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Pulmonary Rehabilitation for Patients With Chronic Pulmonary Disease (COPD): An Evidence-Based Analysis

COPD Working Group

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About the Medical Advisory Secretariat

Effective April 5, 2011, the Medical Advisory Secretariat (MAS) became a part of Health Quality Ontario (HQO), an independent body funded by the Ministry of Health and Long-Term Care. The mandate of MAS is to provide evidence-based recommendations on the coordinated uptake of health services and health technologies in Ontario to the Ministry of Health and Long-Term Care and to the health care system. This mandate helps to ensure that residents of Ontario have access to the best available and most appropriate health services and technologies to improve patient outcomes.

To fulfill its mandate, MAS conducts systematic reviews of evidence and consults with experts in the health care services community. The resulting evidence-based analyses are reviewed by the Ontario Health Technology Advisory Committee—to which MAS also provides a secretariat function—and published in the *Ontario Health Technology Assessment Series*.

About the *Ontario Health Technology Assessment Series*

To conduct its comprehensive analyses, MAS systematically reviews the available scientific literature, making every effort to consider all relevant national and international research; collaborates with partners across relevant government branches; consults with clinical and other external experts and developers of new health technologies; and solicits any necessary supplemental information.

In addition, the Secretariat collects and analyzes information about how a new technology fits within current practice and existing treatment alternatives. Details about the technology's diffusion into current health care practices add an important dimension to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist decision-makers in making timely and relevant decisions to optimize patient outcomes.

The public consultation process is available to individuals wishing to comment on an analysis prior to publication. For more information, please visit: http://www.hqontario.ca/en/mas/ohtac_public_engage_overview.html.

Disclaimer

This evidence-based analysis was prepared by MAS for the Ontario Health Technology Advisory Committee and developed from analysis, interpretation, and comparison of scientific research and/or technology assessments conducted by other organizations. It also incorporates, when available, Ontario data and information provided by experts and applicants to MAS to inform the analysis. While every effort has been made to reflect all scientific research available, this document may not fully do so. Additionally, other relevant scientific findings may have been reported since completion of the review. This evidence-based analysis is current to the date of the literature review specified in the methods section. This analysis may be superseded by an updated publication on the same topic. Please check the MAS website for a list of all evidence-based analyses:
http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

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List of Abbreviations

6MWT	6 Minute Walking Test
AECOPD	Acute exacerbation of COPD
COPD	Chronic obstructive pulmonary disease
CI	Confidence interval(s)
CRQ	Chronic Respiratory Questionnaire
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HRQOL	Health-related quality of life
ITT	Intention-to-treat
MCID	Minimal clinically important difference
RCT	Randomized controlled trial
SD	Standard deviation
SGRQ	St. George's Respiratory Questionnaire
UC	Usual care

Executive Summary

In July 2010, the Medical Advisory Secretariat (MAS) began work on a Chronic Obstructive Pulmonary Disease (COPD) evidentiary framework, an evidence-based review of the literature surrounding treatment strategies for patients with COPD. This project emerged from a request by the Health System Strategy Division of the Ministry of Health and Long-Term Care that MAS provide them with an evidentiary platform on the effectiveness and cost-effectiveness of COPD interventions.

After an initial review of health technology assessments and systematic reviews of COPD literature, and consultation with experts, MAS identified the following topics for analysis: vaccinations (influenza and pneumococcal), smoking cessation, multidisciplinary care, pulmonary rehabilitation, long-term oxygen therapy, noninvasive positive pressure ventilation for acute and chronic respiratory failure, hospital-at-home for acute exacerbations of COPD, and telehealth (including telemonitoring and telephone support). Evidence-based analyses were prepared for each of these topics. For each technology, an economic analysis was also completed where appropriate. In addition, a review of the qualitative literature on patient, caregiver, and provider perspectives on living and dying with COPD was conducted, as were reviews of the qualitative literature on each of the technologies included in these analyses.

The Chronic Obstructive Pulmonary Disease Mega-Analysis series is made up of the following reports, which can be publicly accessed at the MAS website at: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

- Chronic Obstructive Pulmonary Disease (COPD) Evidentiary Framework
- Influenza and Pneumococcal Vaccinations for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Smoking Cessation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Community-Based Multidisciplinary Care for Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Pulmonary Rehabilitation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Long-term Oxygen Therapy for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Chronic Respiratory Failure Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Hospital-at-Home Programs for Patients With Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Home Telehealth for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model
- Experiences of Living and Dying With COPD: A Systematic Review and Synthesis of the Qualitative Empirical Literature

For more information on the qualitative review, please contact Mita Giacomini at: http://fhs.mcmaster.ca/ceb/faculty_member_giacomini.htm.

For more information on the economic analysis, please visit the PATH website: http://www.path-hta.ca/About-Us/Contact-Us.aspx.

The Toronto Health Economics and Technology Assessment (THETA) collaborative has produced an associated report on patient preference for mechanical ventilation. For more information, please visit the THETA website: http://theta.utoronto.ca/static/contact.

Objective

The objective of this evidence-based review was to determine the effectiveness and cost-effectiveness of pulmonary rehabilitation in the management of chronic obstructive pulmonary disease (COPD).

Technology

Pulmonary rehabilitation refers to a multidisciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy. Exercise training is the cornerstone of pulmonary rehabilitation programs, though they may also include components such as patient education and psychological support. Pulmonary rehabilitation is recommended as the standard of care in the treatment and rehabilitation of patients with COPD who remain symptomatic despite treatment with bronchodilators.

For the purpose of this review, the Medical Advisory Secretariat focused on pulmonary rehabilitation programs as defined by the Cochrane Collaboration—that is, any inpatient, outpatient, or home-based rehabilitation program lasting at least 4 weeks that includes exercise therapy with or without any form of education and/or psychological support delivered to patients with exercise limitations attributable to COPD.

Research Questions

1. What is the effectiveness and cost-effectiveness of pulmonary rehabilitation compared with usual care (UC) for patients with stable COPD?

2. Does early pulmonary rehabilitation (within 1 month of hospital discharge) in patients who had an acute exacerbation of COPD improve outcomes compared with UC (or no rehabilitation)?

3. Do maintenance or postrehabilitation programs for patients with COPD who have completed a pulmonary rehabilitation program improve outcomes compared with UC?

Research Methods

Literature Search

Search Strategy

For Research Questions 1and 2, a literature search was performed on August 10, 2010 for studies published from January 1, 2004 to July 31, 2010. For Research Question 3, a literature search was performed on February 3, 2011 for studies published from January 1, 2000 to February 3, 2011. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists and health technology assessment websites were also examined for any additional relevant studies not identified through the systematic search.

Inclusion Criteria

Research questions 1 and 2:

- published between January 1, 2004 and July 31, 2010
- randomized controlled trials, systematic reviews, and meta-analyses
- COPD study population
- studies comparing pulmonary rehabilitation with UC (no pulmonary rehabilitation)
- duration of pulmonary rehabilitation program ≥ 6 weeks
- pulmonary rehabilitation program had to include at minimum exercise training

Research question 3:

- published between January 1, 2000 and February 3, 2011
- randomized controlled trials, systematic reviews, and meta-analyses
- COPD study population
- studies comparing a maintenance or postrehabilitation program with UC (standard follow-up)
- duration of pulmonary rehabilitation program ≥ 6 weeks
- initial pulmonary rehabilitation program had to include at minimum exercise training

Exclusion Criteria

Research questions 1, 2, and 3:

- grey literature
- duplicate publications
- non-English language publications
- study population ≤ 18 years of age
- studies conducted in a palliative population
- studies that did not report primary outcome of interest

Additional exclusion criteria for research question 3:

- studies with ≤ 2 sessions/visits per month

Outcomes of Interest

The primary outcomes of interest for the stable COPD population were exercise capacity and health-related quality of life (HRQOL). For the COPD population following an exacerbation, the primary outcomes of interest were hospital readmissions and HRQOL. The primary outcomes of interest for the COPD population undertaking maintenance programs were functional exercise capacity and HRQOL.

Quality of Evidence

The quality of each included study was assessed taking into consideration allocation concealment, randomization, blinding, power/sample size, withdrawals/dropouts, and intention-to-treat analyses.

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria. The following definitions of quality were used in grading the quality of the evidence:

High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Summary of Findings

Research Question 1: Effect of Pulmonary Rehabilitation on Outcomes in Stable COPD

Seventeen randomized controlled trials met the inclusion criteria and were included in this review.

The following conclusions are based on moderate quality of evidence.

- Pulmonary rehabilitation including at least 4 weeks of exercise training leads to clinically and statistically significant improvements in HRQOL in patients with COPD.[1]
- Pulmonary rehabilitation also leads to a clinically and statistically significant improvement in functional exercise capacity[2] (weighted mean difference, 54.83 m; 95% confidence interval, 35.63–74.03; $P < 0.001$).

Research Question 2: Effect of Pulmonary Rehabilitation on Outcomes Following an Acute Exacerbation of COPD

Five randomized controlled trials met the inclusion criteria and are included in this review. The following conclusion is based on moderate quality of evidence.

- Pulmonary rehabilitation (within 1 month of hospital discharge) after acute exacerbation significantly reduces hospital readmissions (relative risk, 0.50; 95% confidence interval, 0.33–0.77; $P = 0.001$) and leads to a statistically and clinically significant improvement in HRQOL.[3]

Research Question 3: Effect of Pulmonary Rehabilitation Maintenance Programs on COPD Outcomes

Three randomized controlled trials met the inclusion criteria and are included in this review. The conclusions are based on a low quality of evidence and must therefore be considered with caution.

- Maintenance programs have a nonsignificant effect on HRQOL and hospitalizations.
- Maintenance programs have a statistically but not clinically significant effect on exercise capacity ($P = 0.01$). When subgrouped by intensity and quality of study, maintenance programs have a statistically and marginally clinically significant effect on exercise capacity.

[1] As measured by all domains of the Chronic Respiratory Questionnaire
[2] As measured by the 6 Minute Walking Test
[3] As measured by all domains of the Chronic Respiratory Questionnaire and total, impact, and activity scores of the St. George's Respiratory Questionnaire

Background

In July 2010, the Medical Advisory Secretariat (MAS) began work on a Chronic Obstructive Pulmonary Disease (COPD) evidentiary framework, an evidence-based review of the literature surrounding treatment strategies for patients with COPD. This project emerged from a request by the Health System Strategy Division of the Ministry of Health and Long-Term Care that MAS provide them with an evidentiary platform on the effectiveness and cost-effectiveness of COPD interventions.

After an initial review of health technology assessments and systematic reviews of COPD literature, and consultation with experts, MAS identified the following topics for analysis: vaccinations (influenza and pneumococcal), smoking cessation, multidisciplinary care, pulmonary rehabilitation, long-term oxygen therapy, noninvasive positive pressure ventilation for acute and chronic respiratory failure, hospital-at-home for acute exacerbations of COPD, and telehealth (including telemonitoring and telephone support). Evidence-based analyses were prepared for each of these topics. For each technology, an economic analysis was also completed where appropriate. In addition, a review of the qualitative literature on patient, caregiver, and provider perspectives on living and dying with COPD was conducted, as were reviews of the qualitative literature on each of the technologies included in these analyses.

The Chronic Obstructive Pulmonary Disease Mega-Analysis series is made up of the following reports, which can be publicly accessed at the MAS website at: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

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- Smoking Cessation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
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- Long-term Oxygen Therapy for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Chronic Respiratory Failure Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Hospital-at-Home Programs for Patients With Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Home Telehealth for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model
- Experiences of Living and Dying With COPD: A Systematic Review and Synthesis of the Qualitative Empirical Literature

For more information on the qualitative review, please contact Mita Giacomini at: http://fhs.mcmaster.ca/ceb/faculty_member_giacomini.htm.

For more information on the economic analysis, please visit the PATH website: http://www.path-hta.ca/About-Us/Contact-Us.aspx.

The Toronto Health Economics and Technology Assessment (THETA) collaborative has produced an associated report on patient preference for mechanical ventilation. For more information, please visit the THETA website: http://theta.utoronto.ca/static/contact.

Objective of Analysis

The objective of this evidence-based review was to determine the effectiveness and cost-effectiveness of pulmonary rehabilitation in the management of chronic obstructive pulmonary disease (COPD).

Technology

Pulmonary rehabilitation refers to a multidisciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy. Pulmonary rehabilitation is recommended as the standard of care in the treatment and rehabilitation of patients with COPD who remain symptomatic despite treatment with bronchodilators.

Exercise training, the cornerstone of pulmonary rehabilitation programs, may include both aerobic and strength training. Other possible components of pulmonary rehabilitation include psychological support, patient education, nutritional counselling, occupational therapy, medication information, and smoking cessation.

While pulmonary rehabilitation can be delivered in multiple settings for varying durations, the optimal delivery site, components, duration, target populations, and timing remain in question.

For the purpose of this review, the Medical Advisory Secretariat focused on pulmonary rehabilitation programs as defined by the Cochrane Collaboration (1)—that is, any inpatient, outpatient, or home-based rehabilitation program lasting at least 4 weeks that includes exercise therapy with or without any form of education and/or psychological support delivered to patients with exercise limitations attributable to COPD.

Evidence-Based Analysis

Research Question(s)

1. What is the effectiveness and cost-effectiveness of pulmonary rehabilitation compared with usual care (UC) for patients with stable COPD?

2. Does early pulmonary rehabilitation (within 1 month of hospital discharge) in patients who had an acute exacerbation of COPD (AECOPD) improve outcomes compared with UC (or no rehabilitation)?

3. Do maintenance or postrehabilitation programs for patients with COPD who have completed a pulmonary rehabilitation program improve outcomes compared with UC?

Research Methods

Literature Search

Search Strategy

Research Questions 1 and 2: A literature search was performed on August 10, 2010 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published from January 1, 2004 to July 31, 2010 (Appendix 1).

Research Question 3: A literature search was performed on February 3, 2011 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published from January 1, 2000 to February 3, 2011 (Appendix 2).

Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search. Articles of uncertain eligibility were reviewed with a second clinical epidemiologist and then a group of epidemiologists until consensus was established. The quality of evidence was assessed as high, moderate, low, or very low according to GRADE methodology.

Definition of a Pulmonary Rehabilitation Program

As noted previously, there is much clinical heterogeneity in the literature with respect to the duration, intensity, components, and delivery of pulmonary rehabilitation programs. In order to reduce the heterogeneity across studies included in this review we adopted the definition of pulmonary rehabilitation used in a Cochrane review (1) of pulmonary rehabilitation: any inpatient, outpatient, or home based-rehabilitation program lasting at least 4 weeks that includes exercise therapy with or without any form of education and/or psychological support delivered to patients with exercise limitations attributable to COPD.

Inclusion Criteria

Research Questions 1 and 2:

- published between January 1, 2004 and July 31, 2010
- randomized controlled trials (RCTs), systematic reviews, and meta-analyses
- COPD study population
- studies comparing pulmonary rehabilitation with UC (no pulmonary rehabilitation)
- duration of pulmonary rehabilitation program ≥ 6 weeks
- pulmonary rehabilitation program had to include at minimum exercise training

Research Question 3:

- published between January 1, 2000 and February 3, 2011
- RCTs, systematic reviews, and meta-analyses
- COPD study population
- studies comparing a maintenance or postrehabilitation program with UC (standard follow-up)
- duration of pulmonary rehabilitation program ≥ 6 weeks
- initial pulmonary rehabilitation program had to include at minimum exercise training

Exclusion Criteria

Research Questions 1, 2, and 3:

- grey literature
- duplicate publications
- non-English language publications
- study population ≤ 18 years of age
- studies conducted in a palliative population
- studies that did not report primary outcome of interest

Additional Exclusion Criteria for Research Question 3:

- studies with ≤ 2 sessions/visits a month

Outcomes of Interest

The primary outcomes of interest for the stable COPD population were exercise capacity and health-related quality of life (HRQOL). For the COPD population following an exacerbation, the primary outcomes of interest were hospital readmissions and HRQOL. Other health outcomes examined in this population were mortality, emergency department visits, and exercise capacity. The primary outcomes of interest for the COPD population undertaking maintenance programs were functional exercise capacity and HRQOL. Other outcomes examined were hospital admissions and length of hospital stay.

Statistical Analysis

Statistical Challenges: Meta-analysis

Meta-analyzing continuous measurements, such as functional exercise capacity using the 6 Minute Walking Test (6MWT), presents statistical challenges, as studies quite often report only baseline (pre) and final values (post) for intervention and control groups without reporting change-from-baseline values. While the absolute difference between pre and post values is easy to obtain (final value minus baseline value), the standard deviation (SD) necessary for meta-analysis is often lacking.

To clarify the statistical challenges relevant to this report, it is important to define some terms:

The *intra-group change from baseline to final* refers to the mean difference between baseline and final values **within** intervention or **within** control groups (i.e., the difference in pre and post measurements within groups).

The *inter-group difference* refers to the mean difference in intra-group change from baseline to final values (as defined above) **between** intervention and control (i.e., the difference in change from baseline values between groups).

Solutions to Challenges

To solve the problem of missing SDs, the Cochrane Handbook for Systematic Reviews has identified 2 solutions (http://www.cochrane-handbook.org/), both of which are usually explored in any one meta-analysis:

Meta-analyze only the inter-group difference in mean final values between intervention and control. This approach assumes that, if baseline values do not significantly differ between intervention and control, the inter-group difference in mean final values will be similar to the inter-group difference of the intra-group change from baseline to final. One can test for significant differences at baseline; if they do not differ, this approach is valid.

Use statistical calculations to derive the standard deviations for the intra-group change from baseline to final, then meta-analyze these data. Repeated (pre and post) measurements made on the same participants tend to be correlated, thus lowering standard errors and creating tighter confidence intervals in comparison to single measurements. A correlation coefficient quantifies the correlation between measurements. This explains why meta-analyzing the change from baseline to final is preferable to meta-analyzing final values only, particularly if there are significant differences between intervention and control at baseline.

There are 2 ways to derive the standard deviations for the intra-group change from baseline to final when information is lacking:

Derive the standard deviation of the intra-group change from baseline to final using P values, confidence intervals, or standard errors reported from a t-test for the intra-group change from baseline to final. It should be noted, however, that if a study does not report standard deviations for the intra-group change from baseline to final, it is unlikely (though not impossible) that the study will report relevant t-test values. This approach is thus rare.

Calculate the standard deviation of the intra-group change from baseline to final by imputing a correlation coefficient. Correlation coefficients can be calculated from studies that report all relevant data (baseline ± SD, final ± SD, difference ± SD). These correlation coefficients can then be applied to studies lacking relevant information to derive appropriate SDs. Alternatively, one can impute varying correlation coefficients and run multiple sensitivity meta-analyses to observe any changes in effect. It should be noted, however, that imputation has been historically shown to have little effect on the summary estimates and conclusions of a meta-analysis. (2;3)

For this particular analysis, changes from baseline values were meta-analyzed. Standard deviations for these changes were generated by imputing a correlation coefficient of 0.5.

Quality of Evidence

The quality of each included study was assessed taking into consideration the following 7 study design characteristics:

- adequate allocation concealment,
- randomization (study must include a description of the randomization procedure used and this must be a proper method),
- power/sample size (adequate sample size based on a priori calculations; underpowered studies were identified, when possible, using post-hoc sample size power calculations),
- blinding (if double blinding was not possible, a single-blind study with unbiased assessment of outcome was considered adequate for this criterion),
- Fewer than 20% withdrawals/dropouts,
- intention-to-treat (ITT) analysis conducted and done properly (withdrawals/dropouts considered in analysis), and
- other criteria as appropriate for the particular research question and study design.

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria (4) as presented below.

- Quality refers to criteria such as the adequacy of allocation concealment, blinding and follow-up.
- Consistency refers to the similarity of estimates of effect across studies. If there are important and unexplained inconsistencies in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the magnitude of the difference in effect, and the significance of the differences guide the decision about whether important inconsistency exists.
- Directness refers to the extent to which the interventions and outcome measures are similar to those of interest.

As stated by the GRADE Working Group, the following definitions of quality were used in grading the quality of the evidence:

High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Results of Evidence-Based Analysis

Research Question 1: Effect of Pulmonary Rehabilitation on Outcomes in Stable COPD

The database search yielded 2,069 citations published between January 2004 and July 2010. Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment. Figure 1 shows the breakdown of when citations were excluded in the analysis.

Twenty studies met the inclusion criteria described above; of these, 1 paper was a health technology assessment, 2 studies were systematic reviews, and the remaining 17 studies were RCTs (Table 1).

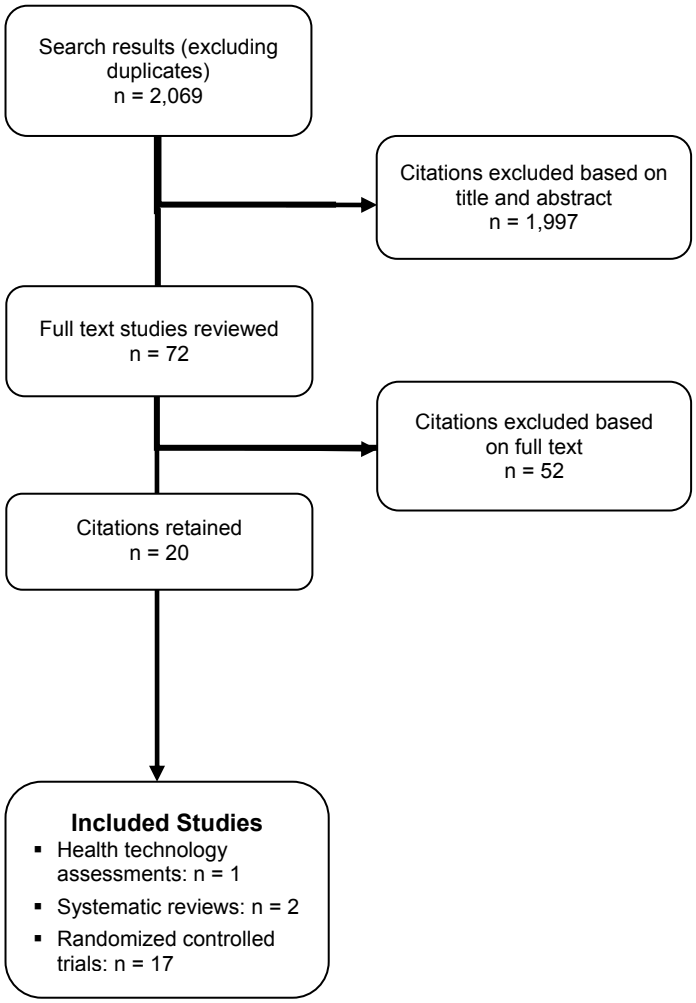

Figure 1: Citation Flow Chart

For each included study, the study design was identified and is summarized below in Table 1, which is a modified version of a hierarchy of study design by Goodman. (5) The additional designation "g" was added for preliminary reports of studies that had been presented to international scientific meetings. Table 1 lists the body of evidence examined according to study design and the number of studies identified.

Table 1: Body of Evidence Examined According to Study Design*

Study Design	Number of Eligible Studies
RCT Studies	
Systematic review of RCTs	3
Large RCT†	3
Small RCT	14
Observational Studies	
Systematic review of non-RCTs with contemporaneous controls	
Non-RCT with contemporaneous controls	
Systematic review of non-RCTs with historical controls	
Non-RCT with historical controls	
Database, registry, or cross-sectional study	
Case series	
Retrospective review, modelling	
Studies presented at an international conference or other sources of grey literature	
Expert opinion	
Total	20

*Abbreviation: RCT, randomized controlled trial.
†Large RCT is defined as having a sample size of at least 100.

The literature search identified 3 reviews focusing on pulmonary rehabilitation for COPD. A summary of the reviews can be found below (Table 2). Two of them were narrative reviews, (6;7) of which 1 focused solely on home-based pulmonary rehabilitation. The remaining review, conducted in 2006 by Lacasse et al, (8) included a meta-analysis of the effects of pulmonary rehabilitation on exercise capacity and HRQOL based on 31 studies from the years 1966 to 2004. The authors concluded that pulmonary rehabilitation featuring at least 4 weeks of exercise training leads to clinically and statistically significant improvements in important domains of quality of life including dyspnea, fatigue, emotional function, and mastery. For exercise capacity, the results favoured the pulmonary rehabilitation group over the UC group, with a weighted mean 6MWT difference of 48 m (95% confidence interval [CI], 32–65 m). (Sixteen studies were included in this pooled estimate.) Subgroup analyses based on a priori reasons for clinical heterogeneity did not have an effect on study results.

Table 2: Summary of Existing Evidence on Pulmonary Rehabilitation Interventions for Stable COPD*

Study (Type)	Number of Trials Search Years	Conclusions
CADTH, 2010 (HTA) (6)	102 1998 onwards	Pulmonary rehabilitation improves short-term exercise capacity, HRQOL, and mental health outcomes for patients with COPD.
Lacasse et al, 2006 (MA) (8)	31 1966–2004	Pulmonary rehabilitation including at least 4 weeks of exercise training leads to clinically and statistically significant improvements in important domains of quality of life including dyspnea, fatigue, emotional function, and mastery.
Viera et al, 2010 (SR) (7)	8	Self-monitored, home-based pulmonary rehabilitation is useful and, if properly done, may be an equivalent alternative to outpatient pulmonary rehabilitation. Many programs with endurance training have been found beneficial in improving HRQOL and exercise capacity.

*Abbreviations: CADTH, Canadian Agency for Technologies and Health; COPD, chronic obstructive pulmonary disease; HRQOL, health-related quality of life; HTA, health technology assessment; MA, meta-analysis; SR, systematic review.

Randomized Controlled Trials

A total of 17 RCTs that met the inclusion criteria were identified and included in this review. (9-24) The sample size of the studies ranged from 28 to 200, with a total of 1,155 participants in the 17 studies. The mean reported age of the participants was 66 years. All studies reported gender, and the mean percentage of females was 67 percent. The percent predicted forced expiratory volume in 1 second (% predicted FEV_1) in the study populations ranged from 27 to 72. Few studies characterised the study sample in terms of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) COPD stage criteria (see below) based on FEV_1 and forced vital capacity (FVC). Using these criteria, the population of the remaining studies was assessed. In total, 77% of studies were conducted in a severe COPD population, 18% in a moderate COPD population, and 5% in a very severe COPD population.

The GOLD COPD stage criteria are as follows:

Stage I (Mild COPD): Mild airflow limitation ($FEV_1/FVC < 70\%$; $FEV_1 \geq 80\%$ predicted) and sometimes, but not always, chronic cough and sputum production. (At this stage, the individual may not be aware that his or her lung function is abnormal.)

Stage II (Moderate COPD): Worsening airflow limitation ($FEV_1/FVC < 70\%$; $50\% > FEV_1 < 80\%$ predicted), with shortness of breath typically developing on exertion. (This is the stage at which patients typically seek medical attention because of chronic respiratory symptoms or exacerbations.)

Stage III (Severe COPD): Further worsening of airflow limitation ($FEV_1/FVC < 70\%$; $30\% > FEV_1 < 50\%$ predicted), greater shortness of breath, reduced exercise capacity, and repeated exacerbations that have an impact on patients' quality of life.

Stage IV (Very Severe COPD): Severe airflow limitation ($FEV_1/FVC < 70\%$; $FEV_1 < 30\%$ predicted) or $FEV_1 < 50\%$ predicted plus chronic respiratory failure. When this complication is present, patients may have very severe (Stage IV) COPD even if the FEV_1 is greater than 30% predicted. (At this stage, quality of life is very appreciably impaired and exacerbations may be life-threatening.)

Nine studies excluded patients with comorbidities that precluded participation in a rehabilitation program or that could limit exercise training. Some of these trials specifically excluded patients with neurological or musculoskeletal disease, cancer and/or diabetes. Eight trials specifically excluded patients with heart failure, ischemic heart disease, or a history of heart disease.

Study Characteristics

Studies were conducted between 1990 and 2009. Two studies were conducted in Canada, with the remainder from the United Kingdom, Europe, India, and Australia. Sample sizes ranged from 28 to 200 participants. A detailed description of the studies can be found in Appendix 2. The individual quality of the studies varied, with differences in quality mainly due to methodological issues such as inadequate description of randomization, sample size calculation, allocation concealment, blinding, and uncertainty around the use of ITT analysis (Appendix 3). Pulmonary rehabilitation programs were delivered through a variety of settings, although the majority of studies (71%) were conducted in an outpatient setting of a hospital. All 17 studies reported a UC control group and 3 reported a wait-list control group.

Intervention Characteristics

All the interventions examined in the studies included a minimum of exercise training. Exercise programs consisted of aerobic training and in many cases included a strength-training component. Some interventions also featured disease education, dietary education/advice, self-care, smoking cessation advice, endurance training, self-management skills, breathing and relaxation exercises, referrals to social services, and/or psychological support. Many of the programs also included an individualized home training program that participants were encouraged to follow. All the studies examined the outcomes of HRQOL and exercise capacity. Despite homogeneity in outcome assessment, clinical heterogeneity was evident in intervention characteristics such as duration, intensity, setting, and interventionist.

Duration and Intensity

Intervention durations ranged from 4 weeks to 1 year. The majority of interventions lasted 6 to12 weeks (13 studies), while the rest fell into categories of 4 weeks (1 study), 6 months (2 studies), or 1 year (1 study). The intensity of the interventions varied between trials, although the majority of studies had pulmonary rehabilitation programs that were 3 to 6 hours per week.

Interventions and Setting

The majority of interventions were carried out by a multidisciplinary team of physiotherapists, occupational therapists, dieticians, and nurses. However, a physiotherapist and/or physical therapist alone carried out the intervention in 5 studies, and a sole nurse in 1 other study. In 3 studies, a primary care physician was involved in supervision of the rehabilitation group during outpatient care. Three studies had an unclear description of who delivered the intervention. The majority of interventions occurred in an outpatient setting (71%).

Outcomes

Duration of follow-up ranged from 8 weeks to 2 years, with the most common reported length being 12 weeks. In addition, 41% of studies followed patients at a minimum of 2 time points.

All studies reported 6MWT results as a measure of exercise capacity. (Two studies reporting functional exercise capacity in terms of the shuttle walk test were not included in the meta-analysis.) Eighty-two percent of trials measured HRQOL using the Chronic Respiratory Questionnaire (CRQ) or St. George's Respiratory Questionnaire (SGRQ). Additional outcomes examined in the trials included patient satisfaction, fatigue, lung function, anxiety and depression, functional dyspnea, psychological general well-being, health status, exacerbations, and hospitalizations.

The results of the meta-analyses identified in the literature search are summarized below in Table 3. Forest plots are found in Appendix 4.

Table 3: Summary of Findings of Meta-Analyses of Studies Investigating the Effectiveness of Pulmonary Rehabilitation on HRQOL and Functional Exercise Capacity in Patients With COPD*

Outcome	Number of Studies	Number of Participants	Effect Size Mean Difference (95% CI)	GRADE
Quality of Life – Change in SGRQ				
Total Score	8	514	-8.40 (-13.30, -3.50)	Moderate
Symptoms	8	514	-3.40 (-7.85, 1.04)	
Impacts	8	514	-3.41 (11.03, 4.21)	
Activity	8	514	-7.73 (-14.24, -1.22)	
Quality of Life – Change in CRQ				
Fatigue	8	507	0.83 (0.62, 1.04)	Moderate
Emotional Function	8	507	0.70 (0.45, 0.95)	
Mastery	8	507	0.85 (0.63, 1.06)	
Dyspnea	8	507	0.97 (0.77, 1.17)	
Functional Exercise Capacity (6MWT)	15	659	54.83 (35.63, 74.03)	Moderate

*Abbreviations: 6MWT, 6 Minute Walking Test; CI, confidence interval; CRQ, Chronic Respiratory Questionnaire; SGRQ, St. George's Respiratory Questionnaire.

Health-Related Quality of Life

Eight studies reported results of an HRQOL assessment based on the SGRQ. (12-15;17;20;22;23) All studies compared the difference in the mean change scores from baseline to follow-up between the pulmonary rehabilitation and UC groups. A mean decrease in the SGRQ indicates an improvement in quality of life, while a mean increase indicates a deterioration in quality of life. The minimal clinically important difference (MCID)—that is, the smallest difference in score corresponding to the smallest difference perceived by the average patient that would mandate, in the absence of troublesome side effects and excessive costs, a change in patient management—for the SGRQ is 4 units. As seen above (Table 3), there was a statistically and clinically significant improvement in quality of life for the pulmonary rehabilitation group compared with the UC group as reflected in the total score ($P < 0.001$) and activity scores ($P = 0.02$) of the SGRQ.

The GRADE quality of evidence was assessed as moderate for this outcome. Details of this assessment, including reasons for downgrading the quality of evidence, are reported in Appendix 3.

Eight studies reported results of the quality-of-life assessment based on the CRQ. (16-19;24-27) All studies compared the difference in the mean change scores from baseline to follow-up between the pulmonary rehabilitation and UC groups. A mean increase in CRQ indicates an improvement in quality of life, while a mean decrease indicates a deterioration in quality of life. The MCID for the CRQ has been established as 0.5 units. Taking this figure into consideration, pulmonary rehabilitation (including all CRQ domains) was associated with a statistically and clinically significant improvement in quality of life ($P < 0.001$) (Table 3).

Exercise Capacity

Eighty-eight percent of studies reported results of functional exercise capacity assessments based on the 6MWT. All studies compared the difference in the mean change in scores from baseline to follow-up between the pulmonary rehabilitation and UC groups. The MCID for the 6MWT has been reported to be

from 25 to 35 meters. (28;29) As seen above (Table 3), there was a statistically and clinically significant improvement in functional exercise capacity for the pulmonary rehabilitation group compared with the UC group, with an estimated pooled difference of 54.83 meters ($P < 0.001$). The GRADE quality of evidence was assessed as moderate for this outcome.

Details of this assessment, including reasons for downgrading the quality of evidence, are reported in Appendix 3.

Conclusion

Based on moderate-quality evidence, pulmonary rehabilitation including at least 4 weeks of exercise training leads to clinically and statistically significant improvements in HRQOL in patients with COPD.[1]

Pulmonary rehabilitation also leads to a clinically and statistically significant improvement in functional exercise capacity[2] (weighted mean difference, 54.83 m; 95% CI, 35.63–74.03; P < 0.001).

Research Question 2: Effect of Pulmonary Rehabilitation on Outcomes Following an Acute Exacerbation of COPD

The database search yielded 2,069 citations published between January 2004 and July 2010. Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment. Figure 2 shows the breakdown of when citations were excluded in the analysis.

Six studies met the inclusion criteria for this research question; of these, 1 paper was a meta-analysis and the remainder were RCTs (Table 4).

[1] As measured by all domains of the CRQ
[2] As measured by the 6MWT

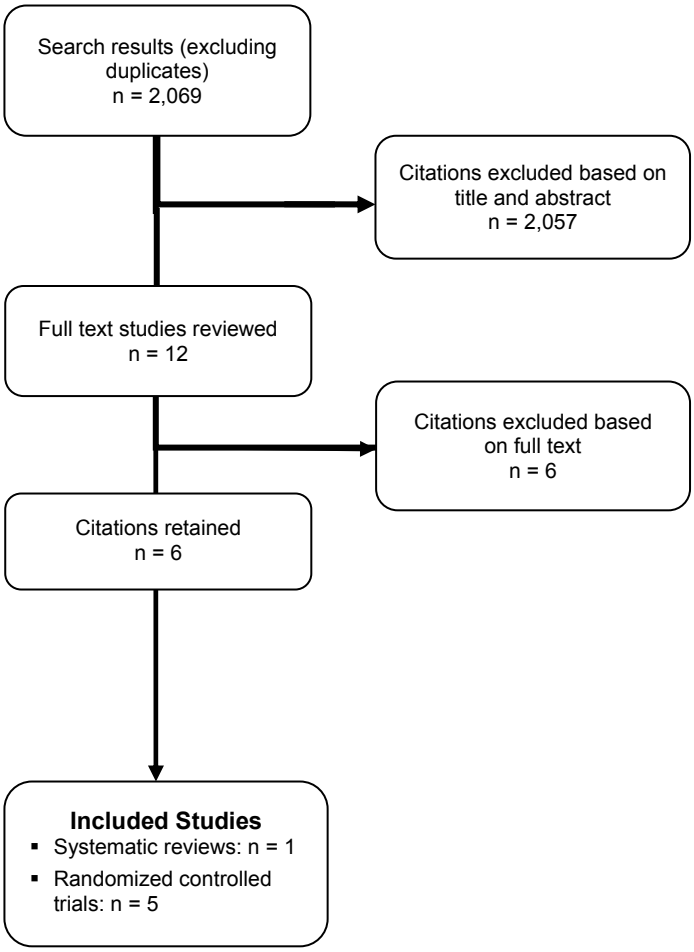

Figure 2: Citation Flow Chart

For each included study, the study design was identified and is summarized below in Table 4, which is modified version of a hierarchy of study design by Goodman. (5)

Table 4: Body of Evidence Examined According to Study Design*

Study Design	Number of Eligible Studies
RCT Studies	
Systematic review of RCTs	1
Large RCT†	
Small RCT	5
Observational Studies	
Systematic review of non-RCTs with contemporaneous controls	
Non-RCT with contemporaneous controls	
Systematic review of non-RCTs with historical controls	
Non-RCT with historical controls	
Database, registry, or cross-sectional study	
Case series	
Retrospective review, modelling	
Studies presented at an international conference or other sources of grey literature	
Expert opinion	
Total	6

*Abbreviation: RCT, randomized controlled trial
†Large RCT is defined as having a sample size of at least 100.

One systematic review, conducted in 2010 by Puhan et al,(30) focused on pulmonary rehabilitation following an AECOPD and included a meta-analysis. The review aimed to evaluate the effects of pulmonary rehabilitation on future hospital admissions (primary outcome) and other important outcomes (mortality, health-related quality of life, and exercise capacity) after COPD exacerbations. Six studies from 1966 to 2008 were included in the review.

The authors concluded that these studies suggest that pulmonary rehabilitation is highly effective and safe in reducing hospital admissions and mortality and improving HRQOL in COPD patients following an exacerbation. There were highly clinically and statistically significant differences between the rehabilitation group and the UC group for all domains of the CRQ and for the total, impact, and activity scores of the SGRQ. Pulmonary rehabilitation also improved exercise capacity measured by the 6MWT or shuttle test.

In assessing the Puhan et al review, (31) the Medical Advisory Secretariat excluded 3 of the 6 RCTs because:

- 2 studies had pulmonary rehabilitation programs lasting no longer than 10 days.
- 1 study excluded patients with an exacerbation in the previous month.

Randomized Controlled Trials

The database search identified citations published between 2004 and August 2010, but the literature was searched from 2008 forward. Five RCTs met the inclusion criteria and were thus included in this review. (9;32-35) The sample size of the studies ranged from 31 to 97, with a total of 276 participants in the 5 studies. The mean age of the participants was about 68 years. All studies reported gender, and the mean percentage of females was about 46 percent. The percent predicted FEV_1 in the study populations ranged from 35 to 59. None of the studies characterised the study sample in terms of the GOLD COPD stage criteria. Using these criteria, 60% of studies included patients with severe COPD while the remaining studies included patients with moderate COPD.

Study Characteristics

Studies were conducted between 2000 and 2010. A detailed description of the studies can be found in Appendix 2. Two studies were conducted in the United Kingdom and the remainder in Germany, Ireland, and New Zealand. Sample sizes ranged from 31 to 97 participants. The individual quality of the studies varied, with differences in quality mainly due to methodological issues such as inadequate description of randomization, sample size calculation, allocation concealment, blinding, and uncertainty around the use of ITT analysis (Appendix 3). Pulmonary rehabilitation programs were delivered through a variety of settings. Two studies had outpatient pulmonary rehabilitation programs (35;36), 2 studies began with an inpatient program followed by an outpatient program (home-based in 1 case) (9;32), and the remaining study had a home-based program for patients discharged from hospital (34). All studies reported a UC control group.

Intervention Characteristics

All the interventions examined in the studies included a minimum of aerobic exercise training, with a strength-training component also included in many cases. Some interventions also featured disease education, dietary education/advice, self-care, smoking cessation advice, endurance training, self-management skills, breathing and relaxation exercises, referrals to social services, and psychological support. All the studies examined the outcomes of hospital readmissions, HRQOL, and exercise capacity. Despite homogeneity in outcome assessment, there was some clinical heterogeneity in intervention characteristics such as duration, intensity, setting, and individuals delivering the intervention.

Duration and Intensity

Intervention durations ranged from 6 weeks to 6 months. Eighty percent of studies had interventions lasting from 6 to 8 weeks. The intensities of the interventions were comparable in the studies, typically involving 2 to 3 two-hour sessions per week for the duration of the rehabilitation program.

Interventions and Setting

Two interventions were carried out by a multidisciplinary team that included 2 or more of the following health care professionals: COPD nurse, physiotherapist, occupational therapist, and dietician. The remaining studies either used a single physiotherapist to carry out the intervention or did not clearly describe who carried out the intervention.

Outcomes

Duration of follow-up ranged from 1 month to 6 months from baseline. Two of the 5 studies followed patients at a minimum of 2 time points. (9;34)

All studies reported hospital readmissions (9;32-35) and 3 reported COPD-specific readmissions. (9;32;35) All 5 trials measured quality of life using the CRQ or the SGRQ. Exercise capacity, (9;32) mortality, (9;33) and emergency department visits, (33;35) were each reported in 2 of the 5 studies. Other outcomes reported in some of the trials included dyspnea, lung function, body mass index (BMI), and

fatigue. The results of the meta-analyses identified in the literature search are summarized below in Tables 5 and 6. Forest plots are found in Appendix 4.

Table 5: Summary of Findings of a Meta-Analysis of Studies Investigating the Effectiveness of Pulmonary Rehabilitation on Hospital Readmission in Patients with COPD Following an Acute Exacerbation*

Outcome	Number of Studies	Number of Participants	Pooled Rate Ratio (95% CI)	GRADE
All hospital readmissions	5	251	0.50 (0.33–0.77)	
COPD-related readmission	3	183	0.41 (0.18–0.93)	Moderate
General readmission	2	68	0.54 (0.29–1.03)	

*Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease.

Table 6: Summary of Findings of Meta-Analyses of Studies Investigating the Effectiveness of Pulmonary Rehabilitation on HRQOL in Patients with COPD Following an Acute Exacerbation*

Outcome	Number of Studies	Number of Participants	Effect Size Mean Difference (95% CI)	GRADE
Quality of Life – Change in SGRQ				
Total Score	3	109	−11.44 (−16.71 to −6.17)	
Symptoms	3	109	−1.59 (−5.16 to 8.35)	Moderate
Impact	3	109	−14.51 (−21.52 to −7.51)	
Activity	3	109	−11.44 (−18..3 to −4.52)	
Quality of Life – Change in CRQ				
Fatigue	4	196	2.54 (2.11, 2.97)	
Emotional Function	4	196	2.11 (1.63, 2.60)	Moderate
Mastery	4	196	3.17 (2.70, 3.64)	
Dyspnea	4	196	3.42 (2.99, 3.85)	

*Abbreviations: CI, confidence interval; CRQ, Chronic Respiratory Questionnaire; HRQOL, health-related quality of life; SGRQ, St. George's Respiratory Questionnaire.

Hospital Readmissions

All studies reported hospital readmissions as an outcome. (9;32-35) Three of the studies reported COPD-related readmissions (9;32;35), while 2 of the studies reported general admissions. (33;34) There was a decrease in all hospital readmissions as seen by the pooled relative risk of 0.50 (95% CI, 0.33–0.77; P = 0.001) favouring pulmonary rehabilitation versus UC. When admissions were subgrouped by type, the effect observed was greater for COPD-related readmissions than for general readmissions.

Health-Related Quality of Life

Three studies reported results of HRQOL assessments based on the SGRQ. (33-35) All studies compared the difference in the mean change scores from baseline to follow-up between the pulmonary rehabilitation and UC groups. (9;32-35) Based on the MCID, there was a statistically and clinically significant improvement in quality of life for the pulmonary rehabilitation group as compared to the UC group reflected in the total ($P < 0.001$), impact ($P < 0.001$), and activity scores ($P = 0.001$) of the SGRQ (Table 6).

The GRADE quality of evidence was assessed as moderate for this outcome. Details of this assessment, including reasons for downgrading the quality of evidence, are reported in Appendix 3.

Four studies reported results of the quality-of-life assessment based on the CRQ. (9;32;33;35) Based on the MCID, there was a statistically and clinically significant improvement in quality of life for the pulmonary rehabilitation group compared with the UC group reflected in all domains of the CRQ ($P < 0.001$) (Table 6).

The GRADE quality of evidence was assessed as moderate for this outcome. Details of this assessment, including reasons for downgrading the quality of evidence, are reported in Appendix 3.

Additional Outcomes

Additional relevant outcomes were reported in several of the studies. Functional exercise capacity as measured by the 6MWT was reported in 2 studies. (9;32) There was a statistically and clinically significant improvement in exercise capacity as measured by the 6MWT favouring the pulmonary rehabilitation group as compared to the UC group (weighted mean difference, 203.14 m; 95% CI, 185.17–221.11; $P < 0.001$). Two studies reported emergency department visits (33;35) and 2 studies reported mortality, (9;33) but no statistically significant differences were found for any of these outcomes between the pulmonary rehabilitation and UC groups.

Conclusion

Based on moderate-quality evidence, pulmonary rehabilitation (within 1 month of hospital discharge) after an AECOPD significantly reduces hospital readmissions (relative risk, 0.34; 95% CI, 0.25– 0.46; $P < 0.001$) and leads to a statistically and clinically significant improvement in HRQOL.[3]

Research Question 3: Effect of Maintenance Programs on COPD Outcomes

The database search yielded 1,000 citations published between January 2000 and February 2011. Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment. Figure 3 shows the breakdown of when citations were excluded in the analysis.

Three studies met the inclusion criteria for this research question. All studies included were RCTs (Table 7).

[3] As measured by all domains of the CRQ and total, impact, and activity scores of the SGRQ

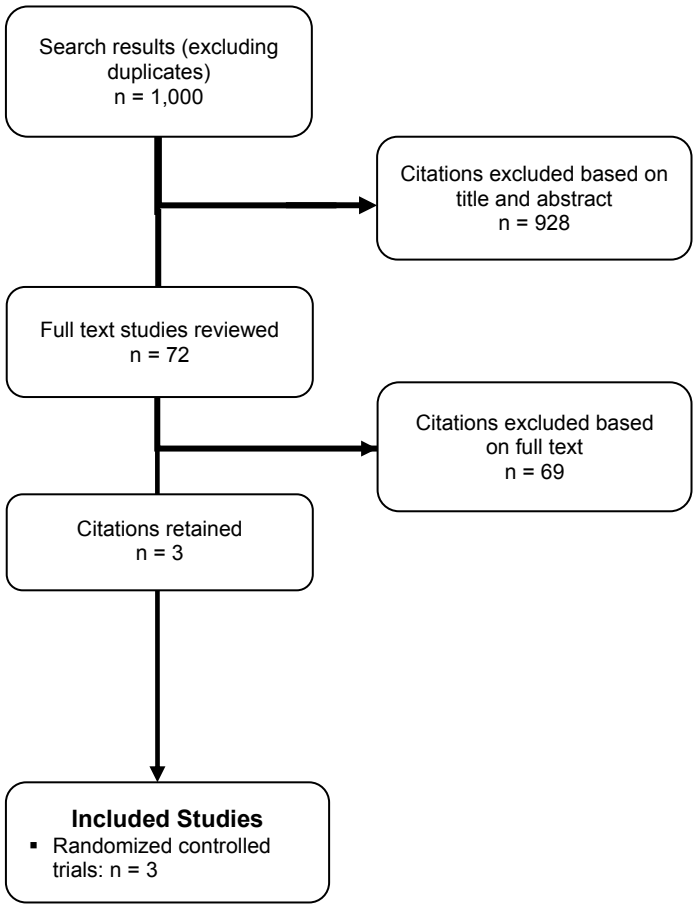

Figure 3: Citation Flow Chart

For each included study, the study design was identified and is summarized below in Table 7, which is a modified version of a hierarchy of study design by Goodman. (5)

Table 7: Body of Evidence Examined According to Study Design*

Study Design	Number of Eligible Studies
RCT Studies	
Systematic review of RCTs	
Large RCT†	1
Small RCT	2
Observational Studies	
Systematic review of non-RCTs with contemporaneous controls	
Non-RCT with contemporaneous controls	
Systematic review of non-RCTs with historical controls	
Non-RCT with historical controls	
Database, registry, or cross-sectional study	
Case series	
Retrospective review, modelling	
Studies presented at an international conference or other sources of grey literature	
Expert opinion	
Total	3

*Abbreviation: RCT, randomized controlled trial
†Large RCT is defined as a sample size of at least 100.

The search did not identify any systematic reviews or meta-analyses focused on maintenance programs following pulmonary rehabilitation for COPD patients.

Randomized Controlled Trials

The database search identified 1,000 citations published between January 2000 and February 2011. Of the 72 full-text articles reviewed, only 3 studies met the inclusion criteria described earlier, of which one was a large RTC and 2 were small RTCs (Table 7). (37-39) Sample sizes in the studies ranged from 48 to 140, with a total of 284 participants in the 3 studies. The mean reported age of the participants was 67 years. All studies reported gender, and the mean percentage of females ranged from 44 to 64 percent. The percent predicted FEV_1 in the study populations ranged from 35 to 59. None of the studies characterised the study sample in terms of the GOLD COPD stage criteria. Using these criteria, 2 studies included patients with moderate COPD (37;39) and 1 included patients with severe COPD. (38)

The majority of studies mentioned exclusion criteria. Criteria included subjects who had experienced an AECOPD in the previous month, required supplemental oxygen, or had comorbidities precluding participation in exercise training, and subjects who had a medical condition limiting their ability to participate in exercise training.

Study Characteristics

Studies were conducted between 2000 and 2010. A detailed description of the studies can be found in Appendix 2. One study was carried out in Australia and the other 2 in Denmark and the United States. Sample sizes ranged from 48 to 140 participants. The individual quality of the studies was generally poor due to methodological issues such as inadequate description of randomization, sample size calculation,

allocation concealment, blinding, and uncertainty around the use of ITT analysis (Appendix 3). All the maintenance programs were delivered in an outpatient setting. All studies reported a UC control group.

Intervention Characteristics

All the interventions examined in the studies included a minimum of aerobic exercise training, while some also included a strength-training component. Two studies included unsupervised home exercise as part of the interventions (38;39), and one of them also supplemented the exercise training with weekly educational sessions. (38) Some clinical heterogeneity was evident in the intervention characteristics, such as duration of the initial program, duration of the maintenance program, and intensity of the maintenance program.

Duration of Initial Pulmonary Rehabilitation Program

The duration of the initial pulmonary rehabilitation programs ranged from 7 to 12 weeks.

Duration and Intensity of Maintenance Programs

The duration of the maintenance programs ranged from 12 to18 months. In 2 of the studies these maintenance programs had comparable intensities, typically involving one 1-to-2-hour session per week plus unsupervised home exercise training. (38;39) The remaining study was more intense, with maintenance sessions carried out 3 times per week. (37)

Outcomes

Outcomes were measured at various time points. One study assessed outcomes at 3, 6, and 12 months post-randomization, (38) another followed patients 3, 6, and 12 months following the intervention, (39) and the remaining study evaluated outcomes 3 months after the intervention as well as at 9, 15, and 18 months from baseline. (37)

Two of the 3 studies reported on exercise capacity as measured by the 6MWT (37;39) and 2 studies also reported on HRQOL. (38;39) The latter 2 studies also included hospitalizations and length of stay as outcomes.

The results of the findings for the maintenance programs identified in the literature search are summarized below in Tables 8 through 10. For studies in which results were meta-analyzed, forest plots can be found in Appendix 4.

Table 8: Summary of Findings of Meta-Analyses of Studies Investigating the Effectiveness of Maintenance Programs on Functional Exercise Capacity*

Outcome	Number of Studies	Number of Participants	Mean Difference (95% CI)	*P* Value	GRADE
Functional Exercise Capacity (6MWT)	2	166	22.93 (5.16–40.71)†	0.01	LOW

*Abbreviations: 6MWT, Six Minute Walking Test; CI, confidence interval.
†Minimally clinically important difference ~25-35 m.

Table 9: Summary of Findings of Studies Investigating the Effectiveness of Maintenance Programs on Health-Related Quality of Life*

Outcome	N	Effect Size Mean Difference (95% CI)	*P* Value	GRADE
HRQOL - Change in SGRQ				
Spencer et al, 2010 (39)	48	5 (−2, 11)	NR	LOW
Ringbaek et al, 2010 (38)	96	NR†	NR	

*Abbreviations; CI, confidence interval; HRQOL, health-related quality of life; N, sample size; NR, not reported; SGRQ, St. George's Respiratory Questionnaire.
†Data not reported; authors concluded there was no significant difference between groups.

Table 10: Summary of Findings of Studies Investigating the Effectiveness of Maintenance Programs on Hospitalizations and Length of Stay*

Outcome	N	Maintenance	Usual Care	*P* Value
Mean Number of Hospital Admissions per Patient Over 12 Months (Mean)				
Ringbaek et al, 2010 (38)	96	0.8	0.8	0.83
Spencer et al, 2010 (39)	48	0.3	0.5	NR†
Mean Number of Days Spent in Hospital per Patient Over 12 Months (Mean)				
Ringbaek et al, 2010 (38)	96	2.8	3.0	0.78
Spencer et al, 2010 (39)	48	Reported no difference in the length of hospital stay between the 2 groups over the 12 months (*P* value not reported)		

*Abbreviations: N, sample size; NR, not reported.
†Data not reported.

Exercise Capacity

Two studies reported results of a functional exercise capacity assessment based on the 6MWT.(37;39) Both studies compared the difference in the mean change in scores from baseline to follow-up between the maintenance and UC groups. Based on the MCID, there was a statistically but not clinically significant improvement in functional exercise capacity for the maintenance group compared with the UC group, with an estimated pooled difference of 22.93 m (95% CI, 5.16–40.71; $P = 0.01$) (Table 8). When higher-intensity maintenance programs were considered individually, the pooled difference reached marginal clinical significance at 25.88 m (95% CI, 25.27–26.49). The GRADE quality of evidence was assessed as low for this outcome. Details of this assessment, including reasons for downgrading the quality of evidence, are reported in Appendix 3.

Health-Related Quality of Life

Two studies reported results of HRQOL assessments based on the SGRQ. (38;39) Both studies compared the difference in the mean change scores from baseline to follow-up between the maintenance program and UC groups. Based on the MCID, one study failed to show a statistically or clinically significant improvement in quality of life for patients receiving the maintenance program compared with those receiving UC. (39) The other study failed to report data for this outcome, although the authors noted that there was no significant difference between the groups. (38) The GRADE quality of evidence was assessed as low for this outcome.

Hospitalizations and Length of Stay

Two studies reported hospitalizations and length of stay as an outcome. (38;39) There was no difference in the mean number of hospital admissions per patient over a 12-month period between patients receiving a maintenance program and those receiving UC (Table 10). There was also no difference in the mean number of days spent in hospital per patient over the 12 months between these 2 groups (Table 10). The GRADE quality of evidence was assessed as low for this outcome.

Conclusion

Based on low-quality evidence, pulmonary rehabilitation maintenance programs have a nonsignificant effect on HRQOL and hospitalizations.

Based on low-quality evidence, pulmonary rehabilitation maintenance programs for COPD patients have a statistically but not clinically significant effect on exercise capacity ($P = 0.01$). When studies are subgrouped by intensity and quality, the difference becomes marginally clinically significant.

Economic Analysis

The results of the economic analysis are summarized in issue 12 of the COPD series entitled *Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model*. This report can be accessed at: www.hqontario.ca/en/mas/tech/pdfs/2012/rev_COPD_Economic_March.pdf.

Glossary

6 Minute Walking Test (6MWT)	A measure of exercise capacity which measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes. A widely used outcome measure in respiratory rehabilitation of patients with COPD.
Acute exacerbations of chronic obstructive pulmonary disease (AECOPD)	A change in baseline symptoms that is beyond day-to-day variation, particularly increased breathlessness, cough, and/or sputum, which has an abrupt onset.
Admission avoidance hospital-at-home program	Treatment program for patients experiencing acute exacerbations of COPD which allows patients to receive treatment in their home and avoid admission to hospital. After patients are assessed in the emergency department for an acute exacerbation, they are prescribed the necessary medications and additional care needed (e.g., oxygen therapy) and then sent home where they receive regular visits from a medical professional until the exacerbation has resolved.
Ambulatory oxygen therapy	Provision of oxygen therapy during exercise and activities of daily living for individuals who demonstrate exertional desaturation.
Bilevel positive airway pressure (BiPAP)	A continuous positive airway pressure mode used during noninvasive positive pressure ventilation (see definition below) that delivers preset levels of inspiratory and expiratory positive airway pressure. The pressure is higher when inhaling and falls when exhaling, making it easier to breathe.
Cost-effectiveness acceptability curve (CEAC)	A method for summarizing uncertainty in estimates of cost-effectiveness.
Cor pulmonale	Right heart failure, as a result of the effects of respiratory failure on the heart.
Dyspnea	Difficulty breathing or breathlessness.
Early discharge hospital-at-home program	Treatment program for patients experiencing acute exacerbations of COPD which allows patients to receive treatment in their home and decrease their length of stay in hospital. After being assessed in the emergency department for acute exacerbations, patients are admitted to the hospital where they receive the initial phase of their treatment. These patients are discharged early into a hospital-at-home program where they receive regular visits from a medical professional until the exacerbation has resolved.
Forced expiratory volume in 1 second (FEV_1)	A measure of lung function used for COPD severity staging; the amount of air that can be forcibly exhaled from the lungs in the first second of a forced exhalation.
Forced vital capacity (FVC)	The amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible.
Fraction of inspired oxygen (FiO_2)	The percentage of oxygen participating in gas exchange.

Hypercapnia	Occurs when there is too much carbon dioxide in the blood (arterial blood carbon dioxide > 45 to 60 mm Hg).
Hypopnea	Slow or shallow breathing.
Hypoxemia	Low arterial blood oxygen levels while breathing air at rest. May be severe ($PaO_2 \leq 55$ mm Hg), moderate (56 mm Hg $\leq PaO_2 <$ 65 mm Hg), or mild-to-moderate (66 mm Hg $< PaO_2 \leq$ 74 mm Hg).[4]
Incremental cost-effectiveness ratio (ICER)	Ratio of the change in costs of a therapeutic intervention to the change in effects of the intervention compared to the alternative (often usual care).
Intention-to-treat analysis (ITT)	An analysis based on the initial treatment the participant was assigned to, not on the treatment eventually administered.
Invasive mechanical ventilation (IMV)	Mechanical ventilation via an artificial airway (endotracheal tube or tracheostomy tube).
Long-term oxygen therapy (LTOT)	Continuous oxygen use for about 15 hours per day. Use is typically restricted to patients fulfilling specific criteria.
Multidisciplinary care	Defined as care provided by a team (compared to a single provider). Typically involves professionals from a range of disciplines working together to deliver comprehensive care that addresses as many of the patient's health care and psychosocial needs as possible.
Nicotine replacement therapy (NRT)	The administration of nicotine to the body by means other than tobacco, usually as part of smoking cessation.
Noninvasive positive pressure ventilation (NPPV)	Noninvasive method of delivering ventilator support (without the use of an endotracheal tube) using positive pressure. Provides ventilatory support through a facial or nasal mask and reduces inspiratory work.
Partial pressure of carbon dioxide ($PaCO_2$)	The pressure of carbon dioxide dissolved in arterial blood. This measures how well carbon dioxide is able to move out of the body.
Partial pressure of oxygen (PaO_2)	The pressure of oxygen dissolved in arterial blood. This measures how well oxygen is able to move from the airspace of the lungs into the blood.
Palliative oxygen therapy	Use of oxygen for mildly hypoxemic or nonhypoxemic individuals to relieve symptoms of breathlessness. Used short term. This therapy is "palliative" in that treatment is not curative of the underlying disease.
Pulmonary rehabilitation	Multidisciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy. Exercise training is the cornerstone of pulmonary rehabilitation programs.
Pulse oximetry	A noninvasive sensor, which is attached to the finger, toe, or ear to detect oxygen saturation of arterial blood.

[4] The mild-to-moderate classification was created for the purposes of the report.

Quality-adjusted life-years (QALYs)	A measure of disease burden that includes both the quantity and the quality of the life lived that is used to help assess the value for money of a medical intervention.
Respiratory failure	Respiratory failure occurs when the respiratory system cannot oxygenate the blood and/or remove carbon dioxide from the blood. It can be either acute (acute respiratory failure, ARF) or chronic, and is classified as either hypoxemic (type I) or hypercapnic (type II) respiratory failure. Acute hypercapnic respiratory failure frequently occurs in COPD patients experiencing acute exacerbations of COPD.
Short-burst oxygen therapy	Short-duration, intermittent, supplemental oxygen administered either before or after exercise to relieve breathlessness with exercise.
Sleep apnea	Interruption of breathing during sleep due to obstruction of the airway or alterations in the brain. Associated with excessive daytime sleepiness.
Smoking cessation	The process of discontinuing the practice of inhaling a smoked substance.
Spirometry	The gold standard test for diagnosing COPD. Patients breathe into a mouthpiece attached to a spirometer which measures airflow limitation.
SpO_2	Oxygen saturation of arterial blood as measured by a pulse oximeter.
Stable COPD	The profile of COPD patients which predominates when patients are not experiencing an acute exacerbation.
Supplemental oxygen therapy	Oxygen use during periods of exercise or exertion to relieve hypoxemia.
Telemedicine (or telehealth)	Refers to using advanced information and communication technologies and electronic medical devices to support the delivery of clinical care, professional education, and health-related administrative services.
Telemonitoring (or remote monitoring)	Refers to the use of medical devices to remotely collect a patient's vital signs and/or other biologic health data and the transmission of those data to a monitoring station for interpretation by a health care provider.
Telephone only support	Refers to disease/disorder management support provided by a health care provider to a patient who is at home via telephone or videoconferencing technology in the absence of transmission of patient biologic data.
Ventilator-associated pneumonia (VAP)	Pneumonia that occurs in patients undergoing mechanical ventilation while in a hospital.

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The role of the expert panel was to provide direction on the scope of the project and the relevant outcomes measures of effectiveness, to review the evidence-based analyses and to identify any societal or systemic issues that are relevant to intervention effectiveness. However, the statements, conclusions and views expressed in this report do not necessarily represent the views of the expert panel members.

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Appendices

Appendix 1: Literature Search Strategies

Initial Literature Search on Pulmonary Rehabilitation for COPD

Search date: August 10, 2010
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, CINAHL, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment

Database: Ovid MEDLINE(R) <1950 to July Week 4 2010>
Search Strategy:
---
1 exp Pulmonary Disease, Chronic Obstructive/ (14057)
2 (chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory) adj (disease* or disorder*)).ti,ab. (20996)
3 (copd or coad).ti,ab. (15985)
4 chronic airflow obstruction.ti,ab. (486)
5 exp Emphysema/ (6925)
6 ((chronic adj2 bronchitis) or emphysema).ti,ab. (22569)
7 or/1-6 (53015)
8 exp Rehabilitation/ (120272)
9 exp Physical Therapy Modalities/ (98967)
10 ((pulmonary or lung* or respirat*) adj2 (physiotherap* or therap* or rehabilitat*)).ti,ab. (8251)
11 rh.fs. (135769)
12 or/8-11 (297725)
13 7 and 12 (3342)
14 limit 13 to (english language and humans and yr="2004 - 2010") (1206)
15 limit 14 to (case reports or comment or editorial or letter) (124)
16 14 not 15 (1082)

Database: EMBASE <1980 to 2010 Week 31>
Search Strategy:
---
1 exp chronic obstructive lung disease/ (47119)
2 (chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory) adj (disease* or disorder*)).ti,ab. (25414)
3 (copd or coad).ti,ab. (20656)
4 chronic airflow obstruction.ti,ab. (548)
5 exp emphysema/ (25316)
6 exp chronic bronchitis/ (6517)
7 ((chronic adj2 bronchitis) or emphysema).ti,ab. (25290)
8 or/1-7 (86799)
9 exp pulmonary rehabilitation/ (993)
10 exp physical medicine/ (288069)
11 ((pulmonary or lung* or respirat*) adj2 (physiotherap* or therap* or rehabilitat*)).ti,ab. (9992)
12 rh.fs. (108684)
13 or/9-12 (387063)

14 8 and 13 (5140)
15 limit 14 to (human and english language and yr="2004 -Current") (1758)
16 limit 15 to (editorial or letter or note) (195)
17 15 not 16 (1563)
18 case report/ (1665922)
19 17 not 18 (1459)

#	Query	Results
S13	S12 Limiters - Published Date from: 20040101-20101231	546
S12	S6 and S11	942
S11	(S7 or S8 or S9 or S10)	54560
S10	pulmonary rehabilitat* or pulmonary therap* or lung rehabilitat* or respiratory therap*	2776
S9	(MH "Home Rehabilitation+")	945
S8	(MH "Physical Therapy+")	50558
S7	(MH "Rehabilitation, Pulmonary+")	1644
S6	S1 or S2 or S3 or S4 or S5	7306
S5	chronic bronchitis or emphysema	1562
S4	(MH "Emphysema+")	954
S3	copd or coad	4032
S2	(chronic obstructive and (lung* or pulmonary or airway* or airflow or respiratory) and (disease* or disorder*))	5524
S1	(MH "Pulmonary Disease, Chronic Obstructive+")	4266

Final Revised Search for COPD-Rehabilitation Revised to Include 2000-2011

Search date: February 3, 2011
Databases Searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, CINAHL, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment

Database: Ovid MEDLINE(R) <1948 to January Week 3 2011>
Search Strategy:
---
1 exp Pulmonary Disease, Chronic Obstructive/ (14676)
2 (chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory) adj (disease* or disorder*)).ti,ab. (21256)
3 (copd or coad).ti,ab. (16373)
4 chronic airflow obstruction.ti,ab. (478)
5 exp Emphysema/ (9400)
6 ((chronic adj2 bronchitis) or emphysema).ti,ab. (22372)
7 or/1-6 (54975)
8 exp Rehabilitation/ (120569)
9 exp Physical Therapy Modalities/ (99270)

10 ((pulmonary or lung* or respirat*) adj2 (physiotherap* or therap* or rehabilitat*)).ti,ab. (8341)
11 rh.fs. (135921)
12 or/8-11 (298194)
13 7 and 12 (3404)
14 limit 13 to (english language and humans and yr="2000 -Current") (1730)
15 limit 14 to (case reports or comment or editorial or letter) (164)
16 14 not 15 (1566)

Database: EMBASE <1980 to 2011 Week 04>
Search Strategy:
---
1 exp chronic obstructive lung disease/ (49584)
2 (chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory) adj (disease* or disorder*)).ti,ab. (26878)
3 (copd or coad).ti,ab. (22292)
4 chronic airflow obstruction.ti,ab. (553)
5 exp emphysema/ (25972)
6 exp chronic bronchitis/ (6645)
7 ((chronic adj2 bronchitis) or emphysema).ti,ab. (25749)
8 or/1-7 (90366)
9 exp pulmonary rehabilitation/ (1194)
10 exp physical medicine/ (300551)
11 ((pulmonary or lung* or respirat*) adj2 (physiotherap* or therap* or rehabilitat*)).ti,ab. (10482)
12 rh.fs. (110909)
13 or/9-12 (401639)
14 8 and 13 (5385)
15 limit 14 to (human and english language and yr="2000 -Current") (2478)

CINAHL

#	**Query**	**Results**
S12	S6 AND S11 Limiters - Published Date from: 20000101-20111231 English Language	787
S11	S7 or S8 or S9 or S10	60613
S10	pulmonary rehabilitat* or pulmonary therap* or lung rehabilitat* or respiratory therap*	7241
S9	(MH "Home Rehabilitation+")	976
S8	(MH "Physical Therapy+")	52603
S7	(MH "Rehabilitation, Pulmonary+")	1682
S6	S1 or S2 or S3 or S4 or S5	7702
S5	chronic bronchitis or emphysema	1623
S4	(MH "Emphysema+")	994
S3	copd or coad	4205
S2	(chronic obstructive and (lung* or pulmonary or airway* or airflow or respiratory) and (disease* or disorder*))	5860
S1	(MH "Pulmonary Disease, Chronic Obstructive+")	4568

Appendix 2: Study Characteristics of Included Studies

Table A1: Description of Studies Examining Pulmonary Rehabilitation in the Stable COPD Population* (n = 18)

Study	Population	Setting	Groups	Delivered By	Length of Intervention	Description	Follow-up	Outcomes of Interest	Other Outcomes	Quality
Theander et al (23) 2009 Sweden	N = 30 Rehab: 15 Control: 15 Subject characteristics: ~65 years FEV_1 % predicted ~33 BMI ~25 Optimized on pharmacological treatment prior to study initiation	Pulmonary outpatient department Optimized on pharmacological treatment prior to study initiation	Control group Rehab group Control group did not receive any of the rehab program or care from professionals who performed the program	Physiotherapist, dietician, occupational therapist, nurse	12 weeks physiotherapy 1 hr, 2–5 days/week dietician/ occupational therapist 1 hr, 3x during program	Multi-disciplinary Aerobic training, strength training; after 1 month, pts received an individualized home training program Dietary education/ advice, self-care, smoking cessation advice	12 weeks from baseline	QOL (SGRQ) Functional exercise capacity (6MWT)	Fatigue; fatigue- related functional limitations; functional performance and satisfaction; lung function; grip strength	Not adequately powered; significant difference in gender distribution between groups; no blinding in outcome assessment; calculated sample size based on CRQ but used SGRQ; Dropout: 3/15 in rehab group, 1/15 in control group
Elci et al (13) 2008 Turkey	N = 78 Rehab: 39 Control: 39 Subject characteristics: ~59 years ~85% male FEV_1 % predicted ~47 ~51% GOLD stage III	Outpatient department of community hospital Lacked specialist pulmonary rehab services	Control group Rehab group Control group received standard medical care including instructions on the use of respiratory medicines	Nurses Received training in the pulmonary rehab program 2 weeks prior 1 session supervised by nurse (the remaining sessions supervised by a family member) Standard telephone questionnaire once weekly	12 weeks	Educational activities aimed at improving self-management skills Individualized rehab plan Exercises at home: 24 sessions of up to 90 min 2x/week Endurance training: abdominal, upper and lower limb muscle strengthening	4, 8, 12 weeks from baseline	QOL (SGRQ) Functional exercise capacity (6MWT)	Lung function; anxiety and depression; functional dyspnea No difference in lung function between control and rehab groups	Outcome assessors not blinded; unclear allocation concealment; no sample size calculation; no mention of droupouts Emailed author for individual data from SGRQ, 4-week data assumed to be baseline (according to author); potential underestimation of effect

Study	Population	Setting	Groups	Delivered By	Length of Intervention	Description	Follow-up	Outcomes of Interest	Other Outcomes	Quality
Karapolat et al (20) 2007 Turkey	N = 49 Rehab: 27 Control: 22 Subject characteristics: ~65 years ~87% male FEV_1 % predicted ~72, ~57% GOLD stage II	Outpatient program	Control group Rehab group	Physiotherapist	8 weeks	Educational component (1-hour session weekly for 16 weeks): respiratory physiology, disease education, dietary advice, relaxation, etc. Exercise training component (3x/week): aerobic, strength training, breathing and relaxation, etc.	8 and 12 weeks from baseline	QOL (SGRQ) Functional exercise capacity (6MWT)	Lung function; arterial blood gas analysis; dyspnea	Outcome assessors not blinded; unclear allocation concealment; no sample size calculation; no mention of dropouts Emailed author for individual data from SGRQ, 4-week data assumed to be baseline (according to author); potential underestimation of effect
Guell et al (18) 2000 Spain	N = 60 Rehab: 30 Control: 30 Subject characteristics: ~65 years ~100% male FEV_1 % predicted ~35	Outpatient clinic of hospital	Control group Rehab group	Unclear	6 months	Breathing retraining: chest wall exercises, abdominal exercises, etc. Exercise training: aerobic, home exercise Maintenance group sessions: breathing exercises, no formal exercise program	3, 6, 9, 12, 18, and 24 months from baseline	QOL (CRQ) Functional exercise capacity (6MWT) Maximal exercise capacity	Lung function; dyspnea; breathlessness; exacerbations; hospitalizations	Generalizable to men only; no allocation concealment; formal exercise component began after 3 months

Study	Population	Setting	Groups	Delivered By	Length of Intervention	Description	Follow-up	Outcomes of Interest	Other Outcomes	Quality
Engstrom et al (14) 1999 Sweden	N = 55 Rehab: 28 Control: 27 Subject characteristics: ~ 66 years ~52% male FEV_1 % predicted: Rehab, 35.8 (11.9) Control, 34.1 (10.2)	Outpatient	Usual outpatient care Rehabilitation program	Physiotherapist, occupational therapist, dietician Information program (self-care, smoking cessation): COPD outpatient team (respiratory nurse, physician)	12 months 45-min sessions 2x/week for 6 weeks; 1x every 2nd week for 6 weeks; 1x/month thereafter	Physiotherapy program: breathing techniques, aerobic exercise, arm training, muscle strength training, instruction to walk daily, individual 30-min home training program, education	12 months from baseline	QOL (SGRQ) Functional exercise capacity (6MWT) Days in hospital	Sickness impact profile; Mood Adjective Check List; maximum symptoms; limited incremental exercise test	Unclear randomization and allocation concealment; blinded outcome assessors with the exception of the 6MWT; no sample size calculation
Ringbaek et al (22) 2000 Denmark	N = 45 Rehab: 24 Control: 21 Subject characteristics: ~ 63 years ~15% male FEV_1 % predicted: Rehab: 49.5 (17.4) Control: 44.3 (13.7)	Outpatient	Control group Rehabilitation program	Physiotherapist, nutritional therapist, occupational therapist Patient education: physician and nurse	8 weeks 2-hour sessions 2x/week	Aerobic and strength training; dietary counselling; relaxation; breathing techniques; patient education; nutritional counselling	8 weeks from baseline	QOL (SGRQ) Functional exercise capacity (6MWT)	Psychological general well-being index; Borg Dyspnea Score	Unclear randomization and allocation concealment; no sample size calculation; high dropout rate
Borghi-Silva et al (11) 2009	N = 40 Rehab: 20 Control: 20 Subject characteristics: ~ 67 years ~74% male FEV_1 % predicted: Treatment: 64 (16.0) Control: 64 (18) Moderate to severe COPD	Outpatient	Usual care Supervised aerobic training program *All pts received regular treatment consisting of inhaled bronchodilators and steroids. Patients in UC received no physical training	Physiotherapist, physical therapist	6 weeks 3x/week for 6 weeks	Supervised program with: stretching of lower and upper limbs and treadmill ambulation (30 min); stretching exercises (back, hamstrings, shoulders, neck, etc.); breathing exercises	6 weeks from baseline	Functional exercise capacity (6MWT)	Borg Dyspnea Score; lung function; cardio-pulmonary exercise testing	Unclear randomization and allocation concealment; no sample size calculation; high dropout in control group

Study	Population	Setting	Groups	Delivered By	Length of Intervention	Description	Follow-up	Outcomes of Interest	Other Outcomes	Quality
Singh (26) 2002 India	N = 40 Rehab: 20 Control: 20 Subject Characteristics: ~ 59 years ~80% male FEV_1 % predicted: Treatment: 28 (7.5) Control: 26 (7.1) Severe airway obstruction	Outpatient	Pulmonary rehab Usual care Usual care patients were asked to continue their activities as usual	Not reported Supervised weekly	4 weeks 30 min 2x /day	Removal of secretions; lower extremity exercises (walking 2x/day); breathing strategies; energy conservation and work simplification	4 weeks from baseline	Functional exercise capacity (6MWT) QOL (CRQ)	FEV_1	Unclear randomization and allocation concealment; no sample size calculation; no mention of blinding
Lake et al (21) 1990 Australia	N = 28 Treatment: 20 Control: 8 Subject characteristics: ~ 66 years ~85% male FEV_1: Treatment 1: 0.97 (±0.29) Treatment 2: 0.73 (±0.24) Treatment 3: 0.83 (±0.25) Control: 0.97 (±0.29) FEV1 % predicted < 55	Outpatient	Training group 1 (upper limb) Training group 2 (lower limb) Training group 3 (combined) Control group Control group offered active program at end of study	Supervised by physiotherapist 1 hour 3x/week	8 weeks	Upper limb group: 10-min warm-up, 20-min circuit training, 10-min cool-off Lower-limb group: 10-min warm-up, 20-min walking, and 10-min cool-off Combined group: 10-min warm-up, 15-min circuit training, 12-min walking, and 10-min cool-off	8 weeks from baseline	Functional exercise capacity (6MWT) QOL (Self-Efficacy Scale)	FEV_1; FVC; maximal exercise tolerance	Unclear randomization and allocation concealment; no sample size calculation; no mention of blinding; population may not be representative of COPD
Goldstein et al (16) 1994 Canada	N = 89 Rehab: 45 Control: 44 Subject characteristics: ~ 66 years ~49 % male FEV_1 % predicted:	Inpatient rehab followed by outpatient care	Conventional community care Rehabilitation Conventional care group received care from their family doctors and respiratory specialists	Multidisciplinary, medically supervised team	24 weeks Inpatient: 8 weeks, ~3x/week Outpatient care: 16 weeks; home training routine; graduated discharge	Stretching; breathing techniques; interval training (40 min 3x/week); treadmill (2–3 x/week); upper-extremity training; leisure walking (30 min 1x/week)	12, 18, and 24 weeks from baseline	Functional exercise capacity (6MWT) QOL (CRQ) Incremental exercise capacity	Pulmonary function	Unclear randomization and allocation concealment; no sample size calculation; no mention of blinding; high dropout rate

Study	Population	Setting	Groups	Delivered By	Length of Intervention	Description	Follow-up	Outcomes of Interest	Other Outcomes	Quality
	Treatment: 34.8 (14.5); Control: 34.6 (11.8) Severe stable COPD FEV_1 < 40%				program supervised by a member of rehab staff; periodic visits by a home care physiotherapist)					
Simpson and Rocker (25) 1992 Canada	N = 34 Rehab: 17 Control: 17 Subject characteristics: ~ 72 years ~54% male FEV_1 % predicted: Treatment: 39.5 (18.96); Control: 39.2 (21.39)	Community-based, local physiotherapy practices	Control Rehabilitation	Physiotherapist	8 weeks 3x/week	Weightlifting program: arm curls, leg extensions, leg press exercises, resistance training	8 weeks from baseline	QOL (CRQ) Functional exercise capacity (6MWT)	Borg Dyspnea Scale	Unclear allocation concealment; no sample size calculation; no ITT
Wijkstra et al (27) 1994 Netherlands	N = 45 Rehab: 30 Control: 15 Subject characteristics: FEV_1 % pred: Treatment: 34.8 (14.5) Control: 34.6 (11.8) Severe airflow limitation: FEV_1 % pred < 60%	Community-based (home-based program)	Control Rehabilitation	Supervised by multidisciplinary team: physiotherapist, nurse, pulmonologist, family doctor	12 weeks 2x/week visit to physiotherapist	Conventional physiotherapy: relaxation exercises, breathing retraining, upper limb training, exercise training (1 hr/day) Exercise training: 30 min 2x/day according to an individual protocol Patient education: supervised monthly by nurse Supervised clinical status: monthly GP visits	12 weeks after rehab	QOL (CRQ) Cycle ergometer test	FEV_1, IVC	Unclear randomization and allocation concealment; no sample size calculation; no mention of blinding

Study	Population	Setting	Groups	Delivered By	Length of Intervention	Description	Follow-up	Outcomes of Interest	Other Outcomes	Quality
Boxall et al (12) 2005 Australia	N = 60 Rehab: 30 Control: 30 Subject Characteristics ~ 76 years ~56% male FEV_1 % predicted: Treatment: 40.5 (15.9) Control: 37.7 (15.0) House-bound elderly COPD patients > 60 years	Community-based (home-based program)	Control Rehabilitation Control group offered program after initial 12 weeks	Nurse, occupational therapist, physiotherapist	12 weeks 11 total home visits	Graduated walking and arm exercises (1x daily): resistance; strengthening upper limb muscles used for respiration; exercise diaries; weekly physiotherapy visits for the first 6 weeks, then every 2 weeks until end of program; education sessions (~6 total)	12 weeks from baseline	QOL (SGRQ) Exercise tolerance (6MWT)	Dyspnea; hospital admission rates with exacerbation of COPD; average length of stay at readmission	No blinding of outcome assessors; sample size was calculated but study was underpowered due to dropouts
Hernandez et al (19) 2000 Spain	N = 60 Rehab: 30 Control: 30 Subject Characteristics: ~ 64.3 years FEV_1 % predicted: Treatment: 41.7 (15.6) Control: 40 (16.4) All patients were medically optimized	Community-based (home-based program)	Control Rehabilitation Control : standard medical treatment alone, but visited hospital every 2 weeks for a clinical check-up and supervision of treatment	Unclear	12 weeks 1 hour sessions, 6 days/week	Lower extremity training, walking Patients also went to hospital every 2 weeks for supervision of clinical status, treatment, and exercise-training compliance	12 weeks from baseline	QOL (CRQ) Exercise capacity (SWT)	Pulmonary function Resistance Test Dyspnea	Unclear randomization and allocation concealment; no sample size calculation; no/unclear ITT; high dropout rate; unclear description of who delivered rehabilitation
Griffiths et al (17) 2000 United Kingdom	N = 200 Rehab: 99 Control: 101 Subject characteristics: ~ 68 years 60 % male FEV1 % predicted: Treatment: 39.7 (16.2) Control: 39.4 (16.4)	Outpatient	Control Rehabilitation Control: outpatients or primary care patients followed for 1 year and then offered pulmonary rehab	Multidisciplinary: occupational therapists, physiotherapists, dieticians, respiratory nurse, smoking cessation counsellor	6 weeks 3 half-days/week, 2-hour sessions	1/3 time: educational activities: understanding of disease, nutrition, medicines, exercise Individualized sessions; aerobic training, circuit	6 weeks and 1 year from baseline	QOL (SGRQ and CRQ) Exercise capacity (SWT)	Health status (SF-36); hospital anxiety and depression score; number of admissions and days spent in hospital	Well-described randomization and allocation concealment; ITT analysis completed; sample size calculated

Study	Population	Setting	Groups	Delivered By	Length of Intervention	Description	Follow-up	Outcomes of Interest	Other Outcomes	Quality
						training Patients encouraged to follow a home exercise routine Psychological support and education At end of rehab program, patients were invited to join a patient-run group that met weekly at a local recreation centre for social activities and exercise				
Troosters et al (24) 2000 Belgium	N = 100 Rehab: 50 Control: 50 Subject characteristics: ~ 62 years ~85 % male FEV1 % predicted: Treatment: 41 (16) Control: 43 (12) Severe COPD	Outpatient	Control Rehabilitation	Supervised by physiotherapists	6 weeks Outpatient sessions: 1.5 hours 3x/week in first 3 months, 2x/week in subsequent 3 months	Training: aerobic (cycling, treadmill, etc.) and muscle strength training	6 and 18 months from baseline	QOL (CRQ) Functional exercise capacity (6MWT)	Maximal exercise capacity	Unclear randomization and allocation concealment; no sample size calculation; no/unclear ITT
Finnerty et al (15) 2001	N = 100 Rehab: 50 Control: 50 Subject characteristics: ~ 69 years ~68% male FEV_1 % predicted: Rehab: 41.2 (19.2) Control: 41.2 (16.2)	Outpatient	Routine outpatient attendance Rehabilitation program	Physiotherapist, occupational therapist, respiratory specialist nurse, dietician	6 weeks	2 visits/week: 2-hour education visit and 1-hour exercise (aerobic) visit Patients asked to exercise 1 to 2x daily 5x/week	12 and 24 weeks from baseline	QOL (SGRQ) Functional exercise capacity (6MWT)	None	Blinded outcome assessors; no sample size calculation; outcome assessed 6 weeks after program completed

Study	Population	Setting	Groups	Delivered By	Length of Intervention	Description	Follow-up	Outcomes of Interest	Other Outcomes	Quality
						Dietary advice, referrals to social services, coping strategies, psychological input				
Behnke et al, 2000 (9) Behnke et al, 2003 (10)	N = 46 Rehab: 15 Control: 15 Baseline characteristics given for 30 patients who completed the study Subject characteristics: ~66 years 77% male FEV_1 % predicted: Treatment: 34.1 ±7.4 Control: 37.5 ±6.6 N = 30 26 analyzed	Inpatient pulmonary rehab and home-based program	Control group Training group Control group: standard in-patient care with no exercise and standard community care with respirologist	Unclear Investigators visited pts every 2 weeks for the first 3 months, then monthly telephone contact	10 day hospital-based program and 6-month home-based program after discharge Started 4–7 days after admission	10-day hospital-based walking program (5 walking sessions/day for 10 days) + supervised home-based training program (3 walking sessions/day for 6 months) Monthly patient diaries	1, 2, 3, and 6 months after discharge 12 month follow-up	Lung function QOL (CRQ) Functional Exercise capacity (6MWT) Dyspnea scores Hospital readmission		Unclear randomization; allocation concealment; no ITT; high dropout rate; primary outcome not identified; no sample size calculation Follow-up at 12 months on only 26/46 original patients

*Abbreviations: 6MWT, Six Minute Walking Test; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRQ, Chronic Respiratory Questionnaire; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; GP, general practitioner; hr, hour; min, minutes; ITT, intention-to-treat analysis; IVC, inspiratory vital capacity; N, sample size; QOL, quality of life; pts, patients; rehab, rehabilitation; SGRQ, St. George's Respiratory Questionnaire; SF-36, Short form 36; SWT, Shuttle Walking Test; UC, usual care.

Table A2: Description of Studies Examining Pulmonary Rehabilitation Within One Month of an Acute Exacerbation of COPD (n = 4 Plus Behnke et al, 2000)

Study	Population	Setting	Groups	Delivered By	Length of Intervention	Description	Follow-up	Outcomes of Interest	Other Outcomes
Man et al (36) 2004 United Kingdom	N = 42 Rehab: 21 Control: 21 Subject characteristics: ~70 years ~41% male FEV_1 % predicted ~39% after inpatient treatment for acute exacerbation	Outpatient	Control group Rehab group Control: standard community care with respirologist	Multidisciplinary team: physiotherapists, respiratory nurses, occupational therapist, dietician, respiratory doctor, smoking cessation adviser, social worker, pharmacist, lay member of a patients' group	8 weeks	Outpatient PR (within 10 days of discharge) Aerobic and strength exercise and patient education for 12 weeks (two 2-hour sessions/week)	12 weeks	Incremental shuttle walk distance (SGRQ, CRQ, and SF-36)	Hospital readmission; hospital days; emergency admissions; mortality
Murphy et al (34) 2005 Ireland	N = 31 Rehab: 16 Control: 15 Subject characteristics: ~66 years ~65% male Moderate COPD FEV_1 % predicted < 60% Long history of smoking	Supervised home exercise program Admitted to a COPD home-from-hospital treatment program	Control group Rehab group Control group: Standard medical treatment without any form of rehabilitation exercises or lifestyle change advice	Physiotherapist	6 weeks	2x/week for 6 weeks 12 supervised exercise sessions (30–40 min each) Patients were instructed to exercise for at least 15 min on other days Use of diaries Aerobic exercise, upper limb exercises	6 weeks from baseline 3-month follow-up for exacerbations	Functional exercise capacity (shuttle walk test, 3-min step test)	Dyspnea QOL: SGRQ admissions exacerbations
Eaton et al (32) 2009	N = 97 Rehab: 47 Control: 50 Subject characteristics: ~70 years ~44% male FEV_1 % predicted ~35 Elderly	Inpatient followed by outpatient Mean of 2.6 days after admission	Usual Care Rehabilitation program Usual care: received standardized advice on benefits of exercise; COPD nurse administered standardized care	Inpatient program: COPD nurse Outpatient education: multidisciplinary	~8 weeks + inpatient program	Inpatient program: structured, supervised exercise regimen (at least 30 min/day) with aerobic and upper/lower limb strengthening Outpatient program: 1-hour sessions of supervised	3 months from baseline	No. COPD-related readmissions; time to first COPD-related readmission; no. inpatient days; unscheduled ED visits	BMI, airflow obstruction, dyspnea, exercise capacity, functional capacity (6MWT), and HRQOL (CRQ)

Study	Population	Setting	Groups	Delivered By	Length of Intervention	Description	Follow-up	Outcomes of Interest	Other Outcomes
	Severe impairment of pulmonary function, poor HRQOL, and high COPD-related morbidity					exercise training 2x/week for 8 weeks Educational sessions At end of program, prescribed 30 min daily activity with government-funded opportunity to attend local gym			
Seymour et al (35) 2010	N = 60 Rehab: 30 Control: 30 Subject characteristics: ~ 66 years ~45% male FEV_1 % predicted ~52	Outpatient Initiated within 1 week after discharge	Usual Care Rehabilitation program UC and rehab arms offered general information about COPD prior to randomization and outpatient appointments with patients' family doctor or respiratory team	2 physiotherapists	8 weeks	2x /week exercise and education sessions (each lasting 2 hours) for 8 weeks Individually tailored aerobic and limb strengthening	3 months after admission	Primary outcome: hospital admission for exacerbation Hospital or emergency department attendance for exacerbation	Quadriceps strength; exercise capacity (paced incremental and endurance shuttle walking tests); fatigue; HRQOL(SGRQ, CRQ)

*Abbreviations: 6MWT, 6 Minute Walking Test; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRQ, Chronic Respiratory Questionnaire; Ctrl, control; ED, emergency department; FEV_1, forced expiratory volume in 1 second; HRQOL, health-related quality of life; min, minutes; N, sample size; no., number; PR, pulmonary rehabilitation; rehab, rehabilitation; SF-36, Short form 36, SGRQ, St. George's Respiratory Questionnaire; UC, usual care.

Table A3: Description of Studies Examining Pulmonary Rehabilitation Maintenance Programs (n = 3)*

Study	Population	Setting	Groups	Delivered By	Length/ Description of Initial PR	Length of Maintenance Program	Description	Follow-up	Outcomes of Interest
Ringbaek et al (38) 2010	N = 96 MT: 55 Control: 41 Subject characteristics: ~ 68 years ~33% male FEV_1 % predicted: Treatment: 35.6 (14.0) Control: 36.9 (16.0) Stable COPD Excluded: patients with significant cardiac, musculoskeletal, or cognitive problems	Outpatient	Maintenance training Control group Both groups requested to continue	No mention	7-week outpatient program Supervised walking and cycling 2x/week combined with unsupervised daily training at home Educational sessions 1x/week Patients instructed to continue the unsupervised training at home after program end	1 year supervised training (every week in first 6 months and every second week in next 6 months) + 6 months unsupervised	Supervised training sessions (assumed to be similar to initial rehab)	Prior to rehab, at randomization, 3, 6, 12, 18 months after randomization	Functional exercise capacity (SWT) QOL (SGRQ) Other outcomes: adherence to supervised training, dropout rates, hospitalization
Spencer et al (39) 2010	N = 48 MT: 24 Control: 24 Subject characteristics: ~ 67 years ~46% male FEV_1 % predicted: Treatment: 51 ±11 Control: 54 ±11 Moderate COPD Excluded: cardiovascular, neurological, musculoskeletal comorbidities; exacerbation in previous month	Outpatient	Intervention group Control group Control group performed unsupervised home exercise 5 days/ week and received home exercise booklet and diary	No mention	8-week program 20 min walking, 20 min cycling, 10 min arm cycling and upper and lower limb strength training exercises using weight equipment and free weights	1 year	Supervised exercise 1 day/week plus unsupervised home exercise on 4 other days Supervised exercise same as initial rehab program Unsupervised home exercise: 30 min walking + 30 min upper and lower limb strengthening exercises using free weights and body weight; included exercise booklet and diary	3, 6, and 12 months following pulmonary rehab	Functional exercise capacity (6MWT) QOL (SGRQ) Other outcomes: lung function; incremental shuttle walk test; hospital anxiety and depression scale; hospital admission; length of stay; exacerbations

Study	Population	Setting	Groups	Delivered By	Length/ Description of Initial PR	Length of Maintenance Program	Description	Follow-up	Outcomes of Interest
Berry et al (37) 2003	N = 140 MT: 70 Control: 70 Subject characteristics: ~ 67 years ~56% male FEV_1 % predicted: Treatment: 57.6 (53.2–62.0) Control: 59.1 (55.0–63.2) Excluded: cardiac and peripheral vascular disease, concurrent cancer treatment, uncontrolled diabetes or hypertension	Community and university centre	Long-term intervention Short-term intervention (control group) Control group: All participants completed a 3-month pulmonary rehabilitation program prior to randomization Patients in control group were encouraged to continue exercising on their own	Not reported	3-month supervised centre-based program Exercise sessions with both aerobic and upper-extremity resistance training: included walking, biceps curls, triceps extension, shoulder exercises Sessions were 3x weekly for 1 hour	15 months		After initial 3-month rehab, and 9, 15, and 18 months from this point	Functional exercise capacity (6MWT) Other outcomes: physical disability; physical function (stairs climbed); peak oxygen uptake; pulmonary function; physical activity scale; compliance; training intensity

*Abbreviations: 6MWT, 6 Minute Walking Test; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; min, minutes; MT, maintenance training; N, sample size; PR, pulmonary rehabilitation; QOL, quality of life; rehab, rehabilitation; SGRQ, St. George's Respiratory Questionnaire; SWT, Shuttle Walking Test.

Appendix 3: Methodological Quality and GRADE Profile of Studies

Table A4: Methodological Quality of Studies Examining Stable COPD* (n = 18)

Study	N	Adequate Randomization Methods	Baseline Comparable	Adequate Allocation Concealment	Blinding of Outcome Assessors for Primary Outcome	Sample Size Calculation	Losses to Follow-up	ITT
Theander et al, 2009 (23)	30	?	✓	✓	No	✓†	21% T: 25%; C: 16.5%	No
Elci et al, 2008 (13)		✓	✓	Unclear	No	X	NR	NR
Karapolat et al, 2007 (20)	49	?	✓	✓	NR	X	6% patients	No
Borghi-Silva et al, 2009 (11)	40	Unclear	✓	Unclear	NR	✓‖	15% T:0%; C: 30%	No
Guell et al, 2000 (18)	60	Unclear	✓	no	Yes	X	None at end of program	No
Finnerty et al, 2001 (15)	100	✓	✓	Unclear	Yes	X	27% T: 20%; C: 34%	No
Engstrom et al, 1999 (14)	55	Unclear	✓	Unclear	Yes‡	X	9% T: 7%; C: 11%	No
Ringbaek et al, 2000 (22)	45	Unclear	X§	Unclear	NR	X	16% T: 29%; C: 0%	No
Wijkstra et al, 1994 (27)	45	Unclear	✓	Unclear	NR	X	4.4% T: 6.7%; C: 0%	No
Troosters et al, 2000 (24)	100	Unclear	✓	Unclear	NR	X	38% T: 32%; C: 44%*	No
Behnke et al, 2000 (9)	46	Unclear	✓	✓	X	X	35% T: 35%; C: 35%	No
Boxall et al, 2005 (12)	60	✓	✓	✓	X	✓#	23% T: 23%; C: 23%	X
Simpson and Rocker, 1992 (25)	34	✓	✓	NR	✓	X	17.6% T: 17.6%; C:17.6 %	X

Study	N	Adequate Randomization Methods	Baseline Comparable	Adequate Allocation Concealment	Blinding of Outcome Assessors for Primary Outcome	Sample Size Calculation	Losses to Follow-up	ITT
Lake et al, 1990 (21)	28	Unclear	✓	NR	NR	X	7.1% T: 5%; C: 12.5%	X
Griffiths et al, 2000 (17)	200	✓	✓	✓	✓	✓	10% T: 7%; C: 12.9%	✓
Singh, 2003 (26)	40	Unclear	✓	NR	NR	X	NR	?
Hernandez et al, 2000 (19)	60	Unclear	✓	NR	NR	X	38.3% T: 33.3%; C: 43.3%	?
Goldstein et al, 1994 (16)	89	Unclear	✓	NR	NR	✓¶	20.2% T: 15.5%; C: 9%	?

*Abbreviations: 6 MWT, 6 Minute Walking Test; C, control; COPD, chronic obstructive pulmonary disease; CRQ, Chronic Respiratory Questionnaire; ITT, intention-to-treat analysis; n, number of studies; N: sample size; NR, not reported; SGRQ, St. Georger's Respiratory Questionnaire; T, treatment.
†Theander et al, 2009 (12) was underpowered. The sample size was calculated based on the CRQ, but the SGRQ was used in the study. Also, the baseline gender distribution between the 2 groups was not comparable.
‡Engstrom et al, 1999 (13) had all outcomes blinded with the exception of the 6MWT.
§Ringbaek et al, 2000 (16) had more females in the control group at baseline and more smokers in the treatment group at baseline.
‖Borghi-Silva et al, 2009 (11) was underpowered.
¶Goldstein et al, 1994 (17) was not well-described in terms of power.
#Boxall et al, 2005 (9) was underpowered.

Table A5: Methodological Quality of Studies Following an Acute Exacerbation of COPD* (n = 5)

Study	N	Adequate Randomization Methods	Baseline Comparable	Adequate Allocation Concealment	Blinding of Outcome Assessors for Primary Outcome	Sample Size Calculation	Losses to Follow-up	ITT
Behnke et al, 2000 (9)	46	Unclear	✓	Unclear	Yes	X	35%	No
Man et al, 2004 (36)	42	✓	✓	Unclear	No	✓	19% T: 14%; C: 24%	✓
Murphy et al, 2005 (34)	31	Unclear	✓	Yes	Yes	X	16% T:19%; C: 13%	No
Eaton et al, 2009 (32)	97	✓	✓	Unclear	No	✓†	13% T:17%; C: 10%	✓
Seymour et al, 2010 (35)	60	Unclear	✓	Unclear	No	✓	18% T:23%; C: 13%	✓

*Abbreviations: C, control; COPD, chronic obstructive pulmonary disease; ITT, intention-to-treat analysis; n, number of studies; N, sample size; T, treatment.
†Eaton et al, 2009 (28) was underpowered to show a difference in primary outcome.

Table A6: Methodological Quality of Studies Examining Maintenance Programs* (n = 3)

Study	N	Adequate Randomization Methods	Baseline Comparable	Adequate Allocation Concealment	Blinding of Outcome Assessors for Primary Outcome	Sample Size Calculation	Losses to Follow-up	ITT
Spencer et al, 2010 (39)	48	Unclear	✓	Unclear	No	✓	19% T: 23%; C: 14%	Yes
Ringbaek et al, 2010 (38)	96	Unclear	✓†	Unclear	Unclear	X	At 12 months: 13% T: 15%: C: 24% At 18 months: 29% T: 24%; C: 34%	Unclear
Berry et al, 2003 (37)	140	Unclear	✓	Yes	Yes	X	16% T:19%; C: 13%	No

*Abbreviations: C, control; ITT, intention-to-treat analysis; n, number of studies; N, sample size; T, treatment.
†Ringbaek et al, 2010 (34): Baseline characteristics comparable with the exception of % of heart diseases: treatment group 41.8% versus 9.8% in the Control arm, $P < 0.01$.

Table A7: GRADE Quality of Evidence for Studies Examining Stable COPD*

Number of Studies	Design	Study Quality	Consistency	Directness	Imprecision	Other Modifying Factors	Overall Quality of Evidence
Outcome: Exercise Capacity – 6MWT							
15	RCT	Serious limitations†	No serious limitations	No serious limitations	No serious limitations	n/a	Moderate
Outcome: HRQL – CRQ							
8	RCT	Serious limitations‡	No serious limitations	No serious limitations	No serious limitations	n/a	Moderate
Outcome: HRQL – SGRQ							
8	RCT	Serious limitations§	No serious limitations	No serious limitations	No serious limitations	n/a	Moderate

*Abbreviations: 6MWT, Six Minute Walking Test; CRQ, chronic respiratory questionnaire; HRQOL, health-related quality of life; n/a, not applicable; RCT, randomized controlled trial; SGRQ, St. George's Respiratory Questionnaire

†Study quality was downgraded for the exercise capacity because of serious limitations in many of the studies including: unknown or inadequate allocation concealment (12 of 15 studies); unclear randomization process based on published trials (12 of 15 studies); unclear whether assessor was blinded (single blind) (11 of15 studies); lack of a priori power calculations (11 of 15 studies); inadequately powered studies based on post hoc sample size calculations (3 of 15 studies), withdrawals/dropouts > 20% (5 of 15 studies); and intention-to-treat (ITT) analysis not used or unknown (15 of 15 studies).

‡ Study quality was downgraded for health-related quality of life (CRQ) because of serious limitations in many of the studies including: unknown or inadequate allocation concealment (12 of 15 studies); unclear randomization process based on published trials (7 of 8 studies); unclear whether assessor was blinded (single blind) (5 of 8 studies); lack of a priori power calculations (6 of 8 studies); withdrawals/dropouts > 20% (3 of 8 studies); and intention-to-treat (ITT) analysis not used or unknown (8 of 8 studies).

§Study quality was downgraded for health-related quality of Life (SGRQ) because of serious limitations in many of the studies including: unknown or inadequate allocation concealment (3 of 8 studies); unclear randomization process based on published trials (4 of 8 studies); unclear whether assessor was blinded (single blind) (4 of 8 studies); lack of a priori power calculations (4 of 8 studies); inadequately powered studies based on post hoc sample size calculations (2 of 8 studies); withdrawals/dropouts > 20% (2 of 8 studies); and intention-to-treat (ITT) analysis not used or unknown (8 of 8 studies).

Table A8: GRADE Quality of Evidence for Studies Examining Pulmonary Rehabilitation Following an Acute Exacerbation of COPD*

Number of Studies	Design	Study Quality	Consistency	Directness	Imprecision	Other Modifying Factors	Overall Quality of Evidence
Outcome: Hospital Readmissions							
5	RCT	Serious limitations†	No serious limitations	No serious limitations	No serious limitations	n/a	Moderate
Outcome: HRQL – CRQ							
4	RCT	Serious limitations‡	No serious limitations	No serious limitations	No serious limitations	n/a	Moderate
Outcome: HRQL – SGRQ							
3	RCT	Serious limitations‡	No serious limitations	No serious limitations	No serious limitations	n/a	Moderate

* Abbreviations: 6MWT, Six Minute Walking Test; CRQ, Chronic Respiratory Questionnaire; HRQOL, health-related quality of life; n/a, not applicable; RCT, randomized controlled trial; SGRQ, St. George's Respiratory Questionnaire.

†Study quality was downgraded for the hospital readmissions outcomes because of serious limitations in many of the studies including: unknown or inadequate allocation concealment (4 of 5 studies); unclear randomization process based on published trials (3 of 5 studies); unclear or no blinded outcome assessors (single blind) (3 of 5 studies); lack of a priori power calculations (2 of 5 studies); inadequately powered studies (1 of 5 studies); withdrawals/dropouts > 20% (1 of 5 studies); and intention-to-treat (ITT) analysis not used (2 of 5 studies).

‡Study quality was downgraded for the HRQL outcome because of serious limitations in many of the studies including: unknown or inadequate allocation concealment (CRQ, 4 of 4 studies; SGRQ, 2 of 3 studies); unclear randomization process based on published trials (CRQ, 2 of 4 studies; SGRQ, 2 of 3 studies); unclear or no blinded outcome assessors (single blind) (CRQ, 3 of 4 studies; SGRQ, 2 of 3 studies); lack of a priori power calculations (CRQ, 1 of 4 studies; SGRQ, 1 or 3 studies); inadequately powered studies (CRQ, 1 of 4 studies); withdrawals/dropouts > 20% (CRQ, 1 of 4 studies); and intention-to-treat (ITT) analysis not used (CRQ, 1 of 4 studies; SGRQ, 1 of 3 studies).

Table A9: GRADE Quality of Evidence for Studies Examining Pulmonary Rehabilitation Maintenance Programs*

Number of Studies	Design	Study Quality	Consistency	Directness	Imprecision	Other Modifying Factors	Overall Quality of Evidence
Outcome: Exercise Capacity – 6MWT							
2	RCT	Serious limitations†	Serious limitations†	No serious limitations	No serious limitations	n/a	Low
Outcome: HRQL – SGRQ							
2	RCT	Very serious limitations‡	No serious limitations	No serious limitations	No serious limitations	n/a	Low

*Abbreviations: 6MWT, Six Minute Walking Test; HRQOL, health-related quality of life; n/a, not applicable; RCT, randomized controlled trial; SGRQ, St. George's Respiratory Questionnaire; WMD, weighted mean difference.

†Study quality was downgraded for the exercise capacity outcome because of serious limitations in many of the studies including: unknown or inadequate allocation concealment (1 of 2 studies); unclear randomization process based on published trials (2 of 2 studies); unclear whether assessor was blinded (single blind) (1 of 2 studies); lack of a priori power calculations (1 of 2 studies); inadequately powered studies (2 of 2 studies); and intention-to-treat (ITT) analysis not used (1 of 2 studies). The study quality was also downgraded because of inconsistent findings for the WMD of the 6MWT.

‡Study quality was downgraded for the HRQOL outcome because of very serious limitations in many of the studies including: unknown or inadequate allocation concealment (2 of 2 studies); unclear randomization process based on published trials (2 of 2 studies); unclear whether assessor was blinded (single blind) (1 of 2 studies); lack of a priori power calculations (1 of 2 studies); and intention-to-treat (ITT) analysis not used (1 of 2 studies). The study quality was also downgraded because of missing data reported for the effect size and associated *P* values.

Appendix 4: Forest Plots

Studies of Stable COPD

Quality of Life (St. George's Respiratory Questionnaire)

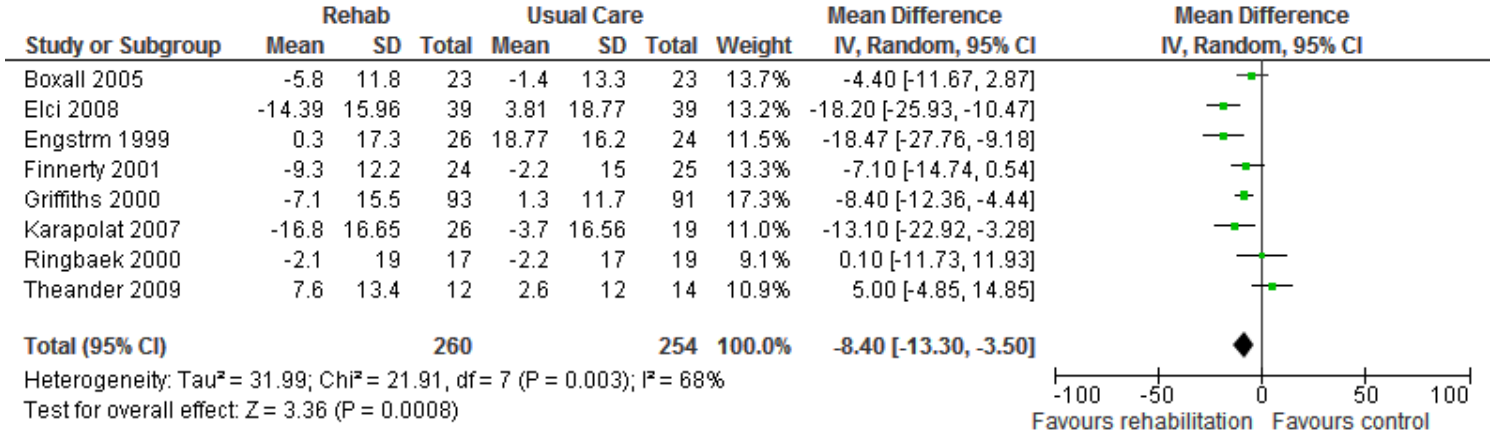

Figure A1: Forest Plot of Pooled Quality of Life Data Measured by the Total Score of the St. George's Respiratory Questionnaire

*Abbreviations: CI, confidence interval; rehab, rehabilitation; SD, standard deviation.

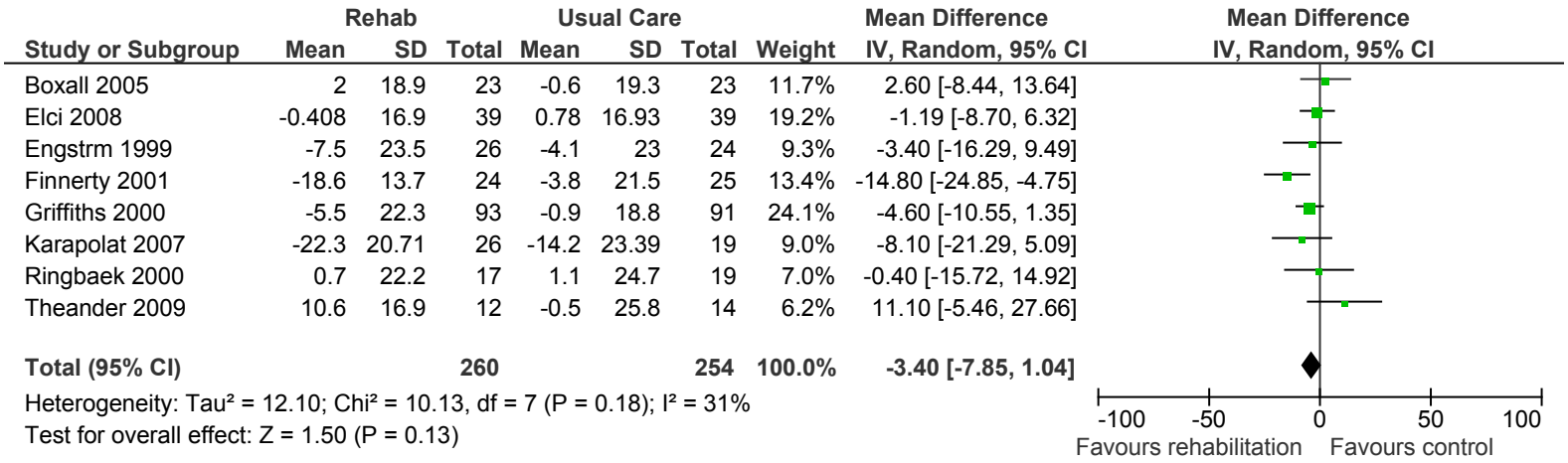

Figure A2: Forest Plot of Pooled Quality of Life Data Measured by the Symptom Score of the St. George's Respiratory Questionnaire

*Abbreviations: CI, confidence interval; rehab, rehabilitation; SD, standard deviation.

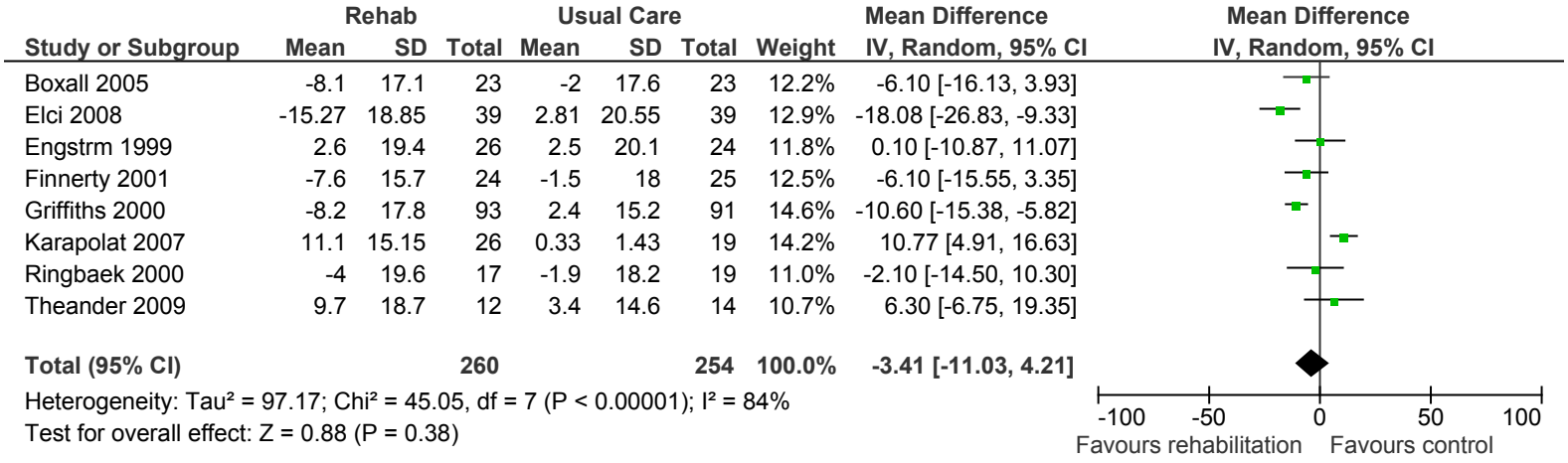

Figure A3: Forest Plot of Pooled Quality of Life Data Measured by the Impacts Score of the St. George's Respiratory Questionnaire

*Abbreviations: CI, confidence interval; rehab, rehabilitation; SD, standard deviation.

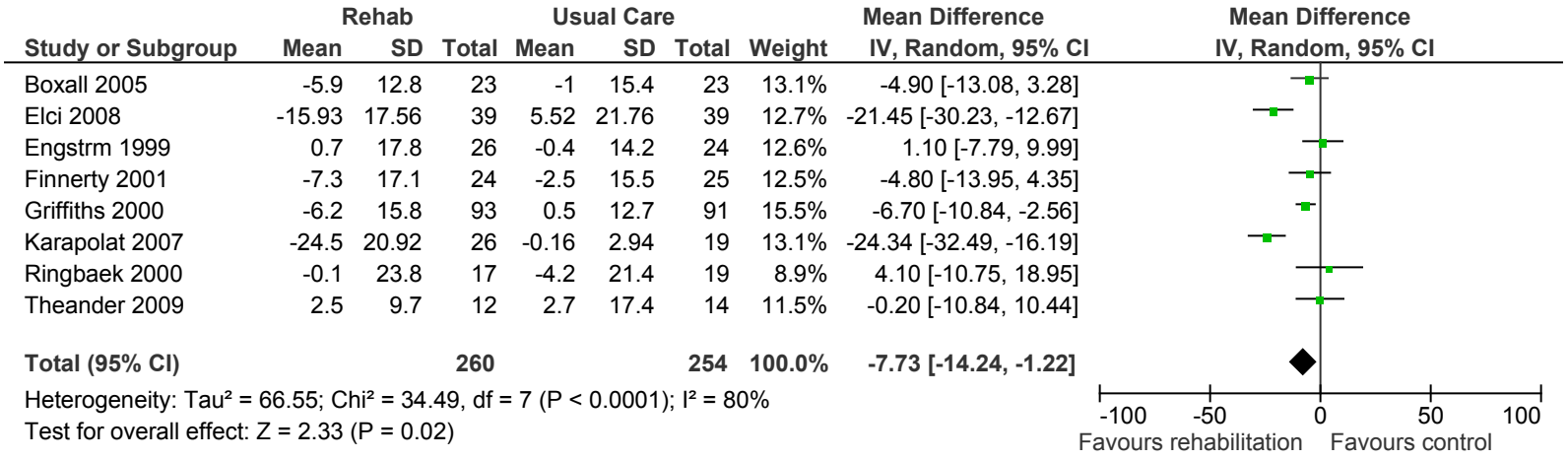

Figure A4: Forest Plot of Pooled Quality of Life Data Measured by the Activity Score of the St. George's Respiratory Questionnaire

*Abbreviations: CI, confidence interval; rehab, rehabilitation; SD, standard deviation.

Quality of Life (Chronic Respiratory Questionnaire)

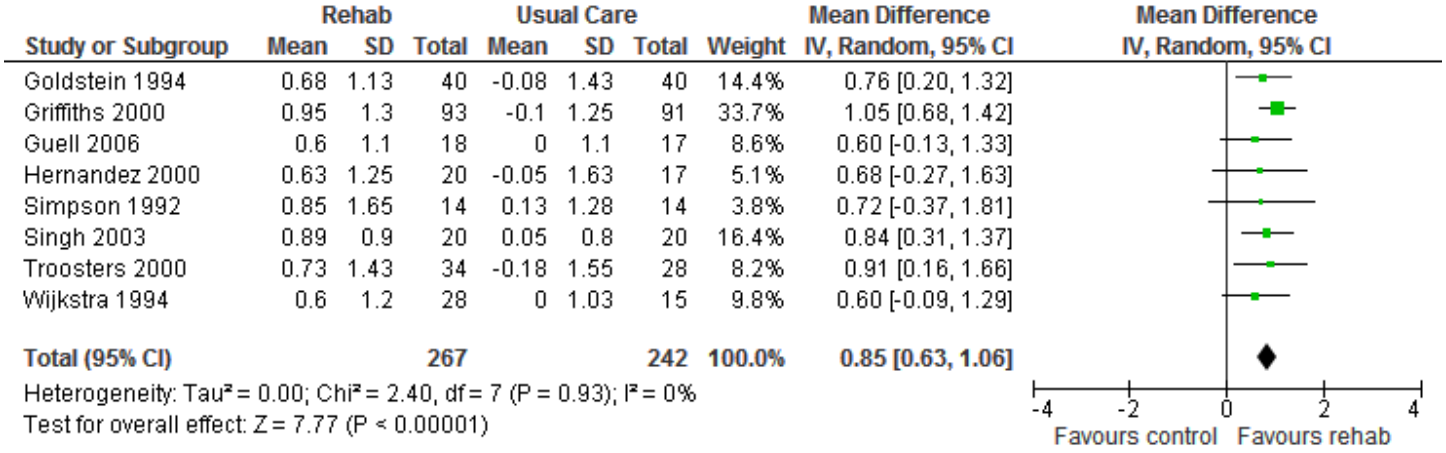

Figure A5: Forest Plot of Pooled Quality of Life Data Measured by the Mastery Score of the Chronic Respiratory Questionnaire

*Abbreviations: CI, confidence interval; rehab, rehabilitation; SD, standard deviation.

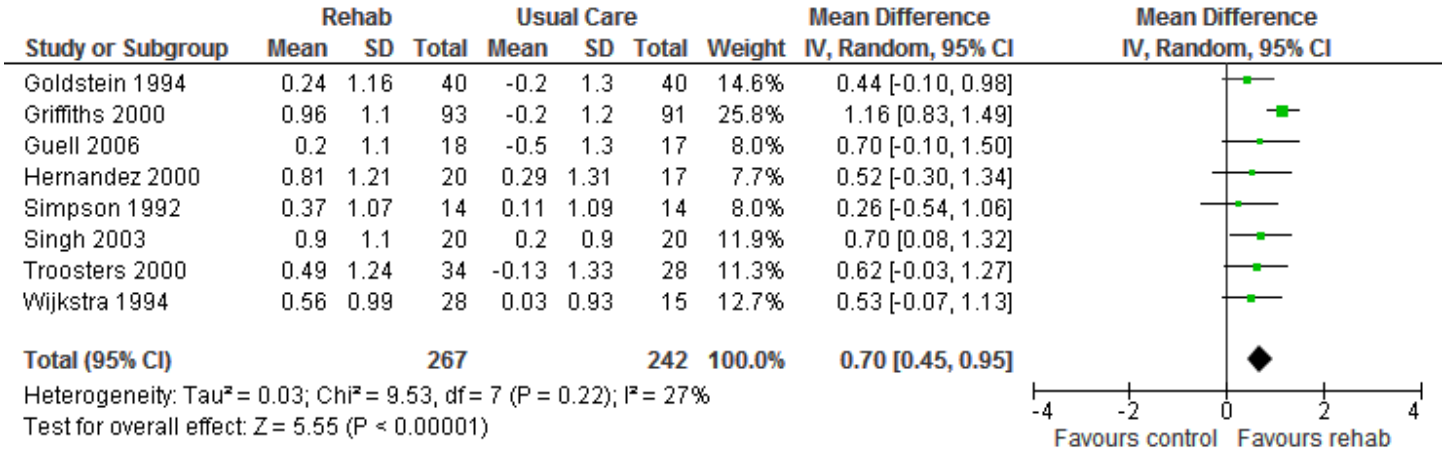

Figure A6: Forest Plot of Pooled Quality of Life Data Measured by the Emotional Function Score of the Chronic Respiratory Questionnaire

*Abbreviations: CI, confidence interval; rehab, rehabilitation; SD, standard deviation.

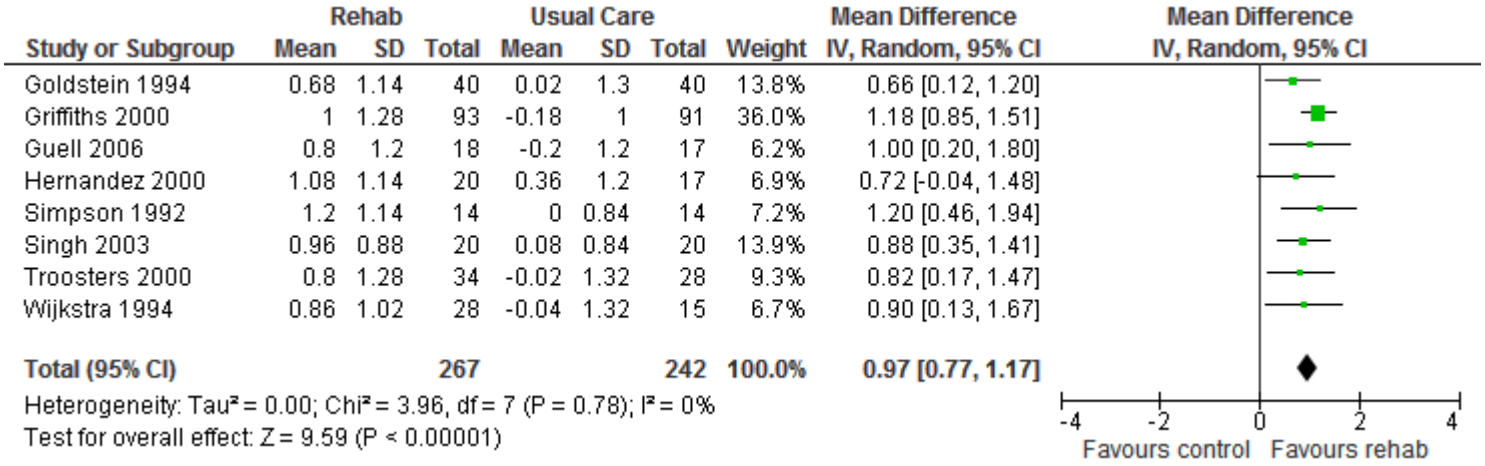

Figure A7: Forest Plot of Pooled Quality of Life Data Measured by the Dyspnea Score of the Chronic Respiratory Questionnaire

*Abbreviations: CI, confidence interval; rehab, rehabilitation; SD, standard deviation.

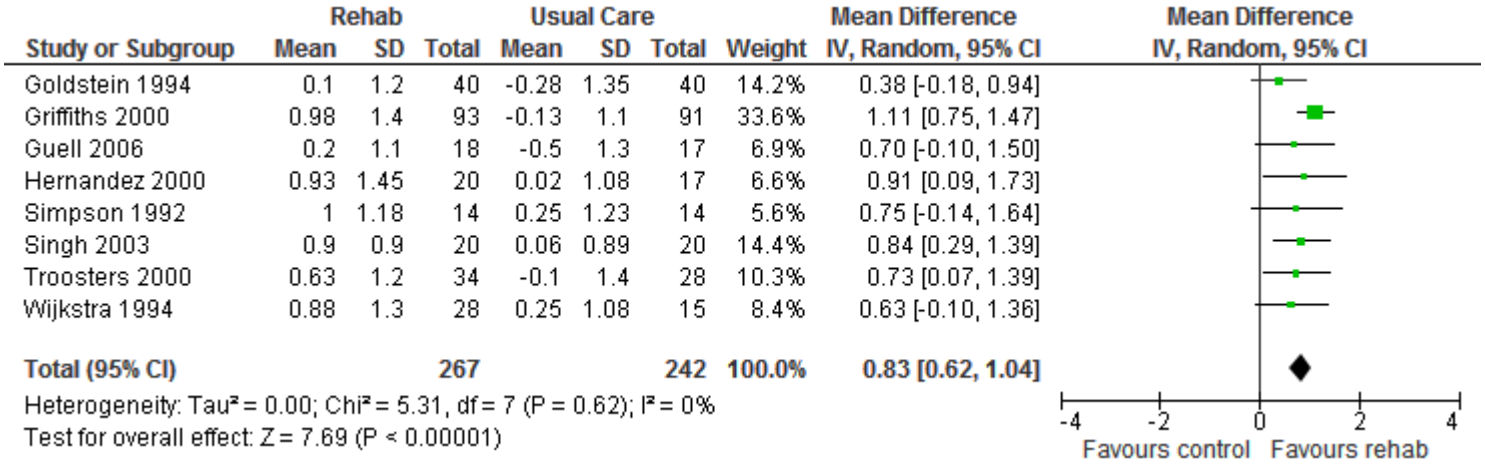

Figure A8: Forest Plot of Pooled Quality of Life Data Measured by the Fatigue Score of the Chronic Respiratory Questionnaire

*Abbreviations: CI, confidence interval; rehab, rehabilitation; SD, standard deviation.

Functional Exercise Capacity (6 Minute Walking Test)

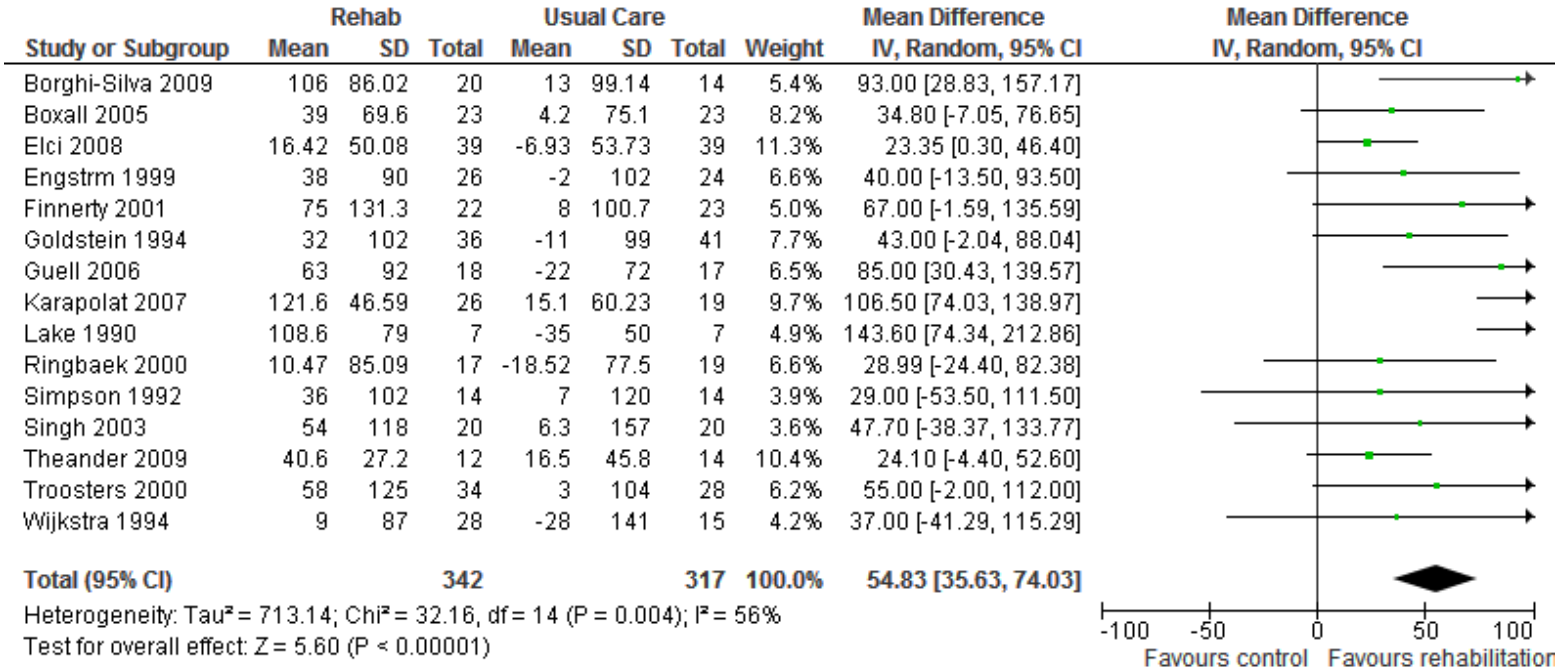

Figure A9: Forest Plot of Pooled Data on Functional Exercise Capacity Measured by the Six Minute Walking Test

*Abbreviations: CI, confidence interval; rehab, rehabilitation; SD, standard deviation.

Studies Examining Pulmonary Rehabilitation Within One Month of an Acute Exacerbation

Hospital Readmissions

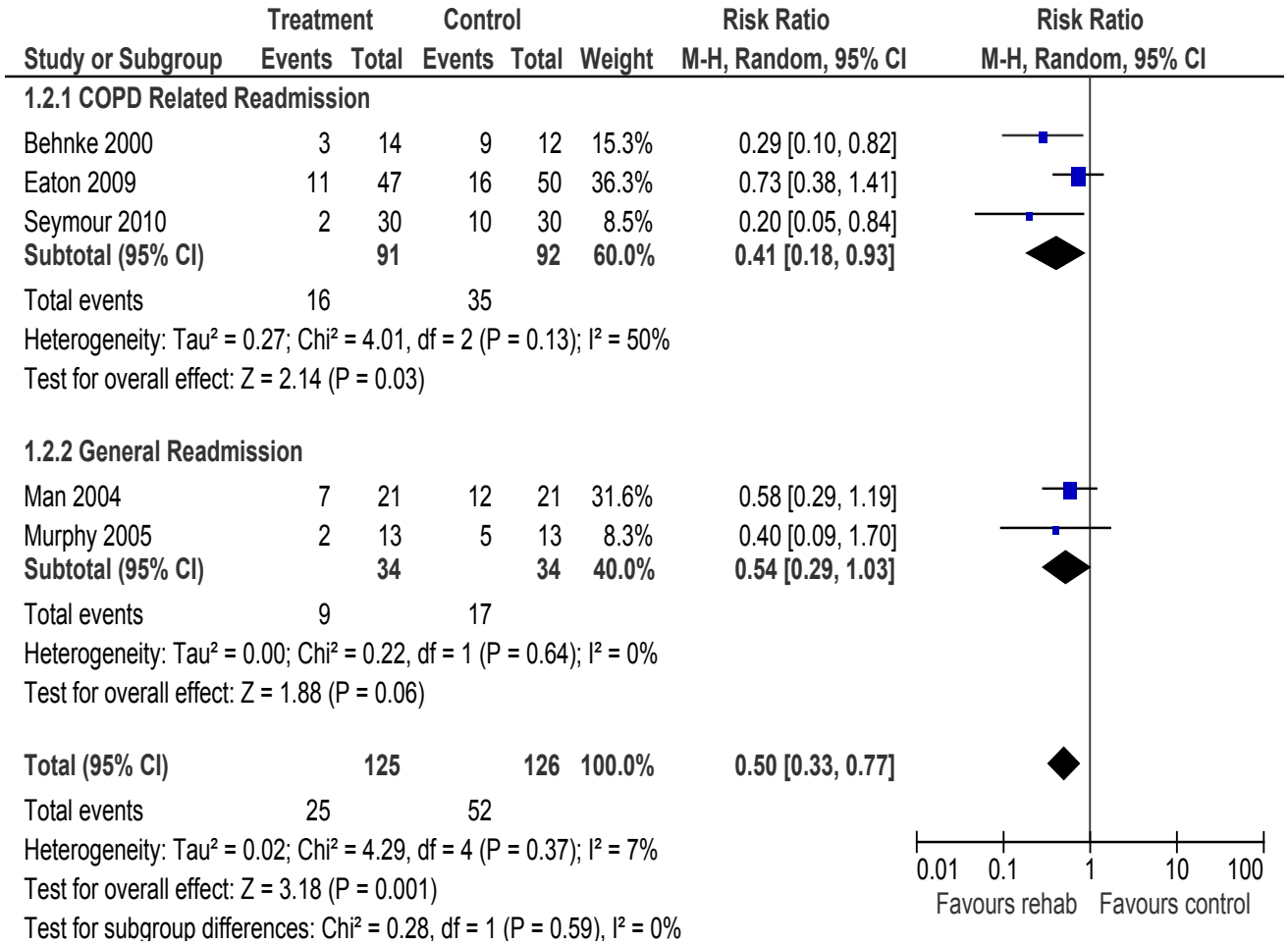

Figure A10: Forest Plot of Pooled Data on Hospital Readmissions Subgrouped by Type of Readmission

*Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; M–H, Mantel–Haenszel.

Health-Related Quality of Life (Chronic Respiratory Questionnaire)

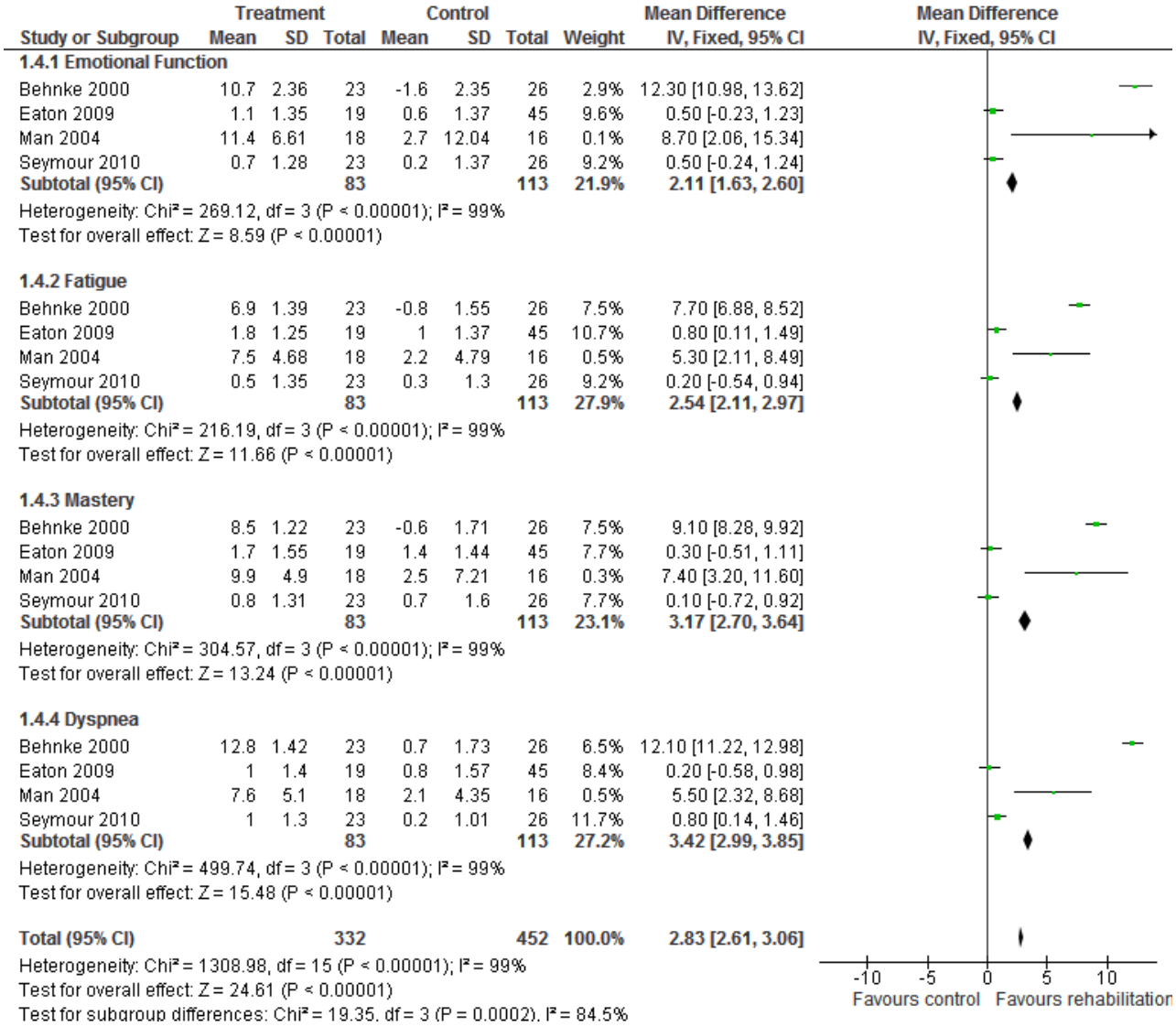

Figure A11: Forest Plot of Pooled Data on Health-Related Quality of Life as Measured by the CRQ, Subgrouped by Components of the CRQ

*Abbreviations: CI, confidence interval; CRQ, Chronic Respiratory Questionnaire; SD, standard deviation.

Health-Related Quality of Life (St. George's Respiratory Questionnaire)

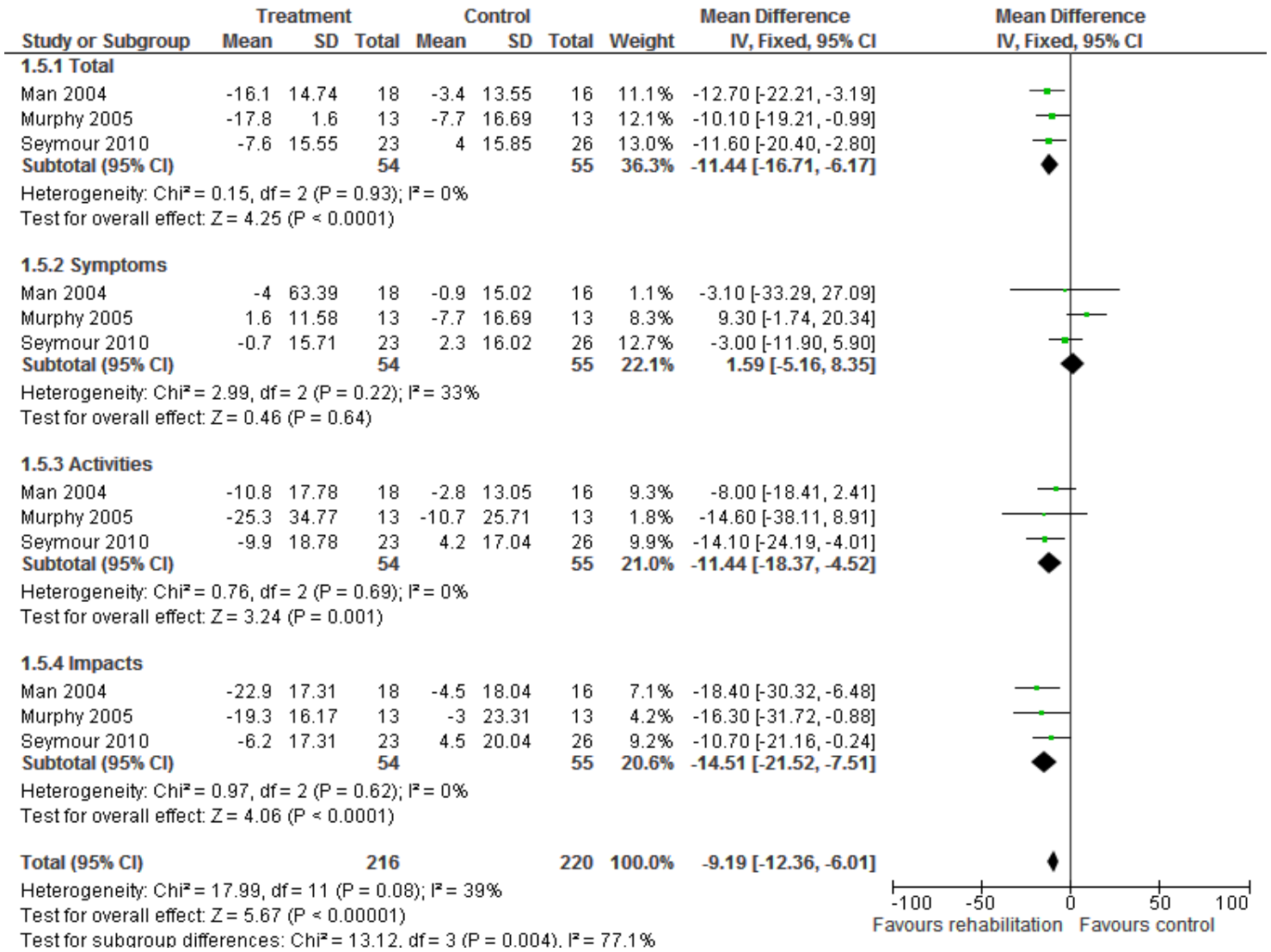

Figure A12: Forest Plot of Pooled Data on Health-Related Quality of Life as Measured by the SGRQ, Subgrouped by Components of SGRQ

*Abbreviations: CI, confidence interval; SD, standard deviation; SQRQ, St. George's Respiratory Questionnaire.

Exercise Capacity

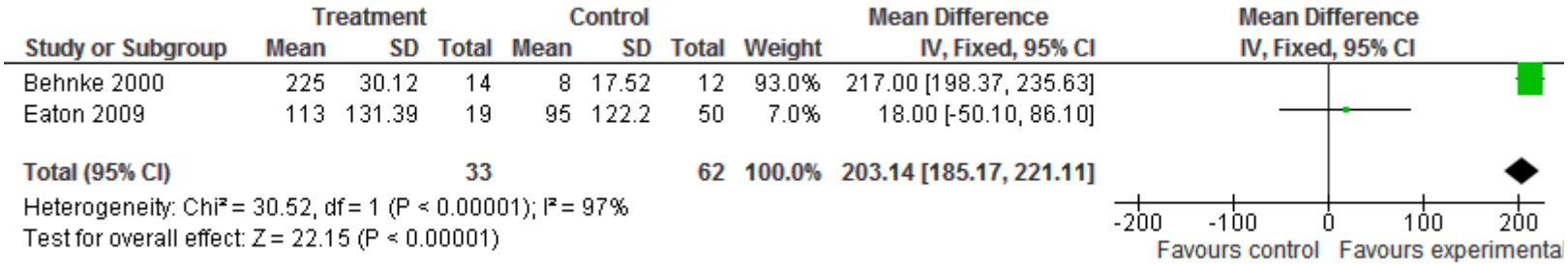

Figure A13: Forest Plot of Pooled Data on Exercise Capacity as Measured by the Six Minute Walking Test

*Abbreviations: CI, confidence interval; SD, standard deviation.

Emergency Department Visits

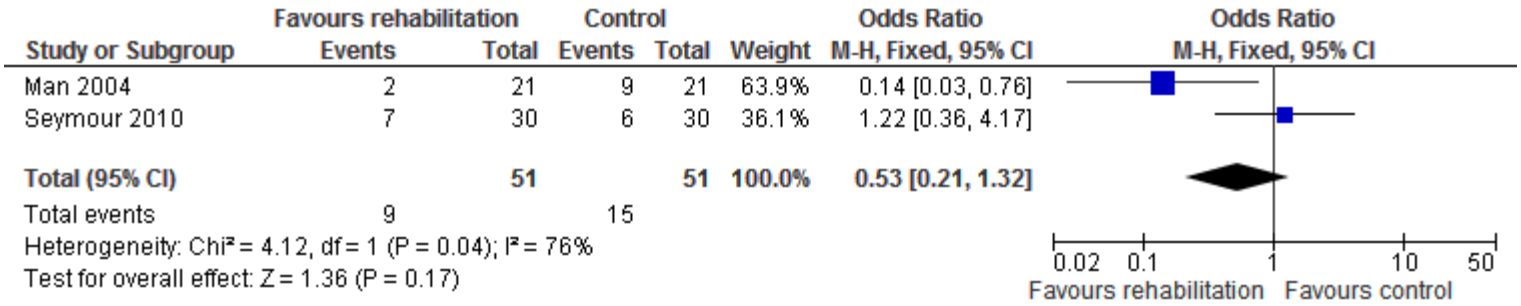

Figure A14: Forest Plot of Pooled Data on Emergency Department Visits

*Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel.

Mortality

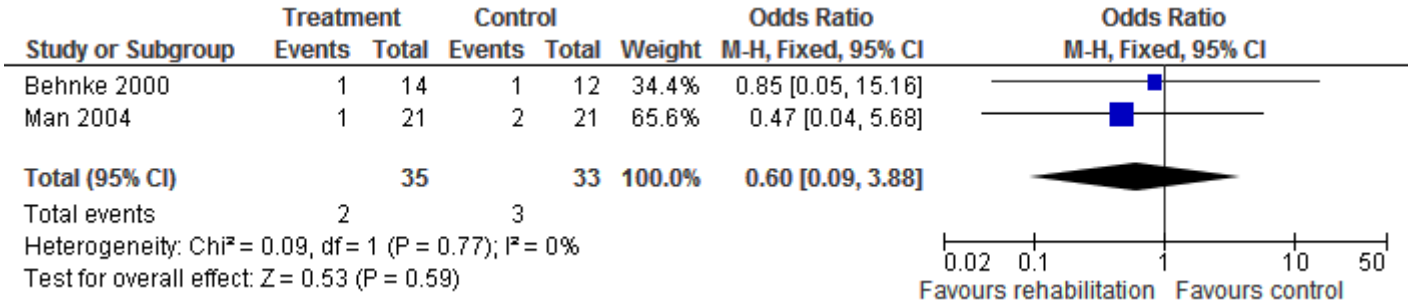

Figure A15: Forest Plot of Pooled Data on Mortality

*Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel.

Studies Examining Pulmonary Rehabilitation Maintenance Programs

Exercise Capacity

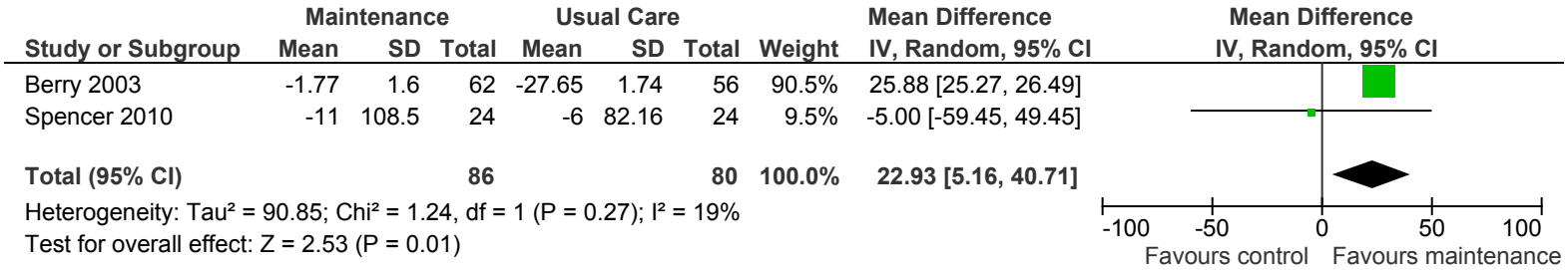

Figure A16: Forest Plot of Pooled Data on Exercise Capacity as Measured by the Six Minute Walking Test

*Abbreviations: CI, confidence interval; SD, standard deviation.

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