points of breathlessness crisis [22, 24-26].

***Implementation considerations**:* All studies evaluated services embedded in palliative care and/or respiratory services, suggesting that implementation is feasible in these settings. The feasibility of implementation in primary care is unknown. Costs for staffing, materials and infrastructure may vary across countries and health systems. It may be more feasible to deliver multicomponent services in higher income countries, where there is an established infrastructure and greater access to a multidisciplinary team.

***Research priorities**:* Understanding the predictors of benefit from multicomponent services would facilitate efficient resource use and delivery of personalised healthcare. Future trials should have extended followup periods, to examine the longer-term impact of multicomponent services, and include participants from diverse racial and ethnic backgrounds. Future research should assess the acceptability and effectiveness of virtual or hybrid multicomponent services. Research is needed to evaluate how best to integrate multicomponent services alongside existing services, such as pulmonary rehabilitation.

Question 2: Should graded exercise therapy be used to reduce fatigue in people with serious respiratory illness?

***Recommendation*:** We suggest that graded exercise therapy be used to reduce fatigue in people with serious respiratory illness (conditional recommendation, low certainty of evidence).

Summary of evidence: Graded exercise therapy (GET) involves establishing a baseline of achievable exercise or physical activity and then making fixed incremental increases in the time spent being physically active. GET is a component of pulmonary rehabilitation, which also includes education and behavior change. We did not include GET conducted in the context of pulmonary rehabilitation in this evidence synthesis, in order to evaluate the effects of GET as a standalone intervention.

The search for systematic reviews identified 1,567 records, of which 38 were screened in full text. 12 relevant systematic reviews were identified with 74 eligible RCTs. The search for additional RCTs identified 6750 records, of which 203 were screened in full text, identifying an additional 2 RCTs.

We included 76 RCTs (3309 participants) including people with COPD (n=41 RCTs), asthma (n=10), ILD (n=7), pulmonary hypertension (n=7), cystic fibrosis (n=4), bronchiectasis (n=2) and mixed respiratory

disease (n=5). Participants were older adults with moderate-to-severe lung disease. Interventions were primarily supervised GET for 8-12 weeks in an outpatient setting, including aerobic exercise. A smaller number of studies evaluated resistance training, water-based exercise or Tai Chi.

For our critical outcome of fatigue, GET improved CRQ fatigue compared to usual care (MD 0.53 points, 95% CI 0.41 to 0.65, 11 RCTs, 624 participants). The mean effect exceeded the MID (0.5 points) [29]. Similar effects were seen in COPD (MD 0.65, 95% CI 0.46 to 0.84; 7 RCTs, 338 participants) and ILD (MD 0.65, 95% CI 0.37 to 0.92; 3 RCTs, 210 participants). In bronchiectasis the mean effect was smaller, but the upper end of the confidence interval exceeded the MID (MD 0.38, 95% CI 0.20 to 0.56; 1 RCT, 76 participants).

Graded exercise therapy improved the important outcome of HrQoL compared to usual care measured using the St George's Respiratory Questionnaire (SGRQ) total score (MD -14.07 points, 95% CI -18.85 to -9.30, 15 RCTs, 627 participants) with the upper end of the CI exceeding the MID (-4 points) [30]. There were improvements in CRQ total score (MD 0.34 points, 95%CI 0.15 to 0.54, 6 RCTs, 419 participants), with a CI that included the MID (0.5 points) [29]. Clinically important effects of GET were evident in COPD (SGRQ MD -16.68, 95%CI -24.05 to -9.31, 9 RCTs, 376 participants) and ILD (MD -8.00, 95%CI -10.57 to -5.43, 4 RCTs, 213 participants).

No serious adverse events related to GET were reported (46 RCTs, 2,030 participants), although a few studies noted mild muscle soreness following exercise. There was no evidence of increased exacerbations, hospitalisations or deaths related to GET (online supplement). Studies in pulmonary hypertension rarely included patients in Functional Class IV, where the risk of adverse events with exercise may be higher. An uncontrolled study of pulmonary rehabilitation (including GET) for pulmonary hypertension reported adverse events in 13.6% of 183 patients, with most being mild [31], including syncope, pre-syncope, respiratory infection and minor haemoptysis.

The overall certainty of evidence was low. Certainty of evidence was affected by detection bias (lack of assessor blinding), reporting bias (trials not registered prospectively) and indirectness (limited data in pulmonary hypertension and bronchiectasis). No studies included people near the very end of life. Fatigue-specific outcome measures were rarely used.

***Justification for the recommendation**:* This recommendation places a high value on consistent improvements in fatigue and HrQoL for people who undertook GET. People living with serious respiratory illness report unmet needs for interventions to reduce fatigue [32, 33] and perceive that supervised, supported and individualized exercise may be useful [32]. The likelihood of undesirable effects was low in RCTs, noting that these studies were conducted in supervised environments using trained staff, and patients with very severe disease were rarely included. GET is within the scope of physical therapists and exercise physiologists and requires no specialised equipment, so could be made widely accessible.

***Implementation considerations**:* GET is a component of pulmonary rehabilitation programs, which are well established in many countries. However, there are disparities in access to pulmonary rehabilitation, which may reduce feasibility in some locations [34]. The patient-related barriers that reduce uptake of pulmonary rehabilitation are likely relevant to GET, including fear of exercise and lack of perceived benefit [35], challenges related to travel and transport, and costs of attendance [36]. Health professionals should explore and address these barriers when referring a patient for GET. For patients with severe pulmonary hypertension or a history of arrhythmia, syncope or pre-syncope during exercise, consider additional monitoring from staff with expertise in delivering GET for this group.

***Recommendations for future research**:* Clinical trials examining the benefits of GET for people with severe lung disease are needed, including those with severe hemodynamic impairment. Many of the participants in existing trials had mild-moderate fatigue, and the impact of GET in those with severe fatigue remains to be examined, including its impact on post-exertional symptoms. Fatigue-specific outcome measures should be used. The cost-effectiveness of GET should be examined, including remote delivery models that could decrease costs and increase accessibility.

Question 3: Should increased airflow be used to reduce breathlessness in people with serious respiratory illness?

Recommendation: We suggest the use of increased airflow to reduce breathlessness in people with serious respiratory illness (conditional recommendation, very low certainty of evidence).

Summary of evidence: Increased airflow was defined as airflow delivered via a fan (handheld or table) or non–oxygen-enriched compressed air, and directed at the cheek of the face, nasal mucosae or mouth [37]. Nasal intermittent positive pressure ventilation was excluded.

The search for systematic reviews identified 742 records, of which 26 were screened in full text. Five relevant systematic reviews were identified [37-39] with 4 eligible studies. The search for additional RCTs identified 487 records, with 23 screened in full text, identifying 2 additional studies. We included four RCTs [40-43] and two crossover trials [44, 45]. One additional RCT (49 participants) could not be included as only 73% of participants had chronic lung disease, and data could not be obtained separately; however, results were similar to included studies [46]. The studies included people with COPD (n=127), ILD (n=56), asthma (n=8), and bronchiectasis (n=7). Interventions were a hand-held fan (5 studies) or pedestal fan (1 study) [45]. The fan was applied to the face, either at rest in the

laboratory (1 study) [45], during an exercise test (2 studies) [40, 44], or during daily life [41-43](3 studies).

For our critical outcome of breathlessness, increased airflow using a hand-held fan to the face during daily life for 28 days did not reduce breathlessness intensity measured using the 0-10 NRS average score over 24 hours (MD 0.90 points, 95% CI -0.95 to 2.75, 1 RCT, 20 participants) or 0-10 NRS worst score over 24 hours (MD 0.80 points, 95% CI -1.01 to 2.61, 1 RCT, 20 participants) [40]. There were similar findings for breathlessness distress and unpleasantness [40]. A hand-held fan did not reduce breathlessness measured using Dyspnoea-12 (D12) at day 14 compared to usual care (MD -2.2 points, 95% CI -6.4 to 1.9 points, 1 RCT, 30 participants) [41]. However the CIs included the MID (-1 units for NRS [28], -3 to -6 units for D12 [47, 48]), so a benefit cannot be excluded. Increased airflow reduced breathlessness on the Visual Analogue Scale after 5 minutes at rest (MD -7.0mm, 95%CI 95% -11.7 to -2.5mm, 1 randomised crossover trial, 27 participants) with the CI including the MID (10mm) [42]. Airflow reduced modified Borg breathlessness score at iso-time during a constant work rate exercise test (MD -3.19, 95%CI -11.55 to 5.17, 1 RCT, 10 participants) [45]. The CI was wide and included the MID (1 unit) [45].

Increased airflow did not improve the important outcome of HrQoL measured using the King's Brief Interstitial Lung Disease (KBILD) Breathlessness and Activities domain at 14 days compared to usual care (MD -1.5 points, 95% CI -8.9 to 5.9, 1 RCT, 30 participants) [41]. However, the CIs included the MID (7 points) [41], so a benefit cannot be excluded. One study reported on adverse events, a short-term crossover trial, with no adverse events during the study period [42].

The overall certainty of evidence was very low. Certainty of evidence was affected by the small number of studies and participants, precluding meta-analysis; detection bias (lack of assessor blinding) and

indirectness (all participants had COPD or ILD). No studies included people near the very end of life. Only one study in ILD measured HrQoL.

***Justification for the recommendation*:** This recommendation places a high value on acute reductions in breathlessness that may be clinically meaningful. However, the paucity of data reduces certainty regarding the effect size. We noted consistent, positive effects on exercise outcomes that were not pre-specified in our protocol (6-minute walk distance, endurance time, recovery time) [44, 45]. Qualitative data demonstrated that hand-held fan use was acceptable to patients, who reported relief of breathlessness, increased relaxation and shorter recovery time after exercise [37, 41, 49]. Consumer members of the task force highlighted that the perceived mechanisms of action included cooling of air as well as increased flow. A positive impact of cool air could occur via stimulation of the trigeminal nerves with activation of central brain regions involved in the anticipation and/or perception of breathlessness, including the insular cortex and amygdala [45]. Trigeminal nerve stimulation may contribute to breathlessness relief by altering the activity of brain regions involved in its central neural processing [50] and reduced neural ventilatory drive [51].

***Implementation considerations*:** Use of a hand-held fan requires little training (e.g., positioning of the fan to direct airflow at the face), so this intervention can be used by a wide range of patients. Environmental costs for fans (manufacturing plastic, battery use etc) should also be considered. The type of fan provided may influence acceptability and uptake, with patient preference for fans delivering increased intensity and pleasantness of airflow and reduced noise [52]. In practice, hand-held fans are implemented widely and provided to patients in a variety of contexts, including breathlessness clinics and by patient support organisations.

***Recommendations for future research*:** Clinical trials that are sufficiently powered to detect the effects of increased airflow on breathlessness and HrQoL are needed, and should include people with

a variety of chronic respiratory diseases and severity of breathlessness. Where increased airflow is applied during exercise testing, breathlessness should be measured at a standardised time point (iso-time), to allow a robust comparison across conditions. Future studies should investigate the optimal flow rate and fan speed for maximal therapeutic benefit.

Question 4: Should supplemental oxygen be used to reduce symptoms in people with serious respiratory illness?

Recommendation: We suggest either administering or not administering supplemental oxygen to reduce symptoms in people with serious respiratory illness (conditional recommendation, low certainty of evidence).

Summary of evidence: We included trials of supplemental oxygen therapy delivered through any non-invasive method at rest or during exertion. We excluded trials in people who were eligible for or treated with long-term oxygen therapy (LTOT), or trials of short-burst oxygen therapy delivered only before or after exertion.

The search for systematic reviews identified 1,710 records, of which 21 were screened in full text. Two relevant systematic reviews were identified [53, 54] with 26 eligible RCTs. The search for additional RCTs identified 1967 records, with 17 screened in full-text, identifying 11 additional RCTs. We included a total of 37 RCTs (42 reports) in the systematic review. We performed meta-analysis including 13 RCTs (245 participants) reporting the effect of supplemental oxygen on breathlessness during laboratory exercise testing [55-66], one RCT (213 participants) reporting breathlessness measured 'right now' in daily life [67], and 14 RCTs (1,062 participants) reporting the effect on HrQoL [67-80]. Participants had mild to moderate hypoxaemia at rest and/or hypoxaemia during exertion only. Most

had COPD or ILD. Given the differences in study design and approach, studies measuring outcomes during laboratory exercise tests or in daily life were not combined.

For the critical outcome of breathlessness, in people with exertional desaturation oxygen therapy (compared with air) decreased breathlessness at iso-time (SMD -0.75, 95% CI -1.23 to -0.28 , 13 RCTs, 245 participants) which is a moderate effect size [81]. In daily life, oxygen (compared with air) had no effect on breathlessness 'right now' over one week (SMD -0.08, 95%CI -0.41 to 0.26, 1 RCT, 213 participants) [67].

In daily life, oxygen (compared with sham treatment with air or no treatment) had no effect on the important outcome of HrQoL (SMD -0.06, -0.17 to 0.05, 14 RCTs, 1,062 participants). Adverse events were evaluated in 9 RCTs [66, 67, 69, 73, 75, 77, 82-84]. These studies reported a high rate of adverse events, but with similar rates across the oxygen and comparison group (air or no treatment) [67, 69, 73, 75]. Trials during exercise testing reported very few or no adverse events. Many adverse events related to nasal irritation or epistaxis, and some related to falls (oxygen tubing presenting a trip hazard). Few patients required hospitalisation for adverse events. Observational studies have shown a high prevalence of adverse events, mainly due to airway dryness or irritation [85, 86]. Risk of these adverse events is likely higher with greater hours of usage.

The overall certainty of evidence was low. Certainty of evidence was affected by selection bias (unclear random sequence generation and allocation concealment), detection bias (lack of assessor blinding) and indirectness (most participants had COPD or ILD). Few studies included people near the very end of life.

Justification of recommendation: In making this recommendation, the task force balanced the positive effects of oxygen on breathlessness in laboratory studies, the paucity of evidence that this

benefit extends into daily life, and the adverse effects and burdens that may be experienced when using oxygen therapy. Oxygen administered in the laboratory setting could improve breathlessness in some people with exertional desaturation. Whether this effect translates to home treatment was not clear. Oxygen treatment might cause adverse events, most of which are minor and can be effectively managed. However, oxygen treatment is related to feelings of shame and restricted physical and social activities in some people [85], which may outweigh any benefits and increase the burden for patients and caregivers. Our recommendation is consistent with guidelines from the British Thoracic Society that supplemental oxygen therapy should not be routinely offered to people who do not meet the criteria for LTOT [87]. The American Thoracic Society (ATS) made a conditional recommendation in favour of ambulatory oxygen therapy for patients with COPD or ILD with exertional desaturation [88], whereas this guideline focuses on the role of oxygen for symptom management.

Implementation considerations: In adults with serious respiratory illness, we suggest that oxygen therapy could be trialled for selected patients with severe breathlessness and exertional desaturation who are likely to use the treatment safely. A trial of oxygen versus air during exertion (e.g. a standardized walking test) may inform decision-making. The oxygen equipment and flow rate should be tailored to the patient's needs, using the lowest oxygen concentration possible to achieve clinical and symptomatic improvement. When supplemental oxygen is being considered to treat breathlessness, clear communication and shared decision-making are required, including the patient's goals, willingness and ability to use the treatment correctly, potential harms including in relation to smoking and contact with flames [89], and the broader impact on the patient's life. Information, interventions and support to reduce and stop smoking are important [89]. Clinicians and caregivers may require education and support regarding the use of oxygen for symptom management. Oxygen need, effectiveness, and harms should be monitored and managed, and oxygen therapy should be discontinued when there is no perceived net benefit.

***Recommendations for future research**:* The current evidence base is limited, with a need for high quality clinical trials testing the effect of oxygen on breathlessness in daily life across different respiratory diagnoses. In studies of exertional breathlessness it is important that the symptom of breathlessness is assessed at a standardised level of exertion (iso-time). Clinical trials should include health utility measures, to facilitate health economic analysis. There is an urgent need for improved oxygen delivery systems with capacity to deliver higher flow rates during ambulatory use.

Question 5: **Should opioids be used to reduce symptoms in people with serious respiratory illness?**

Recommendation: We suggest not using opioids for the treatment of breathlessness in people with serious respiratory illness (conditional recommendation against the intervention, very low certainty of evidence).

Summary of evidence: We considered studies of any opioid drug, given by intravenous, subcutaneous or oral routes in any dose, for the treatment of breathlessness or cough. The effects of opioids were considered separately for (i) opioids self-administered regularly at home for 4 consecutive days or greater with outcomes ideally measured in daily life (e.g., breathlessness 'now') at a singular (either morning or evening, combined averages of morning and evening, or an unspecified time) or multiple timepoints (both morning and evening separately) [90-100], and (ii) opioids administered as one or more doses in the laboratory setting with participants completing an exercise test, and the effect of one or more doses measured at varying times [95, 101-105].

The search for systematic reviews identified 2,736 records, of which 17 were screened in full text. Five relevant systematic reviews were identified, which included 15 eligible trials. The search for additional trials identified 2,332 records, with 14 screened in full text, and two additional trials included. One included trial published after the search date [92] was identified from a qualitative study identified

during the search [106]. We included 17 trials (876 participants). Eleven trials included only people with COPD (11 trials, 316 participants [92, 97-105]) though the majority of participants were from RCTs with mixed cohorts (4 trials, 505 participants [90, 91, 94, 95]). One trial included only people with PAH (19 participants [93]) and another only included people with ILD (36 participants [96]). Seven trials included participants with a modified Medical Research Council (mMRC) dyspnea score ≥3 [92, 94-96, 100, 105, 107], and 2 trials included participants with mMRC ≥2 [99, 108].

For our critical outcome of breathlessness, opioids did not reduce breathlessness intensity measured in daily life compared to the comparator (placebo in all studies, except one which used promethazine) measured either in the morning (SMD -0.10, 95% CI -0.64 to 0.43, 10 trials, 795 participants) or evening (SMD -0.10, 95% CI -0.64 to 0.44, 10 trials, 795 participants) [90-99]. In a meta-analysis of five trials [95, 101, 103-105] examining breathlessness measured at iso-load during laboratory exercise testing, breathlessness intensity was lower following opioids compared with placebo (SMD -0.50, 95% CI -0.84 to -0.16, 5 trials, 70 participants). This translated to approximately a 10mm mean difference on visual analogue scale (VAS), which meets the MID of 10mm, suggesting this effect is clinically significant [109].

For the important outcome of HrQoL, opioids administered regularly at home for ≥4 consecutive days showed no significant effect compared to placebo (SMD -0.42, 95% CI -0.98 to 0.13, 6 trials, 703 participants) [91, 92, 94, 96, 97, 99]. For the important outcome of cough, opioids administered regularly at home for ≥4 consecutive days showed no significant effect on cough scores compared to placebo (SMD -1.42, 95% CI -3.99 to 1.16, 2 trials, 147 participants) [96, 99].

Two separate meta-analyses examining arterial blood gas (ABG) parameters (four trials examining $PaCO_2$ [96, 98-100] and two trials examining PaO_2 [99, 100]), with opioids being administered regularly at home for ≥4 consecutive days compared to placebo, showed no difference in PaO_2 measurements

(SMD -0.22, 95% CI -0.56 to 0.12, 2 trials, 122 participants), but a statistically significant increase in $PaCO_2$ (SMD 0.86, 95% CI 0.03 to 1.69, 4 trials, 165 participants). This translates to 2.2mmHg increase in $PaCO_2$, which is not clinically significant. Meta-analyses of ABG parameters (including two trials examining $PaCO_2$ and PaO_2 [102, 103]), where opioids were administered as one or more doses in the laboratory setting compared to placebo, showed no significant difference for PaO_2 (SMD -0.52, 95% CI -1.14 to 0.10, 2 trials, 21 participants) or $PaCO_2$ (SMD 0.63, 95% CI 0.00 to 1.26, 2 trials, 21 participants).

The frequency of key adverse events was increased amongst people receiving opioids compared to the comparator (placebo in all studies, except one which used promethazine) in studies where opioids were administered regularly at home for ≥4 consecutive days [91-94, 96-100]. This included constipation (OR 3.08, 95% CI 1.69 to 5.61, 9 RCTs, 781 participants), nausea or vomiting (OR 3.32, 95% CI 1.70 to 6.51, 8 trials, 733 participants) and drowsiness (OR 1.37, 95% CI 1.01 to 1.86, 8 trials, 704 participants). In some studies, treatment-emergent adverse events were mild and self-limiting on withdrawal of morphine [90, 91, 93, 94, 96, 98, 100]. However, serious adverse events were reported in two studies [92, 97]; the BEAMS study [92] indicated that 33% (46 of 139) of participants treated with morphine developed serious adverse events, including hospitalisation and death. No differences in frequency of nausea/vomiting were detected between people receiving opioids or placebo in studies where opioids were administered in the laboratory setting [101, 102, 105].

The overall certainty of evidence was very low. Certainty of evidence was affected by reporting bias (lack of prospectively registered protocols), selection bias (unclear random sequence generation and allocation concealment), indirectness (most participants had COPD), lack of sufficient washout periods, and small sample sizes. No studies included people at the very end of life, who are usually highly symptomatic and often prescribed opioids for symptom palliation. Studies mainly included people with COPD.

Justification of recommendation: This recommendation balances the limited evidence for beneficial effects of opioids on symptoms with the increased risk of adverse events, and evidence that opioids may have limited acceptability to patients, caregivers and health professionals. Some people with serious respiratory illness, caregivers and clinicians have concerns regarding safe use, respiratory depression, substance misuse, dependence and addiction, stigma, and the association of opioids with death and dying [110-114]. Opioids may affect capacity to drive and cause many predictable adverse events, which are unacceptable or challenging for some patients [115]. Some participants (4%) withdrew from the included studies due to adverse effects (particularly gastrointestinal), however reporting of withdrawals due to adverse effects was both variable and inconsistent. The inability to recruit patients to some trials in this analysis (even when conducted over numerous years) led to some including patients with only moderate breathlessness, which highlights negative community perceptions to opioids [93, 94, 99]. We found limited data on the use of opioids for cough in people with serious respiratory illness, however since the completion of the meta-analysis a Phase II trial (n=41) demonstrated a 75% decrease in daytime cough frequency with nalbuphine extended-release treatment compared to 23% decrease with placebo in people with IPF [116]. Broader recommendations on management of chronic cough can be found in the 2020 ERS guidelines [117].

Implementation considerations: In people with serious respiratory illness, we do not recommend prescribing opioids to treat chronic breathlessness experienced at home in daily life. However, in cases where opioids are being considered to treat symptoms, clear communication and shared decision making are required. Clinicians should consider patients' goals and willingness to use an opioid medication, their understanding of how to take the medication correctly, and the broader impacts on their lives (including the ability to drive [118]) and other potential harms such as constipation, which is common and if severe may worsen breathlessness. When a clinician and patient with serious respiratory illness decide to trial an opioid to treat symptoms, it is essential before commencing

treatment to: a) ensure all illnesses contributing to breathlessness have been optimally treated, and b) the patient has received education on non-drug, self-management approaches. Other clinicians and informal caregivers may also require education and support regarding safe opioid use. Regular medical follow-up to both titrate the dose and actively prevent (e.g., through prescription of laxatives and anti-emetics) or manage side effects is required. The lowest dose to achieve a clinical improvement in symptoms should be used. If no beneficial effect is perceived, after shared decision making and discussion between clinicians and patients, then cessation of the opioid should occur.

***Recommendations for future research**:* Future clinical trials should examine the impact of opioids on people with serious respiratory illnesses other than COPD, and in those with severe breathlessness (including breathlessness at rest or on minimal exertion), or at the very end of life where the balance of effects may be more favourable. The impact of opioids on other symptoms (particularly cough) and HrQoL requires further investigation.

Question 6: Should breathing techniques be used to reduce symptoms in people with serious respiratory illness?

***Recommendation**:* We suggest that breathing techniques be used to reduce symptoms in people with serious respiratory illness (conditional recommendation, very low certainty of evidence).

***Summary of evidence**:* Breathing techniques were defined as any technique that aimed to alter the respiratory pattern. This could be achieved with or without external devices, either during exercise or at rest. Trials of respiratory muscle training or airway clearance were not included.

The search for systematic reviews identified 508 records, of which 74 were screened in full text. Eight relevant systematic reviews were identified with 43 eligible RCTs. The search for additional RCTs identified 2452 records, with 231 screened in full text and an additional 30 RCTs identified.

We included 73 RCTs (5479 participants) including people with COPD (n=37 RCTs), asthma (n=34), ILD (n=1), and mixed COPD and asthma (n=1). Most participants had moderate to severe lung disease, but no studies included people near the end of life. The most common breathing techniques were Yoga (often Pranayama), breathing exercises (pursed lip breathing and/or diaphragmatic breathing) and addition of breathing exercises to pulmonary rehabilitation (often timing of breathing with exercise). Many studies did not provide details of the intervention, or used a unique intervention that could not be combined with others or replicated in practice.

For our critical outcome of breathlessness, breathing exercises (pursed lip breathing and/or diaphragmatic breathing) reduced mMRC after 4 weeks compared to usual care (MD -0.40 points, 95% CI -0.70 to -0.11, 8 RCTs, 323 participants). However the upper end of the CI did not include the MID (-1 point) and clinical significance is unclear. Reductions in mMRC favoured Yoga over usual care after 2-4 months (MD -1.05 points, 95% CI -2.45 to 0.35, 3 RCTs, 175 participants), with the mean effect exceeding the MID [29]. Addition of breathing exercises to pulmonary rehabilitation improved CRQ dyspnoea at 4-12 weeks, compared to pulmonary rehabilitation alone (MD 0.30 points, 95% CI –0.02 to 0.62, 4 RCTs, 251 participants). However, the CI included the MID [27] and a benefit cannot be excluded.

Breathing exercises improved HrQoL at 4-12 weeks compared to usual care for SGRQ symptoms (MD -8.61 points, 95% CI –16.33 to -0.88, 6 RCTs, 365 participants) and SGRQ impact (MD -9.10 points, 95% CI –16.11 to -2.08, 6 RCTs, 365 participants). The CI for SGRQ activities domain included the MID (-4 points) [30] and a benefit cannot be excluded (online supplement). Yoga (8 RCTs) resulted in

statistically and clinically significant improvements in many domains of HrQoL at the end of the intervention period (6 weeks to 6 months) compared to usual care (online supplement), including mean improvements in the Asthma Quality of Life Questionnaire (AQLQ) symptoms, activities and emotions domains that exceeded the MID (0.5 points) [119], and improvements in the SGRQ impact, activities and total score, where the lower end of the CI exceeded the MID (-4 points) [30]. Addition of breathing exercises to pulmonary rehabilitation (3 RCTs, all COPD) did not improve HrQoL measured using the CRQ (fatigue, emotion, mastery domains) at 4–12 weeks compared to pulmonary rehabilitation alone (online supplement).

No adverse events were reported related to breathing exercises (11 RCTs, 1,433 participants) or Yoga (7 RCTs, 473 participants). Addition of breathing exercises to pulmonary rehabilitation did not increase the odds of exacerbations compared to pulmonary rehabilitation alone (OR 0.37, 95% CI 0.08 to 1.57, 3 RCTs, 260 participants).

The overall certainty of evidence was very low. Certainty of evidence was affected by detection bias (lack of assessor blinding), reporting bias (few trials were registered prospectively), indirectness (limited data in ILD and no data in pulmonary hypertension), and heterogeneity of interventions, outcome measures and timepoints of measurement.

Justification for the recommendation*:* This recommendation places a high value on consistent improvements in HrQoL for people who undertook breathing techniques, and a lower value on uncertainty regarding the effects of breathing techniques on breathlessness. In qualitative studies, people with COPD and asthma report benefits of breathing techniques (Yoga, pursed lip breathing, diaphragmatic breathing) that include better control of breathing, increased confidence in managing symptoms, reduction in panic during episodes of breathlessness, better management of stress, and

enhanced mastery of disease in daily life [120-123]. Breathing techniques were perceived as holistic and unobtrusive [120]. The likelihood of undesirable effects is very low.

***Implementation considerations**:* Breathing techniques are easy to administer, both face-to-face and remotely, and can be delivered in low, middle, and high income settings. Patients need to be adequately instructed regarding correct technique. Breathing techniques are often combined with other interventions in an individualized treatment plan (e.g., positioning to relieve breathlessness). Breathing techniques have a long history of use in many cultures, often as part of Yoga or spiritual practices, which could enhance acceptability and uptake in some cultural groups.

Recommendations for future research: Breathing exercises such as pursed lip breathing and diaphragmatic breathing were originally developed for use in obstructive lung disease, and future research should examine whether these techniques are also useful in patients with restrictive lung diseases such as ILD. The cost-effectiveness of training patients to undertake breathing techniques, including models that involve individual, group-based or remote delivery, should be examined.

Question 7: What is the role of needs assessment tools in people with serious respiratory illness?

Recommendation: We suggest that needs assessment tools may be used as part of a comprehensive needs assessment, but do not replace patient-centred care and shared decision making (conditional recommendation, low certainty of evidence).

Summary of evidence: There is no internationally recognized definition of a needs assessment tool (NAT). Needs assessment is a key component of holistic treatment that aims to alleviate health-related suffering from serious illness [124]. The term NAT has been used to describe tools that can broadly be

categorized into two groups: (i) those developed to assist in the early identification of individuals who would benefit from palliative care or other symptom-directed treatment, and (ii) those developed to identify and monitor unmet palliative and supportive care needs [125, 126]. Only the latter will be considered in this review.

Eleven papers were included in our narrative review [125-135], as well as three systematic reviews [124, 136, 137]. Within these papers, 23 tools are discussed, of which 9 tools aimed to identify unmet needs of patients (7 tools) [125, 127-135] or carers (2 tools) [132, 136] (online supplement).

Of the 9 included NATs, only two were specifically developed for people with serious respiratory illness; the Needs Assessment Tool – Progressive Disease: Interstitial Lung Disease (NAT:PD-ILD) for people with ILD [127-129], and the Needs Near the End of Life Scale modified version (NEST-13) for people awaiting lung transplant [130]. Three were not specific to, but had been investigated in, a cohort of people with serious respiratory illness; the Supportive Needs Approach for Patients (SNAP) in people with COPD [125], the Supportive Care Needs Survey Short Form 34 (SCNS-SF34) in people with cystic fibrosis [131], and the Measure Yourself Medical Outcome Profile (MYMOP) in people with acute exacerbations of bronchitis [135]. Two NATS had been tested in mixed cohorts including a minority of people with serious respiratory illness; the Patient Needs Assessment in Palliative Care (PNAP) [133] and the Integrated Palliative Care Outcome Scale (IPOS) [134]. The final two tools were developed solely to assess needs in carers; an unnamed tool tested in a mixed cohort that included carers of people with COPD [132], and the Carer Support Needs Assessment Tool (CSNAT) tested in carers of people with COPD [136].

Whilst some NATs, including the NAT:PD-ILD, NEST-13, SCNS-SF34, MYMOP, IPOS, and PNAP have undergone face, content, or psychometric validation in people with serious respiratory illness with positive results [126, 137], this has often been in a restricted group such as cystic fibrosis [131] or

chronic bronchitis [135]. Others, such as the SNAP tool, have not undergone formal validation [125]. Test-retest validity and inter-rater reliability has been partially demonstrated for the NAT:PD-ILD [137]. Many validation studies have used prediction of mortality as an endpoint, which may not reflect the capacity of NATs to comprehensively identify unmet patient needs.

At this point, no single NAT could be considered as the optimal tool. Certainty of evidence was low due to risk of bias (limited information on the psychometric properties) and indirectness (most NATs were not originally developed for people with respiratory illness). There is limited evaluation of the feasibility and utility of NATs in clinical practice. Health professionals perceive that the NAT:PD-ILD could improve the care of patients and caregivers, but have highlighted some implementation challenges, including the need for training in psychosocial and spiritual assessment and symptom management, support from other disciplines (palliative care and psychology) and engagement of a multidisciplinary team [129]. The impact of NATs on patient and caregiver outcomes is yet to be determined [125], however, gaps in identifying the needs of carers have been identified [136]. No study has shown harm or undesirable effects.

Justification of the recommendation: This recommendation placed a high value on identifying unmet needs in patients with serious respiratory illness. The benefits of using NATs may include improving patients' understanding of their own needs [125, 126], and increasing healthcare professionals' focus on patient needs, thus facilitating patient centered care and better HrQoL [125, 126]. Comprehensive needs assessment could lead to better organization of health care [136]. However, there are few NATs that were developed specifically for people with serious respiratory illness and existing NATs may not identify all unmet needs in this population. As a result, a NAT cannot replace a thorough assessment of clinical status and unmet needs, shared-decision making, and patient-centred care.

Implementation considerations: Needs assessment is an iterative process that occurs over time, not a one-off task. Clinicians require training to utilize and implement NATS effectively [124, 137]. It should be noted that completion of a NAT does not guarantee improved outcomes, and resources must be dedicated to addressing unmet needs that are identified, including shared decision-making regarding treatment plans. Current NATs do not have capacity to define "all needs" for "all patients or carers". There is no evidence regarding how NATs may perform across social determinants of health (e.g., ethnicity, socioeconomic status). Many NATs have been developed within specialist palliative care [125] and validated within cohorts of patients at the very end of life. For people with serious respiratory illness and their relatives there is an imperative to identify needs earlier [126, 138].

Recommendations for future research: Further development of NATs specific to serious respiratory illness should ensure that consumers (patients, caregivers and clinicians) are active participants in co-design and evaluation. New NATs should capture unmet needs across the care journey of those with serious respiratory illness, not just the end of life. Clinical trials of NATs should include outcomes that are informed by, and important to, patients and caregivers.

DISCUSSION

In this clinical practice guideline, we provide recommendations for symptom management in adults with severe respiratory illness. Strategies that may be beneficial to reduce symptoms include multicomponent services, increased airflow, graded exercise therapy and breathing exercises. There was no clear evidence for the benefit of oxygen therapy to reduce symptoms, and evidence that opioids may not reduce breathlessness. A comprehensive assessment of illness and unmet needs is key to selecting the treatments that may be beneficial for individuals. A suggested approach to manage respiratory symptoms in people with serious respiratory illness is shown in Figure 1.

There is little evidence to guide the timing or order of interventions to manage symptoms in patients with serious respiratory illness. We chose to define serious respiratory illness in relation to its burden [9], rather than by the severity of respiratory function impairment. As a result, our recommendations are relevant to patients experiencing symptoms that have not been alleviated by best disease-specific care, regardless of disease severity. However, it should be acknowledged that most participants in the studies underpinning our recommendations had moderate to severe lung disease, with few having mild impairment or close to the end of life. Some of the interventions (e.g. increased airflow, breathing exercises) are simple and relatively unobtrusive, so they may be acceptable to patients earlier in the disease course, and could be used together. More complex interventions, such as multicomponent services, may be more relevant for patients with a greater symptom burden or those requiring more support with symptom management. It is likely that the acceptability and relevance of these interventions will vary across the care journey, which highlights the importance of regular, repeated assessment to document changing and new unmet needs. A thorough needs assessment provides a starting point for development of an individualised treatment plan.

We have identified several non-pharmacological interventions that were acceptable to patients and feasible to implement, albeit with modest effect sizes. Oxygen therapy and opioids may be

burdensome, but in some patients this may be outweighed by the benefits, particularly when symptoms increase or toward the end of life. There is a clear need for new interventions to address symptom burden in patients with serious respiratory illness, with larger effect sizes and acceptable side effects. This is particularly apparent for cough, where we found little evidence to support the use of any intervention. Patient and public involvement in development of this guideline highlighted the importance of cough and fatigue as outcome measures for future clinical trials. We found few studies in people with breathlessness at rest or in end of life palliative care. These are critical evidence gaps that should be addressed in future research (Table 2).

Most of the studies on which our recommendations were based were conducted in high income countries and at centres with expertise in symptom management and palliative care. Implementation of these recommendations may be more challenging in centres without dedicated symptom management services, and in low and middle income countries where access to non-pharmacological interventions and multidisciplinary teams may be more limited. Few studies considered the effect of social determinants of health or the broader context of care on outcomes, including considerations important to the consumer members of our task force, such as comorbid medical conditions and air quality. We also found limited evidence regarding cost-effectiveness of interventions. Future clinical trials should consider models of care that can be implemented across a variety of settings, including telehealth models, models that are suitable for primary care, and low cost interdisciplinary care models.

Conclusion

This clinical practice guideline provides evidence to guide prescription of symptom management interventions in people with serious respiratory illness, and highlights the importance of comprehensive assessment to individualise treatment. The low certainty of evidence underpinning

these recommendations compels clinicians and researchers to investigate new approaches to reduce symptoms and enhance wellbeing for the many individuals who live with serious respiratory illness.

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Disclaimer: The guidelines published by the European Respiratory Society (ERS) incorporate data obtained from a comprehensive and systematic literature review of the most recent studies available at the time. Health professionals are encouraged to take the guidelines into account in their clinical practice. However, the recommendations issued by this guideline may not be appropriate for use in all situations. It is the individual responsibility of health professionals to consult other sources of relevant information, to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient and the patient's caregiver where appropriate and/ or necessary, and to verify rules and regulations applicable to drugs and devices at the time of prescription.

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Table 1. Clinical Practice Guideline Recommendations

Clinical Practice Guideline Question	Recommendation
Question 1: Should a multicomponent service be used to reduce symptoms in people with serious respiratory illness?	We suggest that multicomponent services should be used to reduce symptoms in people with serious respiratory illness (conditional recommendation, very low certainty of evidence).
Question 2: Should graded exercise therapy be used to reduce fatigue in people with serious respiratory illness?	We suggest that graded exercise therapy be used to reduce fatigue (conditional recommendation, low certainty of evidence).
Question 3: Should increased airflow be used to reduce breathlessness in people with serious respiratory illness?	We suggest the use of increased airflow to reduce breathlessness in people with serious respiratory illness (condtional recommendation, very low certainty of evidence).
Question 4: Should supplemental oxygen be used to reduce symptoms in people with serious respiratory illness?	We suggest either administering or not administering supplemental oxygen to reduce symptoms in people with serious respiratory illness (conditional recommendation, low certainty of evidence).
Question 5: Should opioids be used to reduce symptoms in people with serious respiratory illness?	We suggest not using opioids for the treatment of breathlessness in people with serious respiratory illness (conditional

	recommendation against the intervention, very low certainty of evidence).
Question 6: Should breathing techniques be used to reduce symptoms in people with serious respiratory illness?	We suggest that breathing techniques be used to reduce symptoms in people with serious respiratory illness (conditional recommendation, very low certainty of evidence).
Question 7: What is the role of needs assessment tools in people with serious respiratory illness?	We suggest that needs assessment tools may be used as part of a comprehensive needs assessment, but do not replace patient centred care and shared decision making (conditional recommendation, low certainty of evidence).

Table 2. Research Recommendations

Overarching Research Recommendations	
• Research is needed to develop and evaluate novel interventions and approaches to effectively manage symptoms, including but not limited to breathlessness, fatigue, and cough, in people with serious respiratory illness.	
• Studies need to include people with diverse serious respiratory illnesses, not just COPD.	
• Longer research trials, ideally conducted at home and measuring outcomes experienced in daily life, are required to understand the long-term effectiveness of both current and future approaches to symptom management.	
• Studies are required examining which individuals are most likely to benefit from specific symptom management approaches and to thus facilitate individualised care.	
• Understanding the perspectives, preferences and lived experiences of people with serious respiratory illness, as well as those of the people who care for them, regarding symptoms and management approaches is critical and underpins high-quality research.	
• Implementation science is needed in conjunction with clinical trials to inform meaningful translation of research findings into routine clinical practice.	
• Research is needed to evaluate the effectiveness of and consider implementation processes required for telehealth and digital technologies that may support delivery of symptom management care.	
• Economic evaluation, including assessment of cost-effectiveness and affordability of treatments for all people living with serious respiratory illness, is needed for current and future approaches to symptom management.	
• Symptom management research needs to consider social determinants of health and encompass diverse and representative populations, including people in low and middle-income countries.	
Specific Research Recommendations	
Question 1: Should a multicomponent service be used to reduce symptoms in people with serious respiratory illness?	• Determine which patients are most likely to benefit from a multicomponent service (MCS) • Examine the effectiveness of MCS management on other symptoms e.g., cough or fatigue

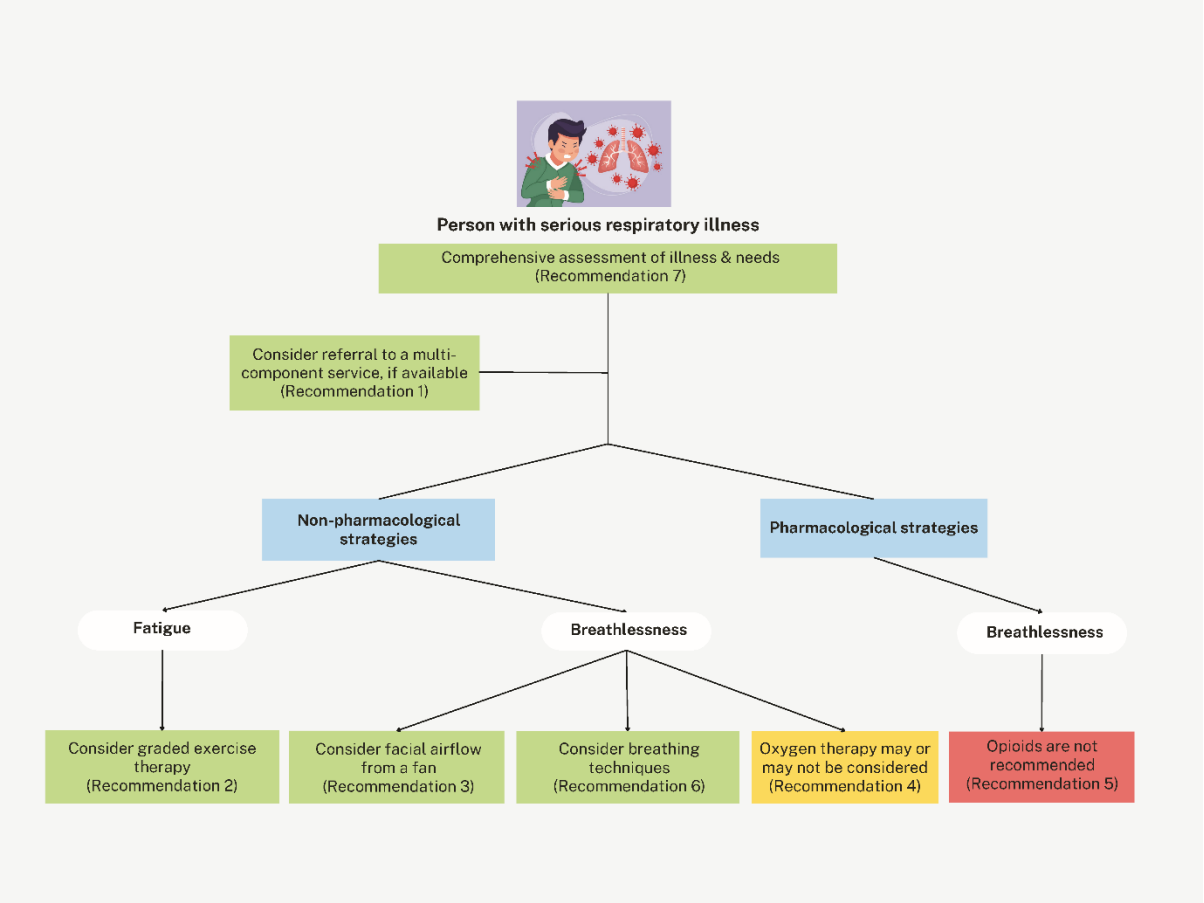
	• Undertake longer RCTs to identify long-term impacts of MCS on symptom management • Consider the role and effectiveness of telehealth and hybrid care models for MCS • Explore how MCS may be best integrated within existing healthcare programs
Question 2: Should graded exercise therapy be used to reduce fatigue in people with serious respiratory illness?	• Conduct clinical trials to examine the effectiveness of GET in people with severe lung disease (including those with severe hemodynamic impairment) and those with severe fatigue • Ensure fatigue-specific outcome measures are used in future studies • Evaluate the cost-effectiveness of GET, including the effects of remote delivery models
Question 3: Should increased airflow be used to reduce breathlessness in people with serious respiratory illness?	• Conduct adequately powered clinical trials to examine the effectiveness of increased airflow on breathlessness and health-related quality of life in people with a variety chronic respiratory diseases • Measure breathlessness at a standardised time-point (iso-time) during exercise testing • Studies are required to determine the optimal flow rate and fan speed for maximal therapeutic benefit
Question 4: Should supplemental oxygen be used to reduce symptoms in people with serious respiratory illness?	• Conduct clinical trials to examine the effectiveness of oxygen on breathlessness experienced in daily across various respiratory conditions

	• Assess exertional breathlessness at a standardised level of exertion (iso-time) • Develop and evaluate oxygen delivery systems capable of delivering higher flow rates during ambulatory use • Include health utility measures in future trials to support economic evaluation
Question 5: Should opioids be used to reduce symptoms in people with serious respiratory illness?	• Examine the effectiveness of opioids on symptom management for people with serious respiratory illnesses other than COPD, and also for those at the very end of life. • Determine the effectiveness of opioids on symptoms such as severe breathlessness (i.e., breathlessness at rest or on minimal exertion) and cough.
Question 6: Should breathing techniques be used to reduce symptoms in people with serious respiratory illness?	• Determine whether people with different lung diseases (such as restrictive lung disease) benefit from breathing exercises • Evaluate the cost-effectiveness (including using remote delivery models) of training patients in breathing techniques
Question 7: What is the role of needs assessment tools in people with serious respiratory illness?	• Involve consumers (patients, caregivers and clinicians) in co-design and evaluation of needs assessments tools (NATs) • Development and evaluation of new NATs that focus on unmet needs earlier in the illness course (not just at end of life) • Clinical trials of NATs should include outcomes that are informed by, and important to, patients and caregivers

FIGURE LEGENDS

Figure 1. Approach to managing symptoms in people with serious respiratory illness.

Recommendations relating to critical outcomes for each PICO question are included. Cough was not included in the diagram as it was an important (secondary) outcome with very limited evidence.



European Respiratory Society Clinical Practice Guideline on symptom management for adults with serious respiratory illness

Online Supplement

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0. Methodology – additional information

Selection of PICO and narrative questions: Task force members proposed nine potential questions for the clinical practice guideline in PICO (Participant, Intervention, Comparison, Outcome) format, along with two potential narrative questions. Using an online survey (Survey Monkey, San Mateo, CA), the task force members rated the importance of each suggested question using a scale between 1 (not important at all) and 10 (extremely important). A similar survey was circulated to members of the European Lung Foundation (ELF) COPD and Pulmonary Fibrosis (PF) Patient Advisory Groups, with 15 responses. Members of the Patient Advisory Groups were also asked to rank the questions in order of priority. Results were presented to online meetings of the task force and the ELF Patient Advisory Groups, and the final questions (6 PICO, 2 narrative) determined by consensus. The second narrative question (timing of opioid therapy) was dropped by consensus of the task force after viewing systematic review results for the related PICO question, which did not support the use of this treatment.

Selection of outcomes: For each PICO question, task force members ranked the importance of relevant outcomes using an online survey, including breathlessness, cough, fatigue, HrQoL and adverse events, on a scale between 1 (not important at all) and 10 (extremely important). Additional outcomes could also be proposed. Results were presented to the task force and the ELF Patient Advisory Groups, with the final ranking agreed by consensus. The highest ranked outcome was the critical outcome for each question, with other outcomes rated as important. None of the proposed items were rated as unimportant.

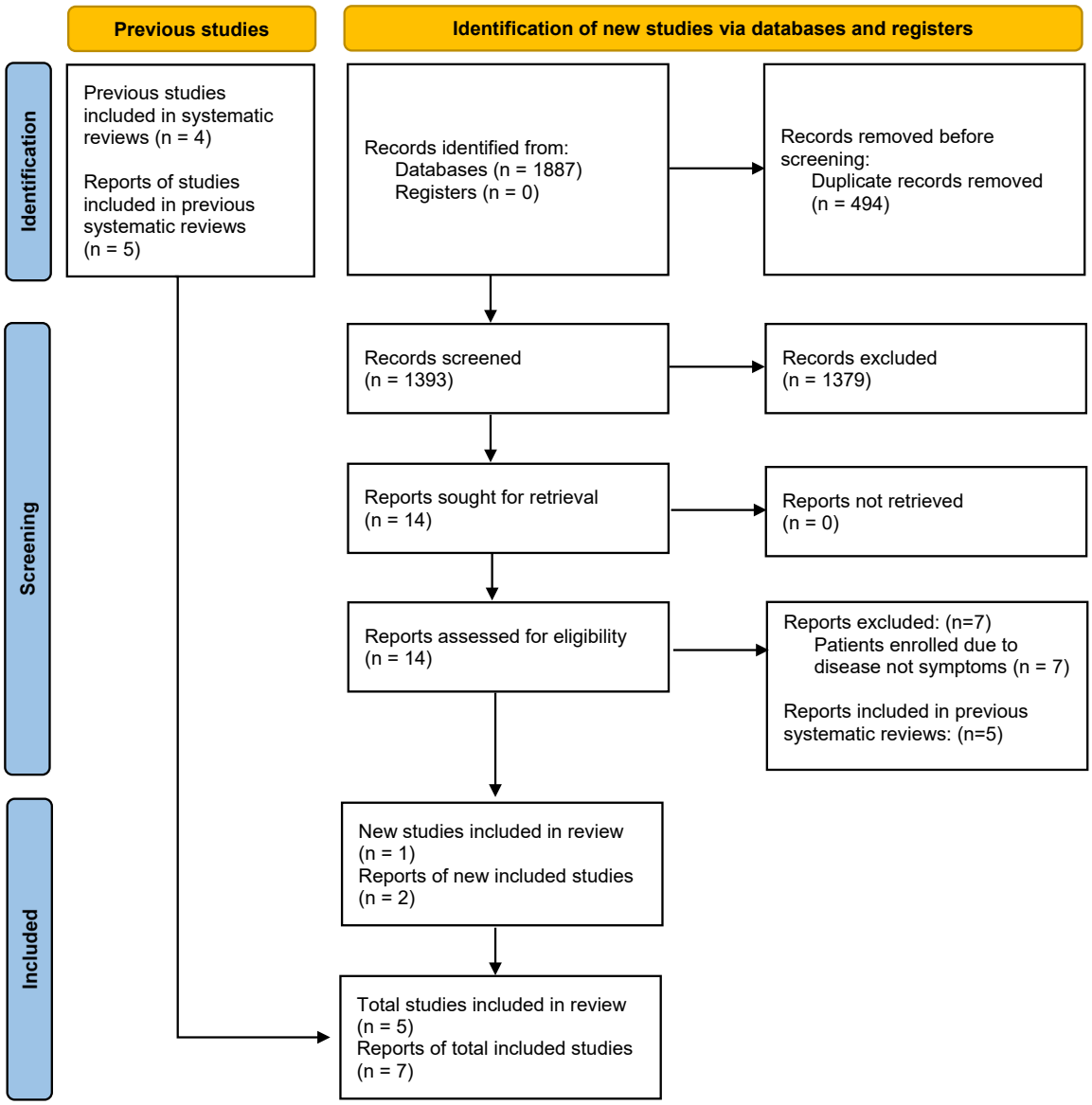
Searching the literature: The search strategies were developed by a medical librarian (LR) based on concepts identified by the task force members. Searches for each question were conducted between July 2022 and November 2022. Searches were conducted in Medline (OVID), Embase (OVID), Cochrane

Database of Systematic Reviews and CENTRAL (The Cochrane Library) for each of the seven questions. The searches were divided into two components for each PICO question. The first component was a search to find relevant systematic reviews. Systematic reviews that provided evidence for at least one of the outcomes of interest were used as a basis for identification of relevant studies. If no relevant systematic review was identified for a question, all original studies were screened for inclusion. The second step was to run searches to identify RCTs that had been published since the search date of the most recent relevant systematic review. Search results were screened independently by two task force members for eligibility. Search dates for each of the questions were as follows:

PICO 1 – systematic review search database inception to July 2022, RCT search 2017 to Jul y 2022
PICO 2 – systematic review search database inception to August 2022, RCT search 2010 to Nov 2022
PICO 3 – systematic review search database inception to August 2022, RCT search 2019 to Feb 2023
PICO 4 – systematic review search database inception to June 2022, RCT search 2016 to June 2022
PICO 5 – systematic review search database inception to June 2022, RCT search 2015 to July 2022
PICO 6 – systematic review search database inception to August 2022, RCT search 2011 to Nov2022
Narrative question: a single search from database inception to June 2022.

1. PICO question 1: Should a multicomponent service be used to reduce symptoms in people with serious illness related to lung disease?

1.1. Identification of studies – PRISMA flow diagram



1.2. Inclusion criteria

- Randomised controlled trials
- Participants were adults aged 18 years or older.
- Participants had serious illness related to lung disease (defined as a condition that carries a high risk of mortality, negatively impacts quality of life and daily function, and/or is burdensome in symptoms, treatments, or caregiver stress). For mixed studies (e.g. studies including those with malignant disease) we asked the authors for data related to the participants with non-malignant disease only. If separate data were unable to be obtained then we included studies only if ≥80% of participants had non-malignant disease.
- Intervention: A multicomponent service, defined as a model of care that offered more than one intervention, including at least one non-pharmacological intervention. Patients needed to be enrolled due to symptoms, not disease; pulmonary rehabilitation and disease-specific services were not included.
- Comparison: Usual care, which could include primary care or secondary care outpatient services.

1.3. Exclusion criteria

- Crossover trials, as the intervention includes behavioural components where carryover of intervention effects to the second period may occur
- Participants with malignant disease.

1.4. Forest plots

Critical outcome - breathlessness

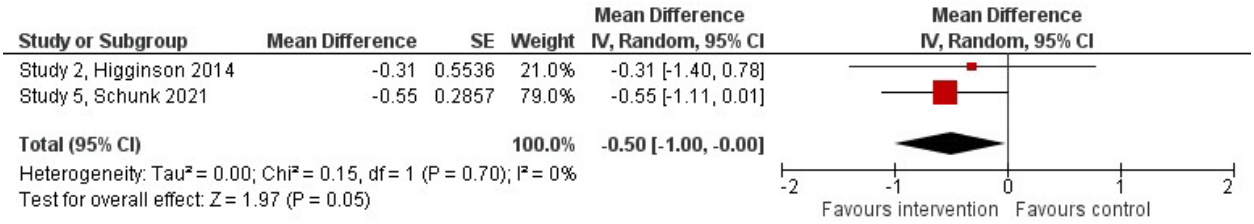


Figure 1.1 Breathlessness - Average breathlessness on numerical rating scale (NRS) 0-10

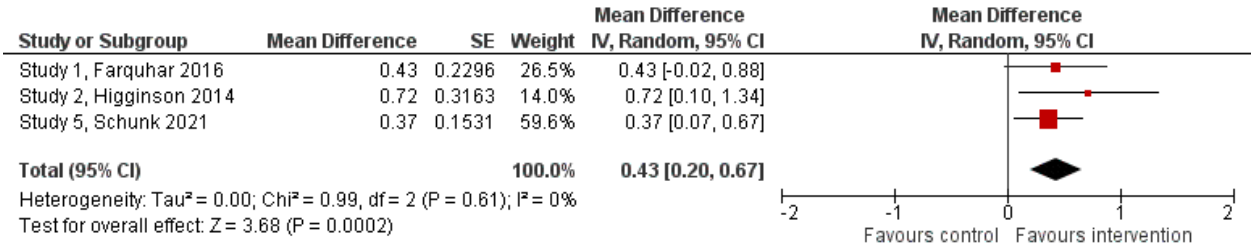


Figure 1.2 Breathlessness - Chronic Respiratory Questionnaire Mastery domain

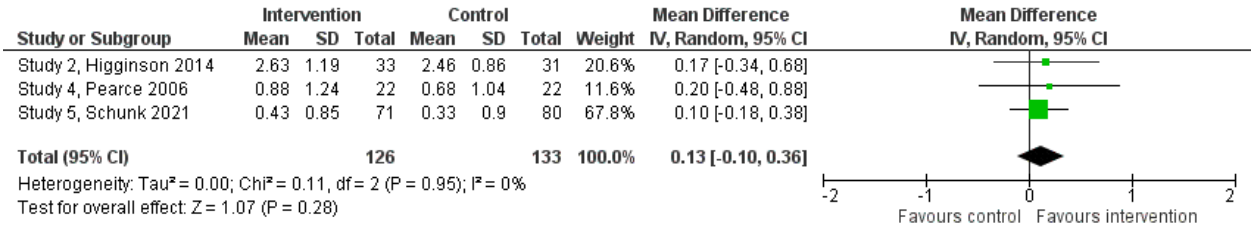


Figure 1.3 Breathlessness - Chronic Respiratory Questionnaire Dyspnoea domain

Important outcome – health-related quality of life

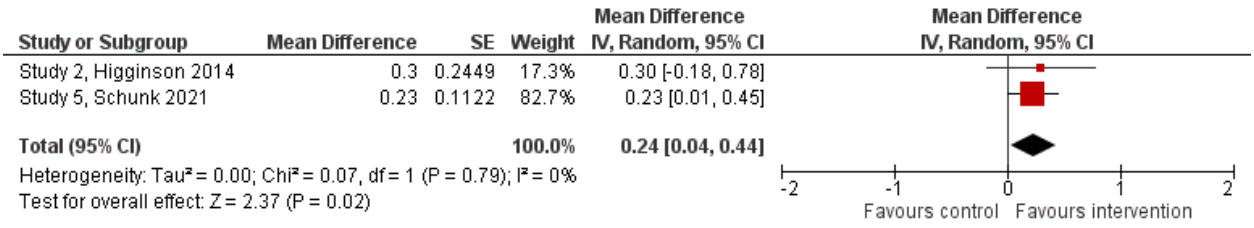


Figure 1.4 Health-related quality of life - Chronic Respiratory Questionnaire Total score

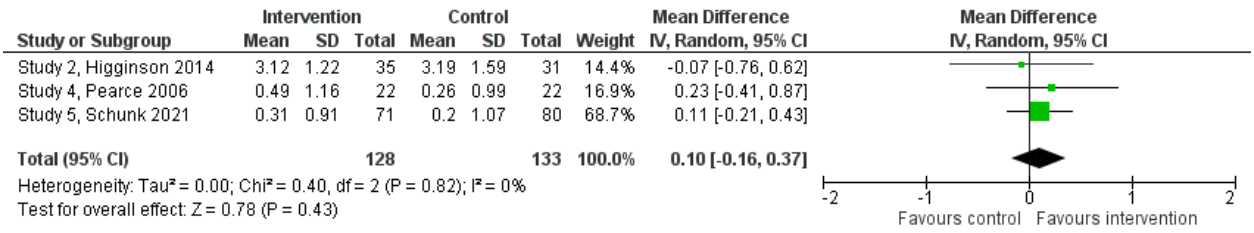


Figure 1.5 Health-related quality of life - Chronic Respiratory Questionnaire fatigue domain

1.5. GRADE Evidence table

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multicomponent service	Usual care	Relative (95% CI)	Absolute (95% CI)		
CRITICAL OUTCOME: Breathlessness												
Breathlessness average NRS												
2	RCT	Serious[a]	Not serious	Not serious	Serious[c]	Serious[d]	123	115		-0.50 (-1.00 to 0.00)	⊕◯◯◯ VERY LOW	CRITICAL
Chronic Respiratory Questionnaire mastery												
3	RCT	Serious[a]	Not serious	Not serious	Serious[c]	Serious[e]	167	160		0.43 (0.20 to 0.67)	⊕◯◯◯ VERY LOW	CRITICAL
Chronic Respiratory Questionnaire dyspnoea												
3	RCT	Serious[a,b]	Not serious	Not serious	Serious[c]	Serious[f]	126	133		0.13 [-0.10, 0.36]	⊕◯◯◯ VERY LOW	CRITICAL
IMPORTANT OUTCOME: Health-related quality of life												
Chronic Respiratory Questionnaire total												
2	RCT	Serious[a]	Not serious	Not serious	Serious[c]	Serious[g]	121	116		0.24 (0.04 to 0.44)	⊕◯◯◯ VERY LOW	IMPORTANT

IMPORTANT OUTCOME: Cough												
No studies reported cough.												
IMPORTANT OUTCOME: Fatigue												
Chronic Respiratory Questionnaire fatigue												
3	RCT	Serious[a,b]	Not serious	Not serious	Serious[c]	Serious[h]	128	133		0.10 (-0.16 to 0.37)	⊕◯◯◯ VERY LOW	IMPORTANT
IMPORTANT OUTCOME: Adverse events												
Adverse events												
1	RCT	Serious[a]	Not serious	Not serious	Very serious[c,i]	Not serious	71	80	In the intervention arm, 44/71 participants experienced a total of 65 events; two were considered related to intervention (one was a skin reaction following an allergy test recommended by the service; the other was a side effect from morphine prescribed by the service). 48/80 participants in the control arm experienced a total of 79 adverse events.		⊕◯◯◯ VERY LOW	IMPORTANT

Explanations:

a. No participant blinding to group allocation, and loss to follow up high or different between arms.

b. One of the three studies no evidence for assessor blinding and published as abstract only.

c. Low numbers of participants.

d. Effect calculated from adjusted mean differences because variation in baseline data from one of the two studies reduces analysis certainty. If change data from this study had been used, effect would be -0.36 [-0.87 to 0.15] and, if end point data, the effect would be -0.65 [-1.17 to -0.14].

e. Effect calculated from adjusted mean differences because variation in baseline data from two of the three studies reduces analysis certainty. Different combinations of end point and change data from four studies would vary the findings from 0.30 [0.05 to 0.51] to 0.47 [0.23 to 0.71].

f. Two of three studies demonstrated baseline variation in the outcome measure. One of the three studies has both change and endpoint data available; reported finding uses change data, but end point data would give a larger, and statistically significant, effect of 0.23 [0.01 to 0.45].

g. Effect calculated from adjusted mean differences because variation in baseline data from one of the two studies reduces analysis certainty. If change data from this study had been used, effect would be 0.18 [-0.03 to 0.39] and, if end point data, the effect would be 0.29 [0.07 to 0.52].

h. Two of three studies demonstrated baseline variation in the outcome measure. One of the three studies has both change and endpoint data available; reported finding uses change data, but end point data would give an effect of 0.14 [-0.13 to 0.41].

i. Cannot judge precision as only a narrative description of adverse events.

1.6. Evidence to Decision Table

PICO1: Should a multicomponent service be used to reduce symptoms in people with serious illness related to lung disease?	
POPULATION:	Adults with serious illness related to lung disease
INTERVENTION:	A multicomponent service, defined as a model of care that offers more than one intervention, including at least one non-pharmacological intervention
COMPARISON:	No multicomponent service
MAIN OUTCOMES:	Critical: Breathlessness, using relevant and validated tool. Measure of any aspect of breathlessness can be included, such as distress due to breathlessness or breathlessness mastery Important: • Health related quality of life, using any validated tool. • Fatigue, using any validated tool. • Cough, using any validated tool. • Adverse events, defined according to the investigators' definition.

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know	Patients with serious illness related to lung disease commonly experience high symptom burden, including chronic breathlessness, cough and fatigue (1), which contribute to a reduced quality of life (2). Breathlessness is frequently ranked by patients as their worst symptom (3) and it is a major contributor to unscheduled healthcare usage (4, 5).	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ● **Small** ○ Moderate ○ Large ○ Varies ○ Don't know	Three studies (Farquhar, Higginson, Schunk) evaluated similar multicomponent interventions, with individualized self-management support. One study (Pearce) involved a similar intervention delivered by nurses in an outpatient setting; information was available in abstract form only. One study (Hutchinson) involving only 13 participants was testing the feasibility of undertaking a trial to test a brief paramedic	Cough was not evaluated in any of the included studies. Three other breathlessness measures from two

	intervention at emergency call out; this study was not included in the meta-analyses. The four studies included in the meta-analyses all used a primary end point of 4 to 8 weeks. **Critical outcome: breathlessness** • Average breathlessness over the last 24 hours (measured by NRS) improved by a mean of 0.50 points (95%CI -1.00 to 0.00), a change that was not statistically significant and below the minimum important difference (MID) (6). The upper confidence interval included the MID (2 studies). • Breathlessness mastery, measured by the Chronic Respiratory Questionnaire mastery domain, improved by 0.43 points (95%CI 0.20 to 0.67), a change that was statistically significant but of borderline clinical relevance(7) (3 studies) • The Chronic Respiratory Questionnaire dyspnoea domain improved by 0.13 points (95%CI -0.10 to 0.36), which was not statistically significant, and the upper end of the confidence interval did not include the MID (3 studies). **Important outcome: health-related quality of life** • Health-related quality of life, measured by the Chronic Respiratory Questionnaire (total score) improved by 0.24 points (0.04 to 0.44), which was statistically significant, but the upper end of the confidence interval did not include the MID (2 studies). **Important outcome: fatigue** • The change in Chronic Respiratory Questionnaire fatigue domain was 0.10 points (-0.16 to 0.37), which was not statistically significant, and the upper end of the confidence interval did not include the MID (3 studies).	studies – all numerical rating scales – could not be included in the meta-analysis. Although all found greater benefit from intervention than control, no changes were statistically significant. However, the upper end of the confidence interval did include the MID, so clinically relevant effects could not be excluded. [NRS distress from breathlessness, -0.24 (-1.30 to 0.82); NRS worst breathlessness in last 24 hours, -0.58 (-2.09 to 0.94); NRS severity of breathlessness on exertion in last 24 hours, -0.84 (-1.92 to 0.25)]
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ○ Moderate ○ Small ●**Trivial** ○ Varies ○ Don't know	**Adverse events** One study (Schunk) reported adverse events. In the intervention arm, 44/71 participants experienced a total of 65 events; two were considered related to intervention (one was a skin reaction following an allergy test recommended by the service; the other was a side effect from morphine prescribed by the service). 48/80 participants in the control arm experienced at total of 79 events. One study (Higginson) reported increased survival in the intervention arm compared to the control arm (whole study population: 72-75% non-malignant lung disease), and direct	

	communication with the research team revealed no adverse events related to the intervention. **Withdrawals** Withdrawals or loss to follow up varied across the studies. One (Higginson) reported 21% and 23% withdrawals from the trial from intervention and control arms respectively; another (Schunk) found that trial withdrawals clustered around the intervention, at a rate of 18% in the intervention group compared to 5% in the control group (data from whole cohorts, rather than population in question). Both studies recruited participants with advanced disease in services provided by palliative care and respiratory specialists, and attrition rates are consistent with those usually found when recruiting in this context.	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● **Very low** ○Low ○ Moderate ○ High ○ No included studies	The very low certainty is based on the GRADE assessment of the evidence. In overview: • The main sources of bias related to lack of blinding of participants to group allocation, and loss to follow up being high or different between groups. • Three studies (Farquhar, Pearce, Schunk) described baseline differences between groups in key outcomes. Where mean differences adjusted for baseline were not available, change data rather than end point data were compared as this increased the likelihood of under-estimating, rather than over-estimating, the effect size.	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ●**No important uncertainty or variability**	The critical outcome for this question is breathlessness, which people with serious respiratory illness consistently report as a major distressing symptom (8, 9, 10). In people with COPD, breathlessness has been found to be a key determinant of low physical and mental health (9, 10). Similarly, in people with pulmonary fibrosis breathlessness has been identified as a major driver of reduced quality of life (11, 12). Fear of exertional breathlessness may result in avoiding exercise, leading to a downward spiral of deconditioning, social isolation with negative physical and emotional consequences (10). There is an immense need to better actively manage chronic breathlessness and other distressing symptoms in people with a variety of non-malignant chronic respiratory diseases.	There was no important uncertainty or variability in the views of the patient members of the Task Force regarding values.

Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ●**Probably favors the intervention** ○ Favors the intervention ○ Varies ○ Don't know	The balance of effects probably favours the intervention. For the critical outcome of breathlessness mastery (CRQ mastery) and the important outcome of quality of life (CRQ total), analyses found statistically significant improvements with intervention compared to control. The size of the benefits is small and of uncertain clinical significance. Harms related to the intervention are infrequent, relatively minor and manageable in clinical practice.	
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ●**Negligible costs and savings** ○ Moderate savings ○ Large savings ○Varies ○ Don't know	Two included studies (Schunk, Farquhar) reported the direct costs of delivering the intervention. In both, the intervention was predominantly non-pharmacological, with pharmacological review, with the main cost being staff time. One study reported that costs to deliver the specialized breathlessness service were on average €357 (SD €132) per patient, with specialist respiratory physiotherapy treatment (€157, SD €59; 44% of costs) and visits to specialists for palliative medicine (€128, SD €47; 36% of costs) as major cost components. Spending on respiratory medicine care (€50), materials (e.g. therapy manual, hand held fan, €16), and psychologists' care (€6) also contributed. Participants received approximately 5-6 contacts with a health professional over up to 8 weeks. The other study reported the average cost of the intervention was £156 (SD £80) per patient. Intervention involved 2-3 in person visit and an average of 3 telephone contacts (with participant or primary care staff) over an average of four weeks delivered by a physiotherapist, occupational therapist and a doctor.	Costs for staffing and materials may vary across countries and health systems. In some lower and middle income countries there may be limited access to members of the multidisciplinary team. Costs may reduce in the future with increasingly hybrid models of healthcare delivery
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ●**Low** ○ Moderate ○ High ○ No included studies	Only two studies have reported costs and resources to deliver the intervention, one from the UK and one from Germany. It is possible that costs will vary in other settings, other countries, and for other models of care.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ●**Varies** ○ No included studies	Three included studies reported on cost effectiveness, with varied findings. One study (Higginson) noted no significant differences in the total formal care costs at 6 weeks between those who received the intervention and those who did not (£1422 in the breathlessness support service group (95% CI £897–£2101) and £1408 in the control group (£899–£2023). Costs varied greatly between individuals. A related study reported on a Markov model for cost effectiveness (Yi) using data from the same trial (Higginson) (13). The model showed that delivering a breathlessness service resulted in lower healthcare costs than usual care, with significant gain in QALYs, resulting in an incremental cost effectiveness ratio (ICER, cost per QALY gained) that strongly favoured the intervention (−£50,789 in men, -£56,242 in women). This was modelled based on the results of a discrete choice experiment to identify the preferred model of care in patients with COPD and ILD. A second study (Farquhar) noted that total formal care costs were higher in the intervention group than the control group, but this did not reach statistical significance (mean £799 higher in the intervention group, 95 % CI -£237 to £1904). There was no significant difference in QALYs gained (0.003, 95% CI -0.001 to 0.007). The intervention resulted in an ICER of £266,333, which would not be considered cost effective. A sensitivity analysis excluding intervention patients with extreme inpatient costs showed an ICER of £33,333.	It is likely that total formal care costs will vary across countries and health systems. Findings of the existing studies on cost-effectiveness show uncertainty, which likely reflects the small number of participants and substantial variation in their formal healthcare needs.

	A third study (Schunk) reported that total formal care costs were higher in the intervention group, but this did not reach statistical significance (€605, 95% CI -1109 to 2550). There was significantly greater gain in QALYs for the intervention group (mean difference 0.05, 95% CI 0.007-0.1). The ICER was €152,433 (95% CI -453,545 to 1,625,903), demonstrating substantial uncertainty (14).	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ●**Don't know**	There is no direct evidence of the impact of multicomponent services on health equity.	It is likely that it would be more feasible to deliver multicomponent services in higher income countries, where there is greater access to a multidisciplinary team. People with cancer diagnoses are more likely to access symptom-directed support through palliative care services than people with non-malignant disease. Therefore increased access to multicomponent services for people with non-malignant disease has potential to reduce this inequity.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ●**Yes**	Four of the five included studies were mixed-methods, with two (Higginson, Schunk) reporting the qualitative data in separate reports (15, 16). Across all studies, qualitative data consistently demonstrated intervention acceptability to patients and	There was no important uncertainty or variability in the

○ Varies ○ Don't know	informal/unpaid carers, along with a qualitatively positive impact on them. A qualitative evaluation of a multicomponent breathlessness support service for people with COPD describes consistent findings (17).	views of the patient members of the Task Force regarding acceptability.
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ●**Probably yes** ○ Yes ○ Varies ○ Don't know	There is no direct evidence for implementation feasibility, and it is likely to vary according to the setting. Feasibility of implementation of multicomponent services within a trial setting is, however, well established (18, 19). For two of the studies (Farquhar, Schunk), the services have continued as part of usual care. All studies evaluated services embedded in palliative care and/or respiratory services, suggesting implementation feasibility in these contexts.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

We suggest multicomponent services should be used to reduce symptoms in people with serious respiratory illness (conditional recommendation, very low certainty of evidence).

Justification

This recommendation places a high value on consistent improvements in breathlessness mastery and HrQoL with multicomponent services, with minimal risk and low direct costs. Although mean effects did not always reach the MID, the confidence interval included the MID for our critical outcome of breathlessness. The accepted MIDs for breathlessness were not generated in people with serious respiratory illness, so it is possible that smaller improvements in breathlessness could be clinically important. Multicomponent services are valued by patients, as they address gaps in current health care and deliver meaningful improvements in daily life and at points of breathlessness crisis.

Subgroup considerations

Not applicable

Implementation considerations

All studies evaluated services embedded in palliative care and/or respiratory services, suggesting that implementation out of a trial context is likely to be feasible in these settings. The feasibility of implementation in primary care is unknown, and programmes of research are underway in the UK and Australia attempting to evaluate this. The low costs, along with possible evidence of cost-effectiveness, should facilitate implementation.

Monitoring and evaluation

Monitoring will require consistent coding for chronic breathlessness as a symptom, rather than relying on coding the underlying respiratory condition. Evaluation of multicomponent services could be achieved pragmatically using standard patient reported outcome measures, such as MRC breathlessness scale. It is important to ensure that multicomponent services provide symptom-focused support in parallel (or after) optimising medical management of the underlying respiratory condition.

Research priorities

Understanding the predictors of benefit from multicomponent services would facilitate efficient resource use and delivery of personalised healthcare. Future trials should have extended followup periods, to examine the longer-term impact of multicomponent services, and include participants from diverse racial and ethnic backgrounds. Future research should assess the acceptability and effectiveness of virtual or hybrid multicomponent services. Research is needed to evaluate how best to integrate multicomponent services alongside existing services, such as pulmonary rehabilitation.

References for ETD table –PICO1

1. Rantala HA, Leivo-Korpela S, Lehtimäki L, Lehto JT. Assessing Symptom Burden and Depression in Subjects With Chronic Respiratory Insufficiency. J Palliat Care. 2022;37(2):134-41.
2. Blinderman CD et al. Symptom distress and quality of life in patients with advanced chronic obstructive pulmonary disease. J Pain Symptom Manage. 2009;38(1):115-23.
3. Gysels MH, Higginson IJ. The lived experience of breathlessness and its implications for care: a qualitative comparison in cancer, COPD, heart failure and MND. BMC Palliative Care. 2011;10(1):15.
4. Hutchinson A, Pickering A, Williams P, Bland JM, Johnson MJ. Breathlessness and presentation to the emergency department: a survey and clinical record review. BMC Pulm Med. 2017;17(1):53.
5. Kelly AM, Keijzers G, Klim S, Graham CA, Craig S, Kuan WS, et al. An Observational Study of Dyspnea in Emergency Departments: The Asia, Australia, and New Zealand Dyspnea in Emergency Departments Study (AANZDEM). Acad Emerg Med. 2017;24(3):328-36.
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8. Swetz KM, Shanafelt TD, Drozdowicz LB, Sloan JA, Novotny PJ, Durst LA, et al. Symptom burden, quality of life, and attitudes toward palliative care in patients with pulmonary arterial hypertension: results from a cross-sectional patient survey. J Heart Lung Transplant. 2012;31(10):1102-8.
9. Janson C, Marks G, Buist S, Gnatiuc L, Gislason T, McBurnie MA, et al. The impact of COPD on health status: findings from the BOLD study. Eur Respir J. 2013;42(6):1472-83.
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14. Seidl H, Schunk M, Le L, Syunyaeva Z, Streitwieser S, Berger U, et al. Cost-Effectiveness of a Specialized Breathlessness Service Versus Usual Care for Patients With Advanced Diseases. Value Health. 2023;26(1):81-90.
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16. Reilly CC, Bausewein C, Pannell C, Moxham J, Jolley CJ, Higginson IJ. Patients' experiences of a new integrated breathlessness support service for patients with refractory breathlessness: Results of a postal survey. Palliat Med. 2015;30(3):313-22.
17. Luckett T, Roberts MM, Smith T, Swami V, Cho J-G, Wheatley JR. Patient perspectives on how to optimise benefits from a breathlessness service for people with COPD. npj Primary Care Respiratory Medicine. 2020;30(1):16.
18. Farquhar M, Higginson I, Fagan P, Booth S. The feasibility of a single-blinded fast-track pragmatic randomised controlled trial of a complex intervention for breathlessness in advanced disease. BMC Palliat Care. 2009;8(9).
19. Schunk M, Berger U, Le L, Rehfuess E, Schwarzkopf L, Streitwieser S, et al. BreathEase: rationale, design and recruitment of a randomised trial and embedded mixed-methods study of a multiprofessional breathlessness service in early palliative care. ERJ Open Res. 2021;7(4).

1.7. List of included studies – PICO1

Farquhar MC, Prevost AT, McCrone P, Brafman-Price B, Bentley A, Higginson IJ, Todd C, Booth S. The clinical and cost effectiveness of a Breathlessness Intervention Service for patients with advanced non-malignant disease and their informal carers: mixed findings of a mixed method randomised controlled trial. Trials 2016;17:185. DOI: 10.1016/S2213-2600(14)70226-7

Higginson I, Bausewein C, Reilly C, Gao W, Gysels M, Dzingina M, McCrone P, Booth S, Jolley C, Moxham J. An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial. Lancet Respiratory Medicine 2014;2(12):979-87. DOI: 10.1016/S2213-2600(14)70226-7

Hutchinson A, Allgar V, Cohen J, Currow DC, Griffin S, Hart S, Hird K, Hodge A, Mason S, Northgraves M, Reeve J, Swan F, Johnson M. Mixed-methods feasibility cluster randomised controlled trial of a paramedic-administered breathlessness management intervention for acute-on-chronic breathlessness (BREATHE): study findings. *European Respiratory Journal Open Research* 2022:00257-2022. DOI: 10.1183/23120541.00257-2022

Pearce L, MacLeod V, Baker A. Randomised controlled trial of nurse-led breathlessness intervention to improve the management of breathlessness in patients with chronic obstructive pulmonary disease at a district general hospital. *Thorax* 2006;61(suppl II):ii84. https://thorax.bmj.com/content/61/suppl_2/ii57

Schunk M, Le L, Syunyaeva Z, Haberland B, Tänzler S, Mansmann U, Schwartzkopf L, Seidl H, Streitwieser S, Hofmann M, Muller T, Weiss T, Morawietz P, Rehfuess EA, Huber RM, Berger U, Bausewein C. Effectiveness of a specialised breathlessness service for patients with advanced disease in Germany: a pragmatic fast track randomised controlled trial (BreathEase). *European Respiratory Journal* 2021:2002139 DOI: 10.1183/13993003.02139-2020

1.8. Search strategies

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions

#	Query
1	Palliative Care/ or Holistic Nursing/ or "Hospice and Palliative Care Nursing"/ or Palliative Medicine/ or terminal care/ or hospice care/ or Terminally Ill/ or Holistic Health/
2	(palliative* or holistic* or wholistic* or "end of life" or hospice or (nonpharmacologic* or non-pharmacologic* or nondrug* or non-drug* or complex intervention*)).mp.
3	((multidisciplinary or multi-disciplinary or multiple disciplines or multispecialt* or multi-specialt* or multiple specialties or multiprofession* or multi-profession* or multiple profession* or interdisciplinary or inter-disciplinary or interprofession* or inter-profession* or transdisciplinary or crossdisciplinary or trans-disciplinary or cross-disciplinary or multisectoral or multi sectoral or multiple key players or multiple sectors) and (care* or healthcare* or service* or clinic? or intervention* or approach or management or shared decision* or "model of care" or care model* or team* or program* or treatment or response or process or therap* or aspect)).mp.
4	((multidimensional or multi-dimensional or multi-element or multielement or multicomponent or multi-component or multi-faceted or multifaceted or multimodal or multi-modal or multi-parameter* or multiparameter*) and (care* or healthcare* or service* or clinic? or intervention* or approach or management or shared decision* or "model of care" or care model* or team* or program* or treatment or response or process or therap* or aspect)).mp.
5	(((multiple or complex or mixed) adj2 (component* or elements or facets or parameter*)) and (care* or healthcare* or service* or clinic? or intervention* or approach or management or shared decision* or "model of care" or care model* or team* or program* or treatment or response or process or therap* or aspect)).mp.
6	((integrated or integrative or collaborative or team based or blended) adj3 (care* or healthcare* or service* or clinic? or intervention* or approach or management or shared decision* or "model of care" or care model* or team* or program* or treatment or response or process or therap* or aspect)).mp.
7	((cooperative or co-operative) adj (care* or healthcare* or service* or clinic? or intervention* or approach or management or shared decision* or "model of care" or care model* or team* or program* or treatment or response or process or therap* or aspect)).mp.
8	("two or more healthcare" or "two or more health care" or "two or more providers" or "two or more components" or "more than one intervention" or "two or more interventions" or "more than two interventions" or ">=two health care providers" or ">=two components" or "working with other healthcare" or "working with other health care" or "working with other professionals" or "work* in partnership" or "from different professions" or "two or more disciplines" or "interaction across

	disciplines" or "from different disciplines" or "disciplines working together" or "team* of experts" or "team of professionals").mp.
9	((doctor* or medical staff or nurse*) adj2 (physiotherapist* or physical therapist* or occupational therapist* or social worker*)).mp.
10	(((physician* or specialist* or provider* or doctor* or medical staff or nurse*) adj2 (physiotherapist* or physical therapist* or occupational therapist* or social worker* or allied health or psychologist*)) or ((physician* or specialist* or provider* or doctor* or medical staff) adj2 nurse*)).mp.
11	((physiotherapist* or physical therapist*) adj2 (occupational therapist* or social worker* or allied health or psychologist*)).mp.
12	Interdisciplinary Research/ or Interprofessional Relations/ or Interdisciplinary Communication/ or Physician-Nurse Relations/ or Interdepartmental Relations/ or Cooperative Behavior/
13	Patient Care Team/
14	or/1-13
15	(dyspn?e* or "short* of breath" or "urge* to breathe*" or breathless* or suffocat*).mp.
16	((labo?red or difficult*) adj3 breath*).mp.
17	(breath* adj1 (distress* or discomfort* or dysfunction*)).mp.
18	(air adj3 (hunger or starv*)).mp.
19	("need for air" or "gasp* for air" or "gasp* to breathe" or "pant* for air").mp.
20	(unsatisf* inspiration or inspiratory difficult* or expiratory difficult*).mp.
21	or/15-20
22	14 and 21
23	((palliative or holistic or wholistic) and breathlessness).mp.
24	((dyspn?e* or "short* of breath" or breathlessness) adj3 (service* or intervention service* or support service* or clinic? or program*)).mp.
25	23 or 24
26	22 or 25
27	(randomized controlled trial or controlled clinical trial).pt. or (randomi?ed or placebo).ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.

28	((cross over or crossover) adj (clinical study or clinical trial or design or method or study or trial or studies)).mp.
29	27 or 28
30	26 and 29

Database: Embase

#	Query
1	palliative nursing/ or palliative therapy/ or holistic care/ or holistic nursing/ or terminal care/ or hospice care/ or terminally ill patient/
2	(palliative* or holistic* or wholistic* or "end of life" or hospice or (nonpharmacologic* or non-pharmacologic* or nondrug* or non-drug* or complex intervention*)).mp.
3	((multidisciplinary or multi-disciplinary or multiple disciplines or multispecialt* or multi-specialt* or multiple specialties or multiprofession* or multi-profession* or multiple profession* or interdisciplinary or inter-disciplinary or interprofession* or inter-profession* or transdisciplinary or crossdisciplinary or trans-disciplinary or cross-disciplinary or multisectoral or multi sectoral or multiple key players or multiple sectors) and (care* or healthcare* or service* or clinic? or intervention* or approach or management or shared decision* or "model of care" or care model* or team* or program* or treatment or response or process or therap* or aspect)).mp.
4	((multidimensional or multi-dimensional or multi-element or multielement or multicomponent or multi-component or multi-faceted or multifaceted or multimodal or multi-modal or multi-parameter* or multiparameter*) and (care* or healthcare* or service* or clinic? or intervention* or approach or management or shared decision* or "model of care" or care model* or team* or program* or treatment or response or process or therap* or aspect)).mp.
5	(((multiple or complex or mixed) adj2 (component* or elements or facets or parameter*)) and (care* or healthcare* or service* or clinic? or intervention* or approach or management or shared decision* or "model of care" or care model* or team* or program* or treatment or response or process or therap* or aspect)).mp.
6	((integrated or integrative or collaborative or team based or blended) adj3 (care* or healthcare* or service* or clinic? or intervention* or approach or management or shared decision* or "model of care" or care model* or team* or program* or treatment or response or process or therap* or aspect)).mp.
7	((cooperative or co-operative) adj (care* or healthcare* or service* or clinic? or intervention* or approach or management or shared decision* or "model of care" or care model* or team* or program* or treatment or response or process or therap* or aspect)).mp.

8	("two or more healthcare" or "two or more health care" or "two or more providers" or "two or more components" or "more than one intervention" or "two or more interventions" or "more than two interventions" or ">=two health care providers" or ">=two components" or "working with other healthcare" or "working with other health care" or "working with other professionals" or "work* in partnership" or "from different professions" or "two or more disciplines" or "interaction across disciplines" or "from different disciplines" or "disciplines working together" or "team* of experts" or "team of professionals").mp.
9	((doctor* or medical staff or nurse*) adj2 (physiotherapist* or physical therapist* or occupational therapist* or social worker*)).mp.
10	(((physician* or specialist* or provider* or doctor* or medical staff or nurse*) adj2 (physiotherapist* or physical therapist* or occupational therapist* or social worker* or allied health or psychologist*)) or ((physician* or specialist* or provider* or doctor* or medical staff) adj2 nurse*)).mp.
11	((physiotherapist* or physical therapist*) adj2 (occupational therapist* or social worker* or allied health or psychologist*)).mp.
12	interdisciplinary research/ or interdisciplinary communication/ or cooperation/ or (Interprofessional Relations or Interdepartmental Relations).mp.
13	Patient Care Team.mp.
14	or/1-13
15	(dyspn?e* or "short* of breath" or "urge* to breathe*" or breathless* or suffocat* or ("need for air" or "gasp* for air" or "gasp* to breathe" or "pant* for air") or (unsatisf* inspiration or inspiratory difficult* or expiratory difficult*)).mp.
16	((labo?red or difficult*) adj3 breath*).mp.
17	(breath* adj1 (distress* or discomfort* or dysfunction*)).mp.
18	(air adj3 (hunger or starv*)).mp.
19	or/15-18
20	14 and 19
21	limit 20 to (randomized controlled trial or controlled clinical trial)
22	randomized controlled trial/ or randomization/ or single blind procedure/ or double blind procedure/ or crossover procedure/ or placebo/ or prospective study/
23	(randomi?ed controlled or RCT or randomly allocated or allocated randomly or random allocation or "allocated at random" or single blind* or double blind* or ((treble or triple) adj blind*) or placebo*).mp.

24	((cross over or crossover) adj (clinical study or clinical trial or design or method or study or trial or studies)).mp.
25	22 or 23 or 24
26	20 and 25
27	21 or 26
28	((palliative or holistic or wholistic) and breathlessness).mp.
29	((dyspn?e* or "short* of breath" or breathlessness) adj3 (service* or intervention service* or support service* or clinic? or program*)).mp.
30	28 or 29
31	limit 30 to (randomized controlled trial or controlled clinical trial)
32	25 and 30
33	31 or 32

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

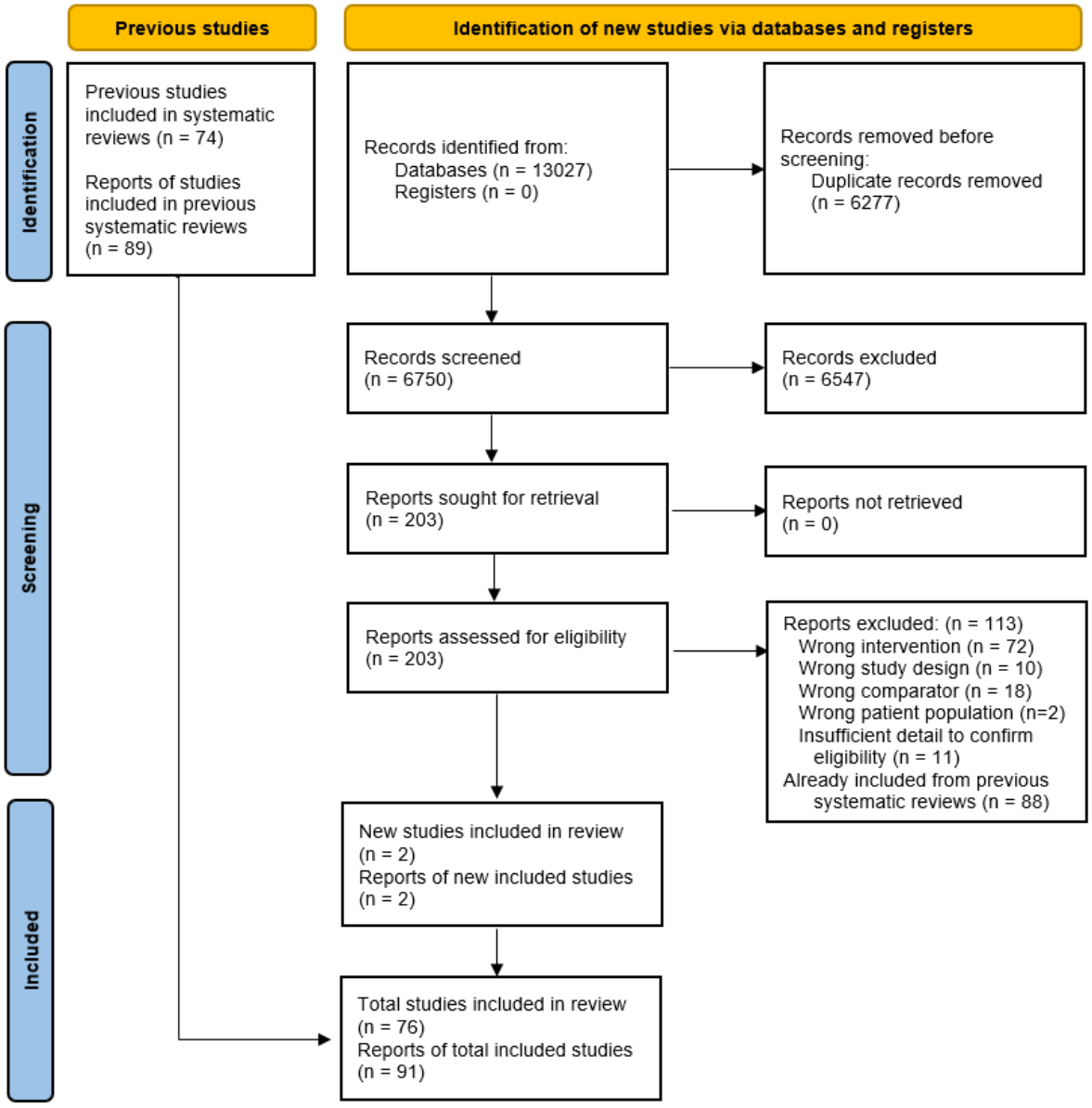
#	Query
1	Palliative Care/ or Holistic Nursing/ or "Hospice and Palliative Care Nursing"/ or Palliative Medicine/ or terminal care/ or hospice care/ or Terminally Ill/ or Holistic Health/
2	(palliative* or holistic* or wholistic* or "end of life" or hospice or (nonpharmacologic* or non-pharmacologic* or nondrug* or non-drug* or complex intervention*)).mp.
3	((multidisciplinary or multi-disciplinary or multiple disciplines or multispecialt* or multi-specialt* or multiple specialties or multiprofession* or multi-profession* or multiple profession* or interdisciplinary or inter-disciplinary or interprofession* or inter-profession* or transdisciplinary or crossdisciplinary or trans-disciplinary or cross-disciplinary or multisectoral or multi sectoral or multiple key players or multiple sectors) and (care* or healthcare* or service* or clinic? or intervention* or approach or management or shared decision* or "model of care" or care model* or team* or program* or treatment or response or process or therap* or aspect)).mp.
4	((multidimensional or multi-dimensional or multi-element or multielement or multicomponent or multi-component or multi-faceted or multifaceted or multimodal or multi-modal or multi-parameter* or multiparameter*) and (care* or healthcare* or service* or clinic? or intervention* or approach or management or shared decision* or "model of care" or care model* or team* or program* or treatment or response or process or therap* or aspect)).mp.

5	(((multiple or complex or mixed) adj2 (component* or elements or facets or parameter*)) and (care* or healthcare* or service* or clinic? or intervention* or approach or management or shared decision* or "model of care" or care model* or team* or program* or treatment or response or process or therap* or aspect)).mp.
6	((integrated or integrative or collaborative or team based or blended) adj3 (care* or healthcare* or service* or clinic? or intervention* or approach or management or shared decision* or "model of care" or care model* or team* or program* or treatment or response or process or therap* or aspect)).mp.
7	((cooperative or co-operative) adj (care* or healthcare* or service* or clinic? or intervention* or approach or management or shared decision* or "model of care" or care model* or team* or program* or treatment or response or process or therap* or aspect)).mp.
8	("two or more healthcare" or "two or more health care" or "two or more providers" or "two or more components" or "more than one intervention" or "two or more interventions" or "more than two interventions" or ">=two health care providers" or ">=two components" or "working with other healthcare" or "working with other health care" or "working with other professionals" or "work* in partnership" or "from different professions" or "two or more disciplines" or "interaction across disciplines" or "from different disciplines" or "disciplines working together" or "team* of experts" or "team of professionals").mp.
9	((doctor* or medical staff or nurse*) adj2 (physiotherapist* or physical therapist* or occupational therapist* or social worker*)).mp.
10	(((physician* or specialist* or provider* or doctor* or medical staff or nurse*) adj2 (physiotherapist* or physical therapist* or occupational therapist* or social worker* or allied health or psychologist*)) or ((physician* or specialist* or provider* or doctor* or medical staff) adj2 nurse*)).mp.
11	((physiotherapist* or physical therapist*) adj2 (occupational therapist* or social worker* or allied health or psychologist*)).mp.
12	Interdisciplinary Research/ or Interprofessional Relations/ or Interdisciplinary Communication/ or Physician-Nurse Relations/ or Interdepartmental Relations/ or Cooperative Behavior/
13	Patient Care Team/
14	or/1-13
15	(dyspn?e* or "short* of breath" or "urge* to breathe*" or breathless* or suffocat*).mp.
16	((labo?red or difficult*) adj3 breath*).mp.
17	(breath* adj1 (distress* or discomfort* or dysfunction*)).mp.
18	(air adj3 (hunger or starv*)).mp.
19	("need for air" or "gasp* for air" or "gasp* to breathe" or "pant* for air").mp.

20	(unsatisf* inspiration or inspiratory difficult* or expiratory difficult*).mp.
21	or/15-20
22	14 and 21
23	((palliative or holistic or wholistic) and breathlessness).mp.
24	((dyspn?e* or "short* of breath" or breathlessness) adj3 (service* or intervention service* or support service* or clinic? or program*)).mp.
25	23 or 24
26	22 or 25

2. PICO question 2: Should graded exercise therapy be used to reduce fatigue in people with serious illness related to lung disease?

2.1. Identification of studies – PRISMA diagram



2.2. Inclusion criteria

- Randomised controlled trials
- Participants were adults aged 18 years or older.
- Participants had serious illness related to lung disease (defined as a condition that carries a high risk of mortality, negatively impacts quality of life and daily function, and/or is burdensome in symptoms, treatments, or caregiver stress). For mixed studies (e.g. studies including those with malignant disease) we asked the authors for data related to the participants with non-malignant disease only. If separate data were unable to be obtained then we included studies only if ≥80% of participants had non-malignant disease.
- Intervention: We defined graded exercise therapy as establishing a baseline of achievable exercise or physical activity and then making fixed incremental increases in the time spent being physically active (NICE 2021 https://www.nice.org.uk/guidance/ng206/chapter/recommendations#graded-exercise-therapy).
- Comparison: we included studies that reported the effects of graded exercise therapy compared to usual care, which could include usual medical care, but did not include pulmonary rehabilitation.

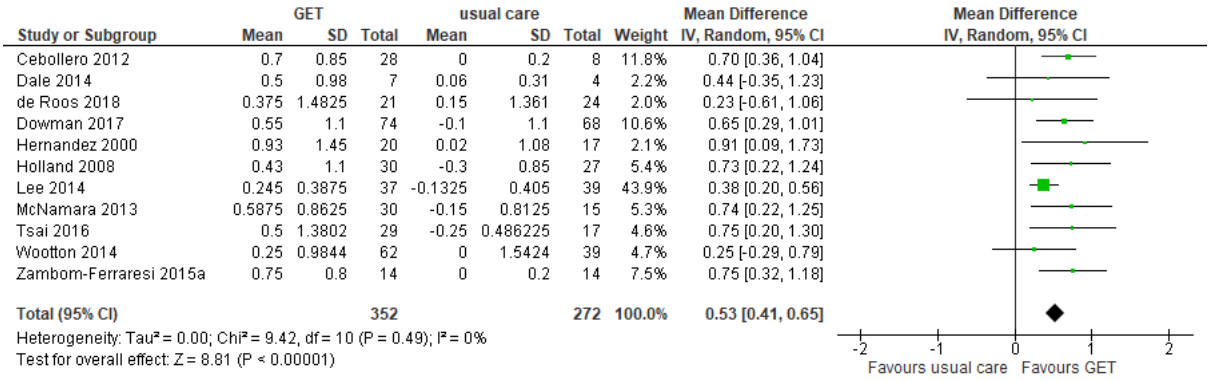
2.3. Exclusion criteria

- Crossover trials, as the intervention includes behavioural components where carryover of intervention effects to the second period may occur
- Participants with malignant disease

- Exercise therapy conducted in the context of pulmonary rehabilitation, which is a broader package of interventions for people with chronic lung disease, 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 behaviour 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 behaviours’ (Spruit AJRCCM 2013)..

2.4. Forest plots

Critical outcome: Fatigue

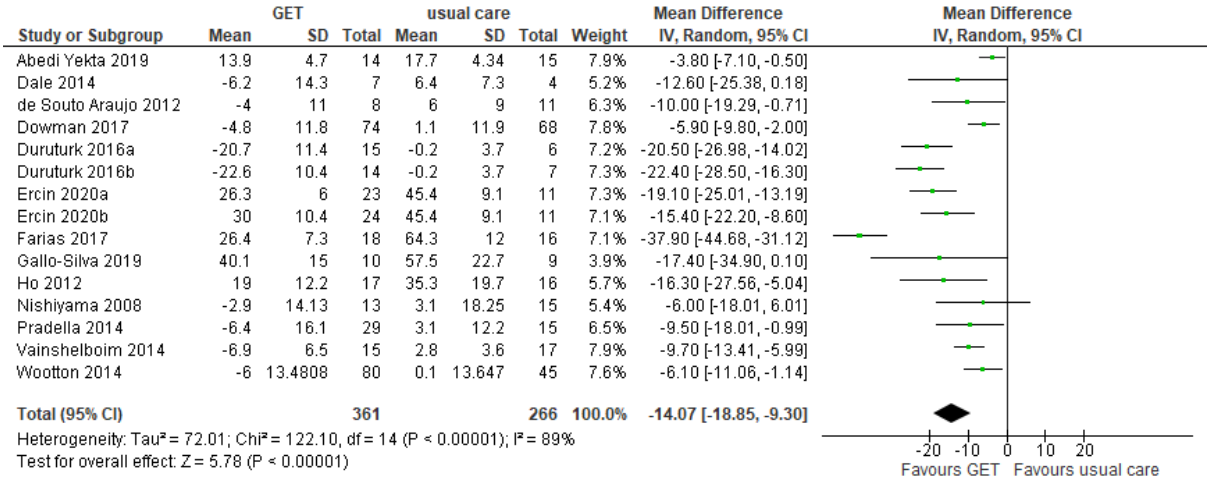


Study or Subgroup	GET Mean	GET SD	GET Total	usual care Mean	usual care SD	usual care Total	Weight	Mean Difference IV, Random, 95% CI
Cebollero 2012	0.7	0.85	28	0	0.2	8	11.8%	0.70 [0.36, 1.04]
Dale 2014	0.5	0.98	7	0.06	0.31	4	2.2%	0.44 [-0.35, 1.23]
de Roos 2018	0.375	1.4825	21	0.15	1.361	24	2.0%	0.23 [-0.61, 1.06]
Dowman 2017	0.55	1.1	74	-0.1	1.1	68	10.6%	0.65 [0.29, 1.01]
Hernandez 2000	0.93	1.45	20	0.02	1.08	17	2.1%	0.91 [0.09, 1.73]
Holland 2008	0.43	1.1	30	-0.3	0.85	27	5.4%	0.73 [0.22, 1.24]
Lee 2014	0.245	0.3875	37	-0.1325	0.405	39	43.9%	0.38 [0.20, 0.56]
McNamara 2013	0.5875	0.8625	30	-0.15	0.8125	15	5.3%	0.74 [0.22, 1.25]
Tsai 2016	0.5	1.3802	29	-0.25	0.486225	17	4.6%	0.75 [0.20, 1.30]
Wootton 2014	0.25	0.9844	62	0	1.5424	39	4.7%	0.25 [-0.29, 0.79]
Zambom-Ferraresi 2015a	0.75	0.8	14	0	0.2	14	7.5%	0.75 [0.32, 1.18]
Total (95% CI)			**352**			**272**	**100.0%**	**0.53 [0.41, 0.65]**

Heterogeneity: Tau² = 0.00; Chi² = 9.42, df = 10 (P = 0.49); I² = 0%
Test for overall effect: Z = 8.81 (P < 0.00001)

GET vs usual care – Chronic Respiratory Questionnaire Fatigue domain score at end intervention

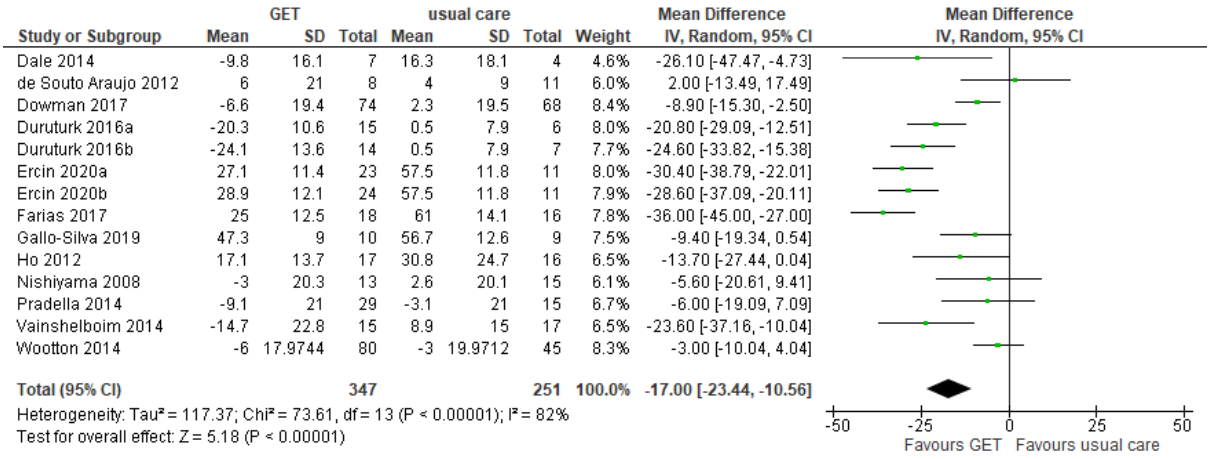
Important outcome: Health-related quality of life



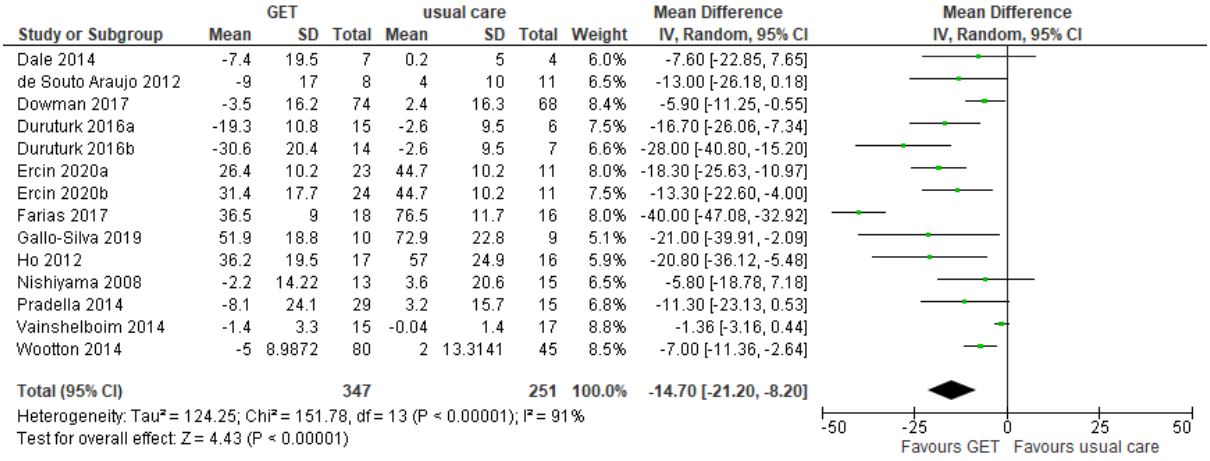
Study or Subgroup	GET Mean	GET SD	GET Total	usual care Mean	usual care SD	usual care Total	Weight	Mean Difference IV, Random, 95% CI
Abedi Yekta 2019	13.9	4.7	14	17.7	4.34	15	7.9%	-3.80 [-7.10, -0.50]
Dale 2014	-6.2	14.3	7	6.4	7.3	4	5.2%	-12.60 [-25.38, 0.18]
de Souto Araujo 2012	-4	11	8	6	9	11	6.3%	-10.00 [-19.29, -0.71]
Dowman 2017	-4.8	11.8	74	1.1	11.9	68	7.8%	-5.90 [-9.80, -2.00]
Durutürk 2016a	-20.7	11.4	15	-0.2	3.7	6	7.2%	-20.50 [-26.98, -14.02]
Durutürk 2016b	-22.6	10.4	14	-0.2	3.7	7	7.3%	-22.40 [-28.50, -16.30]
Ercin 2020a	26.3	6	23	45.4	9.1	11	7.3%	-19.10 [-25.01, -13.19]
Ercin 2020b	30	10.4	24	45.4	9.1	11	7.1%	-15.40 [-22.20, -8.60]
Farias 2017	26.4	7.3	18	64.3	12	16	7.1%	-37.90 [-44.68, -31.12]
Gallo-Silva 2019	40.1	15	10	57.5	22.7	9	3.9%	-17.40 [-34.90, 0.10]
Ho 2012	19	12.2	17	35.3	19.7	16	5.7%	-16.30 [-27.56, -5.04]
Nishiyama 2008	-2.9	14.13	13	3.1	18.25	15	5.4%	-6.00 [-18.01, 6.01]
Pradella 2014	-6.4	16.1	29	3.1	12.2	15	6.5%	-9.50 [-18.01, -0.99]
Vainshelboim 2014	-6.9	6.5	15	2.8	3.6	17	7.9%	-9.70 [-13.41, -5.99]
Wootton 2014	-6	13.4808	80	0.1	13.647	45	7.6%	-6.10 [-11.06, -1.14]
Total (95% CI)			**361**			**266**	**100.0%**	**-14.07 [-18.85, -9.30]**

Heterogeneity: Tau² = 72.01; Chi² = 122.10, df = 14 (P < 0.00001); I² = 89%
Test for overall effect: Z = 5.78 (P < 0.00001)

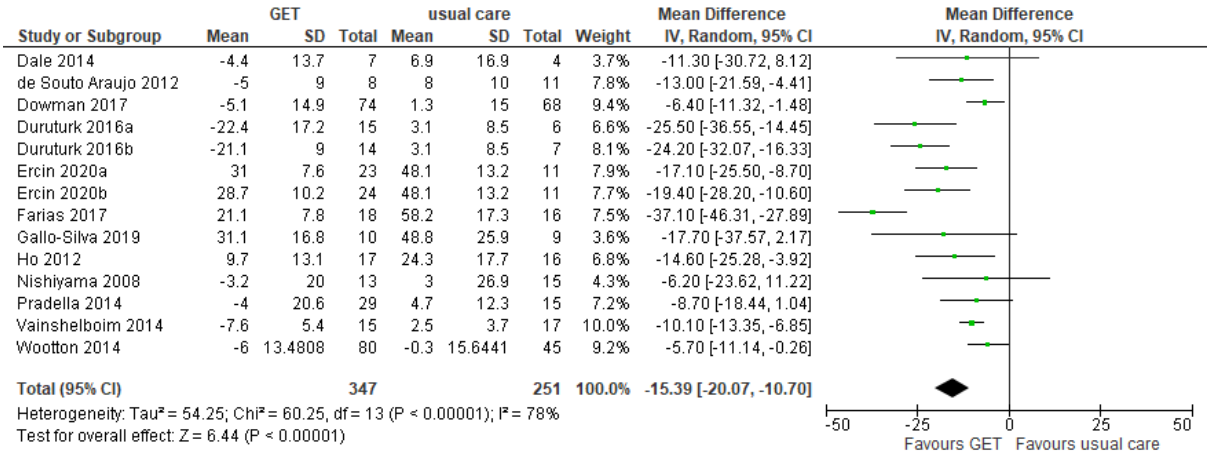
GET vs usual care – SGRQ total score at end intervention



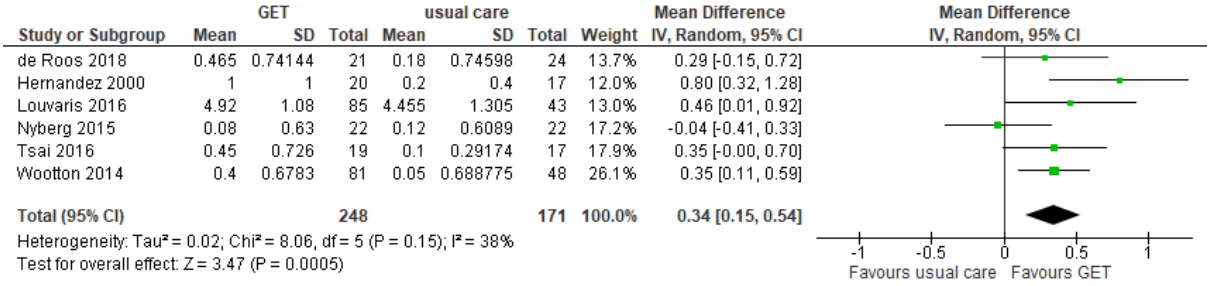
GET vs usual care – SGRQ symptoms domain score at end intervention



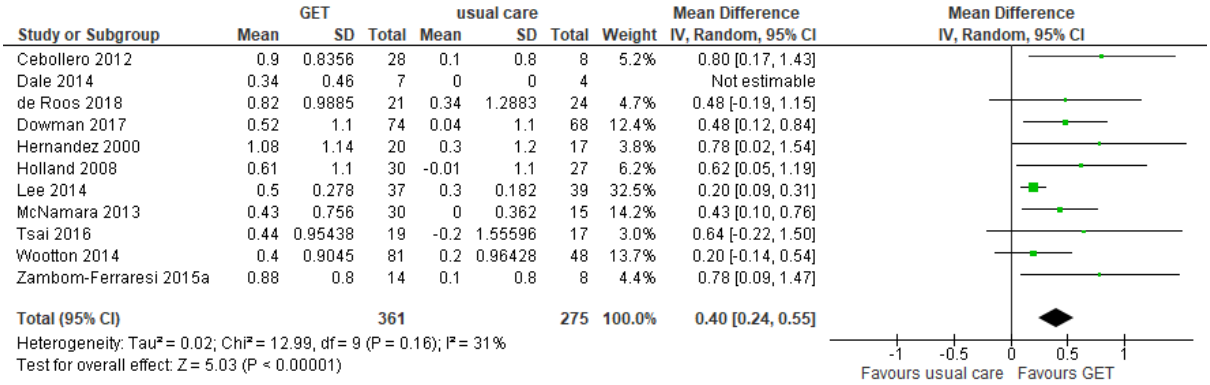
GET vs usual care – SGRQ activities domain score at end intervention



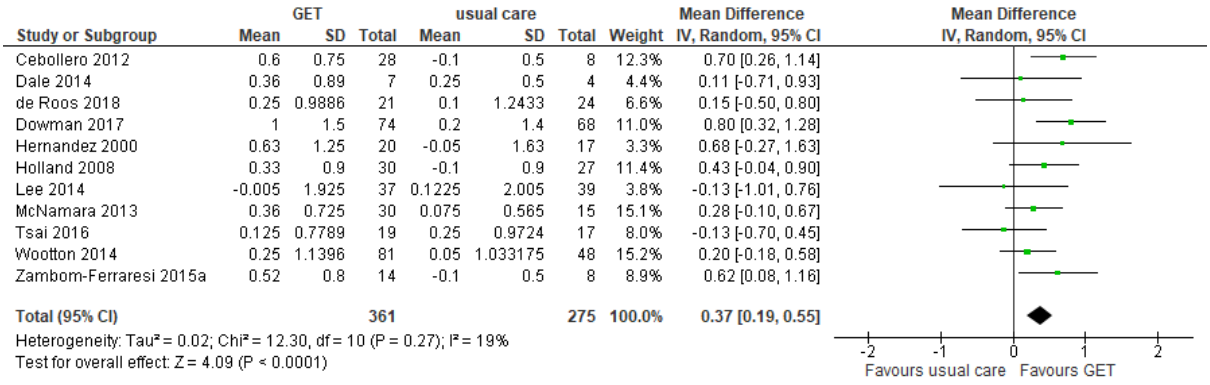
GET vs usual care – SGRQ impact domain score at end intervention



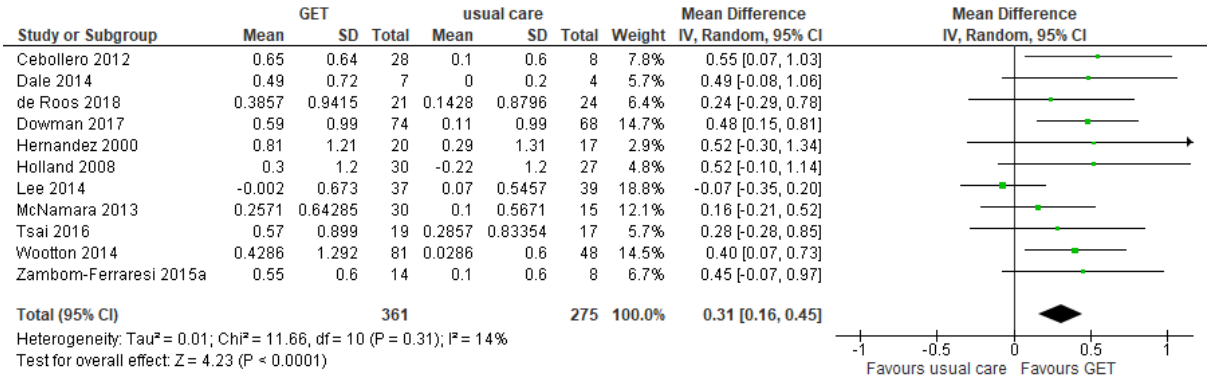
GET vs usual care – CRQ total score at end intervention



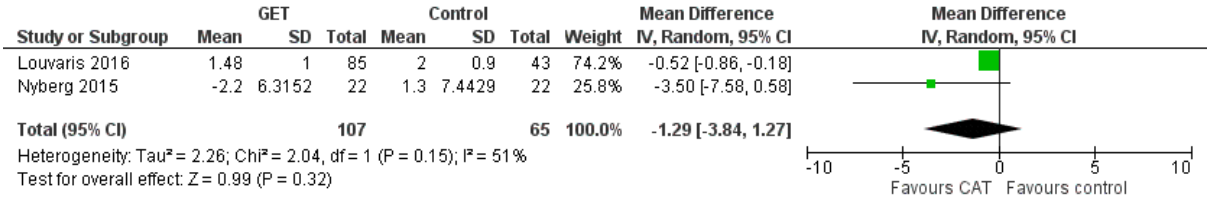
GET vs usual care – CRQ dyspnoea domain score at end intervention



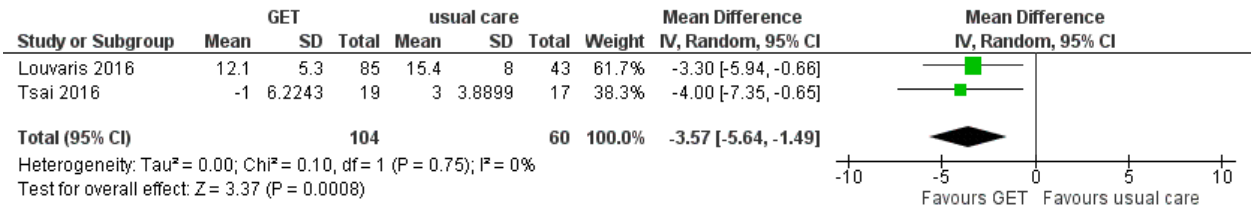
GET vs usual care – CRQ mastery domain at end intervention



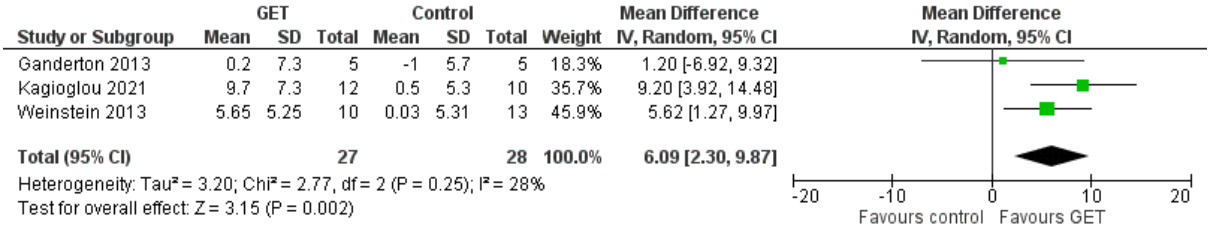
GET vs usual care – CRQ emotional function domain at end intervention



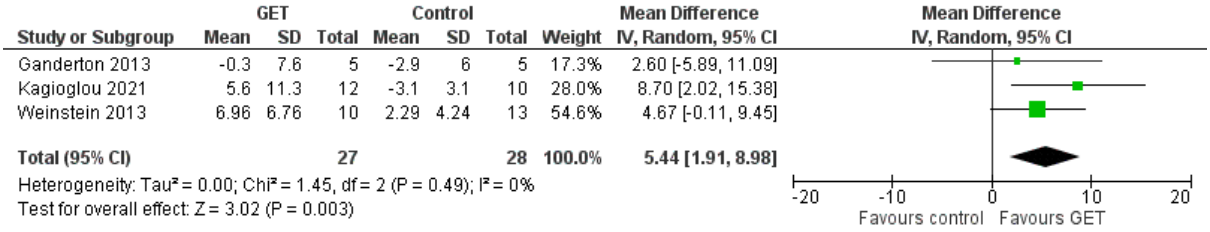
GET vs usual care - Clinical COPD Questionnaire (CCQ) score at end intervention



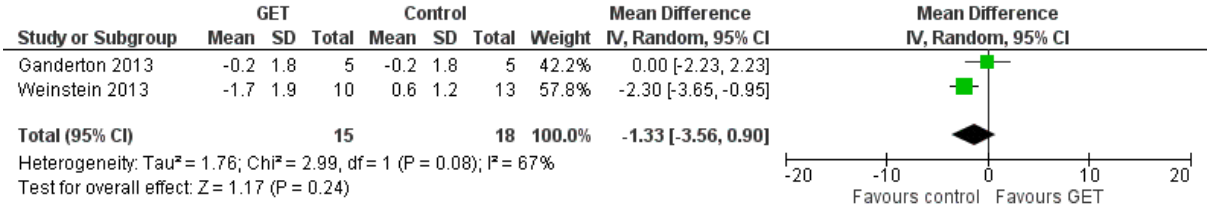
GET vs usual care - COPD assessment test (CAT) score at end intervention



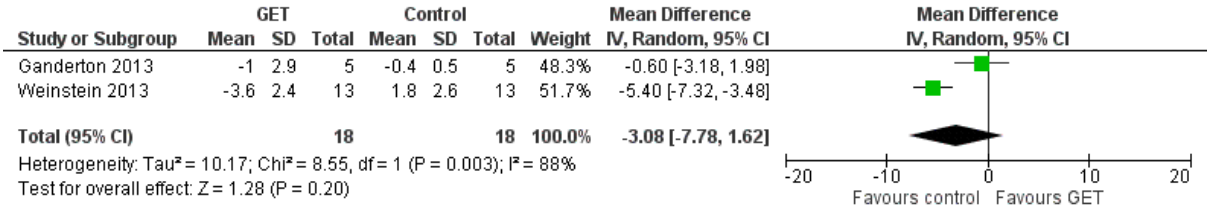
GET vs usual care - SF-36 Physical Component Summary score at end intervention (10weeks to 6 months)



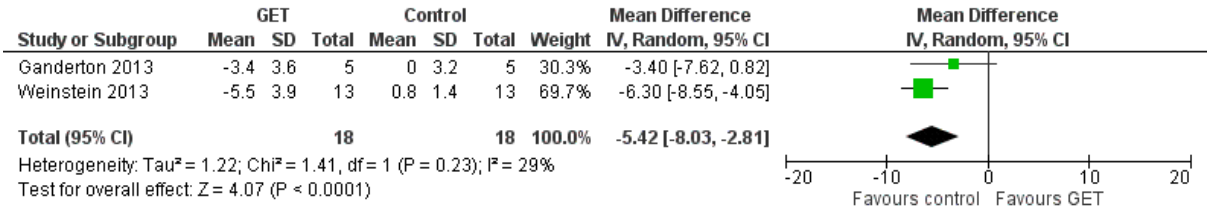
GET vs usual care - SF-36 Mental Component Summary score at end intervention (10weeks to 6 months)



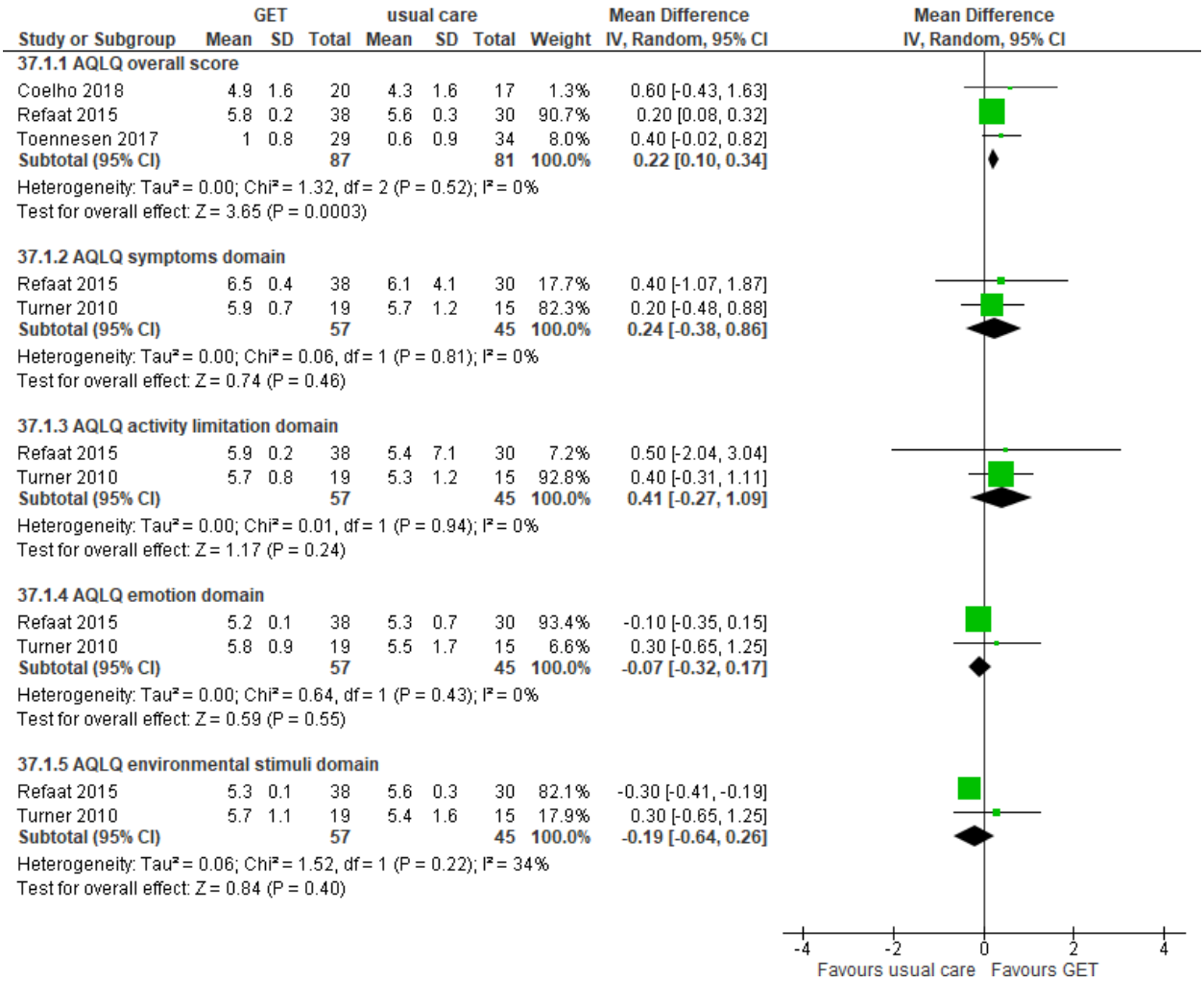
GET vs usual care - CAMPHOR Activities score at end intervention (10- 12 weeks)



GET vs usual care - CAMPHOR Symptoms score at end intervention (10- 12 weeks)



GET vs usual care - CAMPHOR Quality of life at end intervention (10- 12 weeks)



GET vs usual care - AQLQ at end intervention (6 weeks)

Important outcome: Adverse events

No meta-analysis.

2.5. GRADE Evidence table

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GET	Usual care	Relative (95% CI)	Absolute (95% CI)		
INTERVENTION: Graded exercise therapy (GET) including aerobic training												
CRITICAL OUTCOME: Fatigue												
Chronic Respiratory Questionnaire (CRQ) Fatigue domain after 8-12 weeks GET												
11	RCT	Serious[a]	Not serious	Not serious	Serious[b]	Not serious	352	272		0.53 (0.41 to 0.65)	⨁⨁◯◯ LOW	CRITICAL
IMPORTANT OUTCOME: Health-related quality of life												
St George's Respiratory Questionnaire Total after 8-12 weeks GET												
15	RCT	Serious[a]	Serious[c]	Not serious	Not serious	Not serious	361	266		-14.07 (-18.85 to -9.30)	⨁⨁◯◯ LOW	IMPORTANT
St George's Respiratory Questionnaire Symptoms after 8-12 weeks GET												
14	RCT	Serious[a]	Serious[c]	Not serious	Not serious	Not serious	347	251		-17.00 (-23.44 to -10.56)	⨁⨁◯◯ LOW	IMPORTANT
St George's Respiratory Questionnaire Activities after 8-12 weeks GET												
14	RCT	Serious[a]	Serious[c]	Not serious	Not serious	Not serious	347	251		-14.70 (-21.20 to -8.20)	⨁⨁◯◯ LOW	IMPORTANT

St George's Respiratory Questionnaire Impact after 8-12 weeks GET												
14	RCT	Serious[a]	Serious[c]	Not serious	Not serious	Not serious	347	251		-15.39 (-20.07 to -10.07)	⊕⊕◯◯ LOW	IMPORTANT
CRQ Total after 8-12 weeks of GET												
6	RCT	Serious[a]	Not serious	Not serious	Serious[b]	Not serious	248	171		0.34 (0.15 to 0.54)	⊕⊕◯◯ LOW	IMPORTANT
CRQ Dyspnoea after 8-12 weeks of GET												
11	RCT	Serious[a]	Not serious	Not serious	Serious[b]	Not serious	361	275		0.40 (0.24 to 0.55)	⊕⊕◯◯ LOW	IMPORTANT
CRQ Mastery after 8-12 weeks of GET												
11	RCT	Serious[a]	Not serious	Not serious	Serious[b]	Not serious	361	275		0.37 (0.19 to 0.55)	⊕⊕◯◯ LOW	IMPORTANT
CRQ Emotional Function after 8-12 weeks of GET												
11	RCT	Serious[a]	Not serious	Not serious	Serious[b]	Not serious	361	275		0.31 (0.16 to 0.45)	⊕⊕◯◯ LOW	IMPORTANT
COPD Assessment Test after 8-12 weeks GET												
2	RCT	Serious[d]	Not serious	Serious[e]	Not serious	Not serious	104	60		-3.57 (-5.64 to -1.49)	⊕⊕◯◯ LOW	IMPORTANT

Clinical COPD Questionnaire (CCQ) after 8-12 weeks GET												
2	RCT	Serious[a]	Not serious	Serious[e]	Serious[b]	Not serious	107	65		-1.29 (-3.84 to 1.27)	⊕◯◯◯ VERY LOW	IMPORTANT
SF-36 Physical Component Summary immediately post GET (10wks to 6 months)												
3	RCT	Serious[f]	Serious	Serious[g]	Serious[b]	Not serious	27	28		6.09 (2.30 to 9.87)	⊕◯◯◯ VERY LOW	IMPORTANT
SF-36 Mental Component Summary immediately post GET (10wks to 6 months) – Pulmonary Hypertension												
3	RCT	Serious[f]	Not serious	Serious[g]	Serious[b]	Not serious	27	28		5.44 (1.91 to 8.98)	⊕◯◯◯ VERY LOW	IMPORTANT
CAMPHOR Activities immediately post GET (10- 12wks)												
2	RCT	Serious[f]	Not serious	Serious[g]	Serious[b]	Not serious	15	18		-1.33 (-3.56 to 0.90)	⊕◯◯◯ VERY LOW	IMPORTANT
CAMPHOR Symptoms immediately post GET (10- 12wks)												
2	RCT	Serious[f]	Not serious	Serious[g]	Serious[b]	Not serious	18	18		-3.08 (-7.78 to 1.62)	⊕◯◯◯ VERY LOW	IMPORTANT
CAMPHOR Quality of Life immediately post GET (10- 12wks)												
2	RCT	Serious[f]	Not serious	Serious[g]	Serious[b]	Not serious	15	18		-5.42 (-8.03 to -2.81)	⊕◯◯◯ VERY LOW	IMPORTANT

AQLQ symptoms after 6 weeks GET												
2	RCT	Serious[a]	Not serious	Not serious	Serious[b]	Not serious	57	45		0.24 (-0.38 to 0.86))	⊕⊕◯◯ LOW	IMPORTANT
AQLQ activities after 6 weeks GET												
2	RCT	Serious[a]	Not serious	Not serious	Serious[b]	Not serious	57	45		0.41 (-0.27 to 1.09)	⊕⊕◯◯ LOW	IMPORTANT
AQLQ emotion after 6 weeks GET												
2	RCT	Serious[a]	Not serious	Not serious	Serious[b]	Not serious	57	45		0.07 (-0.32 to 0.17)	⊕⊕◯◯ LOW	IMPORTANT
AQLQ environmental stimuli after 6 weeks GET												
2	RCT	Serious[a]	Not serious	Not serious	Serious[b]	Not serious	57	45		-0.19 (-0.64 to 0.26)	⊕⊕◯◯ LOW	IMPORTANT
IMPORTANT OUTCOME: Adverse events												
Adverse events during the intervention period												
46	RCT	Serious[a]	Not serious	Not serious	Serious[h]	Not serious	1099	931		No studies reported serious adverse events related to the intervention. One report of muscle soreness related to resistance training.	⊕⊕◯◯ LOW	IMPORTANT

CI: confidence interval.

Explanations:

a. Majority of studies at high risk for detection bias (lack of assessor blinding) and reporting bias (no prospectively registered protocol).

b. The confidence interval for the pooled estimate of the effect of GET includes both clinically important benefit and no clinically important benefit

c. Significant heterogeneity identified (I^2 >70%), with variable effect estimates across studies

d. Majority of studies at high risk for allocation concealment and selective reporting

e. All studies that measured this outcome were in people with COPD and results cannot be applied to other groups

f. Majority of studies at high risk for allocation concealment and selective reporting.

g. No studies included participants in Functional Class IV

h. Most studies did not report adverse events and we cannot judge the precision of the overall effect

2.6. Evidence to Decision Table

PICO2: Should graded exercise therapy (GET) be used to reduce fatigue in people with serious illness related to lung disease?	
POPULATION:	Adults with serious illness related to lung disease
INTERVENTION:	Graded exercise therapy
COMPARISON:	No graded exercise therapy
MAIN OUTCOMES:	Critical: fatigue Important: health-related quality of life, adverse events

Graded Exercise Therapy (GET) is defined as establishing a baseline of achievable exercise or physical activity and then making fixed incremental increases in the time spent being physically active. Graded exercise therapy is a component of pulmonary rehabilitation, however pulmonary rehabilitation is a package of care that also includes education and behaviour change. We did not include GET conducted in the context of pulmonary rehabilitation in our evidence synthesis, in order to evaluate the effects of GET alone.

ASSESSMENT

Problem Is the problem a priority?		
Judgement	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Fatigue is prevalent in people with serious illness related to lung disease, including COPD, ILD, pulmonary hypertension and bronchiectasis (1-4). Fatigue is more common in those with higher levels of dyspnoea, and in those with anxiety or depression (1, 5). Fatigue has a profound impact on daily life participation and is associated with reduced health related quality of life (1, 6). Fatigue is also associated with poor long-term outcomes including more exacerbations and increased mortality (1, 7). There are few specific treatments for fatigue affecting people with chronic respiratory disease, and the symptom of fatigue is likely under-recognised by health professionals and under-reported by patients (8).	
Desirable Effects How substantial are the desirable anticipated effects?		

Judgement	Research evidence	Additional considerations
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Of 76 included studies, the populations included people with COPD (n=41), asthma (n=10), interstitial lung disease (n=7), pulmonary hypertension (n=7), CF (n=4), bronchiectasis (n=2) and mixed chronic respiratory disease (n=5). Participants were mostly older adults with moderate to severe lung disease. The Interventions were mostly supervised graded exercise programs in an outpatient setting, including aerobic exercise training. A smaller number of studies evaluated resistance training, water-based exercise or Tai Chi. **Critical outcome: Fatigue** GET reduced fatigue (Chronic Respiratory Questionnaire (CRQ) Fatigue domain) at the end of the intervention period (8-12 weeks) compared to usual care (11 RCTs, 624 participants). The mean improvement exceeded the minimal important difference (MID) of 0.5 points. • **Important outcome: Health-related quality of life (HRQoL)** Compared to usual care, 8-12 weeks of GET improved HRQoL (15 RCTs, St George's Respiratory Questionnaire (SGRQ), CRQ) with mean improvements that exceeded MIDs across almost all domains. •	

Undesirable Effects How substantial are the undesirable anticipated effects?		
Judgement	**Research evidence**	**Additional considerations**
2 ○ Large ○ Moderate ○ Small ●Trivial ○ Varies ○ Don't know	**Important outcome: Adverse events** Only half of the studies (46 out of 75) reported on adverse events. No studies reported serious adverse events related to the intervention (46 RCTs, 2030 participants). There was no evidence of adverse effects related to increased exacerbations, hospitalisations or deaths. A few studies reported minor muscle soreness following exercise training. Studies in pulmonary hypertension rarely included patients in Functional Class IV, where the risk of adverse events may be higher.	In pulmonary hypertension, an uncontrolled study of inpatient rehabilitation reported that adverse events occurred in 13.6% of 183 patients, with most being mild and not directly attributable to exercise training (12). These included syncope occurring several hours after

		training (n=2), pre-syncope immediately after cycle training (n=1), pre-syncope not associated with training (n=5), supraventricular tachycardia during training that was self-limiting (n=2), respiratory infection (n=14) and minor haemoptysis (n=1).
Certainty of evidence What is the overall certainty of the evidence of effects?		
Judgement	**Research evidence**	**Additional considerations**
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Based on GRADE assessment, certainty of evidence was low for the critical outcome of fatigue, with most evidence from studies in COPD. Certainty of evidence for the important outcome of HRQoL was low. Certainty of evidence for adverse events was low. Certainty of evidence was affected by detection bias (lack of assessor blinding), reporting bias (trials not registered prospectively) and indirectness (limited data in pulmonary hypertension and bronchiectasis; patients with severe pulmonary hypertension not included in trials). No studies included people near the very end of life. Fatigue-specific outcome measures were rarely used.	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
Judgement	**Research evidence**	**Additional considerations**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability	The critical outcome for this question is fatigue, which people with serious respiratory illness consistently report as a major distressing symptom (1-4). People with chronic respiratory disease describe fatigue as a severe chronic lack of energy, with profound impacts on daily activities and health-related quality of life (13). Despite the overwhelming and ubiquitous nature of fatigue in chronic respiratory disease, patients report that fatigue is often not mentioned by health professionals (8). People living with chronic respiratory disease report unmet needs for effective treatments to reduce fatigue (4, 14).	There was no important uncertainty or variability in the views of the patient members of the Task Force regarding values.

●No important uncertainty or variability		

Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Judgement	**Research evidence**	**Additional considerations**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	The balance of effects favours GET. There were consistent improvements in our critical outcome of fatigue across patient groups, which generally exceeded the MID. There were consistent improvements in the important outcome of HRQoL for people who undertook GET. The likelihood of undesirable effects is low.	

Resources required How large are the resource requirements (costs)?		
Judgement	**Research evidence**	**Additional considerations**
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○Varies ○ Don't know	Costs of supervised exercise programs in chronic respiratory disease are not well documented. However it is likely that costs are modest, particularly for outpatient programs, which is the most common mode of delivery. A community-based exercise program for COPD in the Netherlands reported costs of €1648 over 2 years (15). Graded exercise therapy can be delivered in existing pulmonary rehabilitation programs. The costs of providing pulmonary rehabilitation vary by country and health system. Potential savings may result from reduced hospitalisations in those who complete a graded exercise program (16), although this has only been documented in COPD.	

Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
Judgement	**Research evidence**	**Additional considerations**

● Very low ○ Low ○ Moderate ○ High ○ No included studies	There is very little evidence regarding resource requirements, and the evidence that exists is only in COPD.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
Judgement	**Research evidence**	**Additional considerations**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Limited information is available on the costs of delivering pulmonary rehabilitation, of which GET is a component. Pulmonary rehabilitation for patients with COPD is likely to be cost-effective compared to usual care over 12 months, particularly when it is delivered in an outpatient setting (17), largely due to the reduction in healthcare utilisation over the following 12 months. Pulmonary rehabilitation is also likely to be cost-effective for patients with ILD when compared to no pulmonary rehabilitation if repeated every 6 to 12 months (18). There are no data for other chronic respiratory conditions.	
Equity What would be the impact on health equity?		
Judgement	**Research evidence**	**Additional considerations**
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	There is no direct evidence of the impact of GET on health equity from the included studies.	GET is relatively inexpensive and within the scope of practice for physiotherapists and other exercise professionals, and can be delivered across a wide variety of contexts (outpatient, private clinic, home, remote delivery), which suggests there

		may be potential to improve health equity.
Acceptability Is the intervention acceptable to key stakeholders?		
Judgement	**Research Evidence**	**Additional considerations**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	People with chronic respiratory disease perceive that supervised, supported and individualized exercise may be a useful treatment for fatigue (14). However, some people with chronic respiratory disease may not find GET acceptable. Some may not perceive exercise to be beneficial for them, or may be afraid of exercising due to dyspnoea or other symptoms (19). Exercise programs may not be easily accessible due to difficulties with travel and transport, disabling symptoms or costs of attendance (20). The acceptability of GET to carers is not known. Most research examining exercise therapy for chronic respiratory disease has been undertaken in high income countries, so acceptability in other settings and more diverse cultural groups is not well documented. It is likely that GET is not acceptable in people who are close to the end of life.	There was no important uncertainty or variability in the views of the patient members of the Task Force regarding acceptability.
Feasibility Is the intervention feasible to implement?		
Judgement	**Research evidence**	**Additional considerations**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don’t know	Graded exercise therapy is a component of pulmonary rehabilitation programs, which are well established in many countries. However there are disparities in access to pulmonary rehabilitation across the world, which may reduce feasibility in some locations (21).	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

We suggest that graded exercise therapy be used to reduce fatigue in people with serious respiratory illness (conditional recommendation, low certainty of evidence).

Justification

This recommendation places a high value on consistent improvements in fatigue and HrQoL for people who undertook GET. People living with serious respiratory illness report unmet needs for interventions to reduce fatigue and perceive that supervised, supported and individualized exercise may be useful. The likelihood of undesirable effects was low in RCTs, noting that these studies were conducted in supervised environments using trained staff, and patients with very severe disease were rarely included. GET is within the scope of physical therapists and exercise physiologists and requires no specialized equipment, so could be made widely accessible.

Subgroup considerations

For patients with severe pulmonary hypertension or a history of arrhythmia, syncope or pre-syncope during exercise, consider additional monitoring from staff with expertise in delivering GET for this group.

Implementation considerations

GET is a component of pulmonary rehabilitation programs, which are well established in many countries. However, there are disparities in access to pulmonary rehabilitation, which may reduce feasibility in some locations. The patient-related barriers that reduce uptake of pulmonary rehabilitation are likely relevant to GET, including fear of exercise and lack of perceived benefit, challenges related to travel and transport, and costs of attendance. Health professionals should explore and address these barriers when referring a patient for GET.

Monitoring and evaluation

Fatigue-specific outcome measures shouled be used to evaluate the effect of GET on fatigue. Health professionals delivering GET should monitor for post-exertional malaise and adjust exercise prescription accordingly. Monitoring during GET should be consistent with the principles that are well established in pulmonary rehabilitation, including pulse oximetry.

Research priorities

Clinical trials examining the benefits of GET for people with severe lung disease are needed, including those with severe hemodynamic impairment. Many of the participants in existing trials had mild-moderate fatigue, and the impact of GET in those with severe fatigue remains to be examined, including its impact on post-exertional symptoms. Fatigue-specific outcome measures should be used. The cost-effectiveness of GET should be examined, including remote delivery models that could decrease costs and increase accessibility.

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2.8. Search strategies

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions

#	Query
1	Fatigue Syndrome, Chronic/ or Fatigue/
2	fatigue.mp.
3	1 or 2
4	(graded exercise* or graded activit* or graded aerobic exercis*).mp.
5	((graded adj3 (walk or walking or running or run or steps or stepping or cycling or jog or jogging or physical)) and (exercis* or activit*)).mp.
6	4 or 5
7	3 and 6
8	exercise therapy/ or endurance training/ or muscle stretching exercises/ or plyometric exercise/ or resistance training/ or physical therapy modalities/ or exercise movement techniques/ or physical endurance/ or exercise tolerance/ or physical exertion/ or physical fitness/
9	(exercis* adj1 therap*).mp.
10	(((exercise or endurance or resistance) adj training) or (exercise adj (intensity or tolerance or endurance)) or (physical adj (fitness or endurance or exertion))).mp.
11	8 or 9 or 10
12	3 and 11
13	((exercise* or activit*) adj2 targeted).mp.
14	(Increas* adj2 (challeng* or intensit* or level?) adj5 (exercise* or physical activit* or exertion* or moving or movement* or walking or stepping)).mp.
15	(Increas* adj2 (exercise* or physical activit* or exertion* or aerobic or movement* or moving or walking)).mp.
16	(increas* adj2 (abilit* or duration* or intens*) adj5 (physical activit or exercise* or exertion or movement* or weightlift* or weight-lift* or resistance train* or walking)).mp.
17	((increment* or increas*) adj3 (duration or time or weekly or daily or amount) adj7 (exercise* or physical activit* or exertion* or moving or movement* or walk or walking or step counts or treadmill)).mp.
18	((patient-specific or client-specific or participant* specific or patient-cent* or client-cent*) adj7 (physical activit or exercise* or exertion or movement* or weightlift* or weight-lift* or resistance train* or walking)).mp.
19	((introduc* or increas* or increment*) adj1 gradual* adj3 (physical activit or exercise* or exertion or movement* or weightlift* or weight-lift* or resistance train* or walking)).mp.
20	((physical activit or exercise* or exertion or movement* or weightlift* or weight-lift* or resistance train* or walking) adj5 increase* over time).mp.
21	((progressive* return* or planned approach*) and (physical activit or exercise* or exertion or movement* or weightlift* or weight-lift* or resistance train* or walking)).mp.
22	("return* to" adj2 (physical activit or exercise* or exertion or movement* or weightlift* or weight-lift* or resistance train* or walking)).mp.
23	(fear* and (physical activit or exercise* or exertion or movement* or weightlift* or weight-lift* or resistance train* or walking)).mp.
24	((physical activit or exercise* or exertion or movement* or weightlift* or weight-lift* or resistance train* or walking) adj1 (pace? or pacing)).mp.
25	or/13-24
26	3 and 25
27	7 or 12 or 26
28	(randomized controlled trial or controlled clinical trial).pt.

29	(randomi?ed or placebo).ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.
30	((cross over or crossover) adj (clinical study or clinical trial or design or method or study or trial or studies)).mp.
31	28 or 29 or 30
32	27 and 31

Database: Embase

#	Query
1	fatigue/ or chronic fatigue syndrome/
2	fatigue.mp.
3	1 or 2
4	(graded exercise* or graded activit* or graded aerobic exercis*).mp.
5	((graded adj3 (walk or walking or running or run or steps or stepping or cycling or jog or jogging or physical)) and (exercis* or activit*)).mp.
6	4 or 5
7	3 and 6
8	exercise therapy/ or endurance training/ or muscle stretching exercises/ or plyometric exercise/ or resistance training/ or physical therapy modalities/ or exercise movement techniques/ or physical endurance/ or exercise tolerance/ or physical exertion/ or physical fitness/
9	(exercis* adj1 therap*).mp.
10	(((exercise or endurance or resistance) adj training) or (exercise adj (intensity or tolerance or endurance)) or (physical adj (fitness or endurance or exertion))).mp.
11	8 or 9 or 10
12	3 and 11
13	((exercise* or activit*) adj2 targeted).mp.

14	(Increas* adj2 (challeng* or intensit* or level?) adj5 (exercise* or physical activit* or exertion* or moving or movement* or walking or stepping)).mp.
15	(Increas* adj2 (exercise* or physical activit* or exertion* or aerobic or movement* or moving or walking)).mp.
16	(increas* adj2 (abilit* or duration* or intens*) adj5 (physical activit or exercise* or exertion or movement* or weightlift* or weight-lift* or resistance train* or walking)).mp.
17	((increment* or increas*) adj3 (duration or time or weekly or daily or amount) adj7 (exercise* or physical activit* or exertion* or moving or movement* or walk or walking or step counts or treadmill)).mp.
18	((patient-specific or client-specific or participant* specific or patient-cent* or client-cent*) adj7 (physical activit or exercise* or exertion or movement* or weightlift* or weight-lift* or resistance train* or walking)).mp.
19	((introduc* or increas* or increment*) adj1 gradual* adj3 (physical activit or exercise* or exertion or movement* or weightlift* or weight-lift* or resistance train* or walking)).mp.
20	((physical activit or exercise* or exertion or movement* or weightlift* or weight-lift* or resistance train* or walking) adj5 increase* over time).mp.
21	((progressive* return* or planned approach*) and (physical activit or exercise* or exertion or movement* or weightlift* or weight-lift* or resistance train* or walking)).mp.
22	("return* to" adj2 (physical activit or exercise* or exertion or movement* or weightlift* or weight-lift* or resistance train* or walking)).mp.
23	(fear* and (physical activit or exercise* or exertion or movement* or weightlift* or weight-lift* or resistance train* or walking)).mp.
24	((physical activit or exercise* or exertion or movement* or weightlift* or weight-lift* or resistance train* or walking) adj1 (pace? or pacing)).mp.
25	or/13-24
26	3 and 25
27	7 or 12 or 26
28	randomized controlled trial/ or randomization/ or single blind procedure/ or double blind procedure/ or crossover procedure/ or placebo/ or prospective study/

29	(randomi?ed controlled or RCT or randomly allocated or allocated randomly or random allocation or "allocated at random" or single blind* or double blind* or ((treble or triple) adj blind*) or placebo*).mp.
30	((cross over or crossover) adj (clinical study or clinical trial or design or method or study or trial or studies)).mp.
31	28 or 29 or 30
32	27 and 31
33	limit 27 to (randomized controlled trial or controlled clinical trial)
34	32 or 33

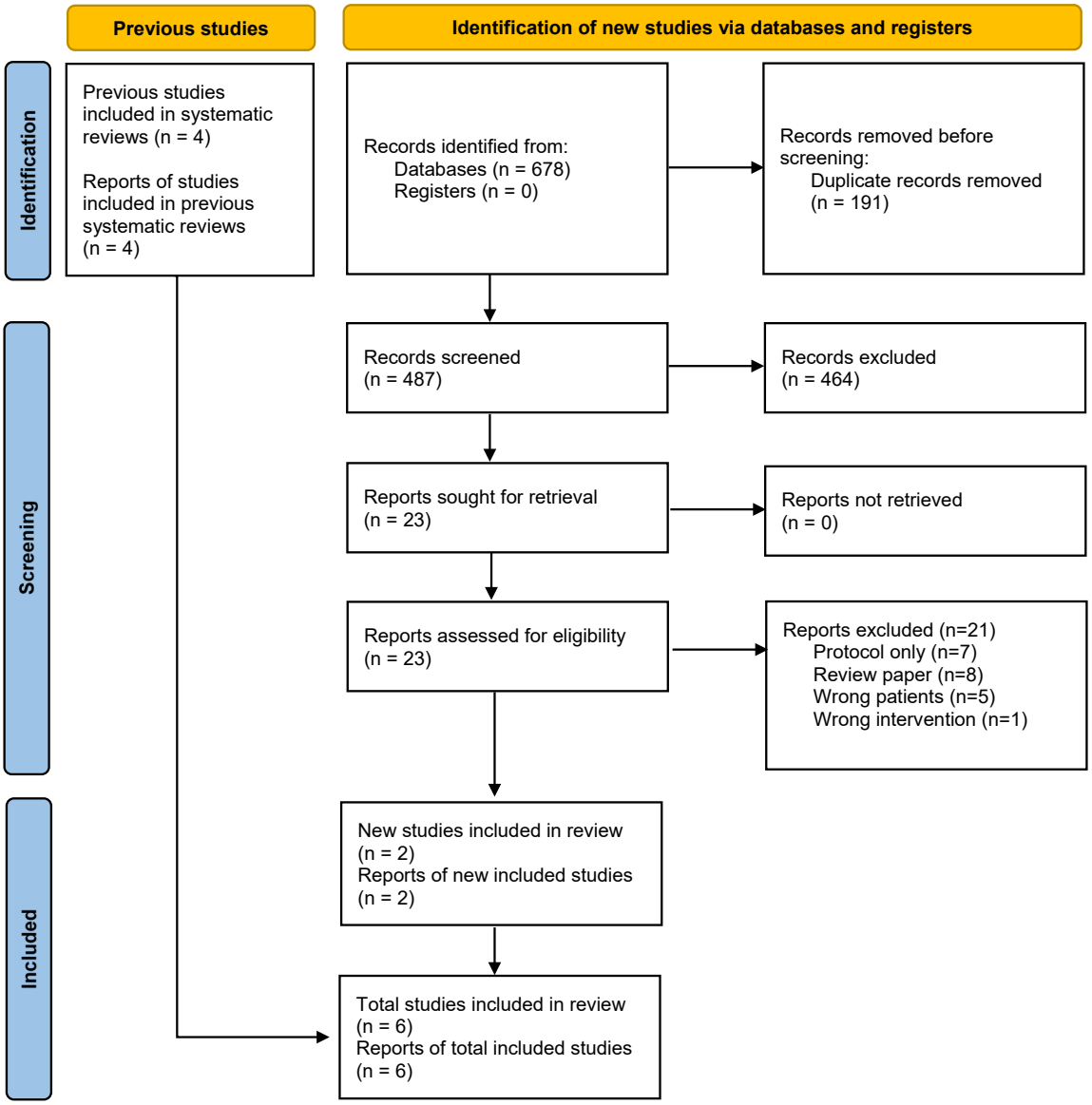
Database: EBM Reviews - Cochrane Central Register of Controlled Trials

#	Query
1	Fatigue Syndrome, Chronic/ or Fatigue/
2	fatigue.mp.
3	1 or 2
4	(graded exercise* or graded activit* or graded aerobic exercis*).mp.
5	((graded adj3 (walk or walking or running or run or steps or stepping or cycling or jog or jogging or physical)) and (exercis* or activit*)).mp.
6	4 or 5
7	3 and 6
8	exercise therapy/ or endurance training/ or muscle stretching exercises/ or plyometric exercise/ or resistance training/ or physical therapy modalities/ or exercise movement techniques/ or physical endurance/ or exercise tolerance/ or physical exertion/ or physical fitness/
9	(exercis* adj1 therap*).mp.
10	(((exercise or endurance or resistance) adj training) or (exercise adj (intensity or tolerance or endurance)) or (physical adj (fitness or endurance or exertion))).mp.
11	8 or 9 or 10
12	3 and 11
13	((exercise* or activit*) adj2 targeted).mp.
14	(Increas* adj2 (challeng* or intensit* or level?) adj5 (exercise* or physical activit* or exertion* or moving or movement* or walking or stepping)).mp.
15	(Increas* adj2 (exercise* or physical activit* or exertion* or aerobic or movement* or moving or walking)).mp.
16	(increas* adj2 (abilit* or duration* or intens*) adj5 (physical activit or exercise* or exertion or movement* or weightlift* or weight-lift* or resistance train* or walking)).mp.
17	((increment* or increas*) adj3 (duration or time or weekly or daily or amount) adj7 (exercise* or physical activit* or exertion* or moving or movement* or walk or walking or step counts or treadmill)).mp.
18	((patient-specific or client-specific or participant* specific or patient-cent* or client-cent*) adj7 (physical activit or exercise* or exertion or movement* or weightlift* or weight-lift* or resistance train* or walking)).mp.

19	((introduc* or increas* or increment*) adj1 gradual* adj3 (physical activit or exercise* or exertion or movement* or weightlift* or weight-lift* or resistance train* or walking)).mp.
20	((physical activit or exercise* or exertion or movement* or weightlift* or weight-lift* or resistance train* or walking) adj5 increase* over time).mp.
21	((progressive* return* or planned approach*) and (physical activit or exercise* or exertion or movement* or weightlift* or weight-lift* or resistance train* or walking)).mp.
22	("return* to" adj2 (physical activit or exercise* or exertion or movement* or weightlift* or weight-lift* or resistance train* or walking)).mp.
23	(fear* and (physical activit or exercise* or exertion or movement* or weightlift* or weight-lift* or resistance train* or walking)).mp.
24	((physical activit or exercise* or exertion or movement* or weightlift* or weight-lift* or resistance train* or walking) adj1 (pace? or pacing)).mp.
25	or/13-24
26	3 and 25
27	7 or 12 or 26

3. PICO question 3: Should increased airflow be used to reduce breathlessness in people with serious illness related to lung disease?

3.1. Identification of studies – PRISMA diagram



3.2. Inclusion criteria

- Randomised controlled trial, including both parallel and crossover trials.
- Participants were adults aged 18 years or older.
- Participants had serious illness related to lung disease (defined as a condition that carries a high risk of mortality, negatively impacts quality of life and daily function, and/or is burdensome in symptoms, treatments, or caregiver stress)
- Intervention: Increased airflow delivered from either a fan (handheld or table) or non–oxygen-enriched compressed air or from a non-invasive ventilatory method (nasal cannula, mask or mouthpiece) and directed at the cheek of the face, nasal mucosae or mouth (Swan et al Pall Med 2019).
- Comparison: No increased airflow - usual care, fan directed at other body part, other gadget (e.g. wristband), placebo.

3.3. Exclusion criteria

- Nasal intermittent positive pressure ventilation
- Participants with malignant disease

3.4. GRADE Evidence table

PICO3: Should airflow be used to reduce breathlessness in people with serious illness related to lung disease?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Increased airflow	No increased airflow	Relative (95% CI)	Absolute (95% CI)		
CRITICAL OUTCOME: Breathlessness												
Breathlessness intensity, NRS average 24 hours at Day 28												
1	RCT	Serious[a]	Not serious	Not serious	Very serious[b]	Not serious	10	10		0.90 [-0.95 to 2.75]	⨁◯◯◯ VERY LOW	CRITICAL
Breathlessness intensity, NRS worst 24 hours at Day 28												
1	RCT	Serious[a]	Not serious	Not serious	Very serious[b]	Not serious	10	10		0.80 [-1.01, 2.61]	⨁◯◯◯ VERY LOW	CRITICAL
Breathlessness distress, NRS average 24 hours at Day 28												
1	RCT	Serious[a]	Not serious	Not serious	Very serious[b]	Not serious	10	10		0.10 [-2.57, 2.77]	⨁◯◯◯ VERY LOW	CRITICAL
Breathlessness distress, NRS worst 24 hours at Day 28												
1	RCT	Serious[a]	Not serious	Not serious	Very serious[b]	Not serious	10	10		0.40 [-2.22, 3.02]	⨁◯◯◯ VERY LOW	CRITICAL

Breathlessness unpleasantness, NRS average 24 hours at Day 28												
1	RCT	Serious[a]	Not serious	Not serious	Very serious[b]	Not serious	10	10		-0.50 [-2.32, 1.32]	⊕◯◯◯ VERY LOW	CRITICAL
Dyspnoea 12 at Day 14												
1	RCT	Serious[c]	Not serious	Serious[d]	Very serious[b]	Not serious	15	15		-2.2 (-6.4 to 1.9) favours fan	⊕◯◯◯ VERY LOW	CRITICAL
Modified Borg at isotime (20 min) on constant work rate test												
1	RXT	Very Serious[e]	Not serious	Serious[f]	Very serious[b]	Not serious[g]	10	10		-3.19 (-11.55 to 5.17)	⊕◯◯◯ VERY LOW	CRITICAL
Visual Analogue Scale at 5 minutes												
1	RXT	Serious[h]	Not Serious	Not serious	Very serious[b]	Not serious	22	22		7mm (2.5 to 11.7mm)	⊕◯◯◯ VERY LOW	CRITICAL
IMPORTANT OUTCOME: Health-related quality of life												
KBILD Breathlessness and activities domain												
1	RCT	Serious[c]	Not serious[b]	Serious[d]	Very serious[b]	Not serious	15	15		-1.5 (-8.9 to 5.9)	⊕◯◯◯ VERY LOW	IMPORTANT

IMPORTANT OUTCOME: Adverse events												
Adverse events												
1	RXT	Serious[c]	Not serious[b]	Not Serious[d]	Very serious[b]	Not serious	49	49		One short-term randomised cross-over study reported on adverse events, stating that 'There were no adverse events during the study'	⊕◯◯◯ VERY LOW	IMPORTANT

Explanations:

a. High risk for performance bias (lack of participant blinding) and detection bias (lack of assessor blinding).
b. 1 RCT with few participants and wide confidence interval for effect
c. High risk for performance bias (lack of participant blinding); success of assessor blinding not clear.
d. All participants had interstitial lung disease
e. High risk of bias for random sequence generation and allocation concealment (not reported); high risk for performance and detection bias (lack of participant and assessor blinding)
f. All participants had COPD
g. No trial registration; selective reporting cannot be excluded.
h. Evidence of inadequate washout between periods; high risk for performance bias (lack of participant blinding); risk of detection bias unclear (assessor blinding not clear, but statisticians were blinded)

3.5. Evidence to Decision Table

PICO3: Should airflow be used to reduce breathlessness in people with serious illness related to lung disease?	
POPULATION:	Adults with serious illness related to lung disease
INTERVENTION:	Increased airflow applied to the face or airways from either a fan (handheld or table) or non–oxygen-enriched compressed air or from a non-invasive ventilatory method (nasal cannula, mask or mouthpiece)
COMPARISON:	No increased airflow applied to the face or airways; fan directed at other body part, placebo (sham)
MAIN OUTCOMES:	Critical: Breathlessness, using relevant and validated tool. This may include measures at rest or during exercise, but exercise measures obtained before and after an intervention must be obtained at iso-workload. Important: • Health related quality of life, using any validated tool. • Adverse events, defined according to the investigators' definition.

Assessment

Problem Is the problem a priority?		
Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know	Patients with serious illness related to lung disease commonly experience high symptom burden, including chronic breathlessness (1), which contributes to a reduced quality of life (2). Breathlessness is frequently ranked by patients as their worst symptom (3) and it is a major contributor to unscheduled healthcare usage (4, 5).	
Desirable Effects How substantial are the desirable anticipated effects?		
Judgement	Research evidence	Additional considerations
○ Trivial ● **Small** ○ Moderate ○ Large ○ Varies ○ Don't know	6 included studies (7 reports) included people with COPD (n=127), interstitial lung disease (n=56), asthma (n=8) and bronchiectasis (n=7). There were 4 randomised controlled trials (6-9) and 2 crossover trials .(10,11) One report was a secondary data analysis using pooled data from the fan arms of two feasibility trials.(6, 13,14)	One additional RCT (49 participants) could not be included as only 73% of participants had chronic lung disease, and data could not be obtained separately. However, results were similar to the included studies.(14)

	Interventions were a hand held fan (5 studies) or a pedestal fan (1 study) (11). The fan was applied to the face, either at rest in the laboratory (1 study), during an exercise test (2 studies) or during daily life (3 studies). **Critical outcome: Breathlessness** Increased airflow using a hand held fan to the face during daily life did not reduce the Numerical Rating Scale for breathlessness at day 28 or Dyspnoea12 at day 14 compared to usual care (6,7). However the confidence intervals included the minimal important difference (1 pt for NRS, 3-6 pt for D12 (15)), so a benefit cannot be excluded. Increased airflow significantly reduced breathlessness on the Visual Analogue Scale after 5 minutes at rest, with the confidence interval including the minimal important difference (10mm).(8) Increased airflow reduced breathlessness at isotime on a constant work rate exercise test. The confidence interval was wide and included the MID (1 pt).(11) A combined analysis of the intervention arms of 2 trials (41 participants who used a hand held fan) reported that 85% of participants reported that the fan helped breathlessness.(13) **Important outcome: Health-related quality of life** Increased airflow did not improve the KBILD Breathlessness and Activities domain at 14 days compared to usual care. However the confidence intervals included the minimal important difference (7 points), so a benefit cannot be excluded.(7)	There were also improvements in exercise outcomes that were not prespecified in our protocol e.g. greater distance walked during the 6 MWT in patients who used a handheld fan and shorter post-exertional recovery time.(10) In another study, patients exercised 34 % longer with the air current applied to the face.(11)
Undesirable Effects How substantial are the undesirable anticipated effects?		
Judgement	Research evidence	Additional considerations
○ Large ○ Moderate ○ Small ●**Trivial** ○ Varies ○ Don't know	Only one study specifically reported on adverse events, stating that no adverse events occurred during the study period.	
Certainty of evidence		

What is the overall certainty of the evidence of effects?		
Judgement	Research evidence	Additional considerations
● **Very low** ○ Low ○ Moderate ○ High ○ No included studies	Based on GRADE assessment.	All studies were randomized trials; few had assessor blinding and none were able to blind participants or researchers. Meta-analysis was not possible due to the small numbers of studies and heterogeneity in outcomes. Several measures of breathlessness during exercise were not measured at isotime and thus could not be included. Only one study measured health-related quality of life. Studies predominantly included people with COPD and ILD. Several studies included mixed populations and it was not possible to obtain separate data for those with lung disease, so they could not be included.
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
Judgement	Research evidence	Additional considerations
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ●**No important uncertainty or**	The critical outcome for this question is breathlessness, which people with serious respiratory illness consistently report as a major distressing symptom (16,17,18). In people with COPD, breathlessness has been found to be a key determinant of low physical and mental health (17,18). Similarly, in people with pulmonary fibrosis breathlessness has been identified as a major driver of reduced quality of life (19,20). Fear of exertional breathlessness may result in avoiding exercise, leading to a downward spiral of deconditioning, social isolation with negative physical and emotional consequences (18). There is an immense need to better actively manage chronic breathlessness and other distressing symptoms in people with a variety of non-malignant chronic respiratory diseases.	There was no important uncertainty or variability in the views of the patient members of the Task Force regarding values.

variability		
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Judgement	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● **Probably favors the intervention** ○ Favors the intervention ○ Varies ○ Don't know	The balance of effects probably favours the intervention. For the critical outcome of breathlessness (NRS, VAS, Dyspnoea 12, modified Borg scale), analyses give mixed results with some showing no benefit of the intervention compared to control (mainly longer term, MCID included in confidence interval) and those with short term measurement demonstrating a benefit with confidence intervals including the minimal important difference. The size of the benefits are small. Onlye on study reported on adverse effects, and reported none.	
Resources required How large are the resource requirements (costs)?		
Judgement	Research evidence	Additional considerations
○ Large costs ○ Moderate costs ● **Negligible costs and savings** ○ Moderate savings ○ Large savings ○Varies ○ Don't know	None of the included studies reported information about the cost of the fans and we did not conduct a separate review on required resources.	Hand held fans are inexpensive (£5-10) and readily accessible. Use of a hand held fan does not require specialist skills and requires little training (e.g. regarding the positioning of fans), so this intervention could be used by a wide range of patients. Health care professionals need some training to instruct patients properly. Environmental costs for fans (manufacturing plastic, battery use etc.) should also be considered.
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		

Judgement	Research evidence	Additional considerations
○ Very low ● Low ○ Moderate ○ High ○ No included studies	No study reported information about cost. There is no information about other associated costs or potential savings.	From clinical practice and patients' experience, it is known that the costs of fans are low.
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
Judgement	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● **No included studies**	No study reported cost effectiveness of increased airflow.	
Equity What would be the impact on health equity?		
Judgement	Research evidence	Additional considerations
○ Reduced ○ Probably reduced ● **Probably no impact** ○ Probably increased ○ Increased ○ Varies ○ Don't know	There is no direct evidence of the impact of the fan on health equity.	Hand held fans are inexpensive and readily accessible. Use of a hand held fan does not require specialist skills and requires little training, so this intervention could be used by a wide range of patients.

Acceptability Is the intervention acceptable to key stakeholders?		
Judgement	Research Evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know	Two of the included seven studies provided qualitative data indicating that patients experience benefit from the use of a handheld fan and that the intervention is acceptable. Patients described the handheld fan as helpful as it relieved breathlessness and provided relaxation, despite initial scepticism about its therapeutic benefit.(7) It also aided recovery and was judged as a useful ‘‘medical’’ device.(6) Acceptability of using the handheld fan was assessed in the RCT by Long et al *via* a Likert scale questionnaire (range 1–5) based on the theoretical framework of acceptability (TFA).(10) Participants were asked to respond to specific questions reflecting the overall acceptability of fan therapy and five subconstructs from the TFA (affective attitude, burden, perceived effectiveness, intervention coherence and self-efficacy). Fan therapy was acceptable to 92% of participants, with a median (IQR) acceptability score of 4 (4 to 5) out of 5. 53% reported no additional burden of fan therapy during the 6MWT. Patients reported they liked the handheld fan (median 4, IQR 3 to 5) and that it was of minimal burden (median 1, IQR 1 to 3). Patients were confident to use the handheld fan (median 5, IQR 4 to 5) In secondary multimethod analysis of interview data from three clinical trials, benefit was described in terms of shorter recovery time, especially after activity, reduced need for home oxygen or inhaled β-agonist medications.(12) Negative perceptions included dislike of the cooling sensation and embarrassment in public.(12) Overall, findings suggest that a hand-held fan is a portable intervention with few disadvantages from which most patients with chronic breathlessness will derive benefit alongside other nonpharmacological and pharmacological strategies.(12) There is only little research in the type of hand-held fans and patients’ preferences. One small study testing five different fans regarding perceived airflow, pleasantness of airflow, noisiness, and ease of use concluded that patient preference was related to increased intensity and pleasantness of airflow and reduced noise.(13)	There was no important uncertainty or variability in the views of the patient members of the Task Force regarding acceptability.
Feasibility Is the intervention feasible to implement?		
Judgement	Research evidence	Additional considerations

○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know	There is no direct evidence for implementation feasibility of a (handheld) fan. However, in clinical practice, hand-held fans are implemented widely and e.g. provided to patients in breathlessness clinics.	As a handheld fan is an easy to use, relatively cheap device which patients can carry with them, implementation seems to be feasible. Simple instructions can be provided by all health care professionals irrespective of setting.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

We suggest the use of increased airflow to reduce breathlessness in people with serious respiratory illness (conditional recommendation, very low certainty of evidence).

Justification

This recommendation places a high value on acute reductions in breathlessness that may be clinically meaningful. However, the paucity of data reduces certainty regarding the effect size. Qualitative data demonstrated that hand-held fan use was acceptable to patients, who reported relief of breathlessness, increased relaxation and shorter recovery time after exercise. Consumer members of the task force highlighted that the perceived mechanisms of action included cooling of air as well as increased flow. A positive impact of cool air on breathlessness could occur via stimulation of the trigeminal nerves with activation of central brain regions involved in the anticipation and/or perception of breathlessness, including the insular cortex and amygdala. Trigeminal nerve stimulation may contribute to breathlessness relief by altering the activity of brain regions involved in its central neural processing and reduced neural ventilatory drive.

Subgroup considerations

N/A

Implementation considerations

All but one study evaluated a handheld fan, only one study tested a pedestal fan. Handheld fans are simple and easy to use devices that patients can carry with them, allowing their use as routine prophylactic intervention for acute exacerbations of breathlessness.

Monitoring and evaluation

Patient-reported outcome measures including breathlessness and health-related quality of life will be critical to understand the impact of increased airflow for individual patients. Where an effect during exercise is evaluated, this should be assessed at isotime.

Research priorities

Further research needs to focus on

- testing the effectiveness of fans in fully powered randomised controlled trials including breathlessness and health-related quality of life as outcomes
- testing the effectiveness of a fans during exercise using appropriate measures (e.g. at isotime)
- studies including people with chronic lung disease across all diagnoses.

References – EtD table, PICO3

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2. Blinderman CD, Homel P, Billings JA, Tennstedt S, Portenoy RK. Symptom distress and quality of life in patients with advanced chronic obstructive pulmonary disease. J Pain Symptom Manage. 2009;38(1):115-23.

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6. Swan F, English A, Allgar V, Hart SP, Johnson MJ. The Hand-Held Fan and the Calming Hand for People With Chronic Breathlessness: A Feasibility Trial. JPSM 2019; 57(6)1051-61

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8. Galbraith S, Fagan P, Perkins P, Lynch A, Booth S. Does the Use of a Handheld Fan Improve Chronic Dyspnea? A Randomized, Controlled, Crossover Trial. JPSM 2010; 39(5): 831-838

9. Bausewein C, Booth S, Gysels M, Kühnbach R, Higginson IJ. Effectiveness of a hand-held fan for breathlessness: a randomised phase II trial. BMC Palliative Care 2010 9:22

10. Long A, Cartwright M, Reilly CC. Impact of fan therapy during exercise on breathlessness and recovery time in patients with COPD: a pilot randomised controlled crossover trial. ERJ Open Res 2021; 7: 00211-2021

11. Marchetti N, Lammi MR, Travaline JM, Ciccolella D, Civic B, Criner GC. Air Current Applied to the Face Improves Exercise Performance in Patients with COPD. Lung (2015) 193:725–731

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14. Johnson M, Booth S, Currow DC, Lam LT, Philips JL. A Mixed-Methods, Randomized, Controlled Feasibility Trial to Inform the Design of a Phase III Trial to Test the Effect of the Handheld Fan on Physical Activity and Carer Anxiety in Patients With Refractory Breathlessness. JPSM 2016; 51(5): 807-815

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3.6. List of included studies – PICO3

Bausewein C, Booth S, Gysels M, Kühnbach R, Higginson IJ. Effectiveness of a hand-held fan for breathlessness: a randomised phase II trial. BMC Palliative Care 2010 9:22. DOI: 10.1186/1472-684X-9-22.

Galbraith S, Fagan P, Perkins P, Lynch A, Booth S. Does the Use of a Handheld Fan Improve Chronic Dyspnea? A Randomized, Controlled, Crossover Trial. JPSM 2010; 39(5): 831-838. DOI:

Khor YH, Saravanan K, Holland AE, Lee JYT, Ryerson CJ, McDonald CF, Goh NSL. A mixed-methods pilot study of handheld fan for breathlessness in interstitial lung disease. Scientific reports 2021;11:6874. DOI: 10.1016/j.jpainsymman.2009.09.024.

Long A, Cartwright M, Reilly CC. Impact of fan therapy during exercise on breathlessness and recovery time in patients with COPD: a pilot randomised controlled crossover trial. ERJ Open Res 2021; 7: 00211-2021. DOI: 10.1183/23120541.00211-2021.

Marchetti N, Lammi MR, Travaline JM, Ciccolella D, Civic B, Criner GC. Air Current Applied to the Face Improves Exercise Performance in Patients with COPD. Lung (2015) 193:725–731. DOI: 10.1007/s00408-015-9780-0.

Swan F, English A, Allgar V, Hart SP, Johnson MJ. The Hand-Held Fan and the Calming Hand for People With Chronic Breathlessness: A Feasibility Trial. JPSM 2019; 57(6)1051-61. DOI: 10.1016/j.jpainsymman.2019.02.017.

3.7. Search strategies

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions

#	Query
1	lung diseases/ or "cystic adenomatoid malformation of lung, congenital"/ or cystic fibrosis/ or hepatopulmonary syndrome/ or lung abscess/ or lung diseases, interstitial/ or alveolitis, extrinsic allergic/ or bird fancier's lung/ or farmer's lung/ or silo filler's disease/ or trichosporonosis/ or anti-glomerular basement membrane disease/ or histiocytosis, langerhans-cell/ or eosinophilic granuloma/ or pneumoconiosis/ or anthracosis/ or anthracosilicosis/ or asbestosis/ or berylliosis/ or byssinosis/ or caplan syndrome/ or siderosis/ or silicosis/ or silicotuberculosis/ or pulmonary fibrosis/ or idiopathic pulmonary fibrosis/ or hamman-rich syndrome/ or idiopathic interstitial pneumonias/ or cryptogenic organizing pneumonia/ or sarcoidosis, pulmonary/
2	lung diseases, obstructive/ or asthma/ or asthma-chronic obstructive pulmonary disease overlap syndrome/ or bronchiolitis obliterans/ or cryptogenic organizing pneumonia/ or bronchitis, chronic/ or pulmonary disease, chronic obstructive/ or pulmonary emphysema/ or plasma cell granuloma, pulmonary/ or bronchial diseases/ or bronchiectasis/
3	respiratory tract diseases/ or respiration disorders/ or dyspnea/
4	(lung disease* or pulmonary disease* or cystic fibrosis or interstitial pneumoni* or extrinsic allergic alveolit* or hypersensitivity pneumoniti* or pneumoconios?s or anthracos?s or anthracosilicos?s or asbestos?s or beryllios?s or byssinos?s or beryllium disease* or caplan syndrome or bird fancier* lung or farmer* lung or silo filler* disease or trichosporonos?s or sideros?s or silicos?s or silicotuberculos?s or fibrosing alveolit* or pulmonary fibros?s or fibrocystic pulmonary dysplasia* or hamman-rich disease or hamman-rich syndrome or cryptogenic organizing pneumonia* or pulmonary sarcoidos?s or bronchiolitis obliterans or constrictive bronchiolit* or exudative bronchiolit* or chronic bronchitis or emphysema* or pulmonary inflammatory pseudotumo?r or pulmonary plasma cell granuloma* or bronchial disease* or bronchiectas?s).mp.
5	((chronic or severe* or unrelenting or obstructive) adj asthma*).mp.
6	(chronic* obstruct* adj3 (lung* or airway* or pulmon* or bronch* or alveolit* or respiratory)).mp.
7	(bronchopulmonary disease* or pneumopath* or pulmonary disorder* or acute pneumonitis or chronic fibrous pneumonia* or fibroid phthisis or interstitial cell pneumonia or interstitial plasma cell pneumonia or interstitial pneumocystic pneumonia or phthisis fibroidea or pneumonia interstitialis or interstitial fibros?s or lung fibros?s or interstitial fibros?s or alveolar fibros?s or respiratory granulomatos?s or pulmonary granulomatos?s or lung granulomatos?s or lung conios?s or pneumoconiotic lesion or pneumokonios?s or pneumono?onios?s).mp.

8	(airway obstructive disease* or obstructive airway disorder* or obstructive respiratory disease* or obstructive respiratory disorder* or pneumatosis pulmonum or interstitial syndrome).mp.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	((air or airflow or air-flow or air current?) adj4 (face or upper airway* or nose or mouth or cheek?)).mp.
11	((air or airflow or air-flow or air current?) adj5 (airway mucosa* or nasal mucosa* or pharynx)).mp.
12	((facial or nasal or upper airway*) adj3 (air or airflow or air-flow or cooling)).mp.
13	(fan or fans).mp.
14	((cool or cold or medical) adj (air or airflow or air-flow)).mp.
15	((draught or draft) adj2 air).mp.
16	((non-oxygen* or nonoxygen*) adj5 air).mp.
17	(((non-invasive or noninvasive) adj (ventilat* or respiratory)) and (nasal cannula? or nasal prong? or mask or mouthpiece)).mp.
18	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19	9 and 18
20	(dyspn?e* or "short* of breath" or "urge* to breathe*" or breathless* or suffocat* or ("need for air" or "gasp* for air" or "gasp* to breathe" or "pant* for air") or (unsatisf* inspiration or inspiratory difficult* or expiratory difficult*)).mp.
21	((labo?red or difficult*) adj3 breath*).mp.
22	(breath* adj1 (distress* or discomfort* or dysfunction*)).mp.
23	(air adj3 (hunger or starv*)).mp.
24	20 or 21 or 22 or 23
25	18 and 24

26	(Air Movements/ or Ventilation/ or Air/) and Dyspnea/
27	19 or 25 or 26
28	(randomized controlled trial or controlled clinical trial).pt. or (randomi?ed or placebo).ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.
29	((cross over or crossover) adj (clinical study or clinical trial or design or method or study or trial or studies)).mp.
30	28 or 29
31	27 and 30

Database: Embase

#	Query
1	lung disease/ or chronic lung disease/ or interstitial lung disease/ or interstitial syndrome/ or lung emphysema/ or lung fibrosis/ or lung sarcoidosis/ or obstructive lung disease/ or fibrosing alveolitis/ or interstitial pneumonia/ or pneumoconiosis/ or asthma/ or chronic obstructive lung disease/ or severe asthma/ or asthmatic state/ or severe persistent asthma/ or pulmonary hypertension/ or chronic thromboembolic pulmonary hypertension/ or cor pulmonale/ or pulmonary capillary hemangiomatosis/ or pulmonary vascular obstructive disease/ or pulmonary veno-occlusive disease/
2	obstructive airway disease/ or occupational lung disease/ or anthracosis/ or asbestosis/ or berylliosis/ or bird breeder lung/ or byssinosis/ or farmer lung/ or occupational asthma/ or pigeon breeder lung/ or pneumoconiosis/ or silicosis/ or bronchus disease/ or bronchiectasis/ or lung granuloma/ or respiratory tract disease/ or dyspnea/
3	(lung disease* or pulmonary disease* or cystic fibrosis or interstitial pneumoni* or extrinsic allergic alveolit* or hypersensitivity pneumoniti* or pneumoconios?s or anthracos?s or anthracosilicos?s or asbestos?s or beryllios?s or byssinos?s or beryllium disease* or caplan syndrome or bird fancier* lung or farmer* lung or silo filler* disease or trichosporonos?s or sideros?s or silicos?s or silicotuberculos?s or fibrosing alveolit* or pulmonary fibros?s or fibrocystic pulmonary dysplasia* or hamman-rich disease or hamman-rich syndrome or cryptogenic organizing pneumonia* or pulmonary sarcoidos?s or bronchiolitis obliterans or constrictive bronchiolit* or exudative bronchiolit* or chronic bronchitis or emphysema* or pulmonary inflammatory pseudotumo?r or pulmonary plasma cell granuloma* or bronchial disease* or bronchiectas?s).mp.
4	((chronic or severe* or unrelenting or obstructive) adj asthma*).mp.
5	(chronic* obstruct* adj3 (lung* or airway* or pulmon* or bronch* or alveolit* or respiratory)).mp.
6	(bronchopulmonary disease* or lung granulomatos?s or pneumopath* or pulmonary disorder* or acute pneumonitis or chronic fibrous pneumonia* or fibroid phthisis or interstitial cell pneumonia or interstitial plasma cell pneumonia or interstitial pneumocystic pneumonia or phthisis fibroidea or pneumonia interstitialis or interstitial fibros?s or lung fibros?s or interstitial fibros?s or alveolar fibros?s or respiratory granulomatos?s or pulmonary granulomatos?s or lung conios?s or pneumoconiotic lesion or pneumokonios?s or pneumono?onios?s).mp.

7	(airway obstructive disease* or obstructive airway disorder* or obstructive respiratory disease* or obstructive respiratory disorder* or pneumatosis pulmonum or interstitial syndrome).mp.
8	((lung or pulmonary) adj (arter* hypertens* or hypertens* or fixed hypertens* or capillary hemangiomatosis or veno-occlusive or venoocclusive or parenchyma* disease*)).mp.
9	(corpulmonale or cor pulmonale or pulmonary cardiac disease* or pulmonary vascular obstructive disease* or obstructive pulmonary vascular disease*).mp.
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	((air or airflow or air-flow or air current?) adj4 (face or upper airway* or nose or mouth or cheek?)).mp.
12	((air or airflow or air-flow or air current?) adj5 (airway mucosa* or nasal mucosa* or pharynx)).mp.
13	((facial or nasal or upper airway*) adj3 (air or airflow or air-flow or cooling)).mp.
14	(fan or fans).mp.
15	((cool or cold or medical) adj (air or airflow or air-flow)).mp.
16	((draught or draft) adj2 air).mp.
17	((non-oxygen* or nonoxygen*) adj5 air).mp.
18	(((non-invasive or noninvasive) adj (ventilat* or respiratory)) and (nasal cannula? or nasal prong? or mask or mouthpiece)).mp.
19	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20	10 and 19
21	(dyspn?e* or "short* of breath" or "urge* to breathe*" or breathless* or suffocat* or ("need for air" or "gasp* for air" or "gasp* to breathe" or "pant* for air") or (unsatisf* inspiration or inspiratory difficult* or expiratory difficult*)).mp.
22	((labo?red or difficult*) adj3 breath*).mp.
23	(breath* adj1 (distress* or discomfort* or dysfunction*)).mp.
24	(air adj3 (hunger or starv*)).mp.
25	21 or 22 or 23 or 24
26	19 and 25
27	(air/ or airflow/) and dyspnea/
28	20 or 26 or 27
29	limit 28 to (randomized controlled trial or controlled clinical trial)
30	randomized controlled trial/ or randomization/ or single blind procedure/ or double blind procedure/ or crossover procedure/ or placebo/ or prospective study/
31	(randomi?ed controlled or RCT or randomly allocated or allocated randomly or random allocation or "allocated at random" or single blind* or double blind* or ((treble or triple) adj blind*) or placebo*).mp.
32	((cross over or crossover) adj (clinical study or clinical trial or design or method or study or trial or studies)).mp.
33	30 or 31 or 32
34	28 and 33
35	29 or 34

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

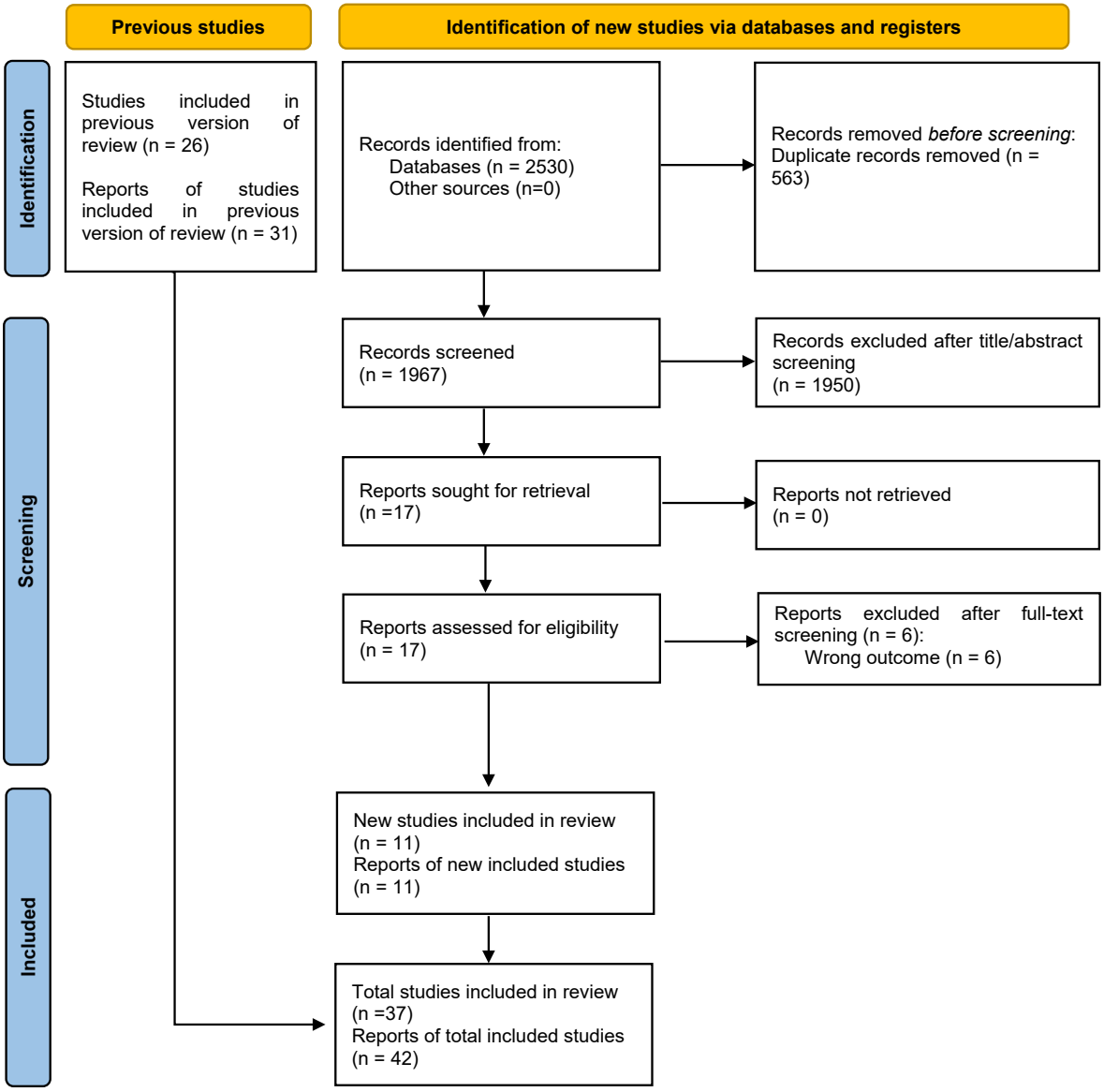
#	Query
1	lung diseases/ or "cystic adenomatoid malformation of lung, congenital"/ or cystic fibrosis/ or hepatopulmonary syndrome/ or lung abscess/ or lung diseases, interstitial/ or alveolitis, extrinsic allergic/ or bird fancier's lung/ or farmer's lung/ or silo filler's disease/ or trichosporonosis/ or anti-glomerular basement membrane disease/ or histiocytosis, langerhans-cell/ or eosinophilic granuloma/ or pneumoconiosis/ or anthracosis/ or anthracosilicosis/ or asbestosis/ or berylliosis/ or

	byssinosis/ or caplan syndrome/ or siderosis/ or silicosis/ or silicotuberculosis/ or pulmonary fibrosis/ or idiopathic pulmonary fibrosis/ or hamman-rich syndrome/ or idiopathic interstitial pneumonias/ or cryptogenic organizing pneumonia/ or sarcoidosis, pulmonary/
2	lung diseases, obstructive/ or asthma/ or asthma-chronic obstructive pulmonary disease overlap syndrome/ or bronchiolitis obliterans/ or cryptogenic organizing pneumonia/ or bronchitis, chronic/ or pulmonary disease, chronic obstructive/ or pulmonary emphysema/ or plasma cell granuloma, pulmonary/ or bronchial diseases/ or bronchiectasis/
3	respiratory tract diseases/ or respiration disorders/ or dyspnea/
4	(lung disease* or pulmonary disease* or cystic fibrosis or interstitial pneumoni* or extrinsic allergic alveolit* or hypersensitivity pneumoniti* or pneumoconios?s or anthracos?s or anthracosilicos?s or asbestos?s or beryllios?s or byssinos?s or beryllium disease* or caplan syndrome or bird fancier* lung or farmer* lung or silo filler* disease or trichosporonos?s or sideros?s or silicos?s or silicotuberculos?s or fibrosing alveolit* or pulmonary fibros?s or fibrocystic pulmonary dysplasia* or hamman-rich disease or hamman-rich syndrome or cryptogenic organizing pneumonia* or pulmonary sarcoidos?s or bronchiolitis obliterans or constrictive bronchiolit* or exudative bronchiolit* or chronic bronchitis or emphysema* or pulmonary inflammatory pseudotumo?r or pulmonary plasma cell granuloma* or bronchial disease* or bronchiectas?s).mp.
5	((chronic or severe* or unrelenting or obstructive) adj asthma*).mp.
6	(chronic* obstruct* adj3 (lung* or airway* or pulmon* or bronch* or alveolit* or respiratory)).mp.
7	(bronchopulmonary disease* or pneumopath* or pulmonary disorder* or acute pneumonitis or chronic fibrous pneumonia* or fibroid phthisis or interstitial cell pneumonia or interstitial plasma cell pneumonia or interstitial pneumocystic pneumonia or phthisis fibroidea or pneumonia interstitialis or interstitial fibros?s or lung fibros?s or interstitial fibros?s or alveolar fibros?s or respiratory granulomatos?s or pulmonary granulomatos?s or lung granulomatos?s or lung conios?s or pneumoconiotic lesion or pneumokonios?s or pneumono?onios?s).mp.
8	(airway obstructive disease* or obstructive airway disorder* or obstructive respiratory disease* or obstructive respiratory disorder* or pneumatosis pulmonum or interstitial syndrome).mp.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	((air or airflow or air-flow or air current?) adj4 (face or upper airway* or nose or mouth or cheek?)).mp.
11	((air or airflow or air-flow or air current?) adj5 (airway mucosa* or nasal mucosa* or pharynx)).mp.
12	((facial or nasal or upper airway*) adj3 (air or airflow or air-flow or cooling)).mp.
13	(fan or fans).mp.
14	((cool or cold or medical) adj (air or airflow or air-flow)).mp.

15	((draught or draft) adj2 air).mp.
16	((non-oxygen* or nonoxygen*) adj5 air).mp.
17	(((non-invasive or noninvasive) adj (ventilat* or respiratory)) and (nasal cannula? or nasal prong? or mask or mouthpiece)).mp.
18	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19	9 and 18
20	(dyspn?e* or "short* of breath" or "urge* to breathe*" or breathless* or suffocat* or ("need for air" or "gasp* for air" or "gasp* to breathe" or "pant* for air") or (unsatisf* inspiration or inspiratory difficult* or expiratory difficult*)).mp.
21	((labo?red or difficult*) adj3 breath*).mp.
22	(breath* adj1 (distress* or discomfort* or dysfunction*)).mp.
23	(air adj3 (hunger or starv*)).mp.
24	20 or 21 or 22 or 23
25	18 and 24
26	(Air Movements/ or Ventilation/ or Air/) and Dyspnea/
27	19 or 25 or 26

4. PICO question 4: Should supplemental oxygen be used to reduce symptoms in people with serious illness related to lung disease?

4.1. Identification of studies – PRISMA diagram



4.2. Inclusion criteria

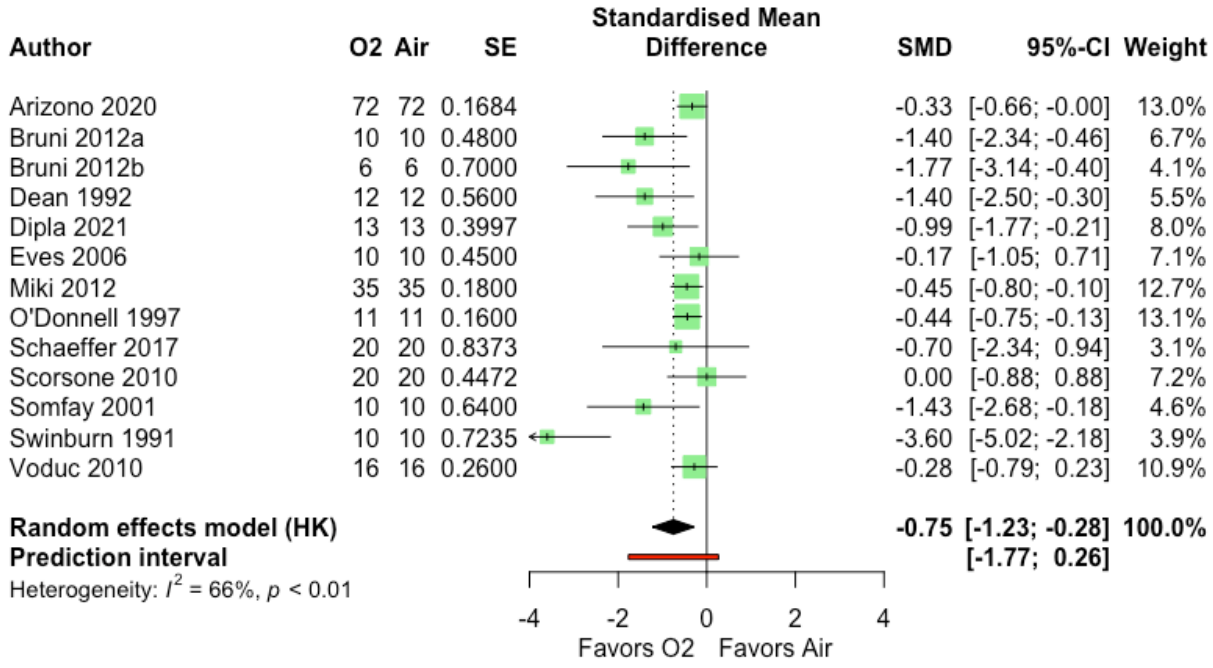
- Randomised controlled trial, including both parallel and crossover trials.
- Participants were adults aged 18 years or older.
- Participants had serious illness related to lung disease (defined as a condition that carries a high risk of mortality, negatively impacts quality of life and daily function, and/or is burdensome in symptoms, treatments, or caregiver stress)
- Intervention: Supplemental oxygen therapy delivered in any dose or by any non-invasive method (mask or nasal prongs) at rest or during exertion.
- Comparison: No oxygen: sham treatment or usual care.

4.3. Exclusion criteria

- Treated with supplemental oxygen already at the time of randomization.
- Meet eligibility criteria for long-term oxygen therapy (LTOT) or ambulatory oxygen therapy (oxygen on exertion).
- Trials of short-burst oxygen therapy delivered only before or after exertion
- Comparisons with other types of oxygen therapy (such as using high-flow nasal canulae [HFNC])

4.4. Forest Plots

Critical outcome: Breathlessness measured at iso-time

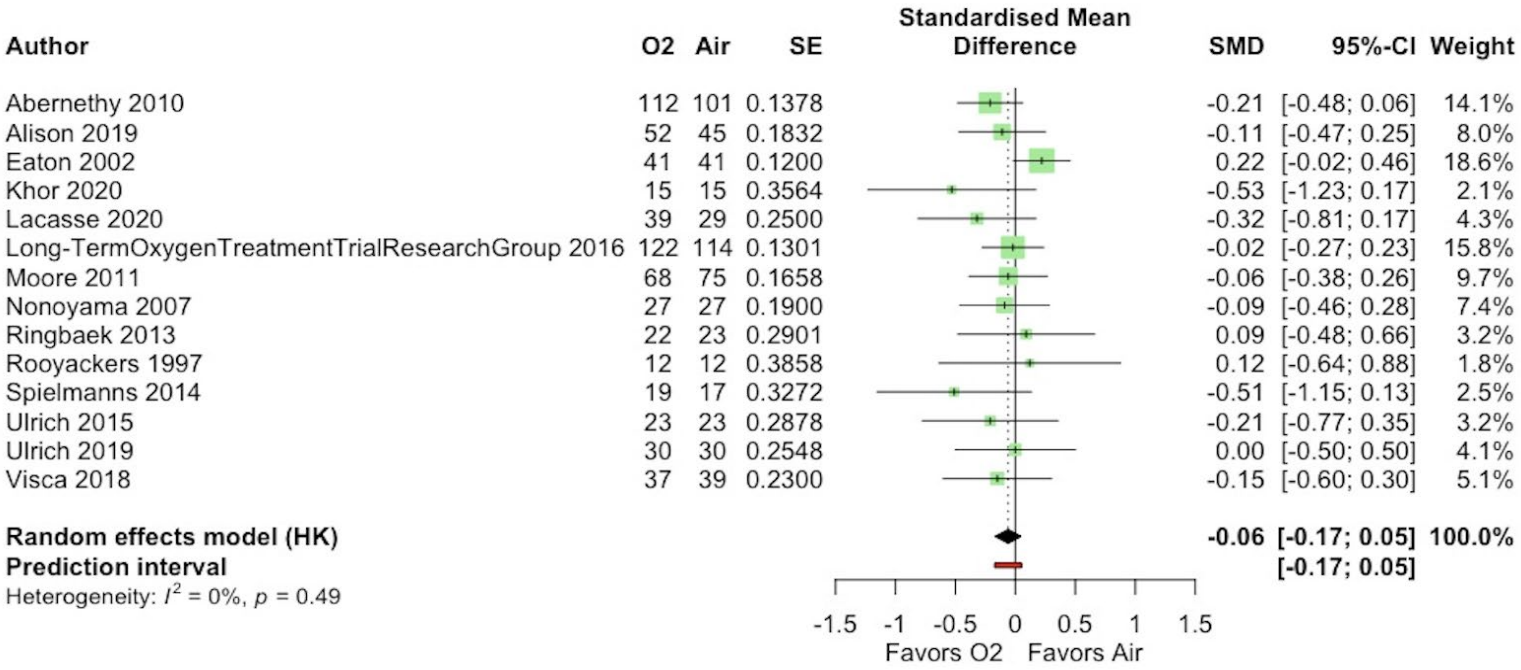


Interpretation of the estimates:

- **The effect estimate = the pooled effect across the included studies**

- **The prediction interval:** *"as a description of the range of observed effect sizes* rather than as a prediction of the range of effect sizes that will be observed in future studies".

Important outcome: Health-related quality of life measured with a validated tool



4.5. GRADE evidence table

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	oxygen	no oxygen	Relative (95% CI)	Absolute (95% CI)		
Breathlessness at iso-time (assessed with: any validated score; lower = better)												
13	randomised trials	serious[a]	not serious[b]	not serious	serious[c]	none	245	245	-	SMD* **0.75 SD lower** (1.23 lower to 0.28 lower)	⨁⨁◯◯ Low	CRITICAL
Breathlessness "right now"; lower = better (assessed with: numerical rating scale (NRS); Scale from: 0 ("none") to 10 ("maximal"))												
1	randomised trials	not serious	not serious	not serious	very serious[d]	none	152	152	-	SMD* **0.08 SD lower** (0.41 lower to 0.26 higher)	⨁⨁◯◯ Low	CRITICAL

Health-related quality of life (assessed with: any validated score; lower = better)

14	randomised trials	serious[e]	not serious	not serious	not serious	none	619	591	-	SMD* **0.06 SD lower** (0.17 lower to 0.05 higher)	⨁⨁⨁◯ Moderate	IMPORTANT

Adverse events (assessed with: any reported side-effects)

10	randomised trials	serious[f]	Serious[g]	not serious	not serious	none	**Abernethy 2010: [O2 vs. air]** Moderate to extreme drowsiness: 31/65 (47%) vs. 36/70 (51%); Moderate to extreme nasal irritation: 19/65 (29%) vs. 25/70 (35%); Moderate to extremely troublesome nosebleeds: 2/65 (3%) vs. 2/70 (3%); Moderate to extreme anxiousness: 17/65 (26%) vs. 28/70 (40%) **Eaton 2002:** None of the participants withdrew from the study for adverse events; No other adverse events reported **Emtner 2003:** None of the participants withdrew from the study for adverse events; No other adverse events reported **Laude 2006:** No adverse effects were reported from breathing heliox gas mixtures **Moore 2011:** 1/66 in the O2 group died; 1/66 in the O2 group became unwell **Ringbaek 2013:** The proportion of patients with acute exacerbation in COPD, hospital admission, or dropout was the same in the O2 and air groups **Spielmanns 2014:** 5/19 in the O2 group discontinued study participation due to comorbidities; 7/17 in the air group discontinued study participation due to comorbidities	⨁⨁◯◯ Low	IMPORTANT

CI: confidence interval; **SMD:** standardised mean difference

* Standardized mean difference (SMD) estimates are interpreted using thresholds defined by Cohen, J. 1988. Statistical Power Analysis for the Behavioral Sciences. Erlbaum Press.

- SMD ≈ 0.20: small effect
- SMD ≈ 0.50: moderate effect
- SMD ≈ 0.80: large effect

Explanations

a. Incomplete allocation concealment (Schaeffer 2017); Incomplete blinding of outcome assessment (Arizono 2022, Dipla 2021, Schaeffer 2017, Swinburn 1991); Incomplete blinding of participants and/or personnel (Schaeffer 2017, Somfay 2001); Incomplete outcome data (Voduc 2010)

b. Heterogeneity suspected (I^2 = 66%); however, could be introduced by differences in risk of bias between studies. Therefore, did not rate down.

c. 95% CI of the pooled estimate of the effect of oxygen on breathlessness crosses thresholds for minor benefit (< -0.2 SMD) and large benefit (< -0.8 SMD)

d. Downgraded twice for imprecision due to the fact that the effect crosses thresholds for both moderate benefit and harm, and the small number of included participants

e. Incomplete allocation concealment (LTOTTRG 2016); Incomplete blinding of participants and/or personnel (LTOTTRG 2016, Ringbaek 2013, Rooyackers 1997); Incomplete blinding of outcome assessment (LTOTTRG 2016, Ringbaek 2013, Rooyackers 1997, Visca. 2018); Incomplete outcome data (LTOTTRG 2016, Ringbaek 2013, Spielmanns 2014)

f. Incomplete outcome data (Ringbaek 2013, Speilmanns 2014, Voduc 2010); Incomplete blinding of participants/personnel and outcome assessment (Ringbaek 2013)

g. Studies reported varying estimations of the rate of adverse events from none to up to 29% of patients receiving the intervention. This could be explained by inconsistent reporting of the type and severity of adverse events.

4.6. Evidence-to-Decision Table

PICO 4: Should supplemental oxygen be used to reduce symptoms in adults with serious respiratory illness?	
POPULATION:	Adults with serious illness related to lung disease
INTERVENTION:	Supplemental oxygen, delivered either at rest or during exercise
COMPARISON:	No supplemental oxygen
MAIN OUTCOMES:	Critical: • Breathlessness using any validated tools. This may include measures at rest or during exercise, but exercise measures obtained before and after an intervention must be obtained at iso-workload. Important: • Health-related quality of life using any validated tool • Adverse events, defined according to the investigators' definition

Problem Is the problem a priority?		
Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Patients with serious illness related to lung disease commonly experience high symptom burden, including chronic breathlessness [1] which contributes to a reduced quality of life [2]. Breathlessness can be frightening and disabling for patients, it is frequently ranked as their worst symptom [3] and is a major contributor to unscheduled healthcare utilization [4, 5].	
Desirable Effects How substantial are the desirable anticipated effects of using Oxygen on breathlessness?		
Judgement	Research evidence	Additional considerations
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Of the 37 studies included overall in the systematic review, the populations under study had predominantly COPD (n=26 studies) with IPF/ILD (n=7) and the remaining 4 a mixture of lung diseases including PAH. There was a variety of delivery devices and Oxygen flow rates and concentration used in the studies reviewed and also in the duration and frequency of Oxygen administered. The majority of studies looked at use of oxygen in an exercise test or ambulatory setting and 3 studies looked at nocturnal oxygen administration. **<u>Breathlessness</u>** 13 studies breathlessness at iso-time SMD* **0.75 SD lower** (1.23 lower to 0.28 lower)1 study of Breathlessness 'right	In the laboratory exercise testing setting, the desirable effects on breathlessness measured at iso-time was judged as moderate, but the overall desirable effects were judged as small due to the lack of evidence for effect on breathlessness in daily life in the home setting and on HRQOL. The group's clinical impression is that the effect of supplemental oxygen

	now' in daily life, SMD* **0.08 SD lower** (0.41 lower to 0.26 higher) **HRQOL** 14 studies - absolute effect 95% CI SMD* **0.06 SD lower** (0.17 lower to 0.05 higher)	therapy on breathlessness and HRQOL varies substantially between individuals.

Undesirable Effects

How substantial are the undesirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	Data from 10 studies were included. A small proportion of studies mention number of drop outs (measured day 3 by telephone contact in one study). One study looked at COPD exacerbations, all hospital admissions, deaths at study end. A very low proportion of patients died or dropped out from the oxygen treatment groups. There was a range of adverse effects including drowsiness and anxiousness reported in the studies - these pertained to environmental and physical hazards as well as direct result of oxygen administration e.g. oxygen usage has a fire/burns risk. Further, many effects reported related to local effects - nasal irritation/epistaxis and some related to falls (0_2 tubing presenting a trip hazard). A small number of patients required hospitalisation for adverse effects. Other factors influence adverse effect of oxygen administration e.g. length of exposure, higher flow rates and concentrations (which may be more prevalent in ILD populations) [9][6].	Studies mainly studied treatment with non-humidified (dry) supplemental oxygen. There is some evidence that treatment with humidified, high-flow oxygen therapy could decrease the risk of adverse events during long-term oxygen therapy [7-9]. Limited information was given about smoking in relation to the oxygen therapy, or about psychosocial adverse events such as decreased physical or social activities. Observational studies have shown a high prevalence and frequency of adverse events, mainly due to dryness or irritation of the airways [10, 11]. Risk of these adverse events is likely higher with longer daily use of the oxygen therapy, and lower with ambulatory treatment.

Certainty of evidence

What is the overall certainty of the evidence of effects?		
Judgement	Research evidence	Additional considerations
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Based on the GRADE assessment, the certainty of evidence was low.	Few studies included people with lung diseases other than COPD. There was heterogeneity in the populations included and the outcomes measured. Few studies included people near the very end of life.
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
Judgement	Research evidence	Additional considerations
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	The critical outcome for this question is breathlessness, which people with serious respiratory illness consistently report as a major distressing symptom [12-14]. In people with COPD, breathlessness has been found to be a key determinant of low physical and mental health [13, 14]. Similarly, in people with pulmonary fibrosis breathlessness has been identified as a major driver of reduced quality of life [15, 16]. Fear of exertional breathlessness may result in avoiding exercise, leading to a downward spiral of deconditioning, social isolation with negative physical and emotional consequences [14]. There is an immense need to better actively manage chronic breathlessness and other distressing symptoms in people with a variety of non-malignant chronic respiratory diseases. There is a decline in health status over time which is expected and in line with the trajectory for serious lung disease. Patient reported outcomes are hence important, the lack of QALY reporting has impact too. In people with COPD oxygen may relieve breathlessness during exercise for those with mild hypoxaemia or no hypoxaemia. Oxygen therapy does not affect health-related quality of life in daily life [17, 18].	Context of shared decision making and patient expectation with respect to chronic breathlessness and diminished quality of life. Patients with ILD have a preference for portable oxygen concentrators to oxygen cylinders (weight, reliability of supply and portability) [6]. There was no important uncertainty or variability in the views of the patient members of the Task Force regarding values.
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		

Judgement	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Based on review of included studies of oxygen, results are mixed with some evidence benefit for short term ambulatory O2 but also trending to no difference when O2 given in other studies [19]. Most oxygen related side effects are not serious and can be managed relatively easily. Patient perception of benefit may not correspond with improvement in scores such as HRQOL and oxygen saturation. Additionally, there is the burden of managing oxygen equipment which may negate any potential positive effects that oxygen therapy may bring [17, 20-23]. Hence, shared decision making with the patient is crucial to discuss realistic risk versus benefit and to ensure responsible use and maximal clinical effect.	Opportunity for shared decision making.

Resources required

How large are the resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Oxygen therapy is costly [24, 25]. Home oxygen therapy is the second most expensive health-care expenditure (after hospitalisation) associated with clinical care for COPD in high-income countries [26]. In the UK, cylinder prescriptions almost doubled in the decade from 1993-2003 with annual costs £10 million (UK Prescription Pricing Authority. Annual Report 2003–2004; 83). • Monetary costs also apply to electricity, consumables, water for humidification, paying for healthcare in some countries, rural v urban and coastal variance • Healthcare utilization costs/visits from community teams also cost of adverse events potentially requiring hospitalization need to be considered.	Safety or effectiveness (both clinical/cost) of continuous flow portable concentrators is not documented. Costs for productivity losses are difficult to quantify and included absenteeism from paid work and voluntary work, but the population are for the most part retired. The main costs drivers are identified as oxygen use and support systems and contact with healthcare professionals with the largest difference in healthcare costs associated with hospital admissions.

Certainty of evidence

What is the certainty of the evidence of resource requirements (costs)?

Judgement	Research evidence	Additional considerations

○ Very low ● Low ○ Moderate ○ High ○ No included studies	Oxygen therapy may be prescribed in clinical practice for mild to moderate hypoxia and exertional desaturation [27], information on the cost-effectiveness is lacking in the studies included in these analyses. Evidence is scarce and data on costs are limited or outdated, e.g. in the US Medicare data and in the UK national prescribing association data.	

Cost effectiveness **Does the cost-effectiveness of the intervention favor the intervention or the comparison?**		
Judgement	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	Whilst home oxygen is expensive, costs if oxygen is not used (in people who are eligible) may be increased, such as due to increased hospitalisations and mortality, a reduction in quality of life and individual productivity [28]. Cost effectiveness is considered to be more than fiscal [28] In the absence of robust evidence of positive outcomes of oxygen therapy, patient perspectives on the benefits, convenience and costs will inform treatment decisions [29, 30].	The potential benefit of oxygen therapy observed was small and there is a moderate cost impact of using it. The benefits vary and are individual and individual environment dependent. ambulatory systems require frequent maintenance and bespoke delivery Home based assessments are expensive but may outweigh the cost of LTOT for patients who do not benefit [27] Different provider/payer set up in different countries – cost of and access to oxygen and cost for (travel) insurances. • Note cost of electricity for Oxygen concentrators in context of cost of living • Reporting in QALYs facilitates health economic analysis but such data not necessarily available.

Equity **What would be the impact on health equity?**		
Judgement	Research evidence	Additional considerations

○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	There were no studies on the effects of symptomatic oxygen therapy on equity, and the group thinks that any effects are likely to vary between settings depending on differences in populations and how oxygen services are available, structured and funded.	• Access to oxygen may depend on payer status/eligibility for healthcare/insurance in some settings • Note there was not commentary on remote versus urban/coastal areas and geographical variation in types of O2 concentrators available. • Oxygen therapy in some settings may effect health equity as it requires infrastructure which has associated costs Smoking has a survival impact, smokers are more likely to progress to requiring oxygen – they may have difficulty accessing smoking cessation interventions which has indirect impact to oxygen eligibility (may be ineligible if current smokers)
Acceptability **Is the intervention acceptable to key stakeholders**?		
Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	There was limited evidence on the acceptability of symptomatic oxygen therapy.	The Task Force thinks that acceptability are likely to vary between settings depending on differences in populations and how oxygen services are available, structured and funded. There was no important uncertainty or variability in the views of the patient members of the Task Force regarding acceptability.

		There is a trade-off of benefit to risks, and acceptability is patient dependent according to their values and lifestyle but also care givers and policymakers who may stipulate smoking cessation before progressing to oxygen therapy. Oxygen is a non-invasive treatment per se, it can be given in controlled manner (concentration, flowrate, device) with a variety of delivery methods to suit the patient (in shared discussion) but there are psychosocial considerations/stigma which is bi-directional, ability to move around take oxygen to work with them etc. Assessments of acceptability could encompass all stakeholders – patients, clinicians, insurance, oxygen suppliers (generally health providers in secondary and primary care). Alternatives to Oxygen therapy for breathlessness include opioids, benzodiazepines, other hand held fans/breathing exercises, mindfulness, CBT – some of which outside of scope of the PICO review criteria.
Feasibility **Is the intervention feasible to implement?**		
Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ○ Yes	Limited evidence on feasibility, but likely varies according to delivery method and local resources.	We acknowledge the different set up and access to healthcare in different

● Varies ○ Don't know		countries and also intra-variation within a country itself.

Summary of judgements

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

We suggest either administering or not administering supplemental oxygen to reduce symptoms in people with serious respiratory illness (conditional recommendation, low certainty of evidence).

Justification

In making this recommendation, the task force balanced the positive effects of oxygen on breathlessness in laboratory studies, the paucity of evidence that this benefit extends into daily life, and the adverse effects and burdens that may be experienced when using oxygen therapy. Oxygen administered in the laboratory setting could improve breathlessness in some people with exertional desaturation. Whether this effect translates to home treatment was not clear. Oxygen treatment might cause adverse events, most of which are minor and can be effectively managed. However, oxygen treatment is related to feelings of shame and restricted physical and social activities in some people, which may outweigh any benefits and increase the burden for patients and caregivers. Our recommendation is consistent with guidelines from the British Thoracic Society that supplemental oxygen therapy should not be routinely offered to people who do not meet the criteria for LTOT. The American Thoracic Society (ATS) made a conditional recommendation in favour of ambulatory oxygen therapy for patients with COPD or ILD with exertional desaturation, whereas this guideline focuses on the role of oxygen for symptom management.

Subgroup considerations

The majority of evidence has focussed on people with COPD, therefore it is challenging to extrapolate the true impacts of oxygen on symptoms in people with other serious, non-malignant, respiratory illnesses.

The patient populations included in the studies to date have been heterogeneous, with some studies including people with only moderate (i.e. not severe) breathlessness, therefore it is not clear if oxygen is beneficial for symptomatic relief in people with more severe breathlessness (i.e. breathlessness occurring at rest or on minimal exertion).

In an observational study of cxygen in Sweden (Bjorklund, ATS Annals 2022) taking a random selection of patients (mainly from a COPD population) and looking at the adverse effects of oxygen, it is clear that other factors influence the adverse effects and frequency of oxygen administration. Length of exposure (>15 hours versus short burst administration), higher flows and concentrations impact the likelihood of adverse events, including local v systemic effects (some of which may be more prevalent in ILD populations). Other considerations for patients related to oxygen therapy include shame of going out of the house, resultant isolation, stigma of disease or treatment visibility /equipment and its portability.

A low number of studies included people at the very end of life, who are usually highly symptomatic patients and who may be prescribed oxygen for symptom palliation.

In a palliative setting concentrated room air does not offer an affordable viable option indicating that oxygen therapy is a substitute but there is no clear evidence showing symptomatic benefit of palliative oxygen and such an intervention entails cost and logistical burden (Abernathy). In the absence of robust evidence of positive.

Implementation considerations

Breathlessness can be frightening and debilitating for patients; whilst oxygen treats hypoxia, it may offer an option for symptomatic relief of breathlessness associated with serious lung disease.

When oxygen is being considered to treat symptoms in people with serious non-malignant, respiratory illness, clear communication that is person centred and shared decision making between clinicians and patients is required. This must include consideration of benefits and harms for the individual (and household where applicable), and active discussion and plans to manage side effects. Oxygen prescription should consider patients' goals and willingness to use it, including their understanding of how to use it correctly and safely, and the broader impacts on their lives and other potential harms. Other clinicians and the patients' informal caregivers may also require education and support regarding the use of oxygen for symptom management in people with serious, non-malignant, respiratory illnesses.

Smoking has a survival impact; smokers are more likely to progress to requiring oxygen – they may have difficulty accessing smoking cessation interventions which has indirect impact to oxygen eligibility (ineligible if current smokers in some countries).

Monitoring and evaluation

If a clinician and patient with serious respiratory illness have decided to trial oxygen therapy to treat symptoms, before treatment commences, it is essential to:

- ensure all illnesses contributing to breathlessness have been optimally treated, and
- the patient has received education on non-drug, self-management approaches.

Regular medical follow up to both titrate the prescription if needed and identify, and actively prevent and manage potential related risks and side effects of therapy is required:

- i.e modification of devices portability, humidification
- identifying and minimising trip hazards, including reducing flammability risk and burns – concurrent smoking, smoker in household, paraffin containing products, cooking with gas)

The lowest concentration of oxygen to achieve a clinical improvement in symptoms should be used. If no beneficial effect is experienced, shared decision making and discussion between clinicians and patients i.e. benefits versus risks, then consideration of cessation should occur.

Research priorities

Further research needs to focus on

- The effect of oxygen on breathlessness in daily life setting across different respiratory diagnoses.
- Other and new interventions (including non-pharmacological approaches) to improve breathlessness and other symptoms in people with serious, non-malignant, respiratory illnesses
- Symptom management in people with non-malignant respiratory illnesses other than COPD, people with more severe breathlessness and people towards the end of life.
- Include a health utility measure in the questionnaire where patients self report to enable better health economic reporting and analysis
- Consideration for study design in studies of exertional breathlessness it is important that the symptom of breathlessness is assessed at a standardised level of exertion

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4.7. List of included studies, PICO4

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disease patients not entitled to long-term oxygen therapy. Clin Physiol Funct Imaging, 2012. 32(1): p. 52-8 DOI: 10.1111/j.1475-097X.2011.01054.x.
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4.8. Search strategies, PICO4

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions

#	Query
1	lung diseases/ or "cystic adenomatoid malformation of lung, congenital"/ or cystic fibrosis/ or hepatopulmonary syndrome/ or lung abscess/ or lung diseases, interstitial/ or alveolitis, extrinsic allergic/ or bird fancier's lung/ or farmer's lung/ or silo filler's disease/ or trichosporonosis/ or anti-glomerular basement membrane disease/ or histiocytosis, langerhans-cell/ or eosinophilic granuloma/ or pneumoconiosis/ or anthracosis/ or anthracosilicosis/ or asbestosis/ or berylliosis/ or byssinosis/ or caplan syndrome/ or siderosis/ or silicosis/ or silicotuberculosis/ or pulmonary fibrosis/ or idiopathic pulmonary fibrosis/ or hamman-rich syndrome/ or idiopathic interstitial pneumonias/ or cryptogenic organizing pneumonia/ or sarcoidosis, pulmonary/
2	lung diseases, obstructive/ or asthma/ or asthma-chronic obstructive pulmonary disease overlap syndrome/ or bronchiolitis obliterans/ or cryptogenic organizing pneumonia/ or bronchitis, chronic/ or pulmonary disease, chronic obstructive/ or pulmonary emphysema/ or plasma cell granuloma, pulmonary/ or bronchial diseases/ or bronchiectasis/
3	respiratory tract diseases/ or respiration disorders/ or dyspnea/
4	(lung disease* or pulmonary disease* or cystic fibrosis or interstitial pneumoni* or extrinsic allergic alveolit* or hypersensitivity pneumoniti* or pneumoconios?s or anthracos?s or anthracosilicos?s or asbestos?s or beryllios?s or byssinos?s or beryllium disease* or caplan syndrome or bird fancier* lung or farmer* lung or silo filler* disease or trichosporonos?s or sideros?s or silicos?s or silicotuberculos?s or fibrosing alveolit* or pulmonary fibros?s or fibrocystic pulmonary dysplasia* or hamman-rich disease or hamman-rich syndrome or cryptogenic organizing pneumonia* or pulmonary sarcoidos?s or bronchiolitis obliterans or constrictive bronchiolit* or exudative

	bronchiolit* or chronic bronchitis or emphysema* or pulmonary inflammatory pseudotumo?r or pulmonary plasma cell granuloma* or bronchial disease* or bronchiectas?s).mp.
5	((chronic or severe* or unrelenting or obstructive) adj asthma*).mp.
6	(chronic* obstruct* adj3 (lung* or airway* or pulmon* or bronch* or alveolit* or respiratory)).mp.
7	(bronchopulmonary disease* or pneumopath* or pulmonary disorder* or acute pneumonitis or chronic fibrous pneumonia* or fibroid phthisis or interstitial cell pneumonia or interstitial plasma cell pneumonia or interstitial pneumocystic pneumonia or phthisis fibroidea or pneumonia interstitialis or interstitial fibros?s or lung fibros?s or interstitial fibros?s or alveolar fibros?s or respiratory granulomatos?s or pulmonary granulomatos?s or lung conios?s or pneumoconiotic lesion or pneumokonios?s or pneumono?onios?s).mp.
8	(airway obstructive disease* or obstructive airway disorder* or obstructive respiratory disease* or obstructive respiratory disorder* or pneumatosis pulmonum or interstitial syndrome).mp.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	Oxygen Inhalation Therapy/
11	((O2 or "O 2" or oxygen*) adj (administration or therap* or inhalation or insufflation or treatment or conserving device* or concentrator* or delivery device* or flow rate or flow metre or cannula?)).mp.
12	((supplement* or home or domicil* or portable or ultraportable or ambulat*) adj3 (oxygen* or oxy-gen or O2 or "O 2" or LOX)).mp.
13	((prescri* or self-fill or liquid or compress* or light-weight or POC) adj3 (oxygen or O2 or "O 2" or LOX)).mp.
14	((noninvasive or non-invasive or therap*) adj (oxygen* or breathing support or respiratory support)).mp.

15	((High flow or highflow or low flow or lowflow) adj (oxygen* or breathing support or nasal or cannula)).mp.
16	(oxygen* adj (flow rate? or breathing support or flow metre or support therapy)).mp.
17	((inhal* or inspir*) adj3 oxygen*).mp.
18	((Humidif* or heated) adj2 oxygen).mp.
19	((nasal cannula? or nasal high flow or nasal prong? or nasal catheter* or nasal tube*) and (oxygen* or "O2" or "O 2")).mp.
20	(Evergo or Inogen One or EverFlo or Millennium M10 or Oxlife Freedom POC or Oxyensure or OxyGo or SimplyFlo or SimplyGo or UltraFill).mp.
21	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22	9 and 21
23	exp lung diseases/th and oxygen/tu
24	22 or 23
25	(randomized controlled trial or controlled clinical trial).pt.
26	(randomi?ed or placebo).ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.
27	((cross over or crossover) adj (clinical study or clinical trial or design or method or study or trial or studies)).mp.
28	25 or 26 or 27
29	24 and 28

Database: Embase

#	Query
1	lung disease/ or chronic lung disease/ or interstitial lung disease/ or interstitial syndrome/ or lung emphysema/ or lung fibrosis/ or lung sarcoidosis/ or obstructive lung disease/ or fibrosing

	alveolitis/ or interstitial pneumonia/ or pneumoconiosis/ or asthma/ or chronic obstructive lung disease/ or severe asthma/ or asthmatic state/ or severe persistent asthma/
2	obstructive airway disease/ or occupational lung disease/ or anthracosis/ or asbestosis/ or berylliosis/ or bird breeder lung/ or byssinosis/ or farmer lung/ or occupational asthma/ or pigeon breeder lung/ or pneumoconiosis/ or silicosis/ or bronchus disease/ or bronchiectasis/ or lung granuloma/ or respiratory tract disease/ or dyspnea/
3	(lung disease* or pulmonary disease* or cystic fibrosis or interstitial pneumoni* or extrinsic allergic alveolit* or hypersensitivity pneumoniti* or pneumoconios?s or anthracos?s or anthracosilicos?s or asbestos?s or beryllios?s or byssinos?s or beryllium disease* or caplan syndrome or bird fancier* lung or farmer* lung or silo filler* disease or trichosporonos?s or sideros?s or silicos?s or silicotuberculos?s or fibrosing alveolit* or pulmonary fibros?s or fibrocystic pulmonary dysplasia* or hamman-rich disease or hamman-rich syndrome or cryptogenic organizing pneumonia* or pulmonary sarcoidos?s or bronchiolitis obliterans or constrictive bronchiolit* or exudative bronchiolit* or chronic bronchitis or emphysema* or pulmonary inflammatory pseudotumo?r or pulmonary plasma cell granuloma* or bronchial disease* or bronchiectas?s).mp.
4	((chronic or severe* or unrelenting or obstructive) adj asthma*).mp.
5	(chronic* obstruct* adj3 (lung* or airway* or pulmon* or bronch* or alveolit* or respiratory)).mp.
6	(bronchopulmonary disease* or pneumopath* or pulmonary disorder* or acute pneumonitis or chronic fibrous pneumonia* or fibroid phthisis or interstitial cell pneumonia or interstitial plasma cell pneumonia or interstitial pneumocystic pneumonia or phthisis fibroidea or pneumonia interstitialis or interstitial fibros?s or lung fibros?s or interstitial fibros?s or alveolar fibros?s or respiratory granulomatos?s or pulmonary granulomatos?s or lung conios?s or pneumoconiotic lesion or pneumokonios?s or pneumono?onios?s).mp.
7	(airway obstructive disease* or obstructive airway disorder* or obstructive respiratory disease* or obstructive respiratory disorder* or pneumatosis pulmonum or interstitial syndrome).mp.

8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	oxygen therapy/ or home oxygen therapy/ or oxygen delivery device/ or oxygen concentrator/ or high flow nasal cannula therapy/ or nasal cannula therapy/ or humidified high flow nasal cannula therapy/
10	((O2 or "O 2" or oxygen*) adj (administration or therap* or inhalation or insufflation or treatment or conserving device* or concentrator* or delivery device* or flow rate or flow metre or cannula?)).mp.
11	((supplement* or home or domicil* or portable or ultraportable or ambulat*) adj3 (oxygen* or oxy-gen or O2 or "O 2" or LOX)).mp.
12	((prescri* or self-fill or liquid or compress* or light-weight or POC) adj3 (oxygen or O2 or "O 2" or LOX)).mp.
13	((noninvasive or non-invasive or therap*) adj (oxygen* or breathing support or respiratory support)).mp.
14	((High flow or highflow or low flow or lowflow) adj (oxygen* or breathing support or nasal or cannula)).mp.
15	(oxygen* adj (flow rate? or breathing support or flow metre or support therapy)).mp.
16	((inhal* or inspir*) adj3 oxygen*).mp.
17	((Humidif* or heated) adj2 oxygen).mp.
18	((nasal cannula? or nasal high flow or nasal prong? or nasal catheter* or nasal tube*) and (oxygen* or "O2" or "O 2")).mp.
19	(Evergo or Inogen One or EverFlo or Millennium M10 or Oxlife Freedom POC or Oxyensure or OxyGo or SimplyFlo or SimplyGo or UltraFill).mp.
20	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21	8 and 20

22	exp lung disease/th and oxygen/ih, na, th
23	21 or 22
24	limit 23 to (randomized controlled trial or controlled clinical trial)
25	randomized controlled trial/ or randomization/ or single blind procedure/ or double blind procedure/ or crossover procedure/ or placebo/ or prospective study/
26	(randomi?ed controlled or RCT or randomly allocated or allocated randomly or random allocation or "allocated at random" or single blind* or double blind* or ((treble or triple) adj blind*) or placebo*).mp.
27	((cross over or crossover) adj (clinical study or clinical trial or design or method or study or trial or studies)).mp.
28	25 or 26 or 27
29	23 and 28
30	24 or 29

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

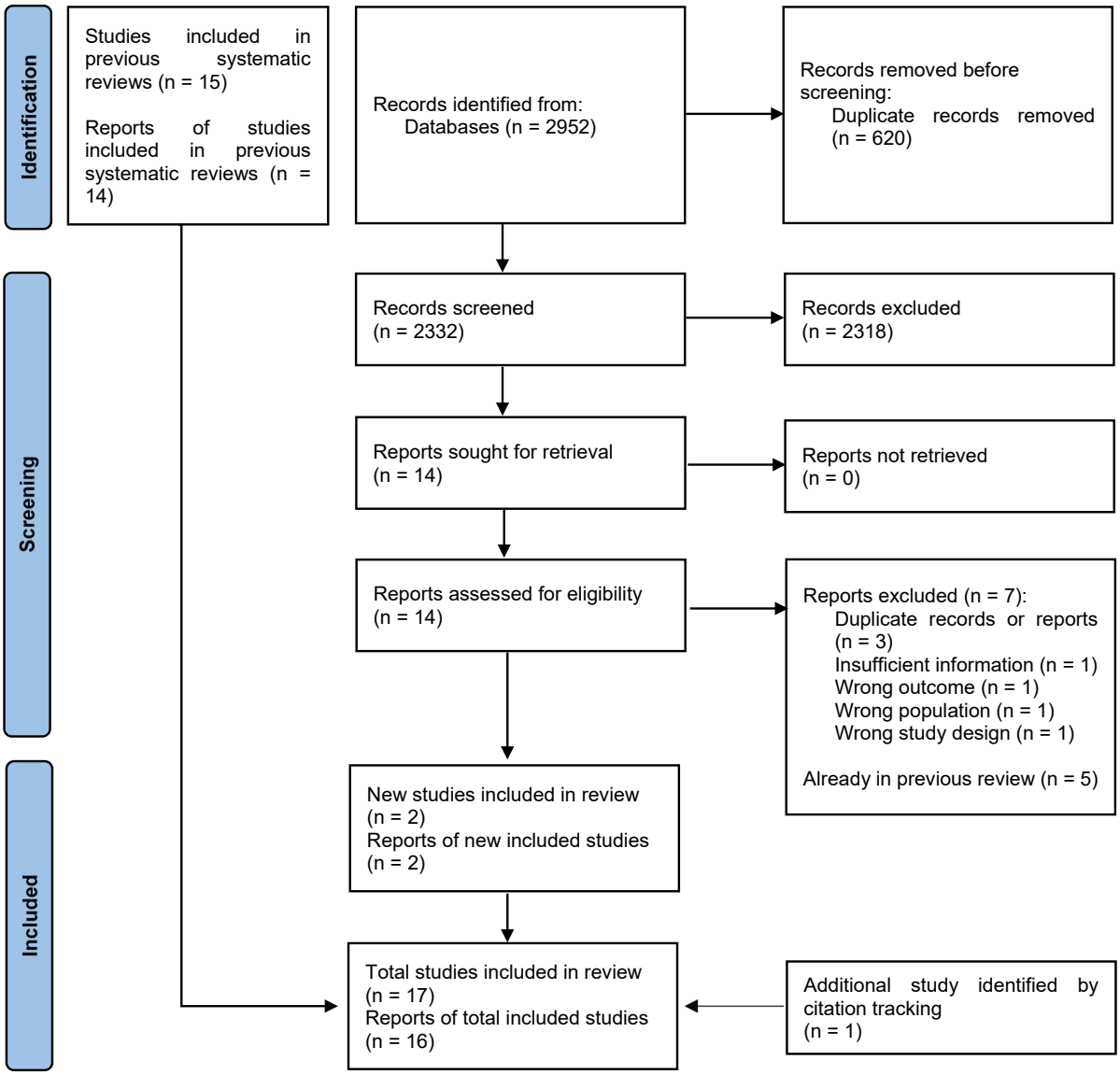
#	Query
1	lung diseases/ or "cystic adenomatoid malformation of lung, congenital"/ or cystic fibrosis/ or hepatopulmonary syndrome/ or lung abscess/ or lung diseases, interstitial/ or alveolitis, extrinsic allergic/ or bird fancier's lung/ or farmer's lung/ or silo filler's disease/ or trichosporonosis/ or anti-glomerular basement membrane disease/ or histiocytosis, langerhans-cell/ or eosinophilic granuloma/ or pneumoconiosis/ or anthracosis/ or anthracosilicosis/ or asbestosis/ or berylliosis/ or byssinosis/ or caplan syndrome/ or siderosis/ or silicosis/ or silicotuberculosis/ or pulmonary fibrosis/ or idiopathic pulmonary fibrosis/ or hamman-rich syndrome/ or idiopathic interstitial pneumonias/ or cryptogenic organizing pneumonia/ or sarcoidosis, pulmonary/

2	lung diseases, obstructive/ or asthma/ or asthma-chronic obstructive pulmonary disease overlap syndrome/ or bronchiolitis obliterans/ or cryptogenic organizing pneumonia/ or bronchitis, chronic/ or pulmonary disease, chronic obstructive/ or pulmonary emphysema/ or plasma cell granuloma, pulmonary/ or bronchial diseases/ or bronchiectasis/
3	respiratory tract diseases/ or respiration disorders/ or dyspnea/
4	(lung disease* or pulmonary disease* or cystic fibrosis or interstitial pneumoni* or extrinsic allergic alveolit* or hypersensitivity pneumoniti* or pneumoconios?s or anthracos?s or anthracosilicos?s or asbestos?s or beryllios?s or byssinos?s or beryllium disease* or caplan syndrome or bird fancier* lung or farmer* lung or silo filler* disease or trichosporonos?s or sideros?s or silicos?s or silicotuberculos?s or fibrosing alveolit* or pulmonary fibros?s or fibrocystic pulmonary dysplasia* or hamman-rich disease or hamman-rich syndrome or cryptogenic organizing pneumonia* or pulmonary sarcoidos?s or bronchiolitis obliterans or constrictive bronchiolit* or exudative bronchiolit* or chronic bronchitis or emphysema* or pulmonary inflammatory pseudotumo?r or pulmonary plasma cell granuloma* or bronchial disease* or bronchiectas?s).mp.
5	((chronic or severe* or unrelenting or obstructive) adj asthma*).mp.
6	(chronic* obstruct* adj3 (lung* or airway* or pulmon* or bronch* or alveolit* or respiratory)).mp.
7	(bronchopulmonary disease* or pneumopath* or pulmonary disorder* or acute pneumonitis or chronic fibrous pneumonia* or fibroid phthisis or interstitial cell pneumonia or interstitial plasma cell pneumonia or interstitial pneumocystic pneumonia or phthisis fibroidea or pneumonia interstitialis or interstitial fibros?s or lung fibros?s or interstitial fibros?s or alveolar fibros?s or respiratory granulomatos?s or pulmonary granulomatos?s or lung conios?s or pneumoconiotic lesion or pneumokonios?s or pneumono?onios?s).mp.
8	(airway obstructive disease* or obstructive airway disorder* or obstructive respiratory disease* or obstructive respiratory disorder* or pneumatosis pulmonum or interstitial syndrome).mp.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8

10	Oxygen Inhalation Therapy/
11	((O2 or "O 2" or oxygen*) adj (administration or therap* or inhalation or insufflation or treatment or conserving device* or concentrator* or delivery device* or flow rate or flow metre or cannula?)).mp.
12	((supplement* or home or domicil* or portable or ultraportable or ambulat*) adj3 (oxygen* or oxy-gen or O2 or "O 2" or LOX)).mp.
13	((prescri* or self-fill or liquid or compress* or light-weight or POC) adj3 (oxygen or O2 or "O 2" or LOX)).mp.
14	((noninvasive or non-invasive or therap*) adj (oxygen* or breathing support or respiratory support)).mp.
15	((High flow or highflow or low flow or lowflow) adj (oxygen* or breathing support or nasal or cannula)).mp.
16	(oxygen* adj (flow rate? or breathing support or flow metre or support therapy)).mp.
17	((inhal* or inspir*) adj3 oxygen*).mp.
18	((Humidif* or heated) adj2 oxygen).mp.
19	((nasal cannula? or nasal high flow or nasal prong? or nasal catheter* or nasal tube*) and (oxygen* or "O2" or "O 2")).mp.
20	(Evergo or Inogen One or EverFlo or Millennium M10 or Oxlife Freedom POC or Oxyensure or OxyGo or SimplyFlo or SimplyGo or UltraFill).mp.
21	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22	9 and 21
23	exp lung diseases/th and oxygen/tu
24	22 or 23

5. PICO question 5: Should opioids be used to reduce symptoms in people with serious illness related to lung disease? (PICO)

5.1. Identification of studies – PRISMA diagram



N.B. one report included two separate clinical trials.

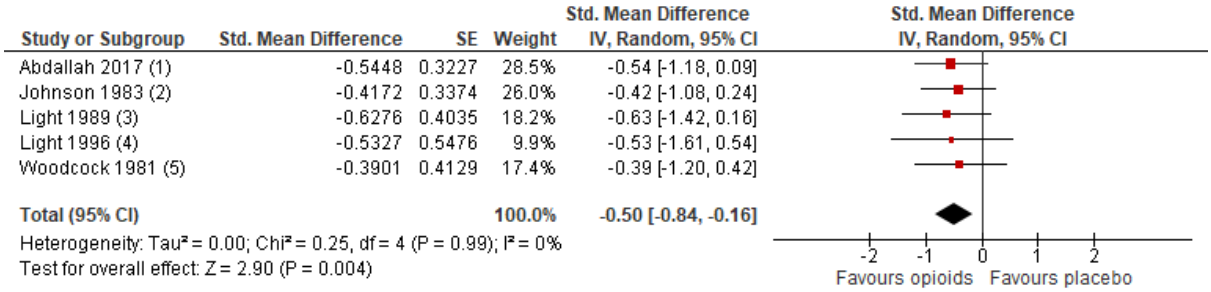
5.2. Inclusion criteria

- Randomised controlled trial, including both parallel and crossover trials.
- Participants are adults aged 18 years or older.
- Participants had serious illness related to lung disease (defined as a condition that carries a high risk of mortality, negatively impacts quality of life and daily function, and/or is burdensome in symptoms, treatments, or caregiver stress)
- Intervention: Any opioid drug, given by intravenous, sub-cutaneous or oral routes in any dose, for the treatment of breathlessness or cough.
- Comparison: placebo, usual care, or any other pharmacological or non-pharmacological interventions that were directly compared with the opioid treatment.

5.3. Exclusion criteria

- Participants with malignant disease. For mixed studies (e.g. studies including those with malignant and non-malignant disease) we asked the authors for data related to the participants with non-malignant disease only. If separate data were unable to be obtained then we included studies only if ≥80% of participants had non-malignant disease
- Nebulised opioid therapies

5.4. Forest Plots

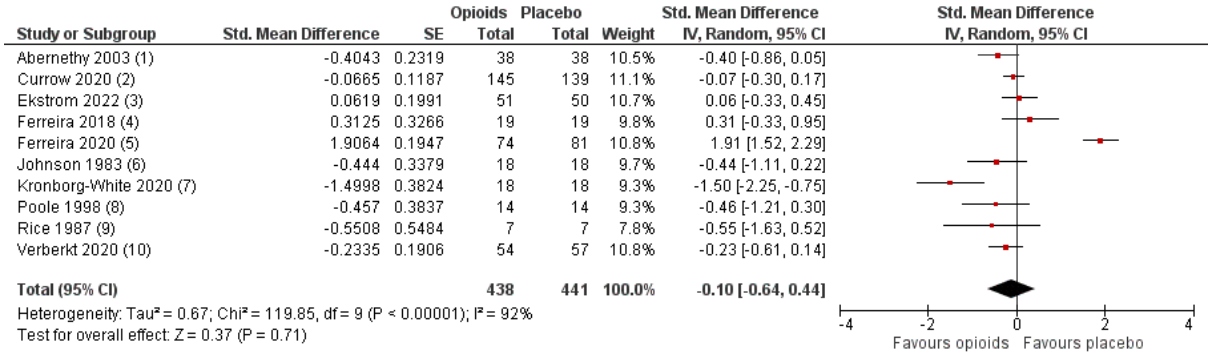


Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
Abdallah 2017 (1)	-0.5448	0.3227	28.5%	-0.54 [-1.18, 0.09]
Johnson 1983 (2)	-0.4172	0.3374	26.0%	-0.42 [-1.08, 0.24]
Light 1989 (3)	-0.6276	0.4035	18.2%	-0.63 [-1.42, 0.16]
Light 1996 (4)	-0.5327	0.5476	9.9%	-0.53 [-1.61, 0.54]
Woodcock 1981 (5)	-0.3901	0.4129	17.4%	-0.39 [-1.20, 0.42]
Total (95% CI)			**100.0%**	**-0.50 [-0.84, -0.16]**

Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 4 (P = 0.99); I² = 0%
Test for overall effect: Z = 2.90 (P = 0.004)

Footnotes
(1) BORG intensity at isotime
(2) 10cm VAS breathlessness at isoload
(3) BORG score at isotime
(4) BORG score at isotime
(5) 10cm VAS breathlessness at isoload

Laboratory-based exercise studies reporting breathlessness at iso-time or iso-load

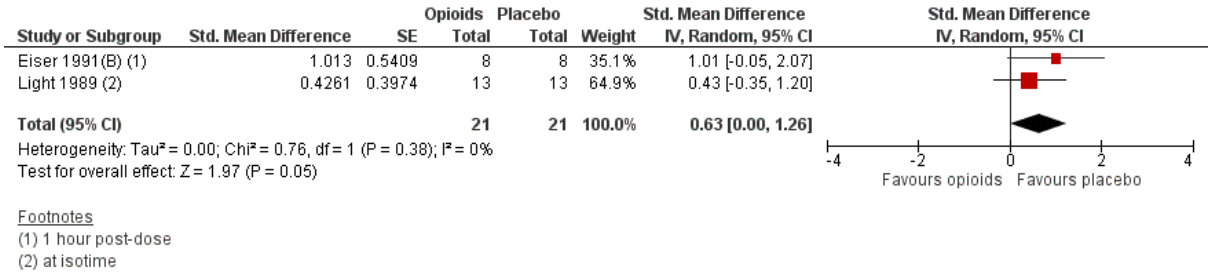


Study or Subgroup	Std. Mean Difference	SE	Opioids Total	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Abernethy 2003 (1)	-0.4043	0.2319	38	38	10.5%	-0.40 [-0.86, 0.05]
Currow 2020 (2)	-0.0665	0.1187	145	139	11.1%	-0.07 [-0.30, 0.17]
Ekstrom 2022 (3)	0.0619	0.1991	51	50	10.7%	0.06 [-0.33, 0.45]
Ferreira 2018 (4)	0.3125	0.3266	19	19	9.8%	0.31 [-0.33, 0.95]
Ferreira 2020 (5)	1.9064	0.1947	74	81	10.8%	1.91 [1.52, 2.29]
Johnson 1983 (6)	-0.444	0.3379	18	18	9.7%	-0.44 [-1.11, 0.22]
Kronborg-White 2020 (7)	-1.4998	0.3824	18	18	9.3%	-1.50 [-2.25, -0.75]
Poole 1998 (8)	-0.457	0.3837	14	14	9.3%	-0.46 [-1.21, 0.30]
Rice 1987 (9)	-0.5508	0.5484	7	7	7.8%	-0.55 [-1.63, 0.52]
Verberkt 2020 (10)	-0.2335	0.1906	54	57	10.8%	-0.23 [-0.61, 0.14]
Total (95% CI)			**438**	**441**	**100.0%**	**-0.10 [-0.64, 0.44]**

Heterogeneity: Tau² = 0.67; Chi² = 119.85, df = 9 (P < 0.00001); I² = 92%
Test for overall effect: Z = 0.37 (P = 0.71)

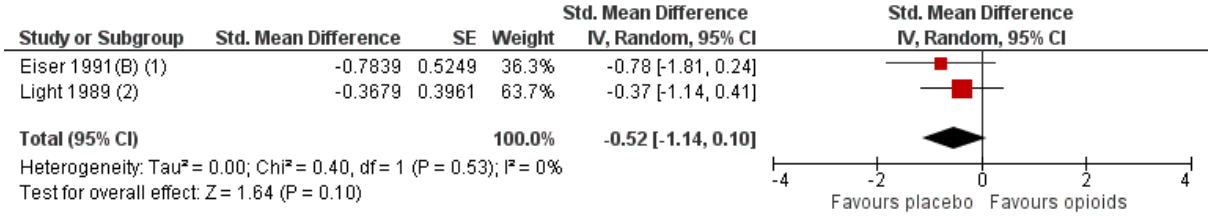
Footnotes
(1) 10cm VAS breathlessness intensity (final evening relative to baseline)
(2) 10cm VAS breathlessness intensity NOW (days 5-7 average of mean morning/evening scores relative to baseline)
(3) NRS intensity of breathlessness (16mg/day dose, days 5 to 7 average scores relative to days -3 to -1 average scores)
(4) 10cm VAS breathlessness intensity NOW (final evening score relative to baseline)
(5) 10cm VAS breathlessness intensity NOW (days 5-7 average of mean morning/evening scores relative to baseline)
(6) 10cm VAS breathlessness (final early evening relative to baseline from alternating weeks period)
(7) 10cm VAS breathlessness during LAST HOUR (change from baseline to followup)
(8) CRQ Dyspnea subscale (change from baseline to 6-weeks)
(9) 10cm VAS breathlessness during PAST 24 HOURS (change from baseline to followup)
(10) NRS over PAST 24 HOURS (change from baseline to followup)

Home studies reporting breathlessness pragmatically during daily life



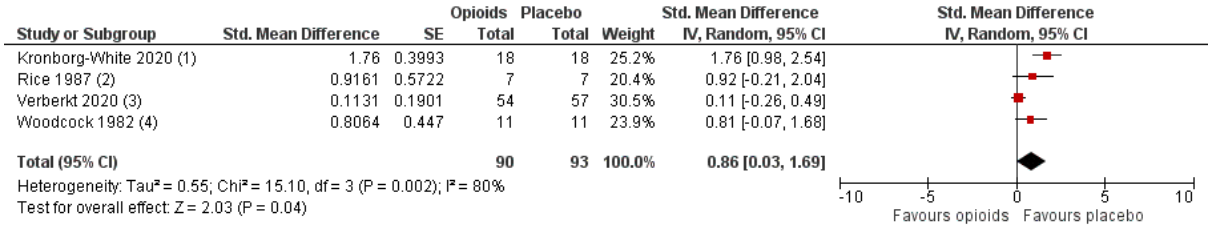
Footnotes
(1) 1 hour post-dose
(2) at isotime

Laboratory-based exercise studies reporting arterial blood gases (partial pressure of carbon dioxide)



Footnotes
(1) 1 hour post-dose
(2) at isotime

Laboratory-based exercise studies reporting arterial blood gases (partial pressure of oxygen)

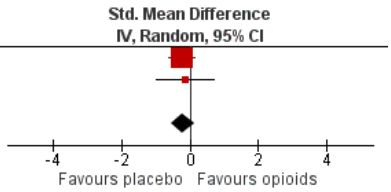


Footnotes
(1) Change from baseline
(2) Raw score at follow up
(3) change from baseline
(4) Raw score at follow up

Home studies reporting arterial blood gases (partial pressure of carbon dioxide)

Study or Subgroup	Std. Mean Difference	SE	Opioids Total	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Verberkt 2020 (1)	-0.2335	0.1906	54	57	83.4%	-0.23 [-0.61, 0.14]
Woodcock 1982 (2)	-0.1431	0.4271	11	11	16.6%	-0.14 [-0.98, 0.69]
Total (95% CI)			**65**	**68**	**100.0%**	**-0.22 [-0.56, 0.12]**

Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.85); I² = 0%
Test for overall effect: Z = 1.26 (P = 0.21)

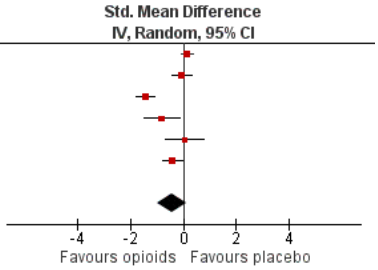


Footnotes
(1) change from baseline
(2) Raw score at follow up

Home studies reporting arterial blood gases (partial pressure of oxygen)

Study or Subgroup	Std. Mean Difference	SE	Opioids Total	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Currow 2020 (1)	0.136	0.1188	145	139	18.4%	0.14 [-0.10, 0.37]
Ekstrom 2022 (2)	-0.064	0.1991	51	50	17.4%	-0.06 [-0.45, 0.33]
Ferreira 2020 (3)	-1.4247	0.1805	74	81	17.7%	-1.42 [-1.78, -1.07]
Kronborg-White 2020 (4)	-0.8196	0.3487	18	18	14.8%	-0.82 [-1.50, -0.14]
Poole 1998 (5)	0.0554	0.378	14	14	14.2%	0.06 [-0.69, 0.80]
Verberkt 2020 (6)	-0.4111	0.192	54	57	17.5%	-0.41 [-0.79, -0.03]
Total (95% CI)			**356**	**359**	**100.0%**	**-0.42 [-0.98, 0.13]**

Heterogeneity: Tau² = 0.42; Chi² = 57.10, df = 5 (P < 0.00001); I² = 91%
Test for overall effect: Z = 1.50 (P = 0.13)

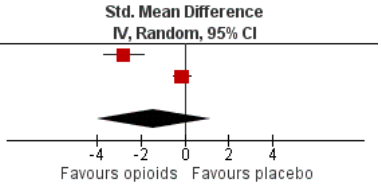


Footnotes
(1) EORTC-QLQ-C15 PAL (change from baseline)
(2) CAT (16mg/day dose, change from baseline)
(3) EORTC-QLQ-C15 PAL (change from baseline)
(4) KBILD (change from baseline)
(5) CRQ (change from baseline)
(6) CAT (change from baseline)

Home studies reporting health-related quality of life

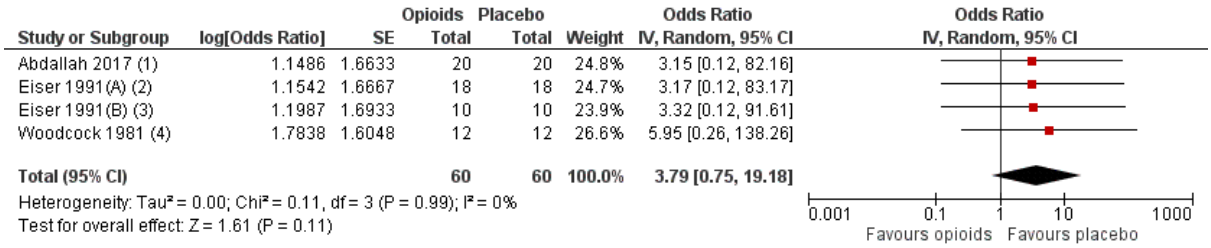
Study or Subgroup	Std. Mean Difference	SE	Opioids Total	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Kronborg-White 2020 (1)	-2.7656	0.48	18	18	48.6%	-2.77 [-3.71, -1.82]
Verberkt 2020 (2)	-0.1389	0.206	44	51	51.4%	-0.14 [-0.54, 0.26]
Total (95% CI)			**62**	**69**	**100.0%**	**-1.42 [-3.99, 1.16]**

Heterogeneity: Tau² = 3.31; Chi² = 25.29, df = 1 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.08 (P = 0.28)



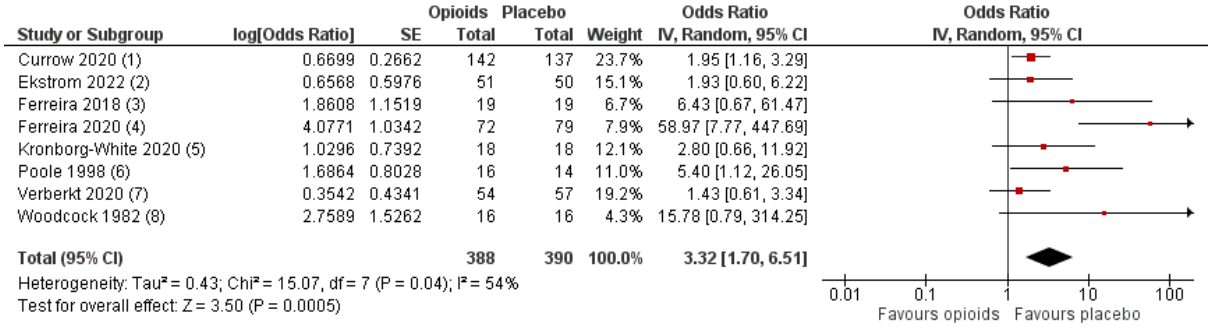
Footnotes
(1) Leicester Cough Score (change from baseline)
(2) CAT Cough subscore (raw score at one month)

Home studies reporting cough



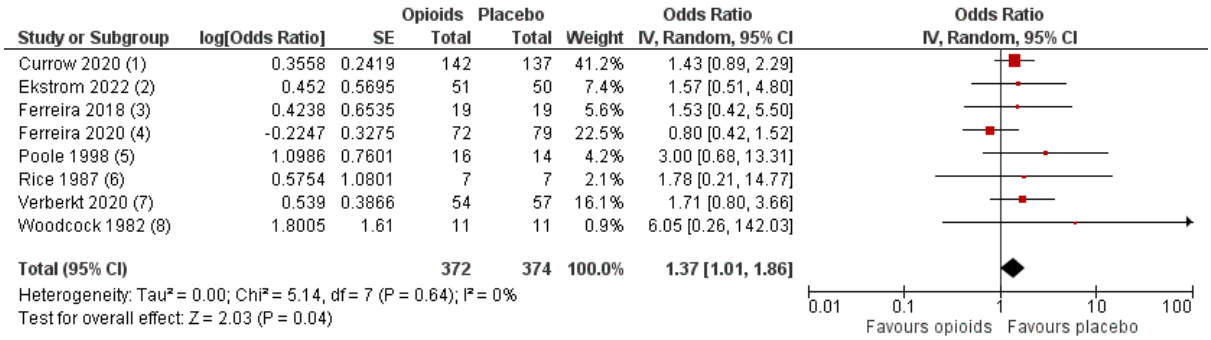
Footnotes
(1) count of self-reported events
(2) count of self-reported events
(3) count of self-reported events
(4) count of self-reported events

Laboratory-based exercise studies reporting adverse events (nausea and/or vomiting



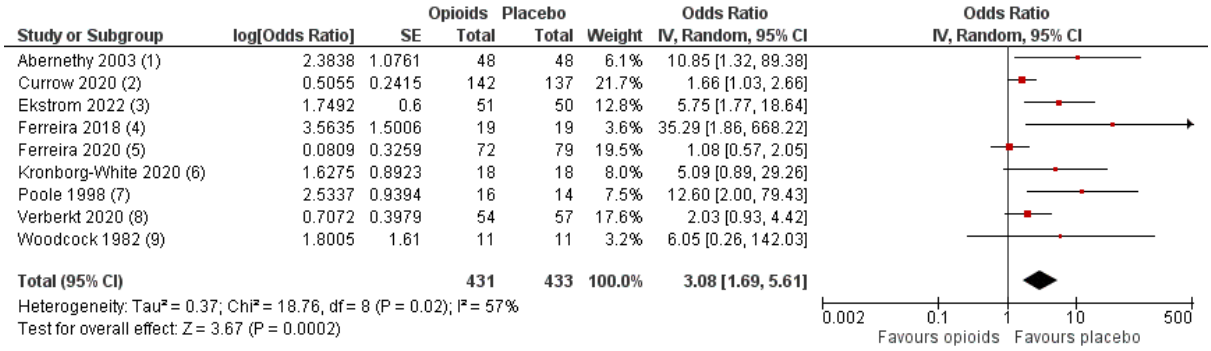
Footnotes
(1) count of self-reported events
(2) count of self-reported events
(3) count of self-reported events
(4) count of self-reported events
(5) count of self-reported events
(6) count of self-reported events
(7) count of participants with increase of 2 or more points on symptom NRS relative to baseline
(8) count of self-reported events

Home studies reporting adverse events (nausea and/or vomiting)



Footnotes
(1) count of self-reported events
(2) count of self-reported events
(3) count of self-reported events
(4) count of self-reported events
(5) count of self-reported events
(6) count of self-reported events
(7) count of participants with increase of 2 or more points on symptom NRS relative to baseline
(8) count of self-reported events

Home studies reporting adverse events (drowsiness)



Footnotes
(1) count of self-reported events
(2) count of self-reported events
(3) count of self-reported events
(4) count of self-reported events
(5) count of self-reported events
(6) count of self-reported events
(7) count of self-reported events
(8) count of participants with increase of 2 or more points on symptom NRS relative to baseline
(9) count of self-reported events

Home studies reporting adverse events (constipation)

5.5. GRADE Evidence Profile

OPIOIDS Daily breathlessness studies (at rest)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	opioids	no opioids	Relative (95% CI)	Absolute (95% CI)		
Home studies - Breathlessness intensity (evening measures or time not stated)												
10	randomised trials – 5 crossover	Serious [a]	Serious [b]	Not serious	Serious [c]	Not serious	438	441	-	**SMD -0.10** -0.64 to 0.44 p=0.71	⊕◯◯◯ very low	CRITICAL
Home studies - Breathlessness intensity (morning measures or time not stated)												
10	randomised trials – 5 crossover	Serious [a]	Serious [b]	Not serious	Serious [c]	Not serious	438	441	-	**SMD -0.10** -0.64 to 0.43 p=0.71	⊕◯◯◯ very low	CRITICAL
Home Studies – Health-Related Quality of Life												
6	randomised trials – 1 crossover	Not serious [a]	Serious [b]	Not serious	Serious [d]	No	356	359	-	**SMD -0.42** -0.98 to 0.13 p=0.13	⊕⊕◯◯ low	IMPORTANT

Home Studies – Cough												
2	randomised trials – 0 crossover	Not serious	Serious [b]	Not serious	Serious [e]	No	62	69	-	**SMD -1.42** -3.99 to 1.16 p=0.28	⊕⊕◯◯ low	IMPORTANT
Home Studies - ABG $PaCO_2$												
4	randomised trials – 2 crossover	Serious [f]	Serious [b]	Serious [g]	Serious [e]	Not serious	90	93	-	**SMD 0.86** 0.03 to 1.69 p=0.04 Favours placebo	⊕◯◯◯ very low	IMPORTANT
Home Studies - ABG PaO_2												
2	randomised trials – 1 crossover	Serious [h]	Not serious	Serious [i]	Serious [j]	Not serious	65	68	-	**SMD -0.22** -0.56 to 0.12 p=0.21	⊕◯◯◯ very low	IMPORTANT
Home Studies - drowsiness												
8	randomised trials – 4 crossover	Serious [k]	Not serious	Not serious	Serious [l]	No	372	374	-	**OR 1.37** 1.01 to 1.86 p=0.04	⊕⊕◯◯ low	IMPORTANT

Home Studies - constipation												
9	randomised trials – 4 crossover	Serious [m]	Serious [n]	Not serious	Not serious	No	431	433	-	**OR 3.08** 1.69 to 5.61 p=0.0002 favours placebo	⊕⊕◯◯ low	IMPORTANT
Home Studies – nausea or vomiting												
8	randomised trials – 3 crossover	Serious [o]	Serious [n]	Not serious	Not serious	No	388	390	-	**OR 3.32** 1.70 to 6.51 p=0.0005 favours placebo	⊕⊕◯◯ low	IMPORTANT

CI: confidence interval; **OR:** risk ratio; **SMD:** standardised mean difference

Explanations:

a. Nearly all studies had an unclear risk regarding selective reporting as most did not publish study protocols before publishing trial outcomes. One study was considered at high risk of bias for selective reporting. 3 of the 5 crossover studies had a risk of carryover effect due to inadequate washout period in crossover design.

b. Significant heterogeneity identified with I^2 >80% and poor overlap of confidence intervals, which is not explained by differences in study design or study populations

c. The pooled estimate of the effect of opioids on breathlessness includes both strong benefit and moderate harm, based on the standardized mean difference

d. The pooled estimate of the effect of opioids on QOL includes both small harm and large benefit

e. Small numbers of patients in the included studies contributes to inprecision in the outcome estimate

f. 45% of weighting comes from studies with uncertainty regarding selection bias and 75% of weighting comes from studies with uncertainty or high risk regarding reporting bias

g. 75% of weighting comes from studies with only people with COPD

h. 17% of weighting comes from studies with uncertainty regarding selection bias and 100% of weighting comes from studies with uncertainty or high risk regarding reporting bias

i. Only patients with COPD included in the studies for this outcome

j. The pooled estimate of the effect of opioids on PaO2 includes both moderate harm and small benefit, based on the standardized mean difference

k. All but 1 study had uncertainty or high risk regarding reporting bias and 30% of the weighting comes from studies with high risk for other bias

l. The pooled estimate of the effect of opioids on drowsiness includes both negligible and large harm, based on the standardized mean difference

m. 79% of the weighting comes from studies with uncertainty or high risk regarding reporting bias and 23% of the weighting comes from studies with high risk for other bias

n. Significant heterogeneity identified I^2 >50%, which is not explained by differences in study design or study populations

o. 73% of the weighting comes from studies with uncertainty or high risk regarding reporting bias and 15% of the weighting comes from studies with high risk for other bias

* Standardized mean difference (SMD) estimates are interpreted using thresholds defined by Cohen, J. 1988. Statistical Power Analysis for the Behavioral Sciences. Erlbaum Press.

- SMD ≈ 0.20: small effect
- SMD ≈ 0.50: moderate effect
- SMD ≈ 0.80: large effect

OPIOIDS Exercise studies

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	opioids	no opioids	Relative (95% CI)	Absolute (95% CI)		
Lab Based Exercise Studies – Breathlessness after exercise (isotime & isoload)												
5	randomised trials – all crossover	Serious [a]	Not serious	Serious [b]	Serious[c]	Not serious	70	70	-	**SMD -0.50** -0.84 to -0.16 p=0.004 Favours opioids	⊕◯◯◯ very low	CRITICAL
Lab Based Exercise Studies – Breathlessness after exercise (isotime only)												
3	randomised trials – all crossover	Serious [a]	Not serious	Serious [b]	Serious[c]	Not serious	40	40	-	**SMD -0.57** -1.02 to -0.12 p=0.01 Favours opioids	⊕◯◯◯ very low	CRITICAL

Lab Based Exercise Studies – Breathlessness after exercise (isoload only)												
2	randomised trials – all crossover	Serious [a]	Not serious	Not serious	Very serious [c,d]	Not Serious	30	30	-	**SMD -0.41** -0.92 to 0.11 p=0.12	⊕◯◯◯ very low	CRITICAL
Lab Based Exercise Studies - ABG PaCO2 after exercise												
2	randomised trials – all crossover	Serious [e]	Not serious	Serious [b]	Very serious [c,f]	Not Serious	21	21	-	**SMD 0.63** 0.0 to 1.26 p=0.05	⊕◯◯◯ very low	IMPORTANT
Lab Based Exercise Studies - ABG PaO2 after exercise												
2	randomised trials – all crossover	Serious [e]	Not serious	Serious [b]	Very serious [c,g]	Not serious	21	21	-	**SMD -0.52** -1.14 to 0.10 p=0.10	⊕◯◯◯ very low	IMPORTANT
Lab Based Exercise Studies – nausea or vomiting												
4	randomised trials – all crossover	Serious [a]	Not serious	Serious [b]	Serious [c]	Not serious	60	60	-	**OR 3.79** 0.75 to 19.18 p=0.11	⊕◯◯◯ very low	IMPORTANT

CI: confidence interval; **OR:** risk ratio; **SMD:** standardised mean difference

Explanations:

a. >=50% of weighting comes from studies with uncertainty or high risk for selection bias and reporting bias. 3 of the 5 crossover studies had a risk of carryover effect due to inadequate washout period in crossover design.

b. All or most studies only include people with COPD

c. Small numbers of patients in the included studies contributes to inprecision in the outcome estimate

e. The pooled estimate of the effect of opioids on breathlessness includes both small harm and large benefit, based on the standardized mean difference

f. All studies have uncertainty regarding for selection bias and reporting bias

g. The pooled estimate of the effect of opioids on ABG $PaCO_2$ includes both large harm and no benefit, based on the standardized mean difference

h. The pooled estimate of the effect of opioids on ABG PaO_2 includes both large harm and small benefit, based on the standardized mean difference

i. The pooled estimate of the effect of opioids on nausea or vomiting includes both large harm and no harm, based on the standardized mean difference

* Standardized mean difference (SMD) estimates are interpreted using thresholds defined by Cohen, J. 1988. Statistical Power Analysis for the Behavioral Sciences. Erlbaum Press.

- SMD ≈ 0.20: small effect. SMD ≈ 0.50: moderate effect. SMD ≈ 0.80: large effect

Conversion of SMD to a familiar instrument to determine clinical significance - Cochrane handbook

The final possibility for interpreting the SMD is to express it in the units of one or more of the specific measurement instruments.

SMD * SD

This will give an estimate of the difference in mean outcome scores (experimental versus control) on that scale.

SD obtained as the pooled standard deviation of baseline scores in one of the studies or from a representative observational study.

The pooled effect is thus re-expressed in the original units of that particular instrument and the clinical relevance and impact of the intervention effect can be interpreted.

Breathlessness score interpretation of SMD

What is MICD for VAS

From 2020 ERJ Ekstrom et al

~10mm

Anchor based MCIDs for VAS: 9.5 - 13.9mm

Distribution-based methods MCIDs: 9.7-16.4mm

A small change: 4.7- 6.3mm

A moderate change: 9.4 -12.5mm

A large change 15.0 and 20.0mm

SE 9.7 - 16.4

Pooled estimate of SD from exercise test studies in this MA using VAS = 2.0

Exercise test studies: Breathlessness intensity all studies (n=7): SMD -0.37 (-0.67 to -0.07) p=0.02 (3 use Borg, 4 use 10cm VAS)

SMD x SD = -0.37 x 2.0 = 0.74cm i.e. VAS 7.4mm less with opioids vs placebo

Exercise tests: Breathlessness intensity isotime/isoload only (n=5): SMD -0.50 (-0.84 to -0.16) p=0.004 (3 use Borg, 2 use 10cmVAS)

SMD x SD = -0.50 x 2.0 = -1.0cm i.e. **VAS 10mm less with opioids vs placebo i.e. this would appear to be clinically significant**

PaCO2 result interpretation of SMD

Pooled estimate of SD from rest studies in this MA using PaCO2 in mmHg = 2.5

Rest studies: PaCO2 (n=4): SMD 0.86 (0.03 to 1.69) p=0.04 (3 use mmHg, 1 uses kPa)

SMD x SD = 0.86 x = 2.2mmHg cm i.e. **ABG PaCO2 is 2.2mmHg higher with opioids vs placebo i.e. this would not be clinically significant**

Pooled estimate of SD from exercise test studies in this MA using PaCO2 in mmHg = 8.18

Exercise tests: PaCO2 (n=2): SMD 0.63 (0.0 to 1.26) p=0.05 (1 uses mmHg, 1 uses kPa)

SMD x SD = 0.63 x 8.18 = 5.2mmHg cm i.e. **ABG PaCO2 is 5.2mmHg higher with opioids vs placebo i.e. this would appear to be clinically significant**

5.6. Evidence-to-Decision Table, PICO 5

PICO5: SHOULD OPIOIDS BE USED TO REDUCE SYMPTOMS IN PEOPLE WITH SERIOUS ILLNESS RELATED TO LUNG DISEASE?	
POPULATION:	Adults with serious illness related to lung disease
INTERVENTION:	Oral, subcutaneous or intravenous opioids
COMPARISON:	No opioids
MAIN OUTCOMES:	Critical: • Breathlessness, using relevant and validated tools. This may include measures at rest or during exercise, but exercise measures obtained before and after an intervention must be obtained at iso-workload. Important: • Health related quality of life, using any validated tool • Cough, using any validated tool • Arterial blood gas • Adverse events, defined according to the investigators' definition

ASSESSMENT

Problem Is the problem a priority?		
Judgement	Research evidence	Additional considerations
No Probably no Probably yes ● Yes Varies Don't know	Patients with serious illness related to lung disease commonly experience high symptom burden, including chronic breathlessness and cough (1), which contribute to a reduced quality of life (2). Breathlessness is frequently ranked by patients as their worst symptom (3) and it is a major contributor to unscheduled healthcare usage (4, 5).	
Desirable Effects How substantial are the desirable anticipated effects?		
Judgement	Research evidence	Additional considerations
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Of 17 included studies, the populations included: people with COPD (11 studies), ILD (1 study), PAH (1 study) and mixed populations with <20% of people having malignancy (4 studies). The effects of opioids were considered according to setting and how outcomes were measured:	(Maher Since the completion of the meta-analysis a Phase II trial (n=41) demonstrated a 75% decrease in daytime cough frequency with nalbuphine extended-release treatment

	○ opioids administered regularly for 4 consecutive days or greater at home (11 studies – 5 COPD; 1 ILD; 1 PAH; 4 mixed) with outcomes in daily life, and ○ opioids administered as one or more doses in the laboratory setting with participants completing an exercise test, with the effect of one or more doses measured at varying times in most studies (7 studies – 6 COPD; 1 mixed), of which 5 studies (4 COPD; 1 mixed) measured effects at either isotime or isoload. Given the differences in study design and approach, studies measuring outcomes at rest in the community or during laboratory exercise tests were not combined. **Critical outcome: breathlessness** ○ In two separate analyses examining either breathlessness scores measured in the evening (10 studies – 5 COPD; 1 PAH; 4 mixed) or morning (10 studies – 5 COPD; 1 PAH; 4 mixed) at home in daily life, there was no significant difference in *breathlessness intensity scores* between opioids and the comparator intervention (placebo in all studies, except one which used promethazine). ○ There was an improvement in *breathlessness intensity scores* measured *at isoload or isotime* during laboratory exercise testing in people receiving opioids compared with placebo (SMD= -0.50, 95%CI= -0.84 to -0.16; p=0.004; studies – 4 COPD; 1 mixed). This translated to approximately a 10mm difference on visual analogue scale (VAS), which suggests this effect is clinically significant (6). **Important outcomes** ○ When opioids were administered regularly at home for 4 consecutive days or greater, there was no significant difference in quality of life (*QOL) scores* between opioids and the comparator intervention (placebo) (6 studies – 3 COPD; 2 mixed; 1 ILD). ○ When opioids were administered regularly at home for 4 consecutive days or greater, there was no significant difference in *cough scores* between opioids and the comparator intervention (placebo) (2 studies – 1COPD; 1 ILD). There was considerable variation in administration frequency and dosing of opioids across studies.	compared to 23% decrease with placebo in people with IPF (Maher et al, NEJM Evidence 2023)

Undesirable Effects **How substantial are the undesirable anticipated effects?**		
Judgement	Research evidence	Additional considerations
○ Large ●Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	Studies measuring outcom**es at home with regular opioid dosing** ○ There was a statistically significant difference in *PaCO2 measurements,* with these being higher in people receiving opioids (SMD 0.86, 95%CI 0.03 – 1.69, p=0.04; 4 studies). This translated to approximately a 2.2mmHg difference in PaCO2, which is not clinically significant. ○ There was no significant difference in *PaO2 measurements* between people receiving opioids or placebo (2 studies). ○ There was a significant increase in the frequency of *constipation* events in people receiving opioids compared with placebo (OR 3.08, 95% CI: 1.69-5.61, p=0.0002; 9 studies). ○ There was a significant increase in the frequency of *nausea or vomiting* events in people receiving opioids compared with placebo (OR 3.32, 95% CI: 1.70-6.51, p=0.0005; 8 studies). ○ There was a significant increase in the frequency of *drowsiness* events in people receiving opioids compared with the comparator intervention (placebo in all studies, except one which used promethazine) (OR 1.37, 95% CI: 1.01-1.86, p=0.04; 8 studies). ○ In some studies, treatment-emergent adverse events were mild and self-limiting on withdrawal of morphine (7-13). However, serious adverse events were reported in two studies (14, 15); data from the BEAMS study (Ekstrom et al, 2022) indicated that 33% (46 of 139) of participants treated with morphine developed serious adverse events, including hospitalisation and death. **Studies measuring outcomes after laboratory exercise testing:** ○ There was a trend but no significant difference in *PaCO2 measurements,* with these being higher in people receiving opioids compared with placebo (SMD 0.63, 95%CI 0 – 1.26, p=0.05; 2 studies). This translated to approximately a 5.2mmHg difference in PaCO2, which is clinically significant. ○ There was no significant difference in the frequency of *nausea or vomiting* events in people receiving opioids compared with placebo (4 studies). ○ There was no significant difference in *PaO2 measurements* between people receiving opioids or placebo (2 studies).	

Certainty of evidence What is the overall certainty of the evidence of effects?		
Judgement	Research evidence	Additional considerations
● Very low ○ Low ○ Moderate ○ High ○ No included studies	Based on GRADE assessment, the certainty of evidence was very low. ○	Very few studies included people with illnesses other than COPD. There was heterogeneity in the populations included – not all studies included people with severe breathlessness (some included mMRC 2). No studies included people near the very end of life, most were limited to chronic daily breathlessness.
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
Judgement	Research evidence	Additional considerations
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	The critical outcome for this question is breathlessness, which people with serious respiratory illness consistently report as a major distressing symptom (16-18). In people with COPD, breathlessness has been found to be a key determinant of low physical and mental health (17, 18). Similarly, in people with pulmonary fibrosis breathlessness has been identified as a major driver of reduced quality of life (19, 20). Fear of exertional breathlessness may result in avoiding exercise, leading to a downward spiral of deconditioning, social isolation with negative physical and emotional consequences (18). There is an immense need to better actively manage chronic breathlessness and other distressing symptoms in people with a variety of non-malignant chronic respiratory diseases.	There was no important uncertainty or variability in the views of the patient members of the Task Force regarding values.

Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Judgement	Research evidence	Additional considerations
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	From these analyses (based on studies mostly in people with COPD), the balance of effects does not favour opioids compared to placebo in people with serious respiratory illness. Opioids had no impact on the intensity of chronic breathlessness when measured in daily life at home. There was a statistically and clinically significant improvement in breathlessness intensity scores when measured during laboratory exercise tests at isotime/isoload. However, there was a significant increase in the frequency of adverse effects (in both studies at home and during laboratory exercise tests), which led many patients to withdraw from studies. There is a lack of evidence for people with illnesses other than COPD.	
Resources required How large are the resource requirements (costs)?		
Judgement	Research evidence	Additional considerations
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○Varies ○ Don't know	Opioids are inexpensive drugs, with low-cost generics widely available. However, no studies in this analysis considered costs or resources required for either opioid prescription to or management of adverse events in people with serious respiratory illness. Data from the Verbekt study (2020) Morphine for Treatment of Dyspnea in Patients With COPD (MORDYC), was evaluated for cost-effectiveness of sustained-release morphine for refractory breathlessness in COPD from the. In some studies, treatment-emergent adverse events were mild and self-limiting on withdrawal of morphine, (12, 21) but inevitably incur costs associated with healthcare consultations and corrective medications. However, serious adverse events were not uncommon amongst larger trials; data from the BEAMS study (Ekstrom et al, 2022) indicated that 33% (46 of 139) of participants treated with morphine developed serious adverse events, including hospitalisaiton and death.	
Certainty of evidence of required resources		

What is the certainty of the evidence of resource requirements (costs)?		
Judgement	Research evidence	Additional considerations
● Very low ○ Low ○ Moderate ○ High ○ No included studies	While opioids are frequently prescribed, information on the cost-effectiveness of morphine treatment for breathlessness is lacking in the studies included in these analyses. A retrospective cost-effectiveness and cost-utility analysis of oral morphine treatment for chronic breathlessness in patients with advanced COPD (22) including a healthcare and societal perspectives, reports on data from a single-centre, randomised, double blind, placebo controlled intervention study (23). Costs for productivity losses included absenteeism from paid work and absenteeism from voluntary work, but the population are for the most part retired. The main costs drivers were identified as medication use and contact with healthcare professionals with the largest difference in healthcare costs associated with hospital admissions.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
Judgement	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Medication use is a known cost driver. The cost-effectiveness analysis of sustained-release morphine for refractory breathlessness in COPD from the Morphine for Treatment of Dyspnoea in Patients with COPD (MORDYC) trial offers limited insights (22). Data collection was only for four weeks and so the long-term effects and costs of morphine treatment remain largely unknown. Total healthcare costs over 4 weeks were lower in the morphine group suggesting regular, low-dose, oral sustained-release morphine treatment is cost-effective, a finding not replicated in other studies. The authors acknowledge that if the cost and frequency of hospitalisations were compared with observational studies healthcare costs might be underestimated in this analysis (22). A study of longer duration is needed.	
Equity What would be the impact on health equity?		

Judgement	Research evidence	Additional considerations
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Effective pharmacological and non-pharmacological treatments (other than pulmonary rehabilitation) for chronic breathlessness are limited and often lack a robust evidence base. Opioids are inexpensive drugs with many low-cost generics available. For these reasons, opioids can be an important component of an individualized breathlessness management strategy. In the included studies, most predominantly included male participants, with little to no reporting of other social determinants of health (24), such as race or socioeconomic status.	
Acceptability Is the intervention acceptable to key stakeholders?		
Judgement	Research evidence	Additional considerations
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	In the included studies, there was no reporting regarding consumer engagement, however, consumers are key stakeholders when considering intervention acceptability. In the wider literature, some people with serious respiratory illness, caregivers and clinicians have negative attitudes or concerns regarding using opioids for the treatment of breathlessness, with concerns regarding safe use, respiratory depression, substance misuse, dependence and addiction, stigma and the association of opioids with death and dying (25-29). Additionally, opioids may affect capacity to drive, and cause many predictable side effects, which are unacceptable or challenging for some patients (30). In the included studies, many participants (n=33) withdrew from the included studies due to significant side effects (particularly gastrointestinal). The inability to recruit patients to some of the trials in this analysis (even though some were conducted over numerous years) highlights negative community perceptions to opioids (8, 9, 31).	There was no important uncertainty or variability in the views of the patient members of the Task Force regarding acceptability.
Feasibility Is the intervention feasible to implement?		
Judgement	Research evidence	Additional considerations

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There is limited research evidence regarding feasibility.	The prescription of opioids to people with serious respiratory illness and significant symptoms is inexpensive and feasible in many healthcare settings. However, managing side effects may be expensive, particularly if adverse effects necessitate additional support from health professionals or hospital admission.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

We suggest not using opioids for the treatment of breathlessness in people with serious respiratory illness (conditional recommendation against the intervention, very low certainty of evidence).

Justification

This recommendation balances the limited evidence for beneficial effects of opioids on symptoms with the increased risk of adverse events, and evidence that opioids may have limited acceptability to patients, caregivers and health professionals. Some people with serious respiratory illness, caregivers and clinicians have concerns regarding safe use, respiratory depression, substance misuse, dependence and addiction, stigma, and the association of opioids with death and dying. Opioids may affect capacity to drive and cause many predictable adverse events, which are unacceptable or challenging for some patients. Many participants (n=33) withdrew from the included studies due to significant side effects (particularly gastrointestinal). The inability to recruit patients to some trials in this analysis (even when conducted over numerous years) led to some including patients with only moderate breathlessness, which highlights negative community perceptions to opioids. We found limited data on the use of opioids for cough in people with serious respiratory illness, however since the completion of the meta-analysis a Phase II trial (n=41) demonstrated a 75% decrease in daytime cough frequency with nalbuphine extended-release treatment compared to 23% decrease with placebo in people with IPF (Maher et al, NEJM Evidence 2023). Broader recommendations on management of chronic cough can be found in the 2020 ERS chronic cough guidelines.

Subgroup considerations

The evidence has focussed on people with COPD, therefore it is impossible to know what the true impacts of opioids are on symptoms in people with other serious, non-malignant, respiratory illnesses.

The patient populations included in the studies to date have been heterogeneous, with some studies including people with only moderate (i.e. not severe) breathlessness, therefore it is not clear if opioids are beneficial in people with more severe breathlessness (i.e. breathlessness occurring at rest or on minimal exertion).

No studies included people at the very end of life, who are usually highly symptomatic and who are often prescribed opioids for symptom palliation.

Implementation considerations

In people with COPD, we do not recommend prescribing opioids to treat chronic breathlessness experienced in daily life. However, when clinicians are considering prescribing opioids to treat symptoms in people with serious non-malignant, respiratory illness, clear communication and shared decision making between clinicians and patients are required. This must include consideration of benefits and harms, and active discussion and plans to manage side effects. Opioid prescription should consider patients' goals and willingness to use an opioid medication, their understanding of how to take the medication correctly, and the broader impacts on their lives (including the ability to drive (32)) and other potential harms. Other clinicians and the patients' informal caregivers may require education and support regarding the use of opioids for symptom management in people with serious, non-malignant, respiratory illnesses

Monitoring and evaluation

If a clinician and patient with serious respiratory illness have decided to trial an opioid to treat symptoms, before the patient commences treatment, it is essential to:

- ensure all illnesses contributing to breathlessness have been optimally treated, and

- the patient has received education on non-drug, self-management approaches.

Regular medical follow up to both titrate the dose and and actively prevent (e.g., through prescription of laxatives and anti-emetics) or manage side effects is required. The lowest dose to achieve a clinical improvement in symptoms should be used. If no beneficial effect is perceived, shared decision making and discussion between clinicians and patients, then consideration of cessation of the opioid should occur.

Research priorities

The current evidence base is limited, further research needs to focus on:

- Other and new interventions (including non-pharmacological approaches) to improve breathlessness and other symptoms in people with serious, non-malignant, respiratory illnesses
- Symptom management in people with non-malignant respiratory illnesses other than COPD, people with more severe breathlessness, people with cough secondary to severe respiratory illness, and people towards the end of life.

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5.8. Search strategies

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions

#	Query
1	lung diseases/ or "cystic adenomatoid malformation of lung, congenital"/ or cystic fibrosis/ or hepatopulmonary syndrome/ or lung abscess/ or lung diseases, interstitial/ or alveolitis, extrinsic allergic/ or bird fancier's lung/ or farmer's lung/ or silo filler's disease/ or trichosporonosis/ or anti-glomerular basement membrane disease/ or histiocytosis, langerhans-cell/ or eosinophilic granuloma/ or pneumoconiosis/ or anthracosis/ or anthracosilicosis/ or asbestosis/ or berylliosis/ or byssinosis/ or caplan syndrome/ or siderosis/ or silicosis/ or silicotuberculosis/ or pulmonary fibrosis/ or idiopathic pulmonary fibrosis/ or hamman-rich syndrome/ or idiopathic interstitial pneumonias/ or cryptogenic organizing pneumonia/ or sarcoidosis, pulmonary/
2	lung diseases, obstructive/ or asthma/ or asthma-chronic obstructive pulmonary disease overlap syndrome/ or bronchiolitis obliterans/ or cryptogenic organizing pneumonia/ or bronchitis, chronic/ or pulmonary disease, chronic obstructive/ or pulmonary emphysema/ or plasma cell granuloma, pulmonary/ or bronchial diseases/ or bronchiectasis/
3	respiratory tract diseases/ or respiration disorders/ or dyspnea/
4	(lung disease* or pulmonary disease* or cystic fibrosis or interstitial pneumoni* or extrinsic allergic alveolit* or hypersensitivity pneumoniti* or pneumoconios?s or anthracos?s or anthracosilicos?s or asbestos?s or beryllios?s or byssinos?s or beryllium disease* or caplan syndrome or bird fancier* lung or farmer* lung or silo filler* disease or trichosporonos?s or sideros?s or silicos?s or silicotuberculos?s or fibrosing alveolit* or pulmonary fibros?s or fibrocystic pulmonary dysplasia* or hamman-rich disease or hamman-rich syndrome or cryptogenic organizing pneumonia* or pulmonary sarcoidos?s or bronchiolitis obliterans or constrictive bronchiolit* or exudative bronchiolit* or chronic bronchitis or emphysema* or pulmonary inflammatory pseudotumo?r or pulmonary plasma cell granuloma* or bronchial disease* or bronchiectas?s).mp.
5	((chronic or severe* or unrelenting or obstructive) adj asthma*).mp.
6	(chronic* obstruct* adj3 (lung* or airway* or pulmon* or bronch* or alveolit* or respiratory)).mp.
7	(bronchopulmonary disease* or pneumopath* or pulmonary disorder* or acute pneumonitis or chronic fibrous pneumonia* or fibroid phthisis or interstitial cell pneumonia or interstitial plasma cell pneumonia or interstitial pneumocystic pneumonia or phthisis fibroidea or pneumonia interstitialis or interstitial fibros?s or lung fibros?s or interstitial fibros?s or alveolar fibros?s or respiratory granulomatos?s or pulmonary granulomatos?s or lung conios?s or pneumoconiotic lesion or pneumokonios?s or pneumono?onios?s).mp.
8	(airway obstructive disease* or obstructive airway disorder* or obstructive respiratory disease* or obstructive respiratory disorder* or pneumatosis pulmonum or interstitial syndrome).mp.

9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	exp narcotics/ or exp analgesics, opioid/ or exp Analgesics/ or exp morphine derivatives/ or morphine/ or fentanyl/ or alfentanil/ or sufentanil/ or exp remifentanil/ or exp sufentanil/ or exp hydromorphone/ or exp oxycodone/ or exp pentazocine/ or exp methadone/ or exp codeine/ or exp dextromoramide/ or exp fentanyl citrate/ or exp diamorphine/ or exp dihydrocodeine/ or exp dextropropoxyphene/ or exp meptazinol/ or exp nalbuphine/ or exp meptazinol/ or exp dipipanone/ or exp pethidine/ or exp tramadol/ or exp buprenorphine/
11	(opiate* or opioid* or analgesic* or morphine or narcotic* or fentanyl or alfentanil or remifentanil or sufentanil or hydromorphone or oxycodone or pentazocine or methadone or codeine or dextromoramide or diamorphine or dihydrocodeine or dextropropoxyphene or meptazinol or nalbuphine or meptazinol or dipipanone or pethidine or tramadol or buprenorphine).mp.
12	(opiat or analgetic or morfin? or morphia or morphin* or fentamyl or fentanil or duragesic or sufentanyl or sulfentanil or sulfentanyl or alfentanyl or remifentanyl or dihydromorphinone or dihydromorphone or hydromorph contin or hydromorphinone or hydromorphon? or dihydrohydroxycodeinone or dihydrohydroxydodeinone or dihydrone or oxicodona or oxicone or oxicontin or oxikodon or oxycodeinonhydrochloride or oxycodon or pentacozine or pentazocin? or methadon or codein or methyl morfine or methylmorfine or methylmorphine or dextro moramide or dextromoramine or actiq or fenodid or fentabbott or acetomorphine or diacephine or diacetyl morphine or diacetylmorphine or heroin? or codhydrin? or dihydroneopine or hydrocodin? or propoxyphen? or propoxyphenhydrochloride or propoxyphine or nalbufin? or piperidyl amidone or meperidin? or meperidol or methylphenylcarbethoxypiperidine or pethedine or tramadolhydrochlorid or buprenorfin or buprenorphin).mp.
13	10 or 11 or 12
14	9 and 13
15	(randomized controlled trial or controlled clinical trial).pt.
16	(randomi?ed or placebo).ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.
17	((cross over or crossover) adj (clinical study or clinical trial or design or method or study or trial or studies)).mp.
18	15 or 16 or 17
19	14 and 18

Database: Embase

#	Query
1	lung disease/ or chronic lung disease/ or interstitial lung disease/ or interstitial syndrome/ or lung emphysema/ or lung fibrosis/ or lung sarcoidosis/ or obstructive lung disease/ or fibrosing

	alveolitis/ or interstitial pneumonia/ or pneumoconiosis/ or asthma/ or chronic obstructive lung disease/ or severe asthma/ or asthmatic state/ or severe persistent asthma/
2	obstructive airway disease/ or occupational lung disease/ or anthracosis/ or asbestosis/ or berylliosis/ or bird breeder lung/ or byssinosis/ or farmer lung/ or occupational asthma/ or pigeon breeder lung/ or pneumoconiosis/ or silicosis/ or bronchus disease/ or bronchiectasis/ or lung granuloma/ or respiratory tract disease/ or dyspnea/
3	(lung disease* or pulmonary disease* or cystic fibrosis or interstitial pneumoni* or extrinsic allergic alveolit* or hypersensitivity pneumoniti* or pneumoconios?s or anthracos?s or anthracosilicos?s or asbestos?s or beryllios?s or byssinos?s or beryllium disease* or caplan syndrome or bird fancier* lung or farmer* lung or silo filler* disease or trichosporonos?s or sideros?s or silicos?s or silicotuberculos?s or fibrosing alveolit* or pulmonary fibros?s or fibrocystic pulmonary dysplasia* or hamman-rich disease or hamman-rich syndrome or cryptogenic organizing pneumonia* or pulmonary sarcoidos?s or bronchiolitis obliterans or constrictive bronchiolit* or exudative bronchiolit* or chronic bronchitis or emphysema* or pulmonary inflammatory pseudotumo?r or pulmonary plasma cell granuloma* or bronchial disease* or bronchiectas?s).mp.
4	((chronic or severe* or unrelenting or obstructive) adj asthma*).mp.
5	(chronic* obstruct* adj3 (lung* or airway* or pulmon* or bronch* or alveolit* or respiratory)).mp.
6	(bronchopulmonary disease* or pneumopath* or pulmonary disorder* or acute pneumonitis or chronic fibrous pneumonia* or fibroid phthisis or interstitial cell pneumonia or interstitial plasma cell pneumonia or interstitial pneumocystic pneumonia or phthisis fibroidea or pneumonia interstitialis or interstitial fibros?s or lung fibros?s or interstitial fibros?s or alveolar fibros?s or respiratory granulomatos?s or pulmonary granulomatos?s or lung conios?s or pneumoconiotic lesion or pneumokonios?s or pneumono?onios?s).mp.
7	(airway obstructive disease* or obstructive airway disorder* or obstructive respiratory disease* or obstructive respiratory disorder* or pneumatosis pulmonum or interstitial syndrome).mp.
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	exp opiate agonist/ or exp opiate/ or exp analgesic agent/ or exp narcotic agent/ or exp fentanyl derivative/ or exp alfentanil/ or exp fentanyl/ or exp remifentanil/ or exp sufentanil/ or exp hydromorphone/ or exp oxycodone/ or exp pentazocine/ or exp methadone/ or exp codeine/ or exp dextromoramide/ or exp fentanyl citrate/ or exp diamorphine/ or exp dihydrocodeine/ or exp dextropropoxyphene/ or exp meptazinol/ or exp nalbuphine/ or exp meptazinol/ or exp dipipanone/ or exp pethidine/ or exp tramadol/ or exp buprenorphine/ or exp morphine derivative/ or exp narcotic analgesic agent/
10	(opiate* or opioid* or analgesic* or morphine or narcotic* or fentanyl or alfentanil or remifentanil or sufentanil or hydromorphone or oxycodone or pentazocine or methadone or codeine or dextromoramide or diamorphine or dihydrocodeine or dextropropoxyphene or meptazinol or nalbuphine or meptazinol or dipipanone or pethidine or tramadol or buprenorphine).mp.

11	(opiat or analgetic or morfin? or morphia or morphin* or fentamyl or fentanil or duragesic or sufentanyl or sulfentanil or sulfentanyl or alfentanyl or remifentanyl or dihydromorphinone or dihydromorphone or hydromorph contin or hydromorphinone or hydromorphon? or dihydrohydroxycodeinone or dihydrohydroxydodeinone or dihydrone or oxicodona or oxicone or oxicontin or oxikodon or oxycodeinonhydrochloride or oxycodon or pentacozine or pentazocin? or methadon or codein or methyl morfine or methylmorfine or methylmorphine or dextro moramide or dextromoramine or actiq or fenodid or fentabbott or acetomorphine or diacephine or diacetyl morphine or diacetylmorphine or heroin? or codhydrin? or dihydroneopine or hydrocodin? or propoxyphen? or propoxyphenhydrochloride or propoxyphine or nalbufin? or piperidyl amidone or meperidin? or meperidol or methylphenylcarbethoxypiperidine or pethedine or tramadolhydrochlorid or buprenorfin or buprenorphin).mp.
12	9 or 10 or 11
13	8 and 12
14	limit 13 to (randomized controlled trial or controlled clinical trial)
15	randomized controlled trial/ or randomization/ or single blind procedure/ or double blind procedure/ or crossover procedure/ or placebo/ or prospective study/
16	(randomi?ed controlled or RCT or randomly allocated or allocated randomly or random allocation or "allocated at random" or single blind* or double blind* or ((treble or triple) adj blind*) or placebo*).mp.
17	((cross over or crossover) adj (clinical study or clinical trial or design or method or study or trial or studies)).mp.
18	15 or 16 or 17
19	13 and 18
20	14 or 19

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

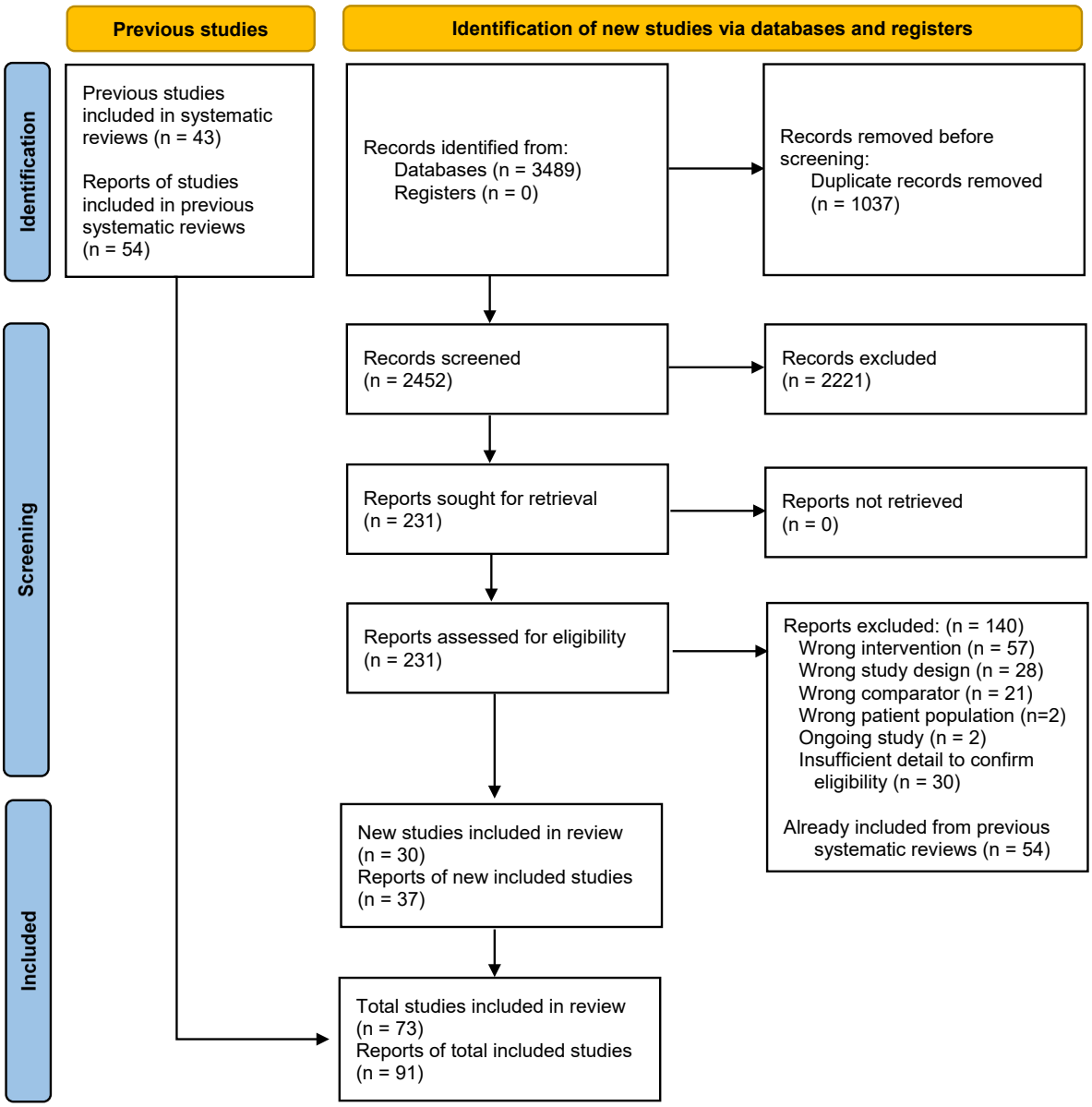
#	Query
1	lung diseases/ or "cystic adenomatoid malformation of lung, congenital"/ or cystic fibrosis/ or hepatopulmonary syndrome/ or lung abscess/ or lung diseases, interstitial/ or alveolitis, extrinsic allergic/ or bird fancier's lung/ or farmer's lung/ or silo filler's disease/ or trichosporonosis/ or anti-glomerular basement membrane disease/ or histiocytosis, langerhans-cell/ or eosinophilic granuloma/ or pneumoconiosis/ or anthracosis/ or anthracosilicosis/ or asbestosis/ or berylliosis/ or byssinosis/ or caplan syndrome/ or siderosis/ or silicosis/ or silicotuberculosis/ or pulmonary fibrosis/ or idiopathic pulmonary fibrosis/ or hamman-rich syndrome/ or idiopathic interstitial pneumonias/ or cryptogenic organizing pneumonia/ or sarcoidosis, pulmonary/
2	lung diseases, obstructive/ or asthma/ or asthma-chronic obstructive pulmonary disease overlap syndrome/ or bronchiolitis obliterans/ or cryptogenic organizing pneumonia/ or bronchitis,

	chronic/ or pulmonary disease, chronic obstructive/ or pulmonary emphysema/ or plasma cell granuloma, pulmonary/ or bronchial diseases/ or bronchiectasis/
3	respiratory tract diseases/ or respiration disorders/ or dyspnea/
4	(lung disease* or pulmonary disease* or cystic fibrosis or interstitial pneumoni* or extrinsic allergic alveolit* or hypersensitivity pneumoniti* or pneumoconios?s or anthracos?s or anthracosilicos?s or asbestos?s or beryllios?s or byssinos?s or beryllium disease* or caplan syndrome or bird fancier* lung or farmer* lung or silo filler* disease or trichosporonos?s or sideros?s or silicos?s or silicotuberculos?s or fibrosing alveolit* or pulmonary fibros?s or fibrocystic pulmonary dysplasia* or hamman-rich disease or hamman-rich syndrome or cryptogenic organizing pneumonia* or pulmonary sarcoidos?s or bronchiolitis obliterans or constrictive bronchiolit* or exudative bronchiolit* or chronic bronchitis or emphysema* or pulmonary inflammatory pseudotumo?r or pulmonary plasma cell granuloma* or bronchial disease* or bronchiectas?s).mp.
5	((chronic or severe* or unrelenting or obstructive) adj asthma*).mp.
6	(chronic* obstruct* adj3 (lung* or airway* or pulmon* or bronch* or alveolit* or respiratory)).mp.
7	(bronchopulmonary disease* or pneumopath* or pulmonary disorder* or acute pneumonitis or chronic fibrous pneumonia* or fibroid phthisis or interstitial cell pneumonia or interstitial plasma cell pneumonia or interstitial pneumocystic pneumonia or phthisis fibroidea or pneumonia interstitialis or interstitial fibros?s or lung fibros?s or interstitial fibros?s or alveolar fibros?s or respiratory granulomatos?s or pulmonary granulomatos?s or lung conios?s or pneumoconiotic lesion or pneumokonios?s or pneumono?onios?s).mp.
8	(airway obstructive disease* or obstructive airway disorder* or obstructive respiratory disease* or obstructive respiratory disorder* or pneumatosis pulmonum or interstitial syndrome).mp.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	exp narcotics/ or exp analgesics, opioid/ or exp Analgesics/ or exp morphine derivatives/ or morphine/ or fentanyl/ or alfentanil/ or sufentanil/ or exp remifentanil/ or exp sufentanil/ or exp hydromorphone/ or exp oxycodone/ or exp pentazocine/ or exp methadone/ or exp codeine/ or exp dextromoramide/ or exp fentanyl citrate/ or exp diamorphine/ or exp dihydrocodeine/ or exp dextropropoxyphene/ or exp meptazinol/ or exp nalbuphine/ or exp meptazinol/ or exp dipipanone/ or exp pethidine/ or exp tramadol/ or exp buprenorphine/
11	(opiate* or opioid* or analgesic* or morphine or narcotic* or fentanyl or alfentanil or remifentanil or sufentanil or hydromorphone or oxycodone or pentazocine or methadone or codeine or dextromoramide or diamorphine or dihydrocodeine or dextropropoxyphene or meptazinol or nalbuphine or meptazinol or dipipanone or pethidine or tramadol or buprenorphine).mp.
12	(opiat or analgetic or morfin? or morphia or morphin* or fentamyl or fentanil or duragesic or sufentanyl or sulfentanil or sulfentanyl or alfentanyl or remifentanyl or dihydromorphinone or dihydromorphone or hydromorph contin or hydromorphinone or hydromorphon? or dihydrohydroxycodeinone or dihydrohydroxydodeinone or dihydrone or oxicodona or oxicone or

	oxicontin or oxikodon or oxycodeinonhydrochloride or oxycodon or pentacozine or pentazocin? or methadon or codein or methyl morfine or methylmorfine or methylmorphine or dextro moramide or dextromoramine or actiq or fenodid or fentabbott or acetomorphine or diacephine or diacetyl morphine or diacetylmorphine or heroin? or codhydrin? or dihydroneopine or hydrocodin? or propoxyphen? or propoxyphenhydrochloride or propoxyphine or nalbufin? or piperidyl amidone or meperidin? or meperidol or methylphenylcarbethoxypiperidine or pethedine or tramadolhydrochlorid or buprenorfin or buprenorphin).mp.
13	10 or 11 or 12
14	9 and 13

6. PICO question 6: Should breathing techniques be used to reduce symptoms in people with serious illness related to lung disease?

6.1. Identification of studies – PRISMA diagram



6.2. Inclusion criteria

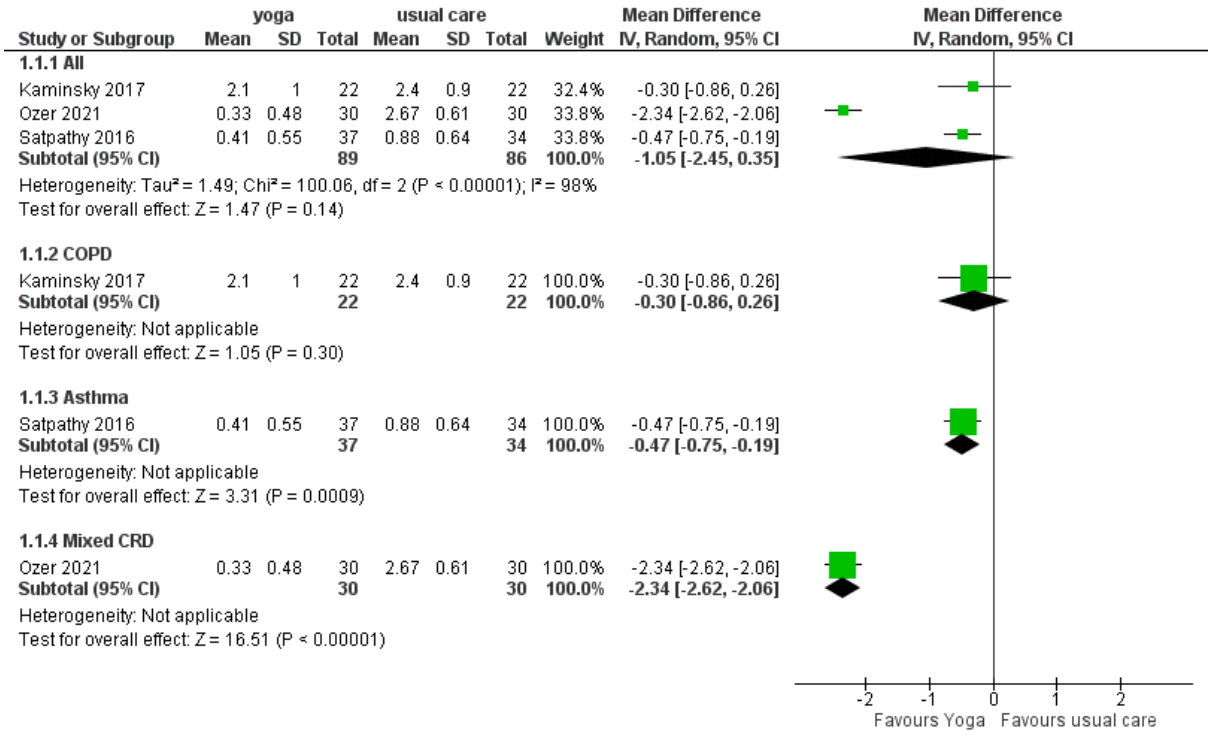
- Randomised controlled trials
- Participants were adults aged 18 years or older.
- Participants had serious illness related to lung disease (defined as a condition that carries a high risk of mortality, negatively impacts quality of life and daily function, and/or is burdensome in symptoms, treatments, or caregiver stress). For mixed studies (e.g. studies including those with malignant disease) we asked the authors for data related to the participants with non-malignant disease only. If separate data were unable to be obtained then we included studies only if ≥80% of participants had non-malignant disease.
- Intervention: Any type of breathing exercises, either supervised or unsupervised. Breathing exercises were defined as any technique that aims to alter the respiratory pattern. This could be achieved with or without external devices, and either during exercise or at rest. Examples include pursed lip breathing, deep breathing, ventilation-feedback training and yoga breathing. As responses to different types of breathing exercises may vary, these interventions were assessed separately. Trials where breathing exercises were combined with another training intervention (e.g. relaxation) were included provided 50% or more of the training consisted of breathing exercises.
- Comparison: no intervention/usual care; sham/placebo intervention; a standard intervention common to both groups (e.g. pulmonary rehabilitation)

6.3. Exclusion criteria

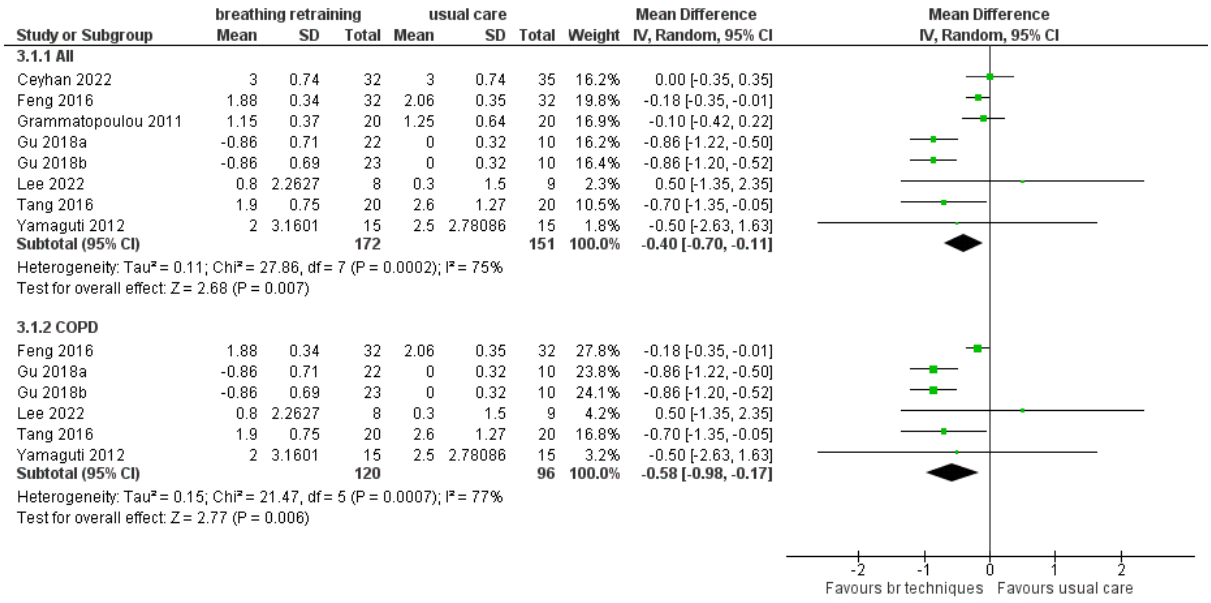
- Crossover trials, as the intervention includes behavioural components where carryover of intervention effects to the second period may occur
- Participants with malignant disease
- Trials of respiratory muscle training, as these interventions aim to improve respiratory muscle strength, rather than alter the respiratory pattern.

6.4. Forest plots

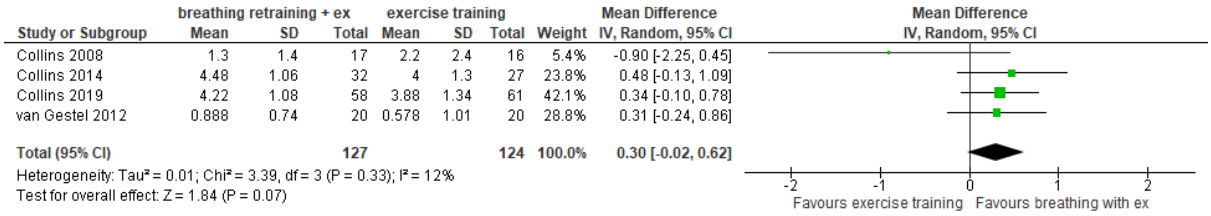
Critical Outcome – Breathlessness



Yoga vs usual care – modified Medical Research Council scale

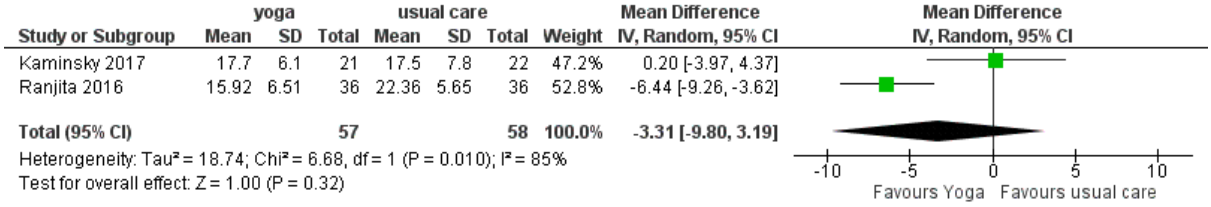


Breathing techniques vs usual care – modified Medical Research Council Scale

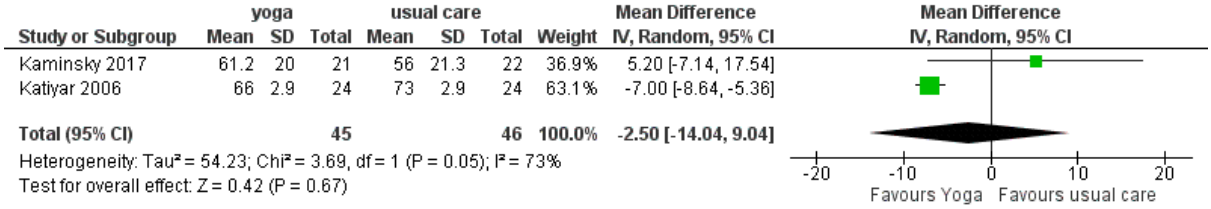


Breathing exercises added to exercise training vs exercise training alone – Chronic Respiratory Questionnaire dyspnoea domain

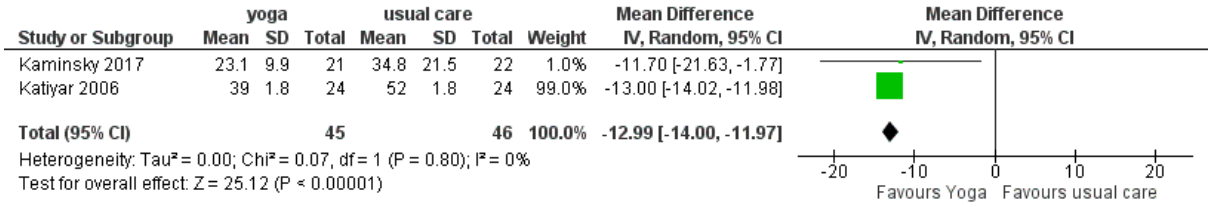
Important outcome – Health-related quality of life



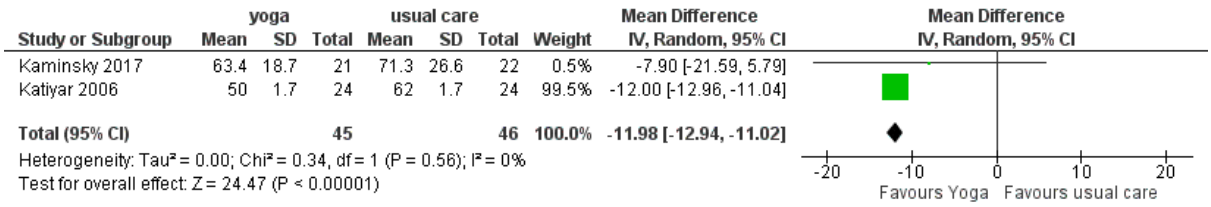
Yoga vs usual care – COPD assessment test



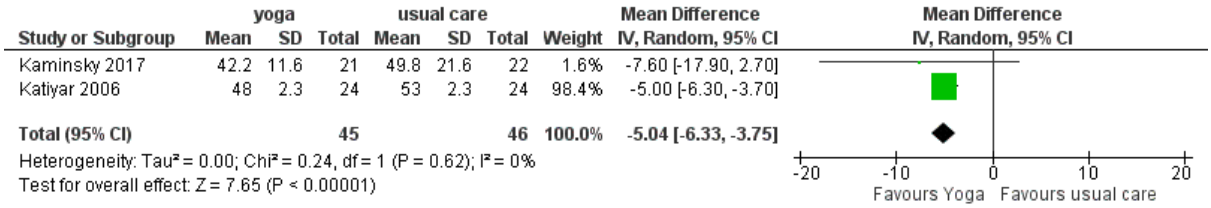
Yoga vs usual care – St George Respiratory Questionnaire symptoms domain



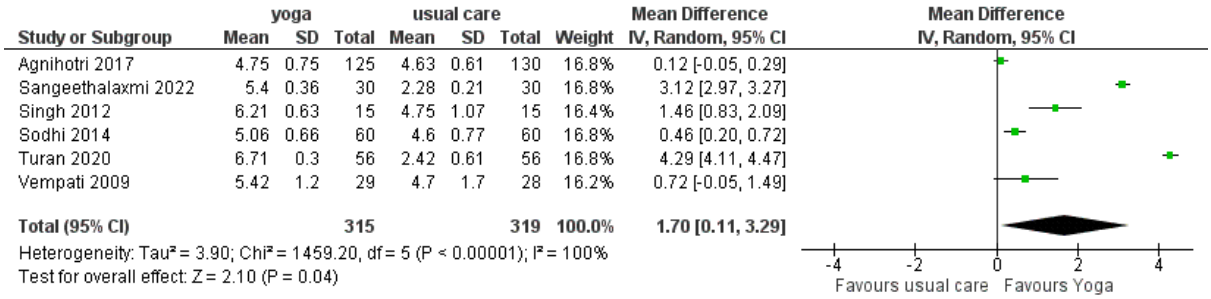
Yoga vs usual care – St George Respiratory Questionnaire impact domain



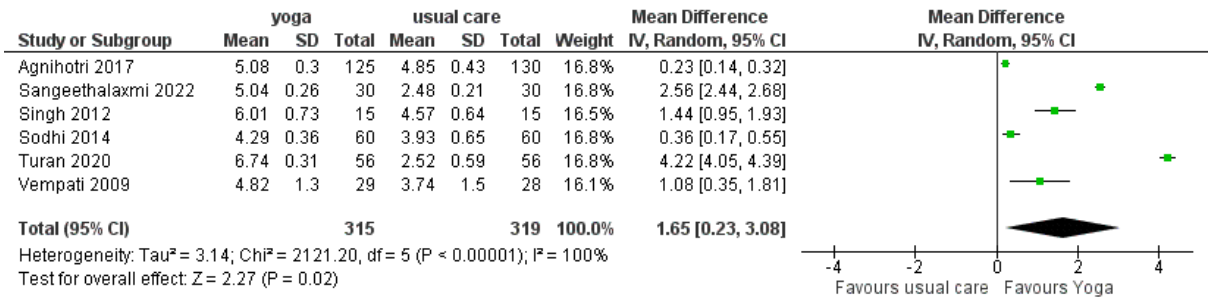
Yoga vs usual care – St George Respiratory Questionnaire activities domain



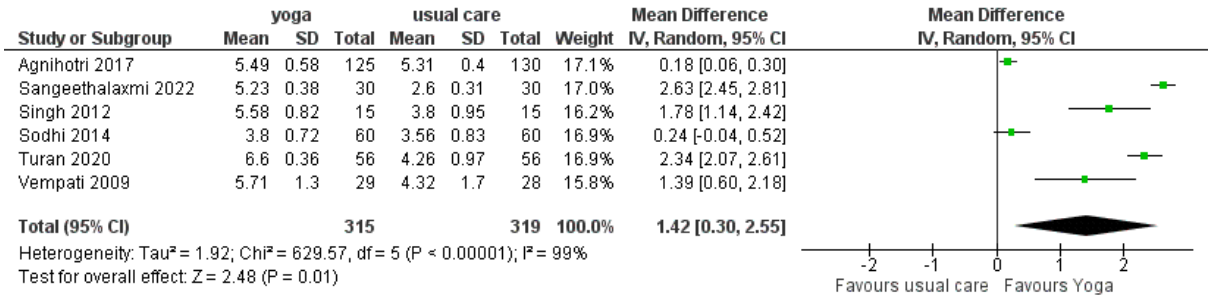
Yoga vs usual care – St George Respiratory Questionnaire total score



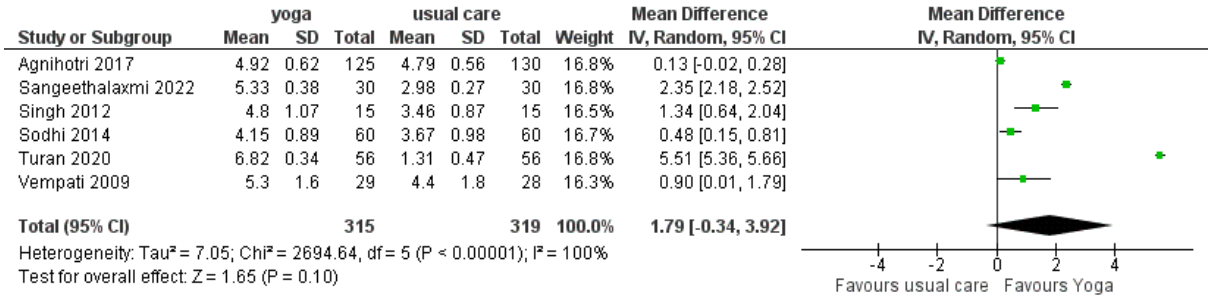
Yoga vs usual care – Asthma Quality of Life Questionnaire symptoms domain



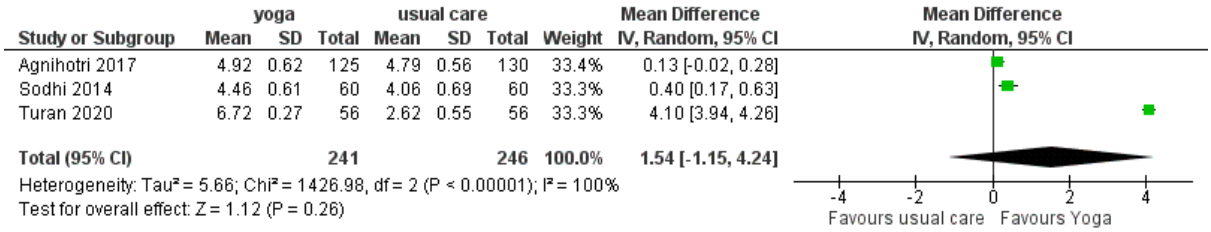
Yoga vs usual care – Asthma Quality of Life Questionnaire activities domain



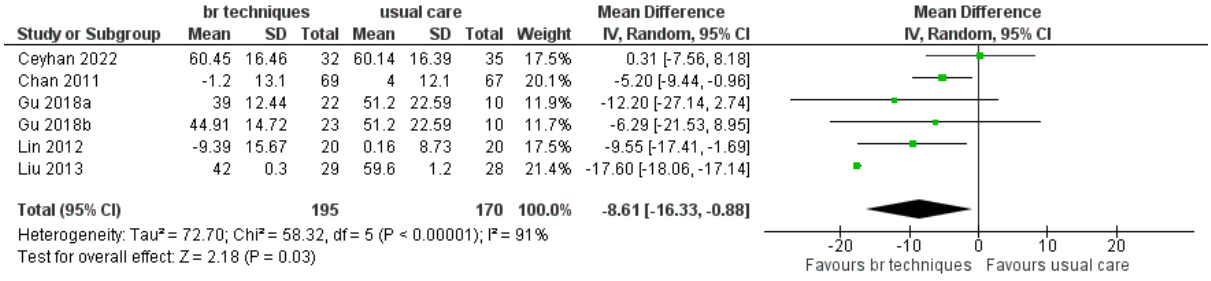
Yoga vs usual care – Asthma Quality of Life Questionnaire emotion domain



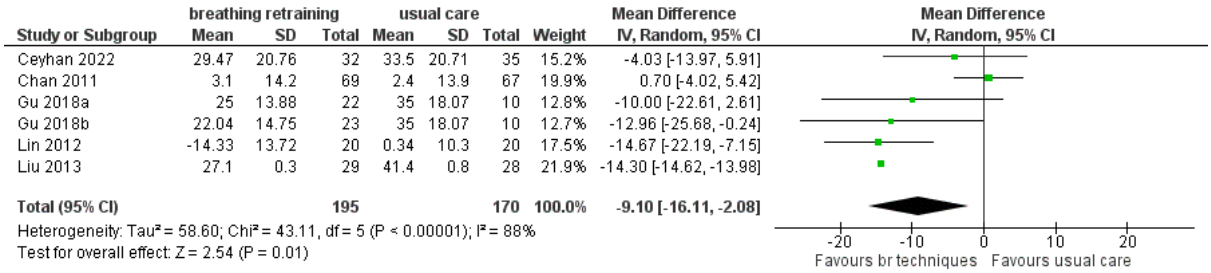
Yoga vs usual care – Asthma Quality of Life Questionnaire environmental stimuli domain



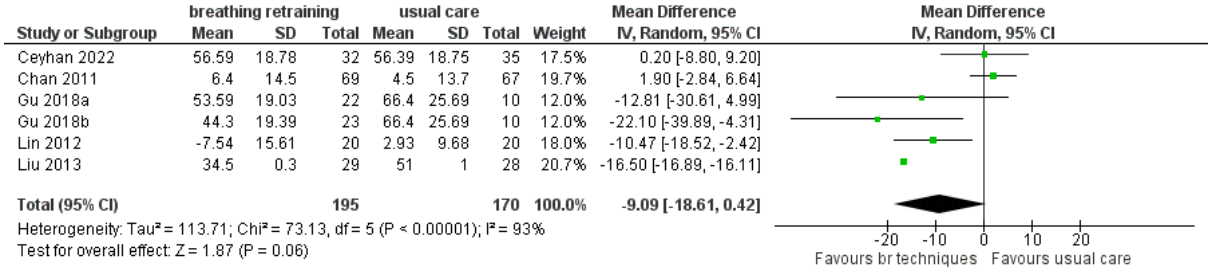
Yoga vs usual care – Asthma Quality of Life Questionnaire total score



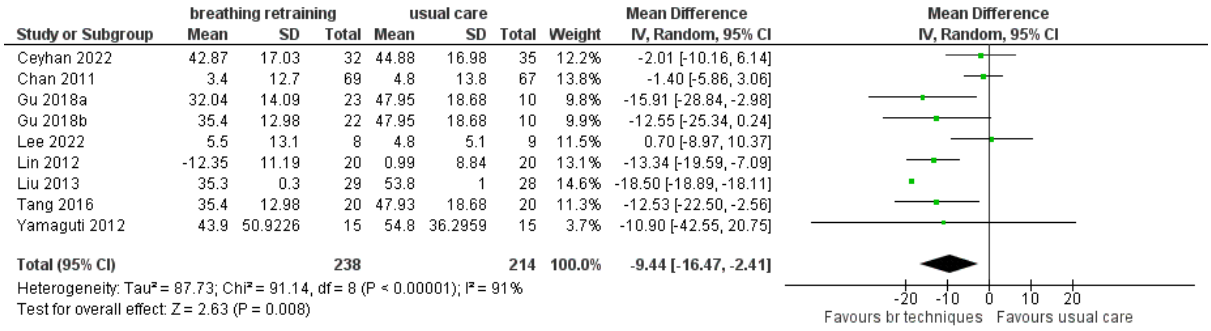
Breathing techniques vs usual care – St George Respiratory Questionnaire symptoms domain



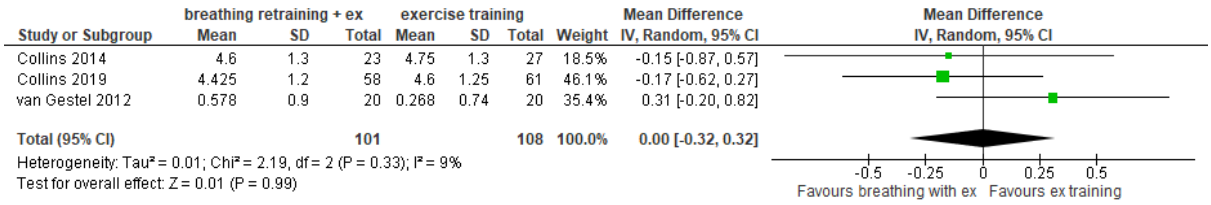
Breathing techniques vs usual care – St George Respiratory Questionnaire impact domain



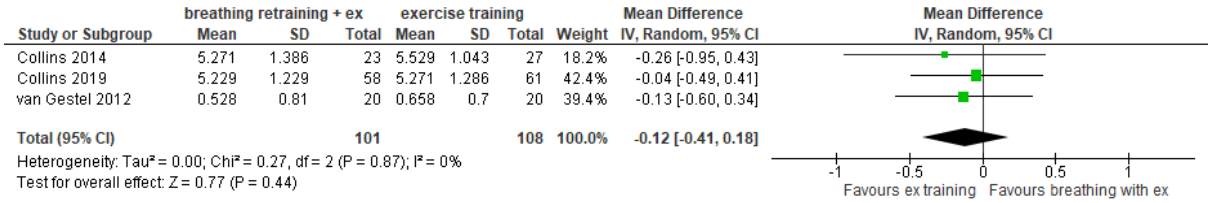
Breathing techniques vs usual care – St George Respiratory Questionnaire activities domain



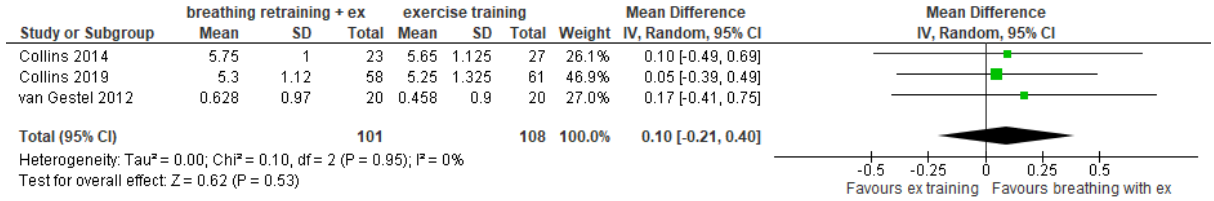
Breathing techniques vs usual care – St George Respiratory Questionnaire total score



Breathing techniques added to exercise training vs exercise training alone – Chronic Respiratory Disease questionnaire fatigue domain

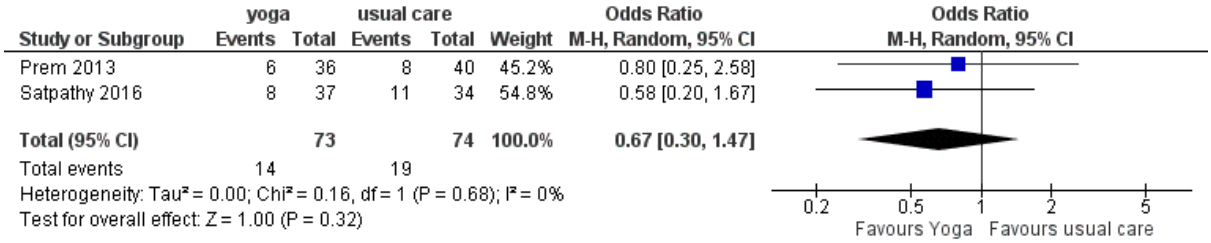


Breathing techniques added to exercise training vs exercise training alone – Chronic Respiratory Disease questionnaire emotional function domain

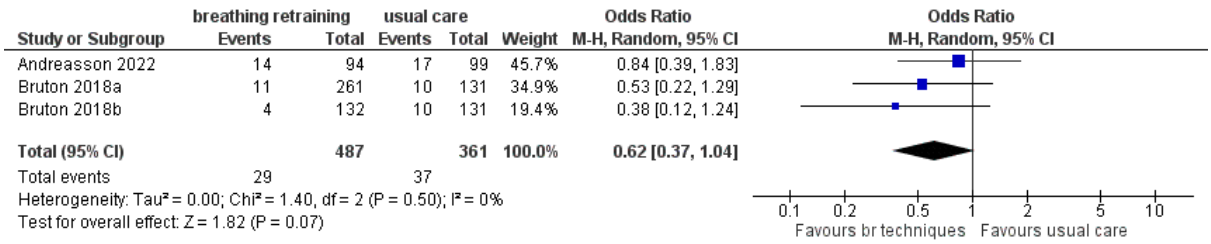


Breathing techniques added to exercise training vs exercise training alone – Chronic Respiratory Disease questionnaire mastery domain

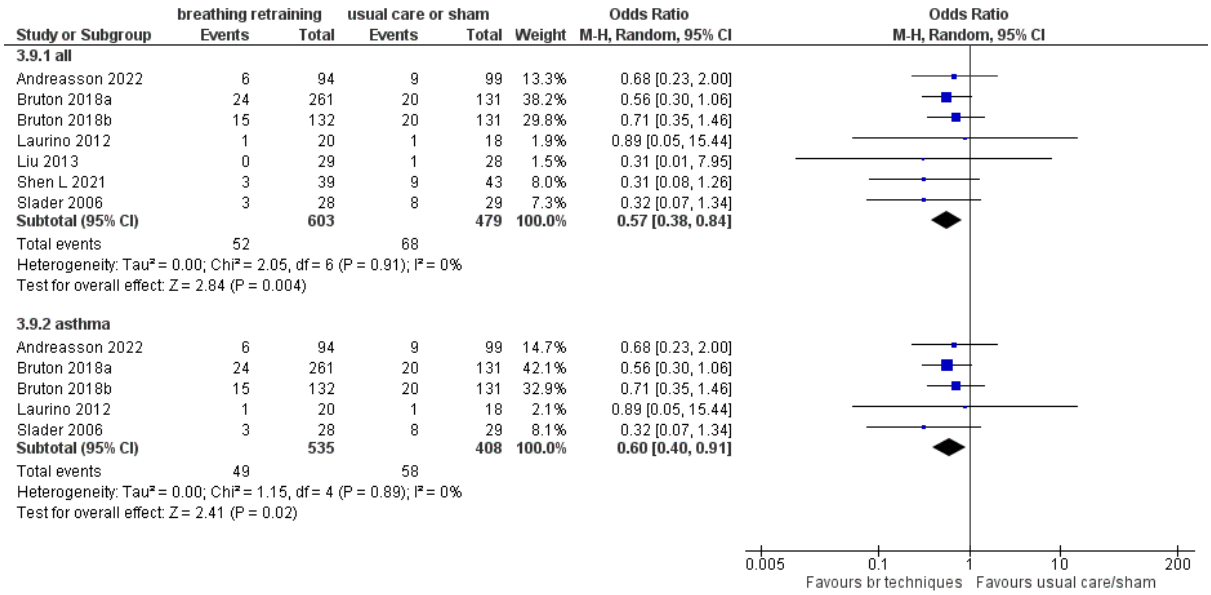
Important outcome – adverse events



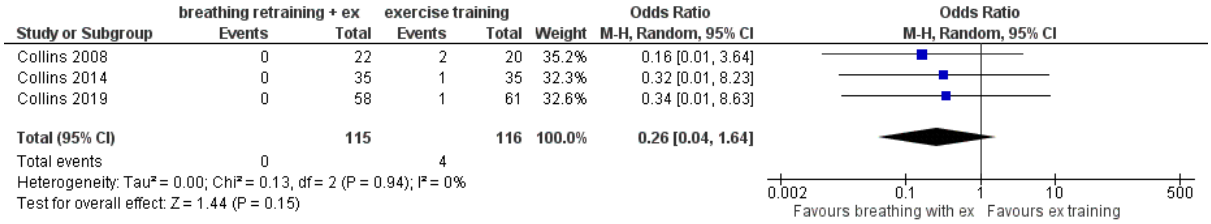
Yoga vs usual care – exacerbations



Breathing techniques vs usual care – serious adverse events



Breathing techniques vs usual care – participants with exacerbations



Breathing techniques added to exercise training vs exercise training alone – participants with exacerbations

6.5. GRADE Evidence table

PICO6: Should breathing techniques be used to reduce symptoms in people with serious respiratory illness?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Yoga	Usual care	Relative (95% CI)	Absolute (95% CI)		
INTERVENTION: Yoga												
CRITICAL OUTCOME: Breathlessness												
Modified Medical Research Council Scale												
3	RCT	Serious[a]	Serious[b]	Serious[c]	Serious[d]	Not serious	89	86		-1.05 (-2.45 to 0.35)	⨁◯◯◯ VERY LOW	CRITICAL
IMPORTANT OUTCOME: Health-related quality of life												
COPD Assessment Test												
2	RCT	Serious[a]	Serious[b]	Serious[c]	Serious[d]	Not serious	57	58		-3.31 (-9.80 to 3.19)	⨁◯◯◯ VERY LOW	IMPORTANT
St George's Respiratory Questionnaire Symptoms												
2	RCT	Serious[a]	Serious[b]	Serious[c]	Serious[d]	Not serious	45	46		-2.50 (-14.04 to 9.04)	⨁◯◯◯ VERY LOW	IMPORTANT

St George's Respiratory Questionnaire Impact												
2	RCT	Serious[a]	Not serious	Serious[c]	Not serious	Not serious	45	46		-12.99 (-14.00 to -11.97)	⊕⊕◯◯ LOW	IMPORTANT
St George's Respiratory Questionnaire Activities												
2	RCT	Serious[a]	Not serious	Serious[c]	Not serious	Not serious	45	46		-11.98 (-12.94 to -11.02)	⊕⊕◯◯ LOW	IMPORTANT
St George's Respiratory Questionnaire Total												
2	RCT	Serious[a]	Not serious	Serious[c]	Not serious	Not serious	45	46		-5.04 (-6.33 to -3.75)	⊕⊕◯◯ LOW	IMPORTANT
AQLQ symptoms												
6	RCT	Serious[a]	Serious[b]	Serious[c]	Not serious	Not serious	315	319		1.70 (0.11 to 3.29)	⊕◯◯◯ VERY LOW	IMPORTANT
AQLQ activities												
6	RCT	Serious[a]	Serious[b]	Serious[c]	Not serious	Not serious	315	319		1.65 (0.23 to 3.08)	⊕◯◯◯ VERY LOW	IMPORTANT
AQLQ emotion												
6	RCT	Serious[a]	Serious[b]	Serious[c]	Serious[e]	Not serious	315	319		1.42 (0.30 to 2.55**)**	⊕◯◯◯ VERY LOW	IMPORTANT
AQLQ environmental stimuli												
6	RCT	Serious[a]	Serious[b]	Serious[c]	Serious[e]	Not serious	315	319		1.79 (-0.34 to -3.92	⊕◯◯◯ VERY LOW	IMPORTANT

IMPORTANT OUTCOME: Adverse events												
Exacerbations during the intervention period (3-4 months)												
2	RCT	Serious[a]	Not serious	Serious[c]	Serious[f]		73	74		OR 0.67 (0.30 to 1.47)	⊕◯◯◯ VERY LOW	IMPORTANT
Adverse events related to the intervention												
7	RCT	Serious[a]	Not serious	Serious[c]	Not serious		233	240		No studies reported adverse events related to the intervention.	⊕⊕◯◯ LOW	IMPORTANT

CI: confidence interval; **OR:** odds ratio

Explanations:

a. Majority of studies at high risk for detection bias (lack of assessor blinding) and reporting bias (no prospectively registered protocol).

b. Significant heterogeneity identified (I^2 >70%), with variable effect estimates across studies and poor overlap of confidence intervals

c. All studies were in people with COPD or asthma

d. The confidence interval for the pooled estimate of the effect of yoga includes both clinically important benefit and no benefit, based on the minimal important difference for the scale.

e. The confidence interval for the pooled estimate of the effect of yoga on health-related quality of life includes both clinically important benefit and no benefit

f. The confidence interval for the pooled estimate of odds of exacerbation includes both clinically important reduction and clinically important increase.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Breathing exercises	Usual care	Relative (95% CI)	Absolute (95% CI)		
INTERVENTION: Breathing Exercises (Pursed lip breathing and / or diaphragmatic breathing)												
CRITICAL OUTCOME: Breathlessness												
Modified Medical Research Council Scale												
8	RCT	Serious[a]	Not serious	Serious[b]	Not serious	Not serious	172	151		-0.40 (-0.70 to -0.11)	⊕⊕◯◯ LOW	CRITICAL
IMPORTANT OUTCOME: Health-related quality of life												
St George's Respiratory Questionnaire Symptoms												
6	RCT	Serious[a]	Not serious	Serious[b]	Not serious	Not serious	195	170		-8.61 (-16.33 to -0.88)	⊕⊕◯◯ LOW	IMPORTANT
St George's Respiratory Questionnaire Impact												
6	RCT	Serious[a]	Serious[c]	Serious[b]	Serious[d]	Not serious	195	170		-9.10 (-16.11 to -2.08)	⊕◯◯◯ VERY LOW	IMPORTANT
St George's Respiratory Questionnaire Activities												
6	RCT	Serious[a]	Serious[c]	Serious[b]	Serious[d]	Not serious	195	170		--9.09 (-18.61 to 0.42)	⊕◯◯◯ VERY LOW	IMPORTANT

St George's Respiratory Questionnaire Total												
9	RCT	Serious[a]	Serious[c]	Serious[b]	Serious[d]	Not serious	238	214		-9.44 (-16.47 to -2.41)	⊕◯◯◯ VERY LOW	IMPORTANT
IMPORTANT OUTCOME: Adverse events												
Serious adverse events												
3	RCT	Serious[e]	Not serious	Serious[c]	Not serious	Not serious	487	361		OR 0.62 (0.37 to 1.04)	⊕⊕◯◯ LOW	IMPORTANT
Exacerbations during the intervention period												
7	RCT	Serious[a]	Not serious	Serious[c]	Not serious	Not serious	603	479		0.57 (0.38 to 0.84)	⊕⊕◯◯ LOW	IMPORTANT
Adverse events related to the intervention												
11	RCT	Serious[a]	Not serious	Not serious	Not serious		777	656		No studies reported adverse events related to the intervention.	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: confidence interval; **OR:** odds ratio

Explanations:

a. Majority of studies at high risk for detection bias (lack of assessor blinding) and reporting bias (no prospectively registered protocol)

b. All studies were in people with COPD or asthma

c. Significant heterogeneity identified (I^2 >70%), with variable effect estimates across studies

d. The confidence interval for the pooled estimate of the effect of breathing retraining includes both clinically important benefit and no benefit

e. Majority of studies at high risk for detection bias (lack of assessor blinding)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Breathing exercises	Control	Relative (95% CI)	Absolute (95% CI)		
INTERVENTION: Breathing exercises added to pulmonary rehabilitation vs pulmonary rehabilitation alone												
CRITICAL OUTCOME: Breathlessness												
Chronic Respiratory Questionnaire Dyspnoea domain												
4	RCT	Serious[a]	Not serious	Serious[b]	Serious[c]	Not serious	127	124		0.30 (-0.02 to 0.62)	⨁◯◯◯ VERY LOW	CRITICAL
IMPORTANT OUTCOME: Health-related quality of life												
Chronic Respiratory Questionnaire Fatigue domain												
3	RCT	Serious[a]	Not serious	Serious[b]	Not serious	Not serious	101	108		0.00 (-0.32 to 0.32)	⨁⨁◯◯ LOW	IMPORTANT
Chronic Respiratory Questionnaire Emotional Function domain												
3	RCT	Serious[a]	Not serious	Serious[b]	Not serious	Not serious	101	108		-0.12 (-0.41 to 0.18)	⨁⨁◯◯ LOW	IMPORTANT
Chronic Respiratory Questionnaire Mastery domain												
3	RCT	Serious[a]	Not serious	Serious[b]	Not serious	Not serious	101	108		0.10 (-0.21 to 0.40)	⨁⨁◯◯ LOW	IMPORTANT

IMPORTANT OUTCOME: Adverse events												
Number of participants with exacerbations during the training period												
4	RCT	Serious[a]	Not serious	Serious[b]	Not serious	Not serious	130	130		0.35 (0.08 to 1.57)	⊕⊕◯◯ LOW	IMPORTANT

CI: confidence interval; **OR:** odds ratio

Explanations:

a. Majority of studies at high risk for detection bias (lack of assessor blinding) and reporting bias (no prospectively registered protocol)

b. All studies were in people with COPD or asthma

c. The confidence interval for the pooled estimate of the effect of breathing retraining includes both clinically important benefit and no benefit

6.6. Evidence to Decision Table

QUESTION

PICO6: Should breathing techniques be used to reduce symptoms in people with serious respiratory illness?	
POPULATION:	Adults with serious respiratory illness
INTERVENTION:	Breathing exercises
COMPARISON:	No breathing exercises or sham/placebo intervention
MAIN OUTCOMES:	Critical: Breathlessness, using relevant and validated tool. This included measures at rest or during exercise, but exercise measures obtained before and after an intervention must be obtained at iso-workload. Important: Health related quality of life, using any validated tool; Adverse events, defined according to the investigators' definition.

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Patients with serious respiratory illness commonly experience high symptom burden, including chronic breathlessness (1), which contributes to reduced health-related quality of life (2). Breathlessness is frequently ranked by patients as their worst symptom (3) and it is a major contributor to unscheduled healthcare usage (4, 5).	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Of 73 included studies, the populations included people with COPD (n=37), asthma (n=34), interstitial lung disease (n=1) and mixed COPD and asthma (n=1). The most common breathing techniques used were Yoga (often Pranayama), training in breathing exercises (pursed lip breathing and/or diaphragmatic breathing) and addition of breathing exercises to pulmonary rehabilitation (often timing of breathing with exercise). Given the differences in approach, these breathing techniques were evaluated separately. Many studies did not provide details of the intervention, or used a unique intervention that could not be combined with others or replicated in practice. **Critical outcome: Breathlessness**	Studies that could not be combined in meta-analysis showed a similar pattern of findings, with inconsistent improvements in breathlessness and consistent improvements in health-related quality of life.

	• Yoga (3 RCTs, 1 in COPD, 1 in asthma, 1 mixed COPD/asthma) reduced modified Medical Research Council score (mMRC) at the end of the intervention period (2-4 months) compared to usual care, with the mean difference exceeding the minimal important difference (MID, -1 point). However the confidence interval included both clinically significant benefit and no benefit. • Breathing exercises (8 RCTs, 6 in COPD, 2 in asthma) reduced mMRC at the end of the intervention period (4-8 weeks) compared to usual care. However the lower end of the confidence interval did not include the MID (-1 point) and the clinical significance is unclear. • Addition of Breathing Techniques to pulmonary rehabilitation (4 RCTs, all COPD) did not result in statistically significant improvement in Chronic Respiratory Questionnaire (CRQ) Dyspnoea domain at the end of the intervention period (4-12 weeks). However, the confidence interval included the MID (0.5 points) and a benefit cannot be excluded. **Important outcome: Health-related quality of life (HRQoL)** • Yoga (8 RCTs, 2 in COPD, 6 in asthma) resulted in statistically and clinically significant improvements in many domains of HRQoL at the end of the intervention period (6 weeks to 6 months) compared to usual care. HRQoL was measured with the Asthma Quality of Life Questionnaire (AQLQ, improvements in symptoms, activities and emotions domains, lower end of the confidence interval did not exceed the MID of 0.5 points) and St George's Respiratory Questionnaire (improvements in impact, activities and total score, lower end of the confidence interval exceeded MID of 4 points). • Breathing Techniques (6 RCTs, all COPD) improved HRQoL measured using SGRQ at the end of the intervention period (4-12 weeks) compared to usual care, and was statistically significant for symptoms and impact domains, and total score. The mean effect for all domains exceeded the MID (4 points). • Addition of Breathing Techniques to pulmonary rehabilitation (3 RCTs, all COPD) did not result in statistically or clinically significant improvements in HRQoL measured using the CRQ (fatigue, emotion, mastery domains) at the end of the intervention period (4 – 12 weeks) compared to pulmonary rehabilitation alone. Studies that could not be combined in meta-analysis showed a similar pattern of findings.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	• Yoga – 7 RCTs (4 asthma, 3 COPD) reported that there were no adverse events related to the intervention. In 2 RCTs (both asthma) Yoga did not increase the number of participants experiencing exacerbations during the intervention period (3-4 months) with results favouring yoga. • Breathing Techniques – 3 RCTs (all asthma) reported fewer serious adverse events in those undertaking breathing techniques compared to usual care. There were fewer participants who experienced exacerbations during the intervention period (4 – 28 weeks) compared to usual care (7 RCTs, 2 COPD, 5 asthma). • Addition of Breathing Techniques to pulmonary rehabilitation did not increase adverse events during the intervention period (6-12 weeks) compared to pulmonary rehabilitation alone (3 RCTs, all COPD).	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	Based on GRADE assessment, certainty of evidence was very low. Certainty of evidence was affected by detection bias (lack of assessor blinding), reporting bias (few trials were registered prospectively), indirectness (limited data in ILD and no data in pulmonary hypertension; asthma may not represent a serious illness in all participants), imprecision, heterogeneity of interventions in terms of type and duration, and heterogeneity of outcome measures and timepoints of measurement.	No studies included people near the very end of life.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	The critical outcome for this question is breathlessness, which people with serious respiratory illness consistently report as a major distressing symptom (1-3). In people with COPD, breathlessness has been found to be a key determinant of low physical and mental health (2, 3). Similarly, in people with ILD breathlessness has been identified as a major driver of reduced quality of life (4, 5). Fear of exertional breathlessness may result in avoiding exercise, leading to a downward spiral of deconditioning, social isolation with negative physical and emotional consequences (3). There is an immense need to better actively manage acute on chronic and chronic breathlessness and other distressing symptoms in people with a variety of non-malignant chronic respiratory diseases.	There was no important uncertainty or variability in the views of the patient members of the Task Force regarding values.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	The balance of effects probably favours breathing exercises. Although there was no clear effect on our critical outcome of breathlessness, confidence intervals were wide and a benefit cannot be excluded. There were consistent improvements in the important outcome of HRQoL for people who undertook breathing exercises. The likelihood of undesirable effects is low.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○Varies ○ Don't know	There is limited evidence on the costs of delivering breathing exercises One included study (6) reported costs to deliver breathing exercises as part of a health economic analysis (7). Costs for delivering 3 sessions of breathing exercises were £83.45 per patient in the face-to-face physiotherapy breathing retraining group and £2.85 in the DVD breathing retraining group. The face-to-face intervention consisted of three sessions, whilst the DVD intervention was self-paced and did not include direct contact with health professionals. Overall healthcare costs	It is likely that costs vary substantially between countries and health systems (e.g. the cost of a staff member to provide training in breathing exercises).

	tended to be lower in those performing breathing exercises in comparison to usual care (difference in costs of –£83 (95% CI –£187 to £12) for the DVD arm and –£45 (95% CI –£134 to £33) for the physiotherapy arm compared with the usual-care arm. However both usual care and technology have changed since this study was conducted.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	There is only one analysis of costs available, for a RCT of breathing exercises in asthma performed in general practice in the United Kingdom (7). It is possible that costs will vary in other settings, other countries, for other patient groups and for other types of breathing exercises. It is likely that the resources required and the associated costs will be higher for breathing exercises that require specialist equipment or training to deliver (e.g. breathing exercises using biofeedback).	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	A cost effectiveness analysis of breathing exercises in asthma (7) showed that costs were lower in those face-to-face physiotherapy breathing retraining or self-paced DVD breathing retraining compared to those receiving usual care, indicating 'dominance' for both of the interventions compared with usual care. The physiotherapy arm cost £877 less per quality adjusted life year (QALY) than the usual-care arm and the DVD arm cost £3057 less per QALY than the usual-care arm. Reduction in costs was related to fewer hospital admissions and fewer outpatient visits in the breathing retraining groups. The Incremental Cost Effectiveness Ratio (ICER) was –£671 (95% confidence interval –£14,269 to £13,814) for face-to-face physiotherapy breathing retraining and –£2754 (–£17,739 to £12,017) for DVD breathing retraining. The confidence intervals for the ICERs were wide and did not reach statistical significance.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	Breathing exercises are easy to administer, both face-to-face and remotely, and can be delivered in low, middle and high income settings. Breathing exercises could be part of an individualized treatment plan for a wide range of patients. Breathing exercises have a long history of use in many cultures, often as part of Yoga or spiritual practices, which could enhance acceptability and uptake in some cultural groups. However there is no direct evidence of the impact of breathing exercises on health equity.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Data from qualitative studies suggest that breathing exercises are acceptable to people with chronic lung disease. People with COPD and asthma reported experiencing benefits of breathing exercises (yoga, pursed lip breathing, diaphragmatic breathing) that included better control of breathing, increased confidence in managing symptoms, reduction in panic during episodes of breathlessness, better management of stress, and enhanced mastery of disease in daily life (8-11). Breathing exercises were perceived as holistic and unobtrusive (8). One study reported that participants who received face-to-face instruction had more positive experiences with breathing exercises and were more likely to continue to practice them at 12 months when compared to DVD instruction, but overall the experiences were positive in both groups (12).	There was no important uncertainty or variability in the views of the patient members of the Task Force regarding acceptability.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Breathing exercises are within the scope of practice for many health professionals involved in care of people with respiratory disease. Many breathing exercises do not require specialized equipment or long periods of training (e.g. pursed lip breathing or diaphragmatic breathing). It is feasible to deliver breathing exercises in a variety of settings, including remote delivery.	Patients need to be adequately informed and instructed regarding the correct technique.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

We suggest that breathing techniques be used to reduce symptoms in people with serious respiratory illness (conditional recommendation, very low certainty of evidence).

Justification

This recommendation places a high value on consistent improvements in HrQoL for people who undertook breathing techniques, and a lower value on uncertainty regarding the effects of breathing techniques on breathlessness. In qualitative studies, people with COPD and asthma report benefits of breathing techniques (Yoga, pursed lip breathing, diaphragmatic breathing) that include better control of breathing, increased confidence in managing symptoms, reduction in panic during episodes of breathlessness, better management of stress, and enhanced mastery of disease in daily life. Breathing techniques were perceived as holistic and unobtrusive. The likelihood of undesirable effects is very low.

Subgroup considerations

The physiological rationale for some breathing exercises (pursed lip breathing and diaphragmatic breathing) was developed in people with COPD, with the aim of reducing hyperinflation, enhancing respiratory muscle efficiency and reducing breathlessness. Whether this rationale is applicable to those with restrictive lung diseases, and whether the same outcomes can be achieved in this group, is unclear.

Implementation considerations

Breathing techniques are easy to administer, both face-to-face and remotely, and can be delivered in low, middle, and high income settings. Patients need to be adequately instructed regarding correct technique. Breathing techniques are often combined with other interventions in an individualized treatment plan (e.g., positioning to relieve breathlessness). Breathing techniques have a long history of use in many cultures, often as part of Yoga or spiritual practices, which could enhance acceptability and uptake in some cultural groups.

Monitoring and evaluation

The risk of harms is low with breathing techniques, and little monitoring is required. Evaluation should include standardized measures of breathlessness, including measures at isotime where breathing techniques are used during exercise.

Research priorities

Breathing exercises such as pursed lip breathing and diaphragmatic breathing were originally developed for use in obstructive lung disease, and future research should examine whether these techniques are also useful in patients with restrictive lung diseases such as ILD. The efficacy of biofeedback to enhance breathing techniques remains to be fully explored. The cost-effectiveness of training patients to undertake breathing techniques, including models that involve individual, group-based or remote delivery, should be examined.

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6.7. List of included studies – PICO6

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6.8. Search strategies

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions

#	Searches
1	lung diseases/ or "cystic adenomatoid malformation of lung, congenital"/ or cystic fibrosis/ or hepatopulmonary syndrome/ or lung abscess/ or lung diseases, interstitial/ or alveolitis, extrinsic allergic/ or bird fancier's lung/ or farmer's lung/ or silo filler's disease/ or trichosporonosis/ or anti-glomerular basement membrane disease/ or histiocytosis, langerhans-cell/ or eosinophilic granuloma/ or pneumoconiosis/ or anthracosis/ or anthracosilicosis/ or asbestosis/ or berylliosis/ or byssinosis/ or caplan syndrome/ or siderosis/ or silicosis/ or silicotuberculosis/ or pulmonary fibrosis/ or idiopathic pulmonary fibrosis/ or hamman-rich syndrome/ or idiopathic interstitial pneumonias/ or cryptogenic organizing pneumonia/ or sarcoidosis, pulmonary/ or hypertension, pulmonary/ or familial primary pulmonary hypertension/ or pulmonary arterial hypertension/ or Pulmonary Heart Disease/ or lung diseases, obstructive/ or asthma/ or asthma-chronic obstructive pulmonary disease overlap syndrome/ or bronchiolitis obliterans/ or cryptogenic organizing pneumonia/ or bronchitis, chronic/ or pulmonary disease, chronic obstructive/ or pulmonary emphysema/ or plasma cell granuloma, pulmonary/ or bronchial diseases/ or bronchiectasis/ or respiratory tract diseases/ or respiration disorders/ or dyspnea/
2	(lung disease* or pulmonary disease* or cystic fibrosis or interstitial pneumoni* or extrinsic allergic alveolit* or hypersensitivity pneumoniti* or pneumoconios?s or anthracos?s or anthracosilicos?s or asbestos?s or beryllios?s or byssinos?s or beryllium disease* or caplan syndrome or bird fancier* lung or farmer* lung or silo filler* disease or trichosporonos?s or sideros?s or silicos?s or silicotuberculos?s or fibrosing alveolit* or pulmonary fibros?s or fibrocystic pulmonary dysplasia* or hamman-rich disease or hamman-rich syndrome or cryptogenic organizing pneumonia* or pulmonary sarcoidos?s or bronchiolitis obliterans or constrictive bronchiolit* or exudative bronchiolit* or chronic bronchitis or emphysema* or pulmonary inflammatory pseudotumo?r or pulmonary plasma cell granuloma* or bronchial disease* or bronchiectas?s).mp.
3	(((chronic or severe* or unrelenting or obstructive) adj asthma*) or (chronic* obstruct* adj3 (lung* or airway* or pulmon* or bronch* or alveolit* or respiratory))).mp.
4	(bronchopulmonary disease* or lung granulomatos?s or pneumopath* or pulmonary disorder* or acute pneumonitis or chronic fibrous pneumonia* or fibroid phthisis or interstitial cell pneumonia or interstitial plasma cell pneumonia or interstitial pneumocystic pneumonia or phthisis fibroidea or pneumonia interstitialis or interstitial fibros?s or lung fibros?s or interstitial fibros?s or alveolar fibros?s or respiratory granulomatos?s or pulmonary granulomatos?s or lung granulomatos?s or lung conios?s or pneumoconiotic lesion or pneumokonios?s or pneumono?onios?s or (airway obstructive disease* or obstructive airway disorder* or obstructive respiratory disease* or obstructive respiratory disorder* or pneumatosis pulmonum or interstitial syndrome)).mp.
5	(((lung or pulmonary) adj (arter* hypertens* or hypertens* or fixed hypertens* or capillary hemangiomatosis or veno-occlusive or venoocclusive or parenchyma* disease*)) or (corpulmonale or cor pulmonale or pulmonary cardiac disease* or pulmonary vascular obstructive disease* or obstructive pulmonary vascular disease*)).mp.
6	1 or 2 or 3 or 4 or 5
7	breathing exercises/ or qigong/
8	(Buteyko or Pranayam* or yoga* or papworth technique or papworth method* or breathing gymnastics or qigong or "ch'i kung" or "qi gong" or breathwork or breath work or holotropic breathing).mp.
9	(breath* adj3 (exercise* or train* or educat* or retrain* or reeducat* or technique*)).mp.
10	(breath* adj3 (coaching or guidance or instruction* or teach* or taught or tutor* or lesson* or learn* or upskill* or reskill* or workshop* or work-shop* or course* or class* or seminar* or drills)).mp.
11	(respirat* adj (exercise* or training or educat* or retrain* or reeducat* or technique* or coaching or guidance or instruction* or teach* or tutor* or lesson* or reskill* or workshop* or work-shop* or drills)).mp.
12	((pursed lip* or diaphragmatic or yogic or deep or slow or relaxation or relaxed) adj (breathing or respiration)).mp.

13	(Breathing control or respiration control or breathing man?uvers or breathing man?uvres).mp.
14	(control* adj3 breath* adj5 (coaching or coached or educat* or guidance or instruction* or practi#e* or practi#ing or teach* or taught or tutor* or lesson* or learn* or upskill* or reskill* or workshop* or work-shop* or course* or class* or seminar* or drills)).mp.
15	((breath* or respiratory) adj5 (physiotherap* or physical therap* or chest physiotherap* or chest physical therap*)).mp.
16	((breath* adj2 pattern) and (computeri#ed feedback or biofeedback)).mp.
17	(Ventilat* feedback or Ventilat* biofeedback or Ventilat* feed-back or Ventilat* bio-feedback).mp.
18	((breath* adj2 pattern) and (computeri#ed feedback or biofeedback or bio feed back or feedback)).mp.
19	or/7-18
20	6 and 19
21	(dyspn?e* or "short* of breath" or "urge* to breathe*" or breathless* or suffocat* or ("need for air" or "gasp* for air" or "gasp* to breathe" or "pant* for air") or (unsatisf* inspiration or inspiratory difficult* or expiratory difficult*)).mp.
22	((labo?red or difficult*) adj3 breath*).mp.
23	(breath* adj1 (distress* or discomfort* or dysfunction*)).mp.
24	(air adj3 (hunger or starv*)).mp.
25	or/21-24
26	19 and 25
27	20 or 26
28	(randomized controlled trial or controlled clinical trial).pt. or (randomi?ed or placebo).ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.
29	((cross over or crossover) adj (clinical study or clinical trial or design or method or study or trial or studies)).mp.
30	28 or 29
31	27 and 30

Database(s): Embase

#	Searches
1	lung disease/ or chronic lung disease/ or interstitial lung disease/ or interstitial syndrome/ or lung emphysema/ or lung fibrosis/ or lung sarcoidosis/ or obstructive lung disease/ or fibrosing alveolitis/ or interstitial pneumonia/ or pneumoconiosis/ or asthma/ or chronic obstructive lung disease/ or severe asthma/ or asthmatic state/ or severe persistent asthma/ or obstructive airway disease/ or occupational lung disease/ or anthracosis/ or asbestosis/ or berylliosis/ or bird breeder lung/ or byssinosis/ or farmer lung/ or occupational asthma/ or pigeon breeder lung/ or pneumoconiosis/ or silicosis/ or bronchus disease/ or bronchiectasis/ or lung granuloma/ or respiratory tract disease/ or dyspnea/
2	(lung disease* or pulmonary disease* or cystic fibrosis or interstitial pneumoni* or extrinsic allergic alveolit* or hypersensitivity pneumoniti* or pneumoconios?s or anthracos?s or anthracosilicos?s or asbestos?s or beryllios?s or byssinos?s or beryllium disease* or caplan syndrome or bird fancier* lung or farmer* lung or silo filler* disease or trichosporonos?s or sideros?s or silicos?s or silicotuberculos?s or fibrosing alveolit* or pulmonary fibros?s or fibrocystic pulmonary dysplasia* or hamman-rich disease or hamman-rich syndrome or cryptogenic organizing pneumonia* or pulmonary sarcoidos?s or bronchiolitis obliterans or constrictive bronchiolit* or exudative bronchiolit* or chronic bronchitis or emphysema* or pulmonary inflammatory pseudotumo?r or pulmonary plasma cell granuloma* or bronchial disease* or bronchiectas?s).mp.
3	(((chronic or severe* or unrelenting or obstructive) adj asthma*) or (chronic* obstruct* adj3 (lung* or airway* or pulmon* or bronch* or alveolit* or respiratory))).mp.
4	(bronchopulmonary disease* or lung granulomatos?s or pneumopath* or pulmonary disorder* or acute pneumonitis or chronic fibrous pneumonia* or fibroid phthisis or interstitial cell pneumonia or interstitial plasma cell pneumonia or interstitial pneumocystic pneumonia or phthisis fibroidea or pneumonia interstitialis or interstitial fibros?s or lung fibros?s or interstitial fibros?s or alveolar

	fibros?s or respiratory granulomatos?s or pulmonary granulomatos?s or lung granulomatos?s or lung conios?s or pneumoconiotic lesion or pneumokonios?s or pneumono?onios?s or (airway obstructive disease* or obstructive airway disorder* or obstructive respiratory disease* or obstructive respiratory disorder* or pneumatosis pulmonum or interstitial syndrome)).mp.
5	(((lung or pulmonary) adj (arter* hypertens* or hypertens* or fixed hypertens* or capillary hemangiomatosis or veno-occlusive or venoocclusive or parenchyma* disease*)) or (corpulmonale or cor pulmonale or pulmonary cardiac disease* or pulmonary vascular obstructive disease* or obstructive pulmonary vascular disease*)).mp.
6	1 or 2 or 3 or 4 or 5
7	breathing exercise/ or breathwork/ or buteyko breathing/ or pranayama/ or qigong/
8	(Buteyko or Pranayam* or yoga* or papworth technique or papworth method* or breathing gymnastics or qigong or "ch'i kung" or "qi gong" or breathwork or breath work or holotropic breathing).mp.
9	(breath* adj3 (exercise* or train* or educat* or retrain* or reeducat* or technique*)).mp.
10	(breath* adj3 (coaching or guidance or instruction* or teach* or taught or tutor* or lesson* or learn* or upskill* or reskill* or workshop* or work-shop* or course* or class* or seminar* or drills)).mp.
11	(respirat* adj (exercise* or training or educat* or retrain* or reeducat* or technique* or coaching or guidance or instruction* or teach* or tutor* or lesson* or reskill* or workshop* or work-shop* or drills)).mp.
12	((pursed lip* or diaphragmatic or yogic or deep or slow or relaxation or relaxed) adj (breathing or respiration)).mp.
13	(Breathing control or respiration control or breathing man?uvers or breathing man?uvres).mp.
14	(control* adj3 breath* adj5 (coaching or coached or educat* or guidance or instruction* or practi#e* or practi#ing or teach* or taught or tutor* or lesson* or learn* or upskill* or reskill* or workshop* or work-shop* or course* or class* or seminar* or drills)).mp.
15	((breath* or respiratory) adj5 (physiotherap* or physical therap* or chest physiotherap* or chest physical therap*)).mp.
16	((breath* adj2 pattern) and (computeri#ed feedback or biofeedback)).mp.
17	(Ventilat* feedback or Ventilat* biofeedback or Ventilat* feed-back or Ventilat* bio-feedback).mp.
18	((breath* adj2 pattern) and (computeri#ed feedback or biofeedback or bio feed back or feedback)).mp.
19	or/7-18
20	6 and 19
21	(dyspn?e* or "short* of breath" or "urge* to breathe*" or breathless* or suffocat* or ("need for air" or "gasp* for air" or "gasp* to breathe" or "pant* for air") or (unsatisf* inspiration or inspiratory difficult* or expiratory difficult*)).mp.
22	((labo?red or difficult*) adj3 breath*).mp.
23	(breath* adj1 (distress* or discomfort* or dysfunction*)).mp.
24	(air adj3 (hunger or starv*)).mp.
25	or/21-24
26	19 and 25
27	20 or 26
28	randomized controlled trial/ or randomization/ or single blind procedure/ or double blind procedure/ or crossover procedure/ or placebo/ or prospective study/
29	(randomi?ed controlled or RCT or randomly allocated or allocated randomly or random allocation or "allocated at random" or single blind* or double blind* or ((treble or triple) adj blind*) or placebo*).mp.
30	((cross over or crossover) adj (clinical study or clinical trial or design or method or study or trial or studies)).mp.
31	or/28-30
32	27 and 31
33	limit 27 to (randomized controlled trial or controlled clinical trial)
34	32 or 33

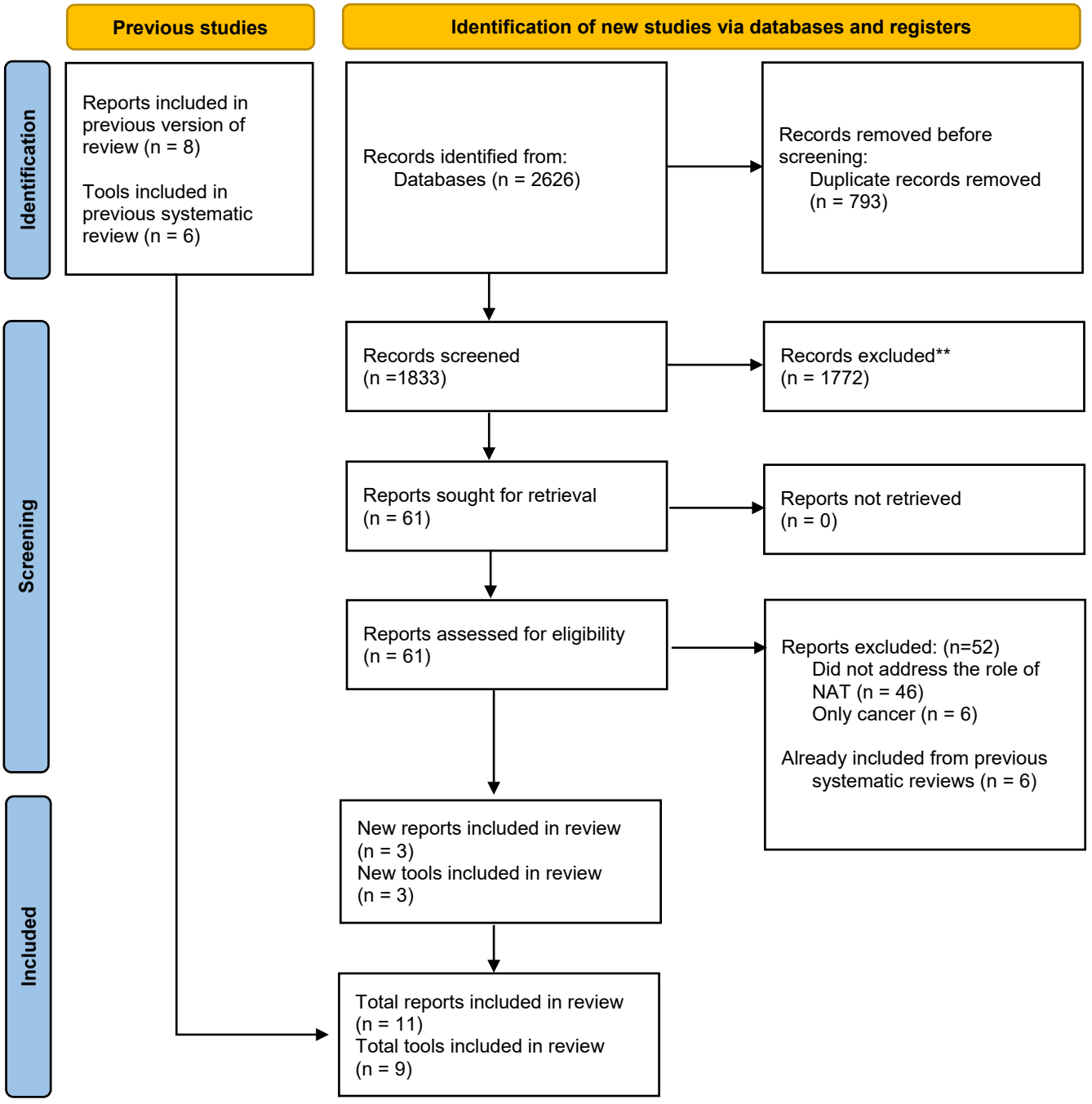
Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials

#	Searches
1	lung diseases/ or "cystic adenomatoid malformation of lung, congenital"/ or cystic fibrosis/ or hepatopulmonary syndrome/ or lung abscess/ or lung diseases, interstitial/ or alveolitis, extrinsic allergic/ or bird fancier's lung/ or farmer's lung/ or silo filler's disease/ or trichosporonosis/ or anti-glomerular basement membrane disease/ or histiocytosis, langerhans-cell/ or eosinophilic granuloma/ or pneumoconiosis/ or anthracosis/ or anthracosilicosis/ or asbestosis/ or berylliosis/ or byssinosis/ or caplan syndrome/ or siderosis/ or silicosis/ or silicotuberculosis/ or pulmonary fibrosis/ or idiopathic pulmonary fibrosis/ or hamman-rich syndrome/ or idiopathic interstitial pneumonias/ or cryptogenic organizing pneumonia/ or sarcoidosis, pulmonary/ or hypertension, pulmonary/ or familial primary pulmonary hypertension/ or pulmonary arterial hypertension/ or Pulmonary Heart Disease/ or lung diseases, obstructive/ or asthma/ or asthma-chronic obstructive pulmonary disease overlap syndrome/ or bronchiolitis obliterans/ or cryptogenic organizing pneumonia/ or bronchitis, chronic/ or pulmonary disease, chronic obstructive/ or pulmonary emphysema/ or plasma cell granuloma, pulmonary/ or bronchial diseases/ or bronchiectasis/ or respiratory tract diseases/ or respiration disorders/ or dyspnea/
2	(lung disease* or pulmonary disease* or cystic fibrosis or interstitial pneumoni* or extrinsic allergic alveolit* or hypersensitivity pneumoniti* or pneumoconios?s or anthracos?s or anthracosilicos?s or asbestos?s or beryllios?s or byssinos?s or beryllium disease* or caplan syndrome or bird fancier* lung or farmer* lung or silo filler* disease or trichosporonos?s or sideros?s or silicos?s or silicotuberculos?s or fibrosing alveolit* or pulmonary fibros?s or fibrocystic pulmonary dysplasia* or hamman-rich disease or hamman-rich syndrome or cryptogenic organizing pneumonia* or pulmonary sarcoidos?s or bronchiolitis obliterans or constrictive bronchiolit* or exudative bronchiolit* or chronic bronchitis or emphysema* or pulmonary inflammatory pseudotumo?r or pulmonary plasma cell granuloma* or bronchial disease* or bronchiectas?s).mp.
3	(((chronic or severe* or unrelenting or obstructive) adj asthma*) or (chronic* obstruct* adj3 (lung* or airway* or pulmon* or bronch* or alveolit* or respiratory))).mp.
4	(bronchopulmonary disease* or lung granulomatos?s or pneumopath* or pulmonary disorder* or acute pneumonitis or chronic fibrous pneumonia* or fibroid phthisis or interstitial cell pneumonia or interstitial plasma cell pneumonia or interstitial pneumocystic pneumonia or phthisis fibroidea or pneumonia interstitialis or interstitial fibros?s or lung fibros?s or interstitial fibros?s or alveolar fibros?s or respiratory granulomatos?s or pulmonary granulomatos?s or lung granulomatos?s or lung conios?s or pneumoconiotic lesion or pneumokonios?s or pneumono?onios?s or (airway obstructive disease* or obstructive airway disorder* or obstructive respiratory disease* or obstructive respiratory disorder* or pneumatosis pulmonum or interstitial syndrome)).mp.
5	(((lung or pulmonary) adj (arter* hypertens* or hypertens* or fixed hypertens* or capillary hemangiomatosis or veno-occlusive or venoocclusive or parenchyma* disease*)) or (corpulmonale or cor pulmonale or pulmonary cardiac disease* or pulmonary vascular obstructive disease* or obstructive pulmonary vascular disease*)).mp.
6	1 or 2 or 3 or 4 or 5
7	breathing exercises/ or qigong/
8	(Buteyko or Pranayam* or yoga* or papworth technique or papworth method* or breathing gymnastics or qigong or "ch'i kung" or "qi gong" or breathwork or breath work or holotropic breathing).mp.
9	(breath* adj3 (exercise* or train* or educat* or retrain* or reeducat* or technique*)).mp.
10	(breath* adj3 (coaching or guidance or instruction* or teach* or taught or tutor* or lesson* or learn* or upskill* or reskill* or workshop* or work-shop* or course* or class* or seminar* or drills)).mp.
11	(respirat* adj (exercise* or training or educat* or retrain* or reeducat* or technique* or coaching or guidance or instruction* or teach* or tutor* or lesson* or reskill* or workshop* or work-shop* or drills)).mp.
12	((pursed lip* or diaphragmatic or yogic or deep or slow or relaxation or relaxed) adj (breathing or respiration)).mp.
13	(Breathing control or respiration control or breathing man?uvers or breathing man?uvres).mp.

14	(control* adj3 breath* adj5 (coaching or coached or educat* or guidance or instruction* or practi#e* or practi#ing or teach* or taught or tutor* or lesson* or learn* or upskill* or reskill* or workshop* or work-shop* or course* or class* or seminar* or drills)).mp.
15	((breath* or respiratory) adj5 (physiotherap* or physical therap* or chest physiotherap* or chest physical therap*)).mp.
16	((breath* adj2 pattern) and (computeri#ed feedback or biofeedback)).mp.
17	(Ventilat* feedback or Ventilat* biofeedback or Ventilat* feed-back or Ventilat* bio-feedback).mp.
18	((breath* adj2 pattern) and (computeri#ed feedback or biofeedback or bio feed back or feedback)).mp.
19	or/7-18
20	6 and 19
21	(dyspn?e* or "short* of breath" or "urge* to breathe*" or breathless* or suffocat* or ("need for air" or "gasp* for air" or "gasp* to breathe" or "pant* for air") or (unsatisf* inspiration or inspiratory difficult* or expiratory difficult*)).mp.
22	((labo?red or difficult*) adj3 breath*).mp.
23	(breath* adj1 (distress* or discomfort* or dysfunction*)).mp.
24	(air adj3 (hunger or starv*)).mp.
25	or/21-24
26	19 and 25
27	20 or 26

7. Narrative Question: What is the role of needs assessment tools in people with serious illness related to lung disease

7.1. Identification of studies – PRISMA diagram



7.2. Inclusion Criteria

- Tools that assess an individual's holistic needs for physical (symptom management), psychological, social and spiritual supportive care
- Instruments used to assess palliative care needs in patients with advanced non-malignant disease, with a focus on those that have been used in lung disease.

7.3. Exclusion Criteria

- Symptom scales, patient-reported outcome measures and decision aids.

7.4. Summary of findings

Our search identified 3 relevant systematic reviews [1-3] and 8 primary papers [4-11] describing 23 tools. An additional 5 reports were sourced from the included systematic reviews and included in this narrative review [12-16].

Of the 23 described tools, 9 were NATs and 14 were palliative care referral clinical decision aids, which are not discussed further in this review. A total of 11 primary reports [4-8, 10, 12, 13, 16] describing 9 NATs are included in this narrative review. Of the 9 included NATs, two were specifically developed for people with serious respiratory illness; the NAT:PD-ILD for people with ILD [4-6], and the NEST-13 for people awaiting lung transplant [8]. Three were not specific to, but had been examined in, a cohort of people with serious respiratory illness; the SNAP in people with COPD [7] and the SCNS-SF34 in people with cystic fibrosis [12], and the MYMOP in people with acute exacerbations of bronchitis [16]. An additional two were not specific to people with serious respiratory illness but had been tested in mixed cohorts containing a small proportion of people with serious respiratory illness; the PNAP [14] and the IPOS [15]. The final two tools were developed to assess needs in carers; an unnamed tool tested in a mixed cohort including carers of people with COPD [13], and the CSNAT tested in a cohort of carers of people with COPD [10].

Whilst some NATs, including the NAT:PD-ILD, NEST-13, SCNS-SF34, MYMOP, IPOS, and PNAP have undergone face, content, or psychometric validation in people with serious respiratory illness with positive results [1, 3], this has often in a restricted cohort such as cystic fibrosis [12] or chronic bronchitis [16] so may not generalise. Others, such as the SNAP, have not undergone formal validation measures [7].

Test-retest validity and inter-rater reliability has only been partially demonstrated for the NAT:PD-ILD [3]. Many validation studies have used prediction of mortality as an endpoint, which may not reflect the capacity of NATs to comprehensively identify unmet patient needs. At this point, no single NAT could be considered as the optimal tool. There is very limited evaluation of the feasibility and utility of NATs in clinical practice. Health professionals perceive that NAT:PD-ILD could improve the care of patients and caregivers, but have highlighted some implementation challenges including the need for training in psychosocial and spiritual assessment and symptom management, support from other disciplines (palliative care and psychology) and engagement of the multidisciplinary team [6]. The impact of NATs on patient and caregiver outcomes is yet to be determined [7], however gaps in need identification for cares have been identified [10]. No study has shown harm or undesirable effects.

Summary Table of Included Needs Assessment Tools

Tool	Acronym	Intended Target	Reference for development and/or validation
Needs Assessment Tool – Progressive Disease: Interstitial Lung Disease	NAT: PT-ILD	Serious respiratory illness	Boland 2016 (adaptation, face and content validation in ILD) [4] Johnson 2018 (psychometric validation in ILD) [5] Reigada 2017 (implementation in ILD) [6]
Needs Near the End of Life Scale modified version	NEST-13	Serious respiratory illness	Pawlow 2020 (adaptation and validity in people awaiting lung transplant) [8]
Supportive Needs Approach for Patients	SNAP	Non-specific advanced disease	Gardener 2021 (qualitative study regarding usage in people with COPD) [7]
Supportive Care Needs Survey Short Form 34	SCNS-SF34	Non-specific advanced disease	Trandel 2020 (validation in people with cystic fibrosis) [12]
Measure Yourself Medical Outcome Profile	MYMOP	Non-specific advanced disease	Paterson 2000 (construct validation in people with exacerbations of bronchitis) [16]
Patient Needs Assessment in Palliative Care	PNAP	Non-specific advanced disease	Buzgova 2016 (validation in cohort that included people with non-malignant serious respiratory illness) [14]
Integrated Palliative Care Outcome Scale	IPOS	Non-specific advanced disease	Murtagh 2019 (validation in cohort that included people with non-malignant serious respiratory illness) [15]
Unnamed measure	-	Carers of people with non-specific advanced disease	Foreva 2014 (mixed cohort of carers) [13]
Carer Support Needs Assessment Tool	CSNAT	Carers of people with non-specific advanced disease	Micklewright 2020 (carers of people with COPD) [10]

7.5. Evidence to Decision table

Narrative question: What is the role of needs assessment tools in people with serious respiratory illness?

This question addresses how an individual's holistic needs for physical (symptom management), psychological, social and spiritual supportive care should be identified.

It includes instruments used to assess unmet needs in patients with advanced non-malignant disease, with a focus on those that have been used in lung disease.

It does not include symptom scales, measures of health-related quality of life, or decision aids.

Domain	Judgement	Research evidence	Additional considerations
Problem Is the problem a priority?	○ No ○ Probably no ○ Probably yes ○ **Yes** ○ Varies ○ Don't know	Patients with serious respiratory illness may have varying needs at different phases of the illness, and there is increasing evidence that an early palliative care plan can improve health-related quality of life. Palliative care is often delivered late in the disease trajectory and access to palliative care is inequitable[2]. Importantly, informal caregivers also often have unmet needs [1, 4-6, 10, 17-19]. One major barrier to providing timely palliative care is the difficulty in identifying patients who could benefit from it [2]. Additionally people with serious respiratory illness may have difficulty expressing their needs [20]. Health professionals should proactively assess unmet needs of patients, and needs assessment tools may assist with this process.	
Desirable Effects How substantial are the desirable anticipated effects?	○ Trivial ○ **Small** ○ Moderate ○ Large ○ Varies ○ Don't know	Eleven papers were included in our narrative review [4-8, 10, 12-16], as well as 3 systematic reviews [1-3]. Within these papers 23 tools are discussed, however, only 9 tools aimed to specifically identify unmet needs of patients (7 tools [4-8, 12, 14-16]) or carers (2 tools [10, 13]). These tools are the focus of this narrative review. An additional 14 tools were described within the papers, which focused on	Some tools highlighted within these papers were actual needs assessment tools (NATs), whereas others were tools to measure patient reported outcomes or patient reported experiences. Additionally, some

		identifying patients who may benefit from palliative care, usually indicated by risk of dying within 12 months. Thus, these did not consider individual needs. These 14 tools were therefore not examined within this narrative review. All studies included in our analysis recommended some form of systematic needs assessment study. Only some tools have undergone rigorous psychometric testing to ensure test-retest reliability, predictive validity, responsiveness, and clinical utility, with varying findings. Key desirable outcomes from adopting a needs assessment tool include: • early identification of palliative care needs • active and improved symptom management • proactive advance care planning • avoiding preventable admissions • facilitating preferred place of death • less family distress. • Facilitating shared decision making aligned with the patients' goals and values. However, here has been very limited evaluation or implementation of NATs in clinical practice therefore their effectiveness to achieve these outcomes is undetermined.	tools were developed for people with non-respiratory illness.
Undesirable Effects How substantial are the undesirable anticipated effects?	○ **Trivial** ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	No study has shown harm or undesirable effects, however, there has been limited evaluation or implementation of NATs in clinical practice. Current NATs do not have capacity to define "all needs" for "all patients or carers". Therefore, clinicians must recognise these limitations and not depend on these tools alone to identify needs.	Many NATs have emerged over the last 20 years, with no tool superior to others, and little guidance or training regarding when, how and with whom to use these tools. One study identified considerable variability in how a

		Needs assessment is an iterative process that occurs over time, not a one-off task. NATs are time consuming and require training for clinicians to implement properly. Spending significant amounts of time completing NATs with patients or carers thus may limit time during clinical consultations to address other important issues. When unmet needs are identified from NATs, there is no guarantee of a clinical response, and/or there may be no clear pathway to enable patients to access the support or care required.	NAT were administered [7]. While standardisation of needs assessment may be helpful, responding to these unmet needs must be individualised. Lack of attention to patient illness narratives may limit utility of NATs. Some clinicians feel that NATs have limited relevance as they believe they already assess patient needs.
Certainty of evidence	What is the overall certainty of the evidence for using the suggested intervention? ○**Very Low** ○ Low ○ Moderate ○ High ○ No included studies	Based on narrative review of evidence	Only some tools have undergone rigorous psychometric testing to ensure test-retest reliability, predictive validity, responsiveness, and clinical utility, with varying findings. However, there has been very limited evaluation or implementation of NATs in clinical practice, and therefore their effectiveness to achieve these outcomes is undetermined.
Current practice		Current practice focuses on prognosis. There are no data regarding the extent to which NATs are currently used in clinical practice.	Many NATs have been developed within specialist palliative care, not within respiratory medicine. Although palliative care is increasingly offered earlier in the illness course to address physical,

			psychosocial and spiritual issues, many NATs have been developed and validated within cohorts of patients at the very end of life. Thus needs are only identified very late in the illness course. For people with serious respiratory illness and their relatives there is an imperative to identify needs earlier.
Values	Is there important uncertainty about or variability in how much people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ **Not important uncertainty or variability** ○ No known undesirable outcomes	Identifying needs is widely described as a crucial first step [17] for patient-centered care [3] and support of informal carers [10].	There was no important uncertainty or variability in the views of the patient members of the Task Force regarding values.
Equity	What would be the impact on health equity? ○ Reduced ○ Probably reduced	There is no evidence regarding how NATs may perform across different social determinants of health (e.g., ethnicity, socioeconomic status) within populations. As such, it is unknown whether NATs may reduce, widen or have no impact on current inequities in health care regarding unmet needs.	A systematic approach to needs assessment may improve access to relevant help and support for people with serious respiratory illness.

	○ Probably no impact ○ **Probably increased** ○ Increased ○ Varies ○ Don't know		
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ● **Probably yes** ○ Yes ○ Varies ○ Don't know	Some studies identified barriers from health professionals regarding using NATs, including lack of time, limited training and resources, and perceived irrelevance when clinicians believed they already comprehensively assessed needs [1, 2, 4, 6, 7, 11, 21-23]. Patients may not perceive that NATs are relevant to their situation and prefer clinicians to be proactive in initiating needs assessments [1, 2, 6, 7, 20-24].	These barriers may represent a lack of understanding regarding what NATs are and how they should be used in clinical practice. There was no important uncertainty or variability in the views of the patient members of the Task Force regarding acceptability.

References – Evidence summary and Evidence-to-Decision Table – Needs assessment tools (Sections 7.4 and 7.5)

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2. ElMokhallalati Y, Bradley SH, Chapman E, Ziegler L, Murtagh FE, Johnson MJ, Bennett MI. Identification of patients with potential palliative care needs: A systematic review of screening tools in primary care. Palliat Med 2020: 34(8): 989-1005.

3. Waller A, Hobden B, Fakes K, Clark K. A Systematic Review of the Development and Implementation of Needs-Based Palliative Care Tools in Heart Failure and Chronic Respiratory Disease. Front Cardiovasc Med 2022: 9: 878428.

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13. Foreva G, Assenova R. Hidden Patients: The Relatives of Patients in Need of Palliative Care. Journal of Palliative Medicine 2014: 17(1): 56-61.

14. Buzgova R, Kozakova R, Sikorova L, Zelenikova R, Jarosova D. Development and psychometric evaluation of patient needs assessment in palliative care (PNAP) instrument. Palliat Support Care 2016: 14(2): 129-137.

15. Murtagh FE, Ramsenthaler C, Firth A, Groeneveld EI, Lovell N, Simon ST, Denzel J, Guo P, Bernhardt F, Schildmann E, van Oorschot B, Hodiamont F, Streitwieser S, Higginson IJ, Bausewein C. A brief, patient- and proxy-reported outcome measure in advanced illness: Validity, reliability and responsiveness of the Integrated Palliative care Outcome Scale (IPOS). Palliat Med 2019: 33(8): 1045-1057.

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7.6. List of included studies, narrative review

Boland JW, Reigada C, Yorke J, Hart SP, Bajwah S, Ross J, Wells A, Papadopoulos A, Currow DC, Grande G, Macleod U, Johnson MJ. The Adaptation, Face, and Content Validation of a Needs Assessment Tool: Progressive Disease for People with Interstitial Lung Disease. J Palliat Med 2016: 19(5): 549-555.

Buzgova R, Kozakova R, Sikorova L, Zelenikova R, Jarosova D. Development and psychometric evaluation of patient needs assessment in palliative care (PNAP) instrument. Palliat Support Care 2016: 14(2): 129-137.

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7.7. Search strategies

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions

#	Searches
1	lung diseases/ or "cystic adenomatoid malformation of lung, congenital"/ or cystic fibrosis/ or hepatopulmonary syndrome/ or lung abscess/ or lung diseases, interstitial/ or alveolitis, extrinsic allergic/ or bird fancier's lung/ or farmer's lung/ or silo filler's disease/ or trichosporonosis/ or anti-glomerular basement membrane disease/ or histiocytosis, langerhans-cell/ or eosinophilic granuloma/ or pneumoconiosis/ or anthracosis/ or anthracosilicosis/ or asbestosis/ or berylliosis/ or byssinosis/ or caplan syndrome/ or siderosis/ or silicosis/ or silicotuberculosis/ or pulmonary fibrosis/ or idiopathic pulmonary fibrosis/ or hamman-rich syndrome/ or idiopathic interstitial pneumonias/ or cryptogenic organizing pneumonia/ or sarcoidosis, pulmonary/ or hypertension, pulmonary/ or familial primary pulmonary hypertension/ or pulmonary arterial hypertension/ or Pulmonary Heart Disease/
2	lung diseases, obstructive/ or asthma/ or asthma-chronic obstructive pulmonary disease overlap syndrome/ or bronchiolitis obliterans/ or cryptogenic organizing pneumonia/ or bronchitis, chronic/ or pulmonary disease, chronic obstructive/ or pulmonary emphysema/ or plasma cell granuloma, pulmonary/ or bronchial diseases/ or bronchiectasis/
3	respiratory tract diseases/ or respiration disorders/ or dyspnea/
4	(lung disease* or pulmonary disease* or cystic fibrosis or interstitial pneumoni* or extrinsic allergic alveolit* or hypersensitivity pneumoniti* or pneumoconios?s or anthracos?s or anthracosilicos?s or asbestos?s or beryllios?s or byssinos?s or beryllium disease* or caplan syndrome or bird fancier* lung or farmer* lung or silo filler* disease or trichosporonos?s or sideros?s or silicos?s or silicotuberculos?s or fibrosing alveolit* or pulmonary fibros?s or fibrocystic pulmonary dysplasia* or hamman-rich disease or hamman-rich syndrome or cryptogenic organizing pneumonia* or pulmonary sarcoidos?s or bronchiolitis obliterans or constrictive bronchiolit* or exudative bronchiolit* or chronic bronchitis or emphysema* or pulmonary inflammatory pseudotumo?r or pulmonary plasma cell granuloma* or bronchial disease* or bronchiectas?s).mp.
5	((chronic or severe* or unrelenting or obstructive) adj asthma*).mp.
6	(chronic* obstruct* adj3 (lung* or airway* or pulmon* or bronch* or alveolit* or respiratory)).mp.
7	(bronchopulmonary disease* or lung granulomatos?s or pneumopath* or pulmonary disorder* or acute pneumonitis or chronic fibrous pneumonia* or fibroid phthisis or interstitial cell pneumonia or interstitial plasma cell pneumonia or interstitial pneumocystic pneumonia or phthisis fibroidea or pneumonia interstitialis or interstitial fibros?s or lung fibros?s or interstitial fibros?s or alveolar fibros?s or respiratory granulomatos?s or pulmonary granulomatos?s or lung granulomatos?s or lung conios?s or pneumoconiotic lesion or pneumokonios?s or pneumono?onios?s).mp.
8	(airway obstructive disease* or obstructive airway disorder* or obstructive respiratory disease* or obstructive respiratory disorder* or pneumatosis pulmonum or interstitial syndrome).mp.
9	((lung or pulmonary) adj (arter* hypertens* or hypertens* or fixed hypertens* or capillary hemangiomatosis or veno-occlusive or venoocclusive or parenchyma* disease*)).mp.
10	(corpulmonale or cor pulmonale or pulmonary cardiac disease* or pulmonary vascular obstructive disease* or obstructive pulmonary vascular disease*).mp.
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	Needs Assessment/
13	"Health Services Needs and Demand"/
14	(needs adj5 (assess* or measure* or analys* or investigat* or identif*)).mp.
15	12 or 13 or 14
16	11 and 15
17	(tool? or survey* or question* or interview* or focus group? or item? or instrument? or inventory or scale? or score? or scoring or form? or webform? or checklist? or check-list? or index or indices or schedule? or self-report* or selfreport* or self-administer* or selfadminister* or self-complete* or selfcomplete* or self-measure* or selfmeasure* or feedback).mp.
18	data collection/ or focus groups/ or health impact assessment/ or interviews as topic/ or "surveys and questionnaires"/ or health surveys/ or patient health questionnaire/ or self report/

19	(data adj1 collect*).mp.
20	(SPICT tool or "Supportive and Palliative Care Indicators" or "Support Needs Approach for Patients" or SNAP tool or Patients Concerns Inventory or PCI tool or patient needs assessment tool or PNAT tool or NAT?PD-ILD or NAT?ILD or Camberwell Assessment of Needs Inventory or Camberwell Assessment Of Needs Questionnaire or Supportive Care Needs Assessment Tool for Indigenous Peoples or SCNAT-IP).mp.
21	(Palliative Care Outcome Scale or Memorial Symptom Assessment Scale Short Form or MSAS-SF or NAT?PD or Needs for Care Assessment Schedule or NFACS tool or Camberwell Assessment of Need Tool or Cardinal Needs Schedule or Salford Needs Assessment Schedule for Adolescents or S?NASA tool or Southampton Needs Assessment Questionnaire or SNAQ tool or HNA surveys or HNA tools or "Sheffield Profile for Assessment and Referral for Care" or SPARC tool or Holistic Screening tool?).mp.
22	(multiple choice or Likert scale or short-answer or open-ended questions or discussion forum* or journal log?).mp.
23	((personal or participant* or carer* or caregiver* or respondent* or patient*) adj3 (story or stories or narrative* or journal* or diary or diaries or verbal response* or written response* or oral response* or answers)).mp.
24	17 or 18 or 19 or 20 or 21 or 22 or 23
25	16 and 24
26	((palliative or terminal care or "end of life") and needs).mp.
27	11 and 24 and 26
28	25 or 27

Database(s): Embase

#	Searches
1	lung disease/ or chronic lung disease/ or interstitial lung disease/ or interstitial syndrome/ or lung emphysema/ or lung fibrosis/ or lung sarcoidosis/ or obstructive lung disease/ or fibrosing alveolitis/ or interstitial pneumonia/ or pneumoconiosis/ or asthma/ or chronic obstructive lung disease/ or severe asthma/ or asthmatic state/ or severe persistent asthma/ or pulmonary hypertension/ or chronic thromboembolic pulmonary hypertension/ or cor pulmonale/ or pulmonary capillary hemangiomatosis/ or pulmonary vascular obstructive disease/ or pulmonary veno-occlusive disease/
2	obstructive airway disease/ or occupational lung disease/ or anthracosis/ or asbestosis/ or berylliosis/ or bird breeder lung/ or byssinosis/ or farmer lung/ or occupational asthma/ or pigeon breeder lung/ or pneumoconiosis/ or silicosis/ or bronchus disease/ or bronchiectasis/ or lung granuloma/ or respiratory tract disease/ or dyspnea/
3	(lung disease* or pulmonary disease* or cystic fibrosis or interstitial pneumoni* or extrinsic allergic alveolit* or hypersensitivity pneumoniti* or pneumoconios?s or anthracos?s or anthracosilicos?s or asbestos?s or beryllios?s or byssinos?s or beryllium disease* or caplan syndrome or bird fancier* lung or farmer* lung or silo filler* disease or trichosporonos?s or sideros?s or silicos?s or silicotuberculos?s or fibrosing alveolit* or pulmonary fibros?s or fibrocystic pulmonary dysplasia* or hamman-rich disease or hamman-rich syndrome or cryptogenic organizing pneumonia* or pulmonary sarcoidos?s or bronchiolitis obliterans or constrictive bronchiolit* or exudative bronchiolit* or chronic bronchitis or emphysema* or pulmonary inflammatory pseudotumo?r or pulmonary plasma cell granuloma* or bronchial disease* or bronchiectas?s).mp.
4	((chronic or severe* or unrelenting or obstructive) adj asthma*).mp.
5	(chronic* obstruct* adj3 (lung* or airway* or pulmon* or bronch* or alveolit* or respiratory)).mp.
6	(bronchopulmonary disease* or lung granulomatos?s or pneumopath* or pulmonary disorder* or acute pneumonitis or chronic fibrous pneumonia* or fibroid phthisis or interstitial cell pneumonia or interstitial plasma cell pneumonia or interstitial pneumocystic pneumonia or phthisis fibroidea or pneumonia interstitialis or interstitial fibros?s or lung fibros?s or interstitial fibros?s or alveolar fibros?s or respiratory granulomatos?s or pulmonary granulomatos?s or lung conios?s or pneumoconiotic lesion or pneumokonios?s or pneumono?onios?s).mp.
7	(airway obstructive disease* or obstructive airway disorder* or obstructive respiratory disease* or obstructive respiratory disorder* or pneumatosis pulmonum or interstitial syndrome).mp.

8	((lung or pulmonary) adj (arter* hypertens* or hypertens* or fixed hypertens* or capillary hemangiomatosis or veno-occlusive or venoocclusive or parenchyma* disease*)).mp.
9	(corpulmonale or cor pulmonale or pulmonary cardiac disease* or pulmonary vascular obstructive disease* or obstructive pulmonary vascular disease*).mp.
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	needs assessment/
12	human needs/
13	(needs adj5 (assess* or measure* or analys* or investigat* or identif*)).mp.
14	11 or 12 or 13
15	10 and 14
16	data collection method/ or interview/ or questionnaire/ or interview/ or delphi study/ or semi structured interview/ or structured interview/ or telephone interview/ or unstructured interview/ or open ended questionnaire/ or structured questionnaire/ or patient health questionnaire/ or self reporting questionnaire 20/ or self report/
17	(tool? or survey* or question* or interview* or focus group? or item? or instrument? or inventory or scale? or score? or scoring or form? or webform? or checklist? or check-list? or index or indices or schedule? or self-report* or selfreport* or self-administer* or selfadminister* or self-complete* or selfcomplete* or self-measure* or selfmeasure* or feedback).mp.
18	(data adj1 collect*).mp.
19	(SPICT tool or "Supportive and Palliative Care Indicators" or "Support Needs Approach for Patients" or SNAP tool or Patients Concerns Inventory or PCI tool or patient needs assessment tool or PNAT tool or NAT?PD-ILD or NAT?ILD or Camberwell Assessment of Needs Inventory or Camberwell Assessment Of Needs Questionnaire or Supportive Care Needs Assessment Tool for Indigenous Peoples or SCNAT-IP).mp.
20	(Palliative Care Outcome Scale or Memorial Symptom Assessment Scale Short Form or MSAS-SF or NAT?PD or Needs for Care Assessment Schedule or NFACS tool or Camberwell Assessment of Need Tool or Cardinal Needs Schedule or Salford Needs Assessment Schedule for Adolescents or S?NASA tool or Southampton Needs Assessment Questionnaire or SNAQ tool or HNA surveys or HNA tools or "Sheffield Profile for Assessment and Referral for Care" or SPARC tool or Holistic Screening tool?).mp.
21	(multiple choice or Likert scale or short-answer or open-ended questions or discussion forum* or journal log?).mp.
22	((personal or participant* or carer* or caregiver* or respondent* or patient*) adj3 (story or stories or narrative* or journal* or diary or diaries or verbal response* or written response* or oral response* or answers)).mp.
23	16 or 17 or 18 or 19 or 20 or 21 or 22
24	15 and 23
25	((palliative or terminal care or "end of life") and needs).mp.
26	10 and 23 and 25
27	24 or 26

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials

#	Searches
1	lung diseases/ or "cystic adenomatoid malformation of lung, congenital"/ or cystic fibrosis/ or hepatopulmonary syndrome/ or lung abscess/ or lung diseases, interstitial/ or alveolitis, extrinsic allergic/ or bird fancier's lung/ or farmer's lung/ or silo filler's disease/ or trichosporonosis/ or anti-glomerular basement membrane disease/ or histiocytosis, langerhans-cell/ or eosinophilic granuloma/ or pneumoconiosis/ or anthracosis/ or anthracosilicosis/ or asbestosis/ or berylliosis/ or byssinosis/ or caplan syndrome/ or siderosis/ or silicosis/ or silicotuberculosis/ or pulmonary fibrosis/ or idiopathic pulmonary fibrosis/ or hamman-rich syndrome/ or idiopathic interstitial pneumonias/ or cryptogenic organizing pneumonia/ or sarcoidosis, pulmonary/ or hypertension, pulmonary/ or familial primary pulmonary hypertension/ or pulmonary arterial hypertension/ or Pulmonary Heart Disease/

2	lung diseases, obstructive/ or asthma/ or asthma-chronic obstructive pulmonary disease overlap syndrome/ or bronchiolitis obliterans/ or cryptogenic organizing pneumonia/ or bronchitis, chronic/ or pulmonary disease, chronic obstructive/ or pulmonary emphysema/ or plasma cell granuloma, pulmonary/ or bronchial diseases/ or bronchiectasis/
3	respiratory tract diseases/ or respiration disorders/ or dyspnea/
4	(lung disease* or pulmonary disease* or cystic fibrosis or interstitial pneumoni* or extrinsic allergic alveolit* or hypersensitivity pneumoniti* or pneumoconios?s or anthracos?s or anthracosilicos?s or asbestos?s or beryllios?s or byssinos?s or beryllium disease* or caplan syndrome or bird fancier* lung or farmer* lung or silo filler* disease or trichosporonos?s or sideros?s or silicos?s or silicotuberculos?s or fibrosing alveolit* or pulmonary fibros?s or fibrocystic pulmonary dysplasia* or hamman-rich disease or hamman-rich syndrome or cryptogenic organizing pneumonia* or pulmonary sarcoidos?s or bronchiolitis obliterans or constrictive bronchiolit* or exudative bronchiolit* or chronic bronchitis or emphysema* or pulmonary inflammatory pseudotumo?r or pulmonary plasma cell granuloma* or bronchial disease* or bronchiectas?s).mp.
5	((chronic or severe* or unrelenting or obstructive) adj asthma*).mp.
6	(chronic* obstruct* adj3 (lung* or airway* or pulmon* or bronch* or alveolit* or respiratory)).mp.
7	(bronchopulmonary disease* or lung granulomatos?s or pneumopath* or pulmonary disorder* or acute pneumonitis or chronic fibrous pneumonia* or fibroid phthisis or interstitial cell pneumonia or interstitial plasma cell pneumonia or interstitial pneumocystic pneumonia or phthisis fibroidea or pneumonia interstitialis or interstitial fibros?s or lung fibros?s or interstitial fibros?s or alveolar fibros?s or respiratory granulomatos?s or pulmonary granulomatos?s or lung granulomatos?s or lung conios?s or pneumoconiotic lesion or pneumokonios?s or pneumono?onios?s).mp.
8	(airway obstructive disease* or obstructive airway disorder* or obstructive respiratory disease* or obstructive respiratory disorder* or pneumatosis pulmonum or interstitial syndrome).mp.
9	((lung or pulmonary) adj (arter* hypertens* or hypertens* or fixed hypertens* or capillary hemangiomatosis or veno-occlusive or venoocclusive or parenchyma* disease*)).mp.
10	(corpulmonale or cor pulmonale or pulmonary cardiac disease* or pulmonary vascular obstructive disease* or obstructive pulmonary vascular disease*).mp.
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	Needs Assessment/
13	"Health Services Needs and Demand"/
14	(needs adj5 (assess* or measure* or analys* or investigat* or identif*)).mp.
15	12 or 13 or 14
16	11 and 15
17	(tool? or survey* or question* or interview* or focus group? or item? or instrument? or inventory or scale? or score? or scoring or form? or webform? or checklist? or check-list? or index or indices or schedule? or self-report* or selfreport* or self-administer* or selfadminister* or self-complete* or selfcomplete* or self-measure* or selfmeasure* or feedback).mp.
18	data collection/ or focus groups/ or health impact assessment/ or interviews as topic/ or "surveys and questionnaires"/ or health surveys/ or patient health questionnaire/ or self report/
19	(data adj1 collect*).mp.
20	(SPICT tool or "Supportive and Palliative Care Indicators" or "Support Needs Approach for Patients" or SNAP tool or Patients Concerns Inventory or PCI tool or patient needs assessment tool or PNAT tool or NAT?PD-ILD or NAT?ILD or Camberwell Assessment of Needs Inventory or Camberwell Assessment Of Needs Questionnaire or Supportive Care Needs Assessment Tool for Indigenous Peoples or SCNAT-IP).mp.
21	(Palliative Care Outcome Scale or Memorial Symptom Assessment Scale Short Form or MSAS-SF or NAT?PD or Needs for Care Assessment Schedule or NFACS tool or Camberwell Assessment of Need Tool or Cardinal Needs Schedule or Salford Needs Assessment Schedule for Adolescents or S?NASA tool or Southampton Needs Assessment Questionnaire or SNAQ tool or HNA surveys or HNA tools or "Sheffield Profile for Assessment and Referral for Care" or SPARC tool or Holistic Screening tool?).mp.
22	(multiple choice or Likert scale or short-answer or open-ended questions or discussion forum* or journal log?).mp.
23	((personal or participant* or carer* or caregiver* or respondent* or patient*) adj3 (story or stories or narrative* or journal* or diary or diaries or verbal response* or written response* or oral response* or answers)).mp.

24	17 or 18 or 19 or 20 or 21 or 22 or 23
25	16 and 24
26	((palliative or terminal care or "end of life") and needs).mp.
27	11 and 24 and 26
28	25 or 27

8.