

Research

Respiratory physiotherapy interventions focused on exercise training and enhancing physical activity levels in people with chronic obstructive pulmonary disease are likely to be cost-effective: a systematic review

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KEY WORDS

Systematic review
Healthcare economics and organisations
Physical therapy modalities
Chronic obstructive pulmonary disease



ABSTRACT

Question: What is the cost-effectiveness of respiratory physiotherapy interventions for people with chronic obstructive pulmonary disease? **Design:** Systematic review of full economic evaluations alongside clinical trials published between 1997 and 2021. Reviewers independently screened studies for inclusion, extracted data and assessed methodological quality. **Participants:** People with chronic obstructive pulmonary disease. **Intervention:** Respiratory physiotherapy interventions as defined in the respiratory physiotherapy curriculum of the European Respiratory Society. **Outcome measures:** Costs expressed in monetary units, effect sizes expressed in terms of disease-specific quality of life (QOL), quality-adjusted life years (QALYs) or monetary units. **Results:** This review included 11 randomised trials with 3,261 participants. The interventions were pulmonary rehabilitation, airway clearance techniques, an integrated disease-management program and an early assisted discharge program, including inpatient respiratory physiotherapy. Meta-analysis was considered irrelevant due to the extensive heterogeneity of the reported interventions. A total of 45 incremental cost-effectiveness ratios (ICERs) were extracted. Regardless of the economic perspectives, 67% of all QOL-related ICERs and 71% of all QALY-related ICERs were situated in the north-east or south-east quadrants of the cost-effectiveness plane. Six studies could be seen as cost-effective when compared with a specified cost-effectiveness threshold per QALY gained. **Conclusion:** Respiratory physiotherapy interventions focusing on exercise training in combination with enhancing physical activity levels are likely to be cost-effective in terms of costs per unit QOL gained and QALYs. Some uncertainty still exists on the various estimates of cost-effectiveness due to differences in the content and intensity of the type of interventions, outcome measures and comparators. **Registration:** PROSPERO CRD42018088699. [Leemans G, Taeymans J, Van Royen P, Vissers D (2021) Respiratory physiotherapy interventions focused on exercise training and enhancing physical activity levels in people with chronic obstructive pulmonary disease are likely to be cost-effective: a systematic review. *Journal of Physiotherapy* 67:271–283]

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Background

Chronic obstructive pulmonary disease (COPD) is a common, often preventable and treatable disease, characterised by persistent respiratory symptoms and airflow limitation. Significant comorbidities may have an impact on morbidity and mortality.¹ Furthermore, COPD has a number of intrapulmonary and extrapulmonary components whose dynamic interactions along time are not linear, and not all of these components are present in all individuals at any given time point.² Besides this complex and heterogeneous nature, COPD is also one of the most prevalent chronic respiratory diseases worldwide and associated with a significant social and economic burden.³ In the European Union alone, the direct cost of COPD amounted to 6% of the total annual healthcare budget in 2011 (380 billion Euros) and

accounted for 42% of the total direct cost of treating respiratory diseases.⁴ For the United States, the cost of COPD in 2010 was projected to be approximately \$50 billion, which included \$20 billion in indirect costs and \$30 billion in direct healthcare expenditures.⁵ Key cost-driving factors for direct medical costs are inpatient hospitalisation and medication due to exacerbations.⁶ In order to release this pressure on healthcare budgets in the future while still increasing the patients' quality of life, it is expected that COPD treatments will increasingly be tailored to individual patients' needs to accommodate the complexity and heterogeneity of this disease.^{7,8}

Individualised approaches for patients with COPD are not new in non-pharmacological therapies. Pulmonary rehabilitation (PR), for example, has been defined as a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies

designed to improve the physical and psychological condition of patients with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviours.⁹ While PR is considered to be one of the most cost-effective therapies for individuals with COPD,¹⁰ comparing various estimates of cost-effectiveness is complicated, and further research in terms of costs per disease-specific quality of life (QOL) and costs per quality-adjusted life years (QALYs) gained by PR is needed to reach definite conclusions.⁹ This also seems to be the case for other respiratory physiotherapy interventions such as airway clearance techniques.

This systematic review aimed to carry out a critical appraisal and synthesis of health economic evaluations that investigated the cost-effectiveness of respiratory physiotherapy interventions in patients with COPD.

Therefore, the research question for this systematic review was:

What is the cost-effectiveness of respiratory physiotherapy interventions for people with COPD?

Method

This systematic review was carried out and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹¹ The five-step approach for preparing a systematic review of economic evaluations by van Mastrigt et al was also used where appropriate.¹² A search of the Cochrane Library revealed no similar published literature reviews.

Identification and selection of studies

A comprehensive literature search was performed in March 2020. The five selected sources were a combination of several general databases (Medline/PubMed, Web of Science, Wiley Online Library), a specific database for economic evaluations of healthcare interventions (NHS EED) and a physiotherapy-specific database (PEDro). In order to increase the sensitivity of the search, references from included articles were checked (backward citation tracking). All databases were searched with the following search terms: 'COPD', 'therapy', 'economics' and 'costs'. Boolean operators were used to combine search terms. Details of the search strategy are presented in Appendix 1 on the eAddenda. For PubMed, MeSH terms were used when available. The searches were adapted and repeated across all databases. Search results were stored in reference management software^a and duplicates were removed. Studies that performed a full health economic evaluation involving people with COPD were included when two or more alternative interventions were compared, and both costs and effects (or benefits) of the compared treatment were taken into account.¹³

Interventions were defined as any skill performed by a respiratory physiotherapist as described in the mandatory modules of the respiratory physiotherapy curriculum of the European Respiratory Society.¹⁴ Multicomponent interventions such as disease management programs, which focused on different health outcomes, were included if physiotherapy interventions as previously defined were a component of the rehabilitation program. The compared treatment was either standard of care or any other respiratory treatment. The outcomes of the included studies were costs, expressed in monetary units, and effect sizes expressed in terms of natural units (eg, change in lung function), disease-specific QOL, healthy years (eg, QALYs) or in monetary units. Box 1 summarises the inclusion criteria for studies in this systematic review.

Regarding study design, all types of full economic evaluations were eligible, namely: cost-effectiveness analyses (CEA), cost-utility analyses (CUA) or cost-benefit analyses if the economic data were collected alongside data from a single prospective clinical trial. Partial and model-based economic evaluations were excluded. Publications in languages other than English, German and French were excluded. Neither the publication date nor timeframe of the economic analyses, the time horizon, was specified. Two independent researchers

Box 1. Inclusion criteria.

Design

- All types of full economic evaluations:
 - cost-effectiveness analyses
 - cost-utility analyses
 - cost-benefit analyses
- The economic data were collected alongside data from a single prospective clinical trial

Participants

- People with chronic obstructive pulmonary disease

Intervention

- Any skills as described in the modules of the European Respiratory Society respiratory physiotherapy curriculum

Outcomes

- Measures of cost-effectiveness, cost-benefit and cost-utility

Comparators

- Standard of care
- Any other respiratory physiotherapy treatment

performed the search, the screening process and the initial inclusion of studies based on title and abstract. Full texts of relevant studies were consulted for definitive inclusion by two independent researchers (GL, DV). A consensus discussion between all researchers took place after title and abstract screening, as well as after full-text consultation.

Assessment of characteristics of studies

Based on Wijnen et al,¹⁵ the following data were extracted from the included studies: study design, characteristics of study participants, details of the intervention/comparator, and measurement and valuation of effects and costs. When studies referred to data sets previously published in other manuscripts, information was extracted from those articles to make a complete data extraction. In the case of missing data, the study authors were contacted. Two independent researchers (GL, DV) extracted data on study characteristics following the criteria in Box 1 and entered the data in a prepared digital form. A consensus discussion took place at the end of the data extraction process with the whole research team.

Quality

The standardised JBI Critical Appraisal Checklist for Economic Evaluation,¹⁶ based on the guidelines developed by Drummond et al,¹³ was used to assess the methodological quality and validity of the relevant economic evaluations. All 11 items of this checklist can be rated as 'yes', 'no' (inadequate methodology), or 'unclear' (insufficient information) and 'not applicable'. All included articles were scored by two researchers independently (GL, DV). Discrepancies were discussed in a consensus meeting.

Study design and setting

The following details were extracted: study design, time horizon, type of economic evaluation, country, perspective of the economic analyses (healthcare, societal or third-party payer) and reported reference year with currency used.

Participants

To describe the participants, the following data were extracted: major inclusion criteria, sample size, age and forced expiratory volume in 1 second (FEV₁) in percent predicted.

Intervention

The details extracted about the interventions from each included study were: type of the (multicomponent) intervention, specific interventions related to respiratory physiotherapy and (where reported) the number of weeks, sessions or hours of one or more

interventions. Data about the control group were: description of usual care, type of (multicomponent) intervention and (where reported) the number of weeks, sessions or hours of one or more interventions.

Outcome measures

The outcome measures considered by this review are listed in [Box 1](#). Detailed breakdowns of the costs per cost item and the outcome parameters used for measuring effectiveness were extracted from the included studies.

Data analysis

Heterogeneity is well recognised in the content, healthcare provider and organisational aspects of respiratory physiotherapy interventions.^{14,17} Taking this heterogeneity into account, it was not plausible to pool effects and, hence, pooling was not undertaken. Therefore, this analysis remained purely descriptive and studies were qualitatively analysed. A summary of incremental costs, incremental effects and incremental cost-effectiveness ratios (ICERs) was tabulated. Where applicable, 95% confidence intervals were reported as well. ICERs were given with their location on the cost-effectiveness plane. The cost-effectiveness plane presents the effectiveness of the intervention on the x-axis and the total costs on the y-axis and consists of four quadrants. ICERs in the south-east quadrant indicate that the intervention compared to the alternative is more effective and less expensive. ICERs in the south-west quadrant indicate that the intervention is less effective and less expensive. In the north-west quadrant, the intervention is less effective and more expensive, while ICERs in the north-east quadrant of the plane indicate more effective but also more expensive interventions as compared to the alternative. In this situation, the cost-effectiveness depends on the willingness to pay, which is defined as the maximum amount of money an individual is willing to pay to avoid or reduce a specific health problem or to gain a specific health benefit.¹³

Nonetheless, to enhance comparability of included studies all study currencies for the ICERs were converted to 2019 Euros by the Campbell and Cochrane Economics Methods Group (CCEMG) and the Evidence for Policy and Practice Information and Coordinating Centre (EPPI-Centre) cost converter^{b,18}. This free web-based tool automatically adjusts estimates for costs and price year, taking purchasing power parities between countries into account.

Results

Flow of studies through the review

After removing 100 duplicates, the database search yielded 435 records, from which 59 articles were identified to review for eligibility. These were obtained in full text and assessed, resulting in the inclusion of 11 studies in this review. The most frequent reasons for exclusion were intervention (eg, no involvement of respiratory physiotherapist as healthcare provider during intervention), outcome (eg, no information about cost-effectiveness) and study design (eg, reviews, abstracts and economic models). A full overview of the flow is provided in [Figure 1](#). Study details of all included studies are presented in [Table 1](#).

Characteristics of included studies

Quality

The results of the critical appraisal of the studies are presented in [Table 2](#). Five of 11 studies fulfilled all 11 criteria on the checklist. All 11 studies: posed a clear research question; provided a clear description of the interventions and comparators; identified and measured all important costs and outcomes and valued those credibly; and

provided an incremental analysis of cost and consequences. The majority of the studies reported clinical effectiveness (nine studies), reflected on issues of concern to users in the study results (eg, decision-makers) (10 studies), discussed transferability of how to generalise results to other settings with similar characteristics (eight studies), adjusted costs for differential timing (eight studies) and conducted sensitivity analysis regarding uncertainty in estimates of costs methods (nine studies). More specifically, the following sensitivity analysis methods were used: probabilistic (nine studies), univariate (six studies) and scenario analysis (one study).

Design, setting and participants

Eleven economic evaluations alongside a clinical trial were included in the final analysis. All were published between 1997 and 2020. All studies were randomised controlled trials, of which two used cluster-randomisation. All cluster-randomised trials took clustering into account for the statistical analysis.^{19,20} Two trials were designed to show equivalence rather than superiority between control and intervention.^{21,22} In light of the research question, we reversed the control (usual care, including inpatient respiratory physiotherapy) and intervention group (early assisted discharge by nurses) of Goossens et al²³ in comparison with the original publication. Studies were carried out in The Netherlands (four studies), United Kingdom (four studies), Australia (one study), Ireland (one study) and Canada (one study). Time horizons ranged from 3 months to 2 years; eight studies used time horizons between 1 and 2 years. Included studies used the healthcare perspective alone (six studies), societal perspective alone (one study), both healthcare and societal perspectives (three studies) and the societal and third-party payer's perspective (one study). Studies consisted of CEA alone (one study), CUA alone (two studies) and both CEA and CUA (eight studies). In most studies, inclusion criteria were stable COPD diagnosed according to GOLD guidelines¹ and a smoking history of ≥ 10 pack-years. Only Cross et al²² and Goossens et al²³ recruited people with COPD during an acute exacerbation. The number of participants across the included studies ranged from 89 to 1,086, with an aggregate total (at time of randomisation) of 3,261. All trials recruited a similar number of participants for both study groups. Participants' mean age at recruitment was 67.1 years (range 49.6 to 71), while mean FEV₁ was 51% predicted (range 35 to 68). Groups were broadly comparable at baseline, albeit with some differences: Boland et al²⁰ reported a higher percentage of males in the usual care group (51 versus 57%) and the control group of Burns et al²⁴ had on average a higher EuroQol five dimensional (EQ-5D) utility (0.7 versus 0.6) than the intervention group.

Interventions

Reported interventions were PR programs (eight studies), airway clearance techniques (ACTs) (one study), an integrated disease management program (one study) and one study on the effect of early assisted discharge by nurses compared with usual care, including inpatient physiotherapy interventions. The majority of the interventions that were studied were compared against usual care (seven studies). Four interventions were compared against another intervention: a home-based PR versus centre-based PR program,²¹ ACTs with manual percussion versus ACTs without percussion,²² PR in hospital versus community settings with and without telephone follow-up,²⁵ and a self-management program versus a community-based exercise program within that self-management program.²⁶ Using the syllabus items of the European Respiratory Society core curriculum in respiratory physiotherapy²⁷ as a framework to report the different interventions, it was observed that 82% of the interventions were exercise training in combination with enhancing physical activity levels (see [Table 3](#)).

The reported content, timing and organisational aspects differed greatly between the exercise programs. First, the intervention

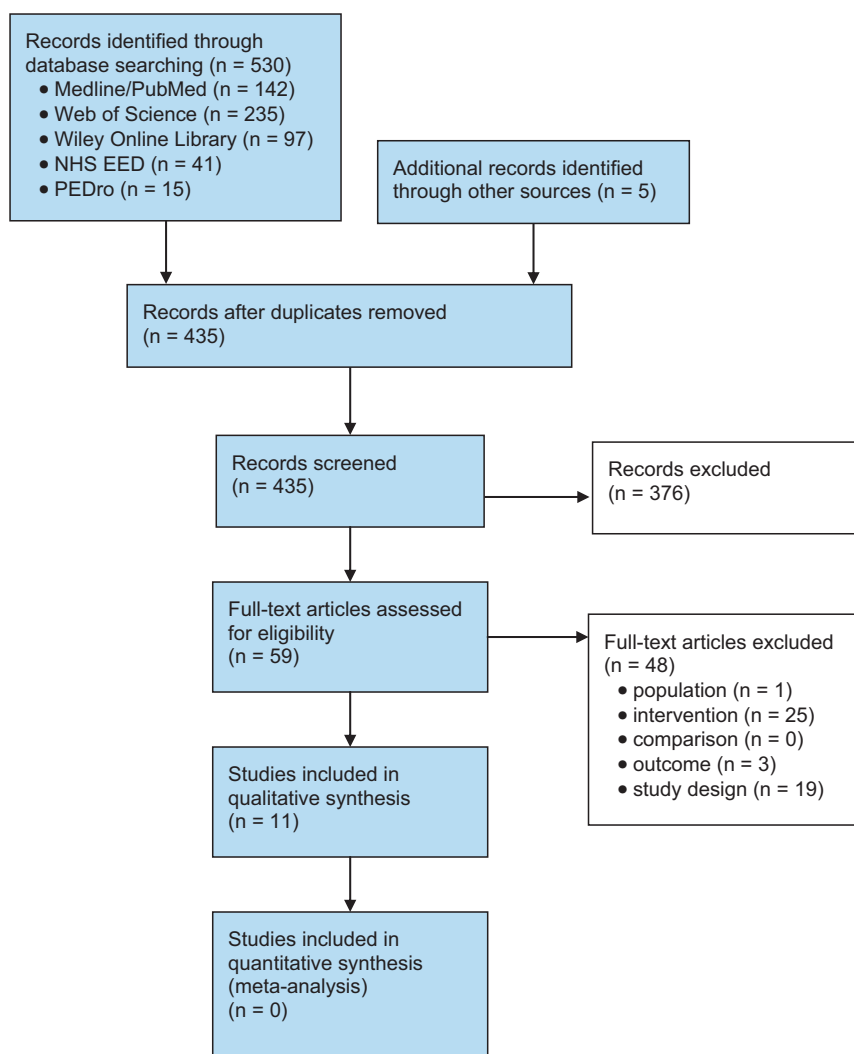


Figure 1. Flow of studies through the review.

programs took place in different healthcare settings: inpatient, outpatient, community-based/primary care, both inpatient and outpatient, a combination of outpatient and primary care and home-based alone (one study each). Second, the duration of the exercise programs varied from short (< 12 weeks, five studies) to a longer duration (> 12 weeks, four studies) with a minimum of 7 days to a maximum of 24 months. Third, heterogeneity in training frequency, intensity and supervision of sessions was observed, ranging from one supervised session per 1 to 3 months for a maintenance program, to two to three supervised sessions per week in combination with one to three additional unsupervised sessions at home to enhance behavioural change towards physical activity. Four out of nine trials with exercise programs specified their exercise intensity, which was considered high intensity according to the recent guideline on PR.⁹ In the study of Boland et al, no duration or training frequency was reported.²⁰ Fourth, the type of exercise training included either endurance (one study), endurance and strength training (seven studies) or was not specified (two studies). The intervention programs also differed in terms of patient education offered, from basic advice by information sheets (one study) to extensive self-management programs (nine studies). Regarding the therapeutic methods for increasing physical activity, interventions were activity counselling, theory-based behavioural medicine interventions, training logs, exercise programs at home, or a combination. However, it was difficult

to evaluate to what extent these techniques were put into practice. Looking to ACTs, two studies examined assisted cough and self-management/education in ACTs.^{22,23} A combination of several ACTs (body positioning, manual percussion, vibration, active cycle of breathing techniques) and breathing exercises were reported once. Interestingly, ACTs were only investigated in clinical trials that recruited COPD patients during an acute exacerbation.^{22,23}

Outcomes

The reported outcomes to assess the effect of the interventions were general health status ($k = 10$), disease-specific QOL (seven studies), exercise capacity (two studies), total number of COPD exacerbations (one study) and daily physical activity (one study). Overall health-related questionnaires were used to derive general health status expressed as QALYs.^{28,29} To calculate QALYs, the majority of the selected studies used the EQ-5D questionnaire to calculate the utilities (seven studies). Three studies derived utility scores for health status by extracting responses from the 36-Item Short Form Health Survey (SF-36) and using them to complete a six-item health state classification, the SF-6D.^{21,25,30} The selected outcome measures for disease-specific QOL across studies were heterogeneous, including St. George Respiratory Questionnaire (SGRQ),^{20,22,31} Chronic Respiratory Questionnaire (CRQ)^{19,24,32} and the Clinical COPD Questionnaire (CCQ).²³ Change in exercise capacity

Table 1
Characteristics of included studies.

Study	Setting	Participants	Control	Intervention	Outcome measures
Boland et al. 2015 ²⁰ - Cluster RCT, time horizon 24 mths - CEA/CUA	- Netherlands - Healthcare and societal perspective 2013 Euros	- COPD based on GOLD guidelines - Con: n = 532, age = 68.4 (SD 11.1), FEV₁ = 67.9 (SD 20.5) - Int: n = 554, age = 68.2 (SD 11.3), FEV₁ = 67 (SD 20.3)	Usual care, based on 2007 national primary care COPD guidelines.	Integrated Disease Management (IDM) ⁴¹ : Multidisciplinary teams consisted of at least three members: GP, practice nurse and PT with specific certified training in COPD care. Elements of this program were proper diagnosis, optimal medical adherence, motivational interviewing, smoking cessation, self-management plans, dietary interventions, and guideline-based physiotherapeutic reactivations. Each team designed their own time-contingent individual practice plan (no standardisation). Dose: an individual patient-specific care plan negotiated in collaboration with patient. Intensity and number of IDM elements depended upon health status and patient's need.	- Costs: - Intervention - Healthcare resources (eg, medication prescriptions) - Travel expenses - Productivity loss - Effectiveness: SGRQ, total number of COPD exacerbations, CCQ - Utility: QALY (EQ-5D) Follow-up: 0, 6, 9, 12, 18 and 24 mths. Exacerbations continuously over specified time horizon.
Burge et al (2020) ²¹ - Equivalence RCT, 12-mth time horizon - CEA/CUA	- Australia - Healthcare and societal perspective 2017 Australian dollars	- Stable COPD based on FEV₁/FVC ratio of < 70% - Smoking history (current or former) of minimum 10 pack-years. - Con: n = 77, age = 69 (SD 9), FEV₁ = 49 (SD 20) - Int: n = 82, age = 71 (SD 9), FEV₁ = 53 (SD 18)	Centre-based, outpatient group-based supervised ⁴² PR course with components of exercise training and self-management education. Dose: 8 weeks, 5 sessions/week with 2/week supervised sessions/week.	Home-based PR course ⁴² : first week a PT home visit to establish exercise goals and supervise first exercise session followed by seven once-weekly structured telephone calls from a PT, using structured modules and motivational interviewing. Dose: 8 weeks, 5/week with 1/week follow-up session by call.	- Costs: - Healthcare resources (eg, staffing) - Personal out-of-pocket expenses - Effectiveness: Δ6MWD (m) - Utility: QALY (SF-6D) - Comorbidities Follow-up: 0, 8 weeks, 12 mths
Burns et al. 2016 ²⁴ - Parallel investigator-blind RCT, 12-mth time horizon - CEA/CUA	- United Kingdom - Healthcare perspective 2012-2013 British pounds sterling	- Stable COPD based on FEV₁ < 70% predicted - smoking history of > 20 pack-years ≥ 60% attendance rate of standard PR course - Con: n = 75, age = 69.3 (SD 8.9), FEV₁ = N/A - Int: n = 73, age = 67.3 (SD 15.1), FEV₁ = N/A	Standard care: encouragement to continue exercises at the conclusion of the initial 2-mth PR course and attend a local support group for people with lung conditions.	Low-intensity maintenance course: 2 hr maintenance session at 3, 6 and 9 mths after completion of standard PR course, comprising 1 hr of education and 1 hr of structured exercise in addition to standard care. Patients received an individually tailored exercise prescription, to be undertaken at home, which was reviewed at each session and modified as appropriate.	- Costs: - Healthcare resources (eg, staffing) - Social services - Out-of-pocket expenses - Productivity loss - Effectiveness: CRQ - Utility: QALY (EQ-5D-3L) Follow-up: 0, 3, 6, 9 and 12 mths
Cross et al. 2010 ²² - Equivalence RCT, 6-mth time horizon - CEA/CUA	- United Kingdom - Healthcare perspective 2007-2008 British pounds sterling	- COPD based on FEV₁ < 80% predicted and FEV₁/FVC < 0.7 - Acute exacerbation - Con: n = 264, age = 69.6 (SD 9.5), FEV₁ = N/A - Int: n = 258, age = 69.1 (SD 9.9), FEV₁ = N/A	Airway clearance technique: advice on positioning, cough and sputum mobilisation in accordance with ACBT. This information was reinforced by providing an information sheet with the advice.	Airway clearance technique: MCP during thoracic expansion exercises and vibration during expiration. Treatment interspersed with periods of relaxed abdominal breathing and FET in accordance with ACBT. Following MCP, the PT provided the patient with advice on positioning, with ACBT. This information was reinforced by providing an information sheet with the advice.	- Costs: - Healthcare resources (eg, staffing) - Personal social services - Effectiveness: SGRQ: symptoms, activity, impact and total score - Utility: QALY (EQ-5D) Follow-up: 0, 6 weeks and 6 mths

Table 1 (Continued)

Study	Setting	Participants	Control	Intervention	Outcome measures
Gillespie et al. 2013 ¹⁹ • Cluster RCT, 5.5-mth time horizon • CEA/CUA	• Ireland • Healthcare perspective • 2009 Euros	• COPD based on GOLD guidelines. • Con: n = 172, age = 68.4 (SD 10.3), FEV ₁ = 59.7 (SD 13.8) • Int: n = 178, age = 68.8 (SD 10.2), FEV ₁ = 57.6 (SD 14.3)	Standard care in Irish general practices	Structured education PR course: 2-hr group-based session each week for 8 weeks delivered jointly by practice nurse and PT. The PT focused on delivering the exercise component. Afterwards, participants were followed up formally via telephone call at 4 weeks after completion of the course and via a 1-hr group session at 10 weeks.	• Costs: ◦ Healthcare resources (eg, GP visit) ◦ Medication ◦ Travel expenses ◦ Time input • Effectiveness: CRQ • Utility: QALY (EQ-5D-3L) Follow-up: 0 and 5.5 mths
Goldstein et al. 1997 ³² • RCT, 6-mth time horizon • CEA	• Canada • Societal perspective • 1989 Canadian dollars	• Severe stable COPD defined by FEV ₁ < 40% pred. ⁴³ • Con: n = 44, age = 65 (SD 8), FEV ₁ = 34.6 (SD 11.8) • Int: n = 45, age = 66 (SD 7), FEV ₁ = 34.8 (SD 14.5)	Usual care: GP and/or respiratory specialist with no special attention to rehabilitation.	Supervised PR: 2 mths inpatient followed by 4 mths combination of outpatient and home exercises. The inpatient activities included supervised exercise training, patient education and psychosocial support. During the next 4 mth, daily home exercise program with 3 to 4 home-care visits and outpatient appointments for 4 to 5 supervised exercise training by PT.	• Costs: ◦ Healthcare resources (eg, medical care, home-care services) ◦ Transportation costs • Effectiveness: CRQ Follow-up: 0 and 6 mths
Goossens et al. 2013 ²³ • RCT, time horizon 3 mths • CEA/CUA	• Netherlands • Healthcare and societal perspective • 2009 Euros	• COPD based on GOLD guidelines • Acute exacerbation • Smoking history ≥ 10 pack-years • Con: n = 69, age = 67.80 (SD 11.30), FEV ₁ = N/A • Int: n = 70, age = 68.31 (SD 10.34), FEV ₁ = N/A	Early assisted discharge with home care: all patients received usual care between days 1 and 3. The PT instructed the patient in breathing, coughing techniques and reactivation. The PT instructed the patient to follow the written instructions at home. The previously described treatment was continued at home and supervised by nurses. ³⁴ Duration: 7 days Usual care: outpatient or primary care follow-up.	Usual inpatient hospital treatment: all patients received usual care between days 1 and 7. The PT instructed the patient in breathing, coughing techniques and reactivation. Duration: 7 days.	• Costs: ◦ Healthcare resources (eg, GP visit) ◦ Non-healthcare costs (eg, unpaid domestic help) ◦ Productivity loss • Effectiveness: CCQ • Utility: QALY (EQ-5D-5L) Follow-up: 0, 7 days and 3 mths
Griffiths et al. 2001 ³⁰ • RCT, time horizon 12 mths • CUA	• United Kingdom • Healthcare perspective • 2001 British pounds sterling	• COPD with FEV ₁ < 60% pred. ⁴⁴ • Con: n = 101, age = 68.3 (SD 8.1), FEV ₁ = 39.4 (SD 16.4) • Int: n = 99, age = 68.2 (SD 8.2), FEV ₁ = 39.7 (SD 16.2)	Usual care: outpatient or primary care follow-up.	Outpatient PR program: patients received rehabilitation on three half days per week for 6 weeks. Each session lasted for approximately 2 hrs and included educational activities, exercise periods and psychosocial sessions. Individual goal setting, dietary intervention, PT and occupational therapy were also included. After the 6-week program, patients were invited to join a patient-run group meeting.	• Costs: ◦ Healthcare resources (eg, PR service) ◦ Transport • Utility: QALY (SF-6D) Follow-up: 0, 6 weeks and 12 mths

Table 1 (Continued)

Study	Setting	Participants	Control	Intervention	Outcome measures
Hoogendoorn et al 2010 ³¹ • RCT, time horizon 24 mths • CEA/CUA	• Netherlands • Societal and third-party payer's perspective • 2007 Euros	• COPD GOLD II-III • Impaired exercise capacity < 70% predicted • Con: n = 88, age = 67 (SD 9), FEV ₁ = 58 (SD 17) • Int: n = 87, age = 66 (SD 9), FEV ₁ = 60 (SD 15)	Usual care: pharmacotherapy according to accepted guidelines, a short smoking cessation advice session from the respiratory physician and short nutritional advice.	Interdisciplinary community-based management course ⁴⁵ : 4-mth, supervised, intensive intervention: 2x/week individual exercise training sessions by PT. Patients were instructed and motivated to perform exercises at home and to walk/cycle 2x/day. Smoking cessation counselling, education, self-management skills provided by respiratory nurses. 20-mth active maintenance: patients visited the PT 1x/mth to monitor exercise capacity and adherence to the training and to provide encouragement to continue the exercise training at home.	• Costs: ◦ Healthcare resources (eg, GP visit) ◦ Non-healthcare costs (eg, unpaid domestic help) ◦ Travel expenses ◦ Productivity loss • Effectiveness: SGRQ, total number of COPD exacerbations • Utility: QALY (EQ-5D) Follow-up: 0, 4, 12 and 24 mths. Exacerbations continuously during 24 mths
Waterhouse et al 2010 ²⁵ • RCT, 2x2 factorial design, time horizon 18 mths • CUA	• United Kingdom • Healthcare perspective • 2010 British pounds sterling	• COPD based on GOLD guidelines • Con: n = 129, age = 69.1 (SD 7.5), FEV ₁ = 48.3 (SD 19.3) • Int: n = 111, age = 68.7 (SD 8.3), FEV ₁ = 45.1 (SD 16.3)	PR in hospital setting: Acute: exercises training in combination with education leading to a total of 2 hrs/session, two times/week, for 6 weeks. Patients were encouraged to exercise between formal classes. They kept an exercise diary at home between sessions. Long-term: telephone follow-up versus 'standard follow-up'. An exercise booklet, individualised for the level of exercise the participant had achieved during the sessions, was provided and the research participants were encouraged to keep up with the booklet exercises. Intervention calls gave encouragement to exercise, not general healthcare advice.	PR in community setting: Acute: exercises training in combination with education leading to a total of 2 hrs/session, two times/week, for 6 weeks. Patients were encouraged to exercise between formal classes. They kept an exercise diary at home between sessions. Long-term: telephone follow-up versus 'standard follow-up'. An exercise booklet, individualised for the level of exercise the participant had achieved during the sessions, was provided and the research participants were encouraged to keep up with the booklet exercises. Intervention calls were orientated to giving encouragement to exercise, not general healthcare advice.	• Costs: ◦ Healthcare resources (eg, GP service) ◦ Non-healthcare costs (eg, home help) • Utility: QALY (SF-6D) Follow-up: 0, 6 weeks, 6, 12 and 18 mths
Zwerink et al 2016 ²⁶ • RCT, time horizon 24 mths • CEA/CUA	• Netherlands • Healthcare perspective • 2009 Euros	• COPD based on GOLD guidelines • ≥ three exacerbations or one hospitalisation respiratory problems in 2 yrs preceding study entry • Con: n = 76, age = 64.1 (SD 7.7), FEV ₁ = 50.5 (SD 17.0) • Int: n = 77, age = 63.1 (SD 8.1), FEV ₁ = 49.6 (SD 14.2)	Self-management program: first mth, patients attended four 2-hr self-management sessions.	Community-based exercise program within a self-management program: first mth, patients attended four 2-hr self-management sessions. Afterwards followed by an exercise program by PT of private practices, consisting of a 6-mth 'compulsory' period (3 sessions/week) and subsequently a 5-mth 'optional' period (2 sessions/week). Since COPE-active was intended to change behaviour with regard to exercise, one session/week in both periods consisted of unsupervised home-based exercise training.	• Costs: ◦ Healthcare resources (eg, medication prescriptions) • Effectiveness: ISWT, daily step count • Utility: QALY (EQ-5D) • Follow-up: 0, 7, 12, 18 and 24 mths

ACBT = active cycle breathing techniques, CCQ = Clinical COPD Questionnaire, CEA = cost-effectiveness analysis, Con = control group, CRQ = Chronic Respiratory Questionnaire, CUA = cost-utility analysis, EQ-5D = EuroQol five dimensional, FET = forced expiration technique, FEV₁ = forced expiratory volume in 1 second (% predicted), GP = general practitioner, IDM = integrated disease management, Int = Interventional group, ISWT = incremental shuttle walk test, MCP = manual chest percussion, N/A = not available in published manuscript, PR = pulmonary rehabilitation, PT = physiotherapist, QALY = quality-adjusted life years, RCT = randomised controlled trial, SGRQ = St. George Respiratory Questionnaire, 6MWD = 6-minute walk distance.

Table 2Critical appraisal of the included clinical trials, assessed using the JBI Critical Appraisal Checklist for Economic Evaluation.¹⁶

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11
Boland et al 2015 ²⁰	+	+	+	+	+	+	+	+	+	+	+
Burge et al 2020 ²¹	+	+	+	+	+	+	+	+	+	+	+
Burns et al 2016 ²⁴	+	+	+	-	+	+	+	+	+	+	+
Cross et al 2010 ²²	+	+	+	-	+	+	+	+	-	0	-
Gillespie et al 2013 ¹⁹	+	+	+	+	+	+	N/A	+	+	+	+
Goldstein et al 1997 ³²	+	+	+	+	+	+	+	+	-	+	-
Goossens et al 2013 ²³	+	+	+	+	+	+	+	+	+	+	+
Griffiths et al 2001 ³⁰	+	+	+	+	+	+	0	+	+	+	+
Hoogendoorn et al 2010 ³¹	+	+	+	+	+	+	+	+	+	+	+
Waterhouse et al 2010 ²⁵	+	+	+	+	+	+	0	+	+	+	-
Zwerink et al 2016 ²⁶	+	+	+	+	+	+	+	+	+	+	+

+ = yes, - = inadequate methodology, 0 = insufficient information, N/A = not applicable.

Q1 = Is there a well-defined question?, Q2 = Is there comprehensive description of alternatives?, Q3 = Are all important and relevant costs and outcomes for each alternative identified?, Q4 = Has clinical effectiveness been established?, Q5 = Are costs and outcomes measured accurately?, Q6 = Are costs and outcomes valued credibly?, Q7 = Are costs and outcomes adjusted for differential timing?, Q8 = Is there an incremental analysis of costs and consequences?, Q9 = Were sensitivity analyses conducted to investigate uncertainty in estimates of cost or consequences?, Q10 = Do study results include all issues of concern to users?, Q11 = Are the results generalisable to the setting of interest in the review?

was assessed by two different field walking tests, with the walking distance covered as the primary outcome. Burge et al²¹ used the distance (6-minute walk distance) of the self-paced 6-minute walk test as a measure of functional exercise capacity, while Zwerink et al²⁶ used the externally paced incremental shuttle walk test to report the maximal exercise capacity. The total number of exacerbations was calculated as the sum of both moderate and severe exacerbations. Similar definitions were used in both clinical trials.^{20,31} Mean daily step count was assessed with a pedometer to unravel any clinical effect on daily physical activity.²⁶

Effect of interventions

Five studies reported statistically significant changes regarding disease-specific QOL^{19,23,31,32} and health status³⁰ (see Tables 4 to 6). Four of these studies compared a structured multicomponent intervention with exercise training versus usual care.^{19,30–32} While Gillespie et al (n = 350) reported only a statistically significant, positive change in the mean total CRQ, both Hoogendoorn et al³¹ (n = 175) and Goldstein et al³² (n = 89) showed statistically and clinically relevant changes in disease-specific QOL. Griffiths et al (n = 200) demonstrated a positive, albeit small, significant change in QALYs.³⁰ Goossens et al (n = 139) compared the usual inpatient hospital care, including respiratory physiotherapy, versus an early assisted discharge program at home. A statistically significant difference was observed between the groups in the probability of having a clinically relevant improvement in the CCQ score between days 3 and 7 (51.3% in the usual hospital care group versus 31.7% in the early discharge group).²³

Costs

Costs reported in the studies could be divided into three subgroups: intervention, direct medical (healthcare, out-of-pocket) and indirect costs (productivity loss). All studies reported the intervention and direct medical cost. Interestingly, only four studies investigated the effect of their intervention on productivity loss.^{20,23,24,31} Only in two out of 11 studies, the mean costs were significantly higher than the alternative interventions ($p < 0.05$).^{19,20} Gillespie et al assessed the cost-effectiveness of a structured education PR program relative to usual practice in primary care from a healthcare perspective. The intervention was estimated to result in a statistically significant increase in mean cost per patient of €944 (95% CI 489 to 1,400) in total healthcare costs.¹⁹ Boland et al compared a disease management program to usual care. The adjusted mean total costs were significantly higher in the disease management group than in the usual care group by €584 (95% CI 86 to 1,046) from a healthcare perspective and €645 (95% CI 28 to 190) from a societal perspective.²⁰

Cost-effective analyses

All 45 ICERs were extracted across the three different perspectives: 25 ICERs from a healthcare perspective, 17 ICERs from a societal perspective and three ICERs from a third-party payer perspective. All ICERs were converted to 2019 Euros (Tables 4 to 6). Based on the extracted data, the intervention was interpreted to be cost-effective in four studies,^{21,23,30,32} while in two it was not.^{25,33} The cost-effectiveness was uncertain or dependent on the willingness to pay in five studies.^{19,22,24,26,31}

Healthcare perspective

More than half of all the reported ICERs for this perspective (15 of 25, 60%) were located in the eastern quadrants of the cost-effectiveness plane, suggesting that the intervention was more effective than the control group. Twenty percent of the ICERs were dominant (south-east quadrant) indicating that the intervention was more effective and less expensive than the comparison. For example, Griffiths et al (n = 200) showed that their 6-week outpatient PR program was more effective (Δ QALY, +0.03, 95% CI 0.002 to 0.058) and potentially cost saving (Δ cost, -£152, 95% CI -880 to 577) compared with standard care.³⁰ In contrast with these unambiguous findings, Burns et al²⁴ (n = 148) concluded that while the 12-month low-intensity maintenance program was less expensive (Δ cost, £-204.04, 95% CI -1,522.18 to 1,114.10), it yielded incremental QALY gains (+0.015, 95% CI -0.050 to 0.079) but had losses in disease-specific QOL (Δ CRQ, -0.007, 95% CI -0.461 to 0.447) (south-west quadrant). Also, only one ICER in Cross et al's study²² (n = 522) on manual percussion dominated the control group for disease-specific QOL (Δ SGRQ, symptoms score, -0.09). Overall, percussion was associated with lower health service costs by savings associated with fewer hospital admissions among participants assigned to receive percussion. However, interpretation of this saving should be examined in the light of the location of the other ICERs, which demonstrated clinical changes in favour of the control group (south-west quadrant).²² The majority of the ICERs in the eastern quadrant were located in the north-east quadrant (40%), indicating that the intervention was more effective but also more costly than the alternatives for positive changes in daily physical activity,²⁶ exercise capacity,²⁶ disease-specific QOL^{19,23} and health status (utilities).^{19,23,26} In contrast to the other studies, the integrated care program by Boland et al (n = 1,086) was not cost-effective in primary care since it was dominated by the alternative (usual care) for all clinical outcomes and related costs (north-west quadrant).²⁰

Societal perspective

Twelve of 17 ICERs (71%) were located in the eastern quadrants of the cost-effectiveness plane, suggesting that the intervention was more effective than the control group. Twenty-four percent of the

Table 3

Use of respiratory physiotherapy interventions per syllabus items described in the European Respiratory Society core curriculum in respiratory physiotherapy.

Core curriculum in respiratory physiotherapy for adult patients		Studies
Module	Syllabus item	
2 Airway clearance techniques	Body positioning	• Cross et al 2010 ²²
	Manual clapping	• Cross et al 2010 ²²
	Vibration	• Cross et al 2010 ²²
	ACBT	• Cross et al 2010 ²²
	Assisted cough	• Cross et al 2010 ²² • Goossens et al 2013 ²³
3 Respiratory muscle training, breathing strategies and techniques for lung expansion	Self-management/education ACT	• Cross et al 2010 ²² • Goossens et al 2013 ²³
	Breathing exercises	• Goossens et al 2013 ²³
4 Exercise training and physical activity	Exercise training	• Boland et al 2015 ²⁰ • Burge et al 2020 ²¹ • Burns et al 2016 ²⁴ • Gillespie et al 2013 ¹⁹ • Goldstein et al 1997 ³² • Griffiths et al 2001 ³⁰ • Hoogendoorn et al 2010 ³¹ • Waterhouse et al 2010 ²⁵ • Zwerink et al 2016 ²⁶
	Physical activity	• Boland et al 2015 ²⁰ • Burge et al 2020 ²¹ • Burns et al 2016 ²⁴ • Goldstein et al 1997 ³² • Goossens et al 2013 ²³ • Griffiths et al 2001 ³⁰ • Hoogendoorn et al 2010 ³¹ • Waterhouse et al 2010 ²⁵ • Zwerink et al 2016 ²⁶

ACBT = active cycle breathing techniques, ACT = airway clearance technique.

ICERs were dominant (south-east quadrant) indicating that the intervention was more effective and less expensive than the comparison. The hospital care in the Goossens et al (n = 139) study included respiratory physiotherapy for all participants with breathing and coughing instructions and reactivation for a treatment period of 7 days. A standardised written instruction was developed, ensuring identical instruction in the participating hospitals.^{23,34} This hospital care was less expensive (Δ mean cost €-880, 95% CI -580 to 2,268) than the early assisted-discharge group after 3 months of follow-up and yielded incremental gains in disease-specific QOL (Δ CCQ -0.041, 95% CI -0.41 to 0.48) and health status (Δ QALY 0.005, 95% CI -0.021 to 0.0095).²³ Although at 3 months all ICERs were located in the south-east quadrant, the ICERs after the 7-day treatment period were located in the north-east quadrant. The cost in the hospital care group was now slightly higher than the early assisted-discharge group, leading to an incremental cost difference of €65 (95% CI -152 to 25) in combination with a positive clinical effect on disease-specific QOL (Δ CCQ -0.290, 95% CI -0.03 to 0.61).²³ The same ICERs were observed for the 24-month INTERdisciplinary COMMunity-based COPD management program (INTERCOM) in the study by Hoogendoorn et al,³¹ leading to a total of 47% ICERs located in the north-east quadrant. More specifically, the INTERCOM group had 30% (95% CI 3 to 56) more patients with a clinically relevant improvement in disease-specific QOL (SGRQ) and 0.08 (95% CI -0.01 to 0.18) more QALYs per patient. Mean total 2-year costs were higher for INTERCOM than for usual care, which resulted in an ICER of €9,960.48 per additional patient with a relevant improvement in SGRQ or €35,577 per QALY.³¹ All ICERs related to the cost per exacerbation avoided within a time horizon of 24 months were located in the south-west

quadrant, meaning that the interventions were dominated by usual care.^{20,31}

Third-party payer's perspective

Only Hoogendoorn et al reported ICERs from a third-party payer's perspective. Two of three ICERs for this perspective were located in the north-east quadrant, and slightly lower than the societal perspective: €7,774.82 per additional patient with a relevant improvement in SGRQ total score or €27,769.26 per QALY. Nevertheless, a higher mean number of exacerbations (0.84, 95% CI -0.07 to 1.78) led to an ICER in the north-west quadrant.³¹

Discussion

Of the 11 included studies, four studies were interpreted to be cost-effective,^{21,23,30,32} while two were not.^{25,33} In five studies, the cost-effectiveness was uncertain or dependent on the willingness to pay.^{19,22,24,26,31} For example, Zwerink et al (n = 153) reported that their community-based exercise program could not be considered cost-effective based on the primary outcome. Nonetheless, the ICERs for the secondary outcomes on physical activity and QALY were generally considered to be acceptable.²⁶ Since respiratory physiotherapy interventions are aimed at improving health-related QOL,³⁵ this specific treatment goal was investigated in more detail. Regardless of the economic perspectives, this systematic review showed that 67% of all QOL-related ICERs were situated in the north-east or south-east quadrants of the cost-effectiveness plane. Moreover, 71% of all the QALYs were also located in these quadrants. When examining potential new treatments and ever-growing medical costs for an efficient healthcare system, cost-effectiveness thresholds are often used. While the advantages and disadvantages of cost-effectiveness thresholds as a formal measure are known, many countries are still using cost-effectiveness thresholds within the World Health Organization guidelines of one-to-three times the gross domestic product per capita.³⁶ Cameron et al confirmed this approach in a recent systematic review and identified an average willingness to pay per QALY of US\$77,509.³⁷ Comparing the ICERs located in the north-east and south-east quadrants with the specified cost-effectiveness threshold of US\$77,509 per QALY, six studies^{21,23,24,26,30,31} could be seen as cost-effective in terms of cost per QALY when offering respiratory physiotherapy interventions focusing on exercise training in combination with enhancing physical activity levels.

Although most ICERs indicated that the interventions were cost-effective and since statistical and clinical significance was hard to demonstrate, even with the applied sensitivity analysis, these ICERs should be interpreted with caution for several reasons. First, the complex and heterogeneous nature of COPD as a disease could limit the generalisability of the reported results. Patients with very severe COPD (FEV₁ < 30% predicted) were not enrolled in the selected trials. Although obtaining a homogeneous sample was prioritised in this study design, it does raise concerns about the generalisability towards those very severe patients seen in clinical practice. Furthermore, Cross et al²² reported that the use of manual chest therapy for airway clearance did not appear to affect QOL, while it was cost-effective. Since much uncertainty was associated with the latter, it would be difficult to justify providing ACT on the basis of cost-effectiveness alone. Nevertheless, ACTs seem to be safe and generate small benefits on short-term reductions in the need for increased ventilatory assistance, duration of ventilatory assistance and hospital length of stay. Therefore, selecting better-defined subgroups in the future (ie, patients prone to the retention of secretions as a treatable trait)³⁸ could potentially demonstrate both the cost-effectiveness and therapeutic value of ACT.^{39,40} Second, from all 11 economic evaluations included in the present review, only five studies reported statistically significant positive changes in disease-specific QOL^{19,23,31} and health status.³⁰ The majority of these studies compared a structured multicomponent intervention with

Table 4

Healthcare perspective: cost and effects (mean) for each group, mean (95% CI) difference between groups, incremental cost-effectiveness ratios and cost-effectiveness plane per outcome.

Study	Outcome, time horizon	Costs			Effect			Cost-effectiveness	
		Intervention	Control	Intervention minus control (95% CI)	Intervention	Control	Intervention minus control (95% CI)	ICERs (2019 Euros) ^b	CE plane
Daily physical activity									
Zwerink et al 2016	Cost per additional patient with 500 steps/day, 24 mths	€6,949	€6,511	€438 (N/A)	0.09	-0.19	0.28 (-0.01 to 0.59)	€1,783.16	N/E
Exercise capacity									
Burge et al 2020	Cost per Δ6MWD, 8 weeks	\$15,447	\$19,944	\$-4,497 (-12,250 to 3,257)	24	11	14 (-11 to 39)	Dominant	S/E
Zwerink et al 2016	Cost per additional patient with a clinically relevant improvement in ISWT, 24 mths	€6,949	€6,511	€438 (N/A)	-0.28	-0.35	0.07 (-0.18 to 0.33)	€7,133.77	N/E
Quality of life									
Goossens et al 2013 ^d	Cost per point additional improvement in mean CCQ score, 7 days	€1,463	€1,219	€244 (-315 to -168)	-0.303	-0.013	-0.290 (-0.03 to 0.61)	€959.99	N/E
Goossens et al 2013 ^d	Cost per additional patient with improved CCQ score, 7 days	€1,463	€1,219	€244 (-315 to -168)	0.513	0.327	0.1941 (-0.3625 to -0.5)*	€1,433.14	N/E
Goossens et al 2013 ^d	Cost per point additional improvement in mean CCQ score, 3 mths	€4,297	€4,129	€168 (-1,253 to 922)	0.024	0.065	-0.041 (-0.41 to 0.48)	€4,672.24	N/E
Goossens et al 2013 ^d	Cost per additional patient with improved CCQ score, 3 mths	€4,297	€4,129	€168 (-1,253 to 922)	0.399	0.358	0.0417 (-0.2194 to 0.1527)	€4,560.51	N/E
Gillespie et al 2013	Cost per CRQ total score, 22 weeks	€2,357	€1,505	€944 (489 to 1,400)* ^a	20.82	19.10	1.11 (0.35 to 1.87)* ^{a,b}	€917.52	N/E
Cross et al 2010	Cost per SQRQ symptoms score, 6 mths	£5,870.31	£6,281.10	£-410.79 (N/A)	-11.28	-11.19	-0.09 (N/A)	Dominant	S/E
Cross et al 2010	Cost per SQRQ activity score, 6 mths	£5,870.31	£6,281.10	£-410.79 (N/A)	-5.50	-6.00	0.50 (N/A)	€1,154.04	S/W
Cross et al 2010	Cost per SQRQ impacts score, 6 mths	£5,870.31	£6,281.10	£-410.79 (N/A)	-5.15	-6.06	0.91 (N/A)	€636.56	S/W
Cross et al 2010	Cost per SQRQ total score, 6 mths	£5,870.31	£6,281.10	£-410.79 (N/A)	-5.22	-6.10	0.89 (N/A)	€654.95	S/W
Burns et al 2016	Cost per ΔCRQ, 12 mths	£3,726	£3,122	£-204.04 (-1,522.18 to 1,114.10) ^a	-0.537	-0.819	-0.007 (-0.461 to 0.447) ^b	€38,006.90	S/W
Boland et al 2015	Cost per additional patient with clinically relevant improvement in CCQ, 24 mths	€5,119	€4,535	€584 (86 to 1,046)*	0.11	0.12	-0.02 (-0.06 to 0.02)	Dominated	N/W
Boland et al 2015	Cost per additional patient with a clinically relevant improvement in SGRQ, 24 mths	€5,119	€4,535	€584 (86 to 1,046)*	0.26	0.27	-0.01 (-0.07 to 0.04)	Dominated	N/W
Utility									
Gillespie et al 2013	Cost per QALY gained, 22 weeks	€2,357	€1,505	€944 (489 to 1,400)*	0.337	0.305	0.002 (-0.006 to 0.011) ^b	€509,492.18	N/E
Burge et al 2020	Cost per QALY, 8 weeks	\$15,447	\$19,944	\$-4,497 (-12,250 to 3,257)	0.645	0.621	0.025 (-0.038 to 0.086)	Dominant	S/E
Goossens et al 2013 ^d	Cost savings per incremental QALY lost, 3 mths	€4,297	€4,129	€168 (-1,253 to 922)	0.175	0.170	0.005 (-0.021 to 0.0095)	€35,470.49	N/E
Cross et al 2010	Cost per QALY, 6 mths	£5,870.31	£6,281.10	£-410.79 (N/A)	0.018	0.020	-0.002 (N/A)	€334,658.35	S/W
Burns et al 2016	Cost per QALY, 12 mths	£4,002	£2,686	£-204.04 (-1,522.18 to 1,114.10) ^a	0.581	0.555	0.015 (-0.050 to 0.079) ^b	Dominant	S/E
Boland et al 2015	Cost per QALY, 24 mths	€5,119	€4,535	€584 (86 to 1,046)*	1.40	1.44	-0.04 (-0.07 to -0.01)*	Dominated	N/W
Zwerink et al 2016	Cost per additional QALY, 24 mths	€6,949	€6,511	€438 (N/A)	1.53	1.49	0.04 (-0.10 to 0.18)	€12,484.39	N/E
Waterhouse et al 2010	Cost per QALY, 18 mths	£3,643.74	£4,511.21	£-867 (-2,366.11 to 631.17)	1.51	1.54	-0.03 (-0.13 to 0.07)	€39,425.41	S/W
Griffiths et al 2001	Cost per QALY, 12 mths	£1,674	£1,826	£-152 (-880 to 577)	0.381	0.351	0.03 (0.002 to 0.058)*	Dominant	S/E
Exacerbations									
Boland et al 2015	Cost per exacerbation avoided, 24 mths	€5,119	€4,535	€584 (86 to 1,046)*	0.78	0.65	-0.14 (-0.30 to 0.06)	Dominated	N/W

^aAdjusted with missing data imputed, ^bEstimation of incremental effectiveness at follow-up was undertaken using GEE regression models, assuming a Gaussian variance function and controlling for treatment arm, baseline EQ5D score and clustering, ^cConversion of original ICERs to 2019 Euros by CCEMG-EPPI-Centre Cost Converter with IMF as source dataset for PPP value and selected country Belgium, ^dControl group and intervention group are reversed compared with original publication since usual care involved physiotherapy interventions.

CCQ = Clinical COPD Questionnaire, CE = cost effectiveness, CRQ = Chronic Respiratory Questionnaire, ICERs = incremental cost-effectiveness ratios, ISWT = incremental shuttle walk test, N/E, north-east, N/W, north-west, QALY = quality-adjusted life years. SGRQ = St. George Respiratory Questionnaire, S/E = south-east, S/W = south-west, 6MWD = 6-minute walk distance.

* Significant, $p < 0.05$.

Table 5

Societal perspective: cost and effects (mean) for each group, mean (95% CI) difference between groups, incremental cost-effectiveness ratios and cost-effectiveness plane per outcome.

Study	Outcome, time horizon	Costs			Effect			Cost-effectiveness	
		Intervention	Control	Intervention minus control (95% CI)	Intervention	Control	Intervention minus control (95% CI)	ICER (<i>2019 Euros</i>) ^a	CE plane
Quality of life									
Goossens et al 2013 ^b	Cost per point additional improvement in mean CCQ score, 7 days	€1,463	€1,398	€65 (–152 to 25)	–0.303	–0.013	–0.290 (–0.03 to 0.61)	€224	N/E
Goossens et al 2013 ^b	Cost per additional patient with improved CCQ score, 7 days	€1,463	€1,398	€65 (–152 to 25)	0.513	0.327	0.1941 (–0.3625 to –0.5)*	€335	N/E
Goossens et al 2013 ^b	Cost per point additional improvement in mean CCQ score, 3 mths	€5,395	€6,304	€–880 (–580 to 2,268)	0.024	0.065	–0.041 (–0.41 to 0.48)	Dominant	S/E
Goossens et al 2013 ^b	Cost per additional patient with improved CCQ score, 3 mths	€5,395	€6,304	€–880 (–580 to 2,268)	0.399	0.358	0.0417 (–0.2194 to 0.1527)	Dominant	S/E
Boland et al 2015	Cost per additional patient with clinically relevant improvement in CCQ, 24 mths	€5,750	€5,105	€645 (28 to 190)*	0.11	0.12	–0.02 (–0.06 to 0.02)	Dominated	N/W
Boland et al 2015	Cost per additional patient with a clinically relevant improvement in SGRQ, 24 mths	€5,750	€5,105	€645 (28 to 190)*	0.26	0.27	–0.01 (–0.07 to 0.04)	Dominated	N/W
Hoogendoorn et al 2010	Cost per additional patient with a clinically relevant improvement in SGRQ, 24 mths	€13,565	€10,814	€2,751 (–631 to 6,372)	0.13	–0.17	0.3 (0.03 to 0.56)*	€9,078	N/E
Goldstein et al 1997	Cost per unit change in CRQ domain dyspnoea, 6 mths	€12,311	€654	\$ 11,597 (N/A)	–	–	0.61 (N/A)*	€19,011	N/E
Goldstein et al 1997	Cost per unit change in CRQ domain fatigue, 6 mths	€12,311	€654	\$ 11,597 (N/A)	–	–	0.33 (N/A)	€35,142	N/E
Goldstein et al 1997	Cost per unit change in CRQ domain emotional function, 6 mths	€12,311	€654	\$ 11,597 (N/A)	–	–	0.44 (N/A)*	€26,357	N/E
Goldstein et al 1997	Cost per unit change in CRQ domain mastery, 6 mths	€12,311	€654	\$ 11,597 (N/A)	–	–	0.70 (N/A)*	€16,567	N/E
Utility									
Goossens et al 2013 ^b	Cost savings per incremental QALY lost, 3 mths	€5,395	€6,304	€–880 (–580 to 2,268)	0.175	0.170	0.005 (–0.021 to 0.0095)	Dominant	S/E
Burge et al 2020	Cost per QALY, 12 mths	N/A	N/A	\$ –4,316 (–16,328 to 6,780)	0.645	0.621	0.025 (–0.038 to 0.086)	Dominant	S/E
Hoogendoorn et al 2010	Cost per QALY, 24 mths	€13,565	€10,814	€2,751 (–631 to 6,372)	1.62	1.54	0.08 (–0.01 to 0.18)	€32,425	N/E
Boland et al 2015	Cost per QALY, 24 mths	€5,750	€5,105	€645 (28 to 190)*	1.40	1.44	–0.04 (–0.07 to –0.01)*	Dominated	N/W
Exacerbations									
Boland et al 2015	Cost per exacerbation avoided, 24 mths	€5,750	€5,105	€645 (28 to 190)*	0.78	0.65	–0.14 (–0.30 to 0.06)	Dominated	N/W
Hoogendoorn et al 2010	Cost per exacerbation avoided, 24 mths	€13,565	€10,814	€2,751 (–631 to 6,372)	3.02	2.18	0.84 (–0.07 to 1.78)	Dominated	N/W

^aConversion of original ICERs to 2019 Euros by CCEMG-EPPI-Centre Cost Converter with IMF as source dataset for PPP value and selected country Belgium, ^bControl group and intervention group are reversed compared with original publication since usual care involved physiotherapy interventions.

CCQ = Clinical COPD Questionnaire, CRQ = Chronic Respiratory Questionnaire, CE = cost effectiveness, ICER = incremental cost-effectiveness ratios, N/E, north-east, N/W, north-west, QALY = quality-adjusted life years, SGRQ = St. George Respiratory Questionnaire, S/E = south-east, S/W = south-west.

* Significant, $p < 0.05$.

Table 6 Third-party payer's perspective: cost and effects (mean) for each group, mean (95% CI) difference between groups, incremental cost-effectiveness ratios and cost-effectiveness plane per outcome.

Study	Outcome, time horizon	Costs			Effect			Cost-effectiveness	
		Intervention	Control	Intervention minus control (95% CI)	Intervention	Control	Intervention minus control (95% CI)	ICER (2019 Euros) ^a	CE plane
Quality of life									
Hoogendoorn et al 2010	Cost per additional patient with a clinically relevant improvement in SGRQ, 24 mths	€12,145	€9,998	€2,147 (-1,091 to 5,649)	0.13	-0.17	0.3 (0.03 to 0.56) ^a	€7,774.82	N/E
Utility									
Hoogendoorn et al 2010	Cost per QALY, 24 mths	€12,145	€9,998	€2,147 (-1,091 to 5,649)	1.62	1.54	0.08 (-0.01 to 0.18)	€27,769.26	N/E
Exacerbations									
Hoogendoorn et al 2010	Cost per exacerbation avoided, 24 mths	€12,145	€9,998	€2,147 (-1,091 to 5,649)	3.02	2.18	0.84 (-0.07 to 1.78) ^a	Dominated	N/W

^aConversion of original ICERs to 2019 Euros by CCEMG-EPPI-Centre Cost Converter with IMF as source dataset for PPP value and selected country Belgium.
CE = cost-effectiveness, ICER = incremental cost-effectiveness ratios, N/E, north-east, N/W, north-west. QALY = quality-adjusted life years, SGRQ = St. George Respiratory Questionnaire.

* Significant, $p < 0.05$.

exercise training and physical activity versus usual care.^{19,30–32} In general, the reported content, timing and organisational aspects between all evaluated exercise interventions also differed greatly, which limited comparison and thus drawing conclusions. Therefore, no particular intervention type was found to be more effective than another intervention. Third, the value for QALYs produced as a result of the described interventions appeared small in absolute terms. This could be explained by the relative insensitivity to change in the generic QOL instruments to detect a clinically meaningful improvement in COPD health status compared with larger changes seen in multi-dimensional disease-specific QOL outcome measures.^{19,30} Fourth, cost-effectiveness ratios were influenced by the chosen time horizon: of the six studies that reported a cost-effectiveness threshold lower than US\$77,509 per QALY, only one had a time horizon of less than 1 year.²³ Although the chosen time horizons of the other five studies were between 1 and 2 years, the cost-effectiveness ratios might still be less favourable in the longer term. Finally, a comparison of the various estimates of cost-effectiveness remains complicated because economic measures depend on other factors as well, like local regulations and national health policies. Consequently, generalisation of the findings to other countries may be limited.

It is believed that this is the first systematic review to focus on economic evaluations of respiratory physiotherapy interventions in COPD. The methodology was enhanced by using both PRISMA guidelines and the five-step approach for systematic reviews on economic evaluations^{11,12} to ensure the comprehensiveness of the systematic literature search. Although this extensive approach resulted in 11 trials of high methodological quality, with the majority focusing on exercise training and physical activity, this small number of studies may have limited the significance of this review. For some interventions such as ACT or respiratory muscle training, no conclusions could be made. Nevertheless, these results may offer a solid basis for future reviews and meta-analyses. Another aspect was the heterogeneous nature of the multicomponent interventions identified in the economic evaluations, which limited comparison and thus drawing conclusions. As expected, it was inappropriate to carry out a meta-analysis. In order to shed light on this heterogeneity, the recent ERS harmonised respiratory physiotherapy curriculum was used as a framework for structuring the different components of all interventions.¹⁴ This enabled the authors to compare the different studies, resulting in a detailed descriptive analysis of health economic outcomes on current practices across different areas of respiratory physiotherapy in COPD. Regarding the external validity of the described costs, to provide a best possible comparison of studies, all costs were reported in 2019 Euros. This systematic review highlights the difficulties in designing and undertaking cost-effectiveness studies and raises the question of whether it is possible to determine the economic measures of individual respiratory physiotherapy interventions versus the total package in multi-modal interventions. For future research, this study supports the recent recommendations by Rodrigues et al⁴⁰ that well-designed respiratory physiotherapy intervention studies are still needed with larger samples based on size estimation (eg, very severe COPD with multi-morbidity), optimal and well-described protocols, improved blinding strategies, responsive outcome measures to demonstrate effectiveness and long-term data collection (eg, costs) across the whole healthcare spectrum.

In conclusion, this sample of 11 studies shows that respiratory physiotherapy interventions focusing on exercise training in combination with enhancing physical activity levels have the potential to be cost-effective in terms of costs per unit QOL gained and QALYs. Despite these results, there is still uncertainty on various estimates of cost-effectiveness, due to differences in content and intensity of the type of interventions, outcome measures and comparators. In the future, more studies investigating cost-effectiveness of respiratory physiotherapy interventions in terms of costs per QALY gained from a societal perspective over a long-term horizon are needed to reach definite conclusions.

What was already known on this topic: Chronic obstructive pulmonary disease is one of the most prevalent chronic respiratory diseases worldwide and associated with a significant social and economic burden.

What this study adds: Respiratory physiotherapy interventions focusing on exercise training in combination with enhancing physical activity levels are likely to be cost-effective in terms of costs per unit gain in health-related quality of life and quality-adjusted life years.

Footnotes: ^a Mendeley Desktop, version 1.19.5, Mendeley Ltd, London, UK. ^b EPPI-Centre Cost Converter, version 1.6, London, UK.

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