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[Intervention Review]

Exercise-based rehabilitation programmes for pulmonary hypertension

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ABSTRACT

Background

Individuals with pulmonary hypertension (PH) have reduced exercise capacity and quality of life. Despite initial concerns that exercise training may worsen symptoms in this group, several studies have reported improvements in functional capacity and well-being following exercise-based rehabilitation in PH.

Objectives

To assess the efficacy and safety of exercise-based rehabilitation for people with PH. Primary outcomes were exercise capacity, adverse events during the intervention period and health-related quality of life (HRQoL). Secondary outcomes included cardiopulmonary haemodynamics, functional class, clinical worsening during follow-up, mortality and changes in B-type natriuretic peptide.

Search methods

We searched the Cochrane Airways Specialised Register of Trials up to August 2016, which is based on regular searches of CINAHL, AMED, Embase, PubMed, MEDLINE, PsycINFO and registries of clinical trials. In addition we searched CENTRAL and the PEDro database up to August 2016 and handsearched relevant journals.

Selection criteria

All randomised controlled trials (RCTs) focusing on exercise-based rehabilitation programmes for PH.

Data collection and analysis

Two reviewers extracted data independently. For binary outcomes, we calculated odds ratios and their 95% confidence interval (CI), on an intention-to-treat basis. For continuous data, we estimated the mean difference (MD) between groups and its 95% CI. We employed a random-effects model for analyses. We assessed risk of bias for included studies and created 'Summary of findings' tables using GRADE.

Main results

We included six RCTs and were able to extract data from five studies. The total number of included participants was 206. The majority of participants were Group I pulmonary artery hypertension (PAH). Study duration ranged from three to 15 weeks. Exercise programmes included both inpatient- and outpatient-based rehabilitation that incorporated both upper and lower limb exercise. The mean six-minute walk distance following exercise training was 60.12 metres higher than control (30.17 to 90.07 metres, $n = 165$, 5 RCTs, low-quality evidence; minimal important difference was 30 metres), the mean peak oxygen uptake was 2.4 ml/kg/minute higher (1.4 to 3.4 ml/kg/min, $n = 145$, 4 RCTs, low-quality evidence) and the mean peak power in the intervention groups was 16.4 W higher (10.9 to 22.0 higher, $n = 145$, 4 RCTs,

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low-quality evidence). The mean change in HRQoL for the SF-36 physical component score was 4.63 points higher (0.80 to 8.47 points, n = 33; 2 RCTs, low-quality evidence) and for the SF-36 mental component score was 4.17 points higher (0.01 to 8.34 points; n = 33; 2 RCTs, low-quality evidence). One study reported a single adverse event, where a participant stopped exercise training due to lightheadedness.

Authors' conclusions

In people with PH, exercise-based rehabilitation results in clinically relevant improvements in exercise capacity. Exercise training was not associated with any serious adverse events. Whilst most studies reported improvements in HRQoL, these may not be clinically important. Overall, we assessed the quality of the evidence to be low. The small number of studies and lack of information on participant selection makes it difficult to generalise these results across the spectrum of people with PH.

PLAIN LANGUAGE SUMMARY

Exercise-based rehabilitation in pulmonary hypertension

What is pulmonary hypertension? Pulmonary hypertension is a condition in which the blood pressure in the arteries that carry blood from the heart to the lungs is elevated well above normal. Often with a gradual onset, it affects individuals of all ages, significantly reduces quality of life and results in premature death.

Bottom Line. We reviewed randomised controlled trials to determine whether exercise training improved short- and long-term patient outcomes in people with pulmonary hypertension. The number of participants in randomised controlled trials of exercise-based rehabilitation for pulmonary hypertension was relatively small. These studies all reported large increases in exercise capacity as evaluated by six-minute walk distance, maximal oxygen consumption and peak power. Health-related quality of life was also improved, but to a lesser extent. Serious adverse events were rare with only one report of a participant being required to stop exercise training due to feeling lightheaded. There were no reports of death or other adverse events with exercise training.

What evidence did we find and how good was it? The review included six studies on 206 people with pulmonary hypertension and we could combine data from five of these studies. We could only use data for 165 participants, however not all of these data could be included in the analysis for all outcome measures. The majority of studies implemented an inpatient exercise rehabilitation programme with only a small number of studies examining an outpatient programme. The methods used to conduct these trials were of low quality. Given this low-quality evidence, it was not possible to generalise the results of this review across the spectrum of people with pulmonary hypertension.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Exercise compared to control for pulmonary hypertension

Exercise compared to control for pulmonary hypertension

Patient or population: people with pulmonary hypertension

Settings: inpatient or outpatient rehabilitation, or both

Intervention: exercise training

Comparison: control: people that had usual care and did not undertake exercise training programme

Outcomes	Illustrative comparative effects* (95% CI)		No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Response on control	Treatment effect			
	Control	Exercise			
Change in functional exercise capacity (6MWD) Distance, metres Follow-up median 12 weeks	Median change = 5 m	The mean exercise capacity 6MWD in the intervention groups was 60.12 higher (30.17 to 90.07 higher)	165 (5 studies)	⊕⊕⊕⊕ low 1,2	Subgroup PAH: (2 studies, n = 36), mean 6MWD for intervention group was 33.84 m higher (0.95 to 66.73 higher); these studies used outpatient exercise rehabilitation whilst other studies contributing to meta-analysis had an inpatient training component Minimal important difference was 30 metres
Exercise capacity: VO₂peak Oxygen uptake, ml/kg/min Follow-up median 13.5 weeks	Median change = -0.25 ml/kg/min	The mean VO ₂ peak in the intervention groups was 2.41 ml/kg/min higher (1.38 to 3.44 higher)	145 (4 studies)	⊕⊕⊕⊕ low 1,2	Subgroup PAH (2 studies, n = 36), the mean VO ₂ peak in the intervention groups was 1.28 ml/kg/min higher (-0.19 to 2.75 higher); these two studies used outpatient exercise rehabilitation whilst other studies contributing to meta-analysis had an inpatient training component
Exercise capacity: peak power watts Follow-up median 13.5 weeks	Median change = 1 watt	The mean exercise capacity: peak power in the intervention groups was 16.44 W higher (10.90 to 21.99 higher)	145 (4 studies)	⊕⊕⊕⊕ low 1,2	Subgroup PAH (2 studies, n = 36), the mean peak power in the intervention groups was 14.24 watts higher (5.78 to 22.70 higher); these two studies used outpatient exercise rehabilitation whilst other studies contributing to meta-analysis had an inpatient training component
HRQoL SF-36: PCS	Median change = -0.49 units	The mean HRQoL SF-36: PCS in the intervention groups	33 (2 studies)	⊕⊕⊕⊕ low 2,3	Both studies were only PAH

units Follow-up median 11 weeks		was 4.63 higher (0.80 to 8.47 higher)			
HRQoL SF-36: MCS units Follow-up median 11 weeks	Median change = -0.31 units	The mean HRQoL SF-36: MCS in the intervention groups was 4.17 higher (0.01 to 8.34 higher)	33 (2 studies)	⊕⊕○○ low 2,3	Both studies were only PAH

*The basis for the response on control is the median control group response across studies

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

1 Two studies did not report random sequence generation, no studies reported allocation concealment

2 Indirectness: 2 studies did not report number of people assessed to achieve sample size; trial participants may represent a highly selected subgroup of people with PH

3 Imprecision (2 small studies of 33 participants) and neither reported allocation concealment

BACKGROUND

Description of the condition

Pulmonary hypertension (PH) is a progressive vasculopathy characterised by extensive remodelling of the pulmonary vasculature resulting in a narrowing of the arterial lumen (Casserly 2009). There is a marked increase in pulmonary vascular resistance resulting in right ventricular remodelling and eventual failure, which, in the majority of cases, results in patient death (Tuder 2013). Confirmatory diagnosis of PH is made via right heart catheterisation in which the patient has a resting mean pulmonary artery pressure of greater than 25 mmHg (Hoepfer 2013). PH may arise in association with a broad range of disease states (over 40) of both known and unknown cause. International guidelines classified PH into the following five clinical groups (Simonneau 2013).

- Group 1: pulmonary arterial hypertension (PAH)
- Group 2: PH due to left heart disease
- Group 3: PH due to lung diseases or hypoxia, or both
- Group 4: chronic thromboembolic PH (CTEPH)
- Group 5: PH with unclear multifactorial mechanisms.

Given the evolving definition of PH, the incidence and prevalence of the disease is difficult to define (Strange 2012). One recent study suggested that this varies markedly between the five clinical groups. In an observational cohort study of over 10,000 individuals from Armadale and the surrounding region in Western Australia, Strange 2012 reported the minimum indicative prevalence for all groups of PH was 326/100,000, with left heart disease associated with Group 2 being the most prevalent. Registries of prevalent and incident cases from around the world have now been published (McGoon 2013), suggesting an increased global awareness of the disease.

Regardless of aetiology, PH is characterised by limited exercise capacity and a progressive increase in breathlessness. Until recently, treatment options for PH remained limited and patient prognosis poor. One early registry of people with PH reported a median survival time of 2.8 years post diagnosis (D'Alonzo 1991). The development of PH-specific drug therapies, targeted at the pulmonary vasculature, has significantly improved prognosis. This improved survival has been reflected in several of the more recently published registries (McGoon 2013). For example, the United States Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) registry of over 3500 prevalent and incident cases recorded between 2006 and 2009, reported five-year survival rates for PAH at 57% (Benza 2010).

Advances in PH-specific therapies have improved survival and slowed disease progression. As a result, other treatment options aimed at improving outcomes such as exercise capacity and quality of life have been explored. In people with other chronic heart and lung diseases, there is strong evidence that exercise training improves functional capacity, quality of life and even long-term survival (Spruit 2013). However, until very recently, exercise rehabilitation has been actively discouraged in people with PH for fear it would worsen symptoms and negatively impact on cardiac function (Galie 2013). Whilst guidelines released in December 2013 recommend exercise training, the guideline authors acknowledge that gaps in the knowledge exist including knowledge of the

optimal training dose, characteristics of supervision, mechanisms of adaptation and the impact of exercise training on long-term survival (Galie 2013).

Description of the intervention

Exercise-based rehabilitation programmes include aerobic and strength training elements designed to improve both aerobic capacity and muscle strength. Aerobic training involves the activation of a large skeletal muscle mass through an extended period of cycling or walking exercise that is between 20 and 40 minutes in duration. Strength training programmes involve upper and lower body muscle groups with the participant completing a number of sets of exercises at a fixed percentage of a repetition maximum (RM) (Spruit 2013). Programmes are typically offered in an outpatient or inpatient setting, involving two to three sessions per week typically over at least a four-week period.

How the intervention might work

In healthy young and older patients, exercise training results in improved oxygen transport and uptake at peak exercise through both central and peripheral adaptations. Central adaptations include an increase in maximal cardiac output, through an increase in stroke volume (Ogawa 1992). Central adaptations are the result of volume overload mediated cardiac remodelling that leads to improved cardiac function at rest and during exercise (Ogawa 1992; Pluim 2000). In the periphery, greater skeletal muscle oxidative capacity occurs with an increase in enzymes associated with cellular respiration, in particular those involved in the citric acid cycle (the Krebs cycle) and oxidative phosphorylation (Gollnick 1973; Coggan 1992). In addition, there is an increase in the capillary density per myofibril (Gollnick 1973; Coggan 1992). As a result of these central and peripheral adaptations, there is not only an increased delivery of oxygen to the exercising myofibril, there is also increased capacity to metabolise oxygen for the production of adenosine triphosphate. Transition between myofibril types typically occurs with an increase in the fast twitch oxidative and a decrease in fast twitch glycolytic fibres following exercise training (Gollnick 1973; Coggan 1992; Ennion 1995). Moreover, there is an increase in the cross sectional area of slow twitch (Type I) and Type IIa fibres in trained individuals (Gollnick 1973; Coggan 1992).

In PH, the factors which contribute to exercise limitation are complex (Fowler 2012; Panagiotou 2015; Babu 2016b). The changes in the pulmonary vasculature associated with PH results in a significant increase in pulmonary artery pressure and right ventricular afterload during exercise (Riley 2000; Provencher 2008). Right ventricular contractility is decreased and there is a reduced capacity for stroke volume and therefore for cardiac output to increase during exercise (Fowler 2012). Moreover, people with PH have a reduced heart rate response to exercise (chronotropic incompetence), which further decreases the ability for cardiac output to increase during exercise (Provencher 2006). As a result, people with PH have a blunted increase in cardiac output during exercise that significantly reduces peak oxygen transport. In the periphery, people with PH appear to have marked skeletal muscle dysfunction consistent with a reduced oxidative capacity (Mainguy 2010a). Compared to controls, people with PH had a lower percentage of Type I fibres and increased concentrations of enzymes associated with glycolytic (anaerobic) metabolism (Mainguy 2010a). These central and peripheral changes would

result in a substantial reduction in the ability to transport and utilise oxygen during exercise.

In people with chronic lung disease, lower limb exercise training and strength training have both been demonstrated to increase exercise capacity and quality of life (Spruit 2013). The primary site of adaptation appears to be the skeletal muscle, with little change in cardiac function following exercise training in people with chronic heart and lung disease (Vogiatzis 2013). For example, in people with chronic obstructive pulmonary disease there is evidence that exercise training results in improved skeletal muscle structure and function with little change in cardiac function (Whitton 1998; Vogiatzis 2013). Whilst preliminary evidence in a small number of people suggests that there is some improvement in skeletal muscle function following exercise training in PH (de Man 2009; Mainguy 2010b), it remains unclear if these changes result in improved exercise capacity or if they relate to improved long-term outcomes. Currently there is limited evidence for any central changes following exercise training in PH.

Why it is important to do this review

The objective of this review was to assess the efficacy and safety of exercise-based rehabilitation for people with PH. In other chronic lung disease populations, for example chronic obstructive pulmonary disease, this form of rehabilitation is safe and has demonstrable benefits in terms of improvement in exercise capacity, lower limb muscle strength and quality of life (Spruit 2013). Until recently there had been a reluctance to recommend exercise-based rehabilitation for PH due to the fact that it may worsen the patient's long-term health outcomes (Galie 2009). Given international guidelines recommending exercise training in PH (Galie 2013, Galie 2015), it is important that the current state of the evidence regarding the efficacy and safety of exercise-based rehabilitation is established. The results of this review will provide essential information to clinicians who may consider referring people with PH for exercise-based rehabilitation, and help guide decisions on which PH patients may be suitable.

OBJECTIVES

To assess the efficacy and safety of exercise-based rehabilitation for people with PH.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs). We included studies reported in full or abstract form as well as any relevant, unpublished data.

Types of participants

We included adults with a diagnosis of PH. We included all five clinical groups of PH (Simonneau 2013), independent of whether the patients were stable on therapy (i.e. change of therapy over the past three months).

Types of interventions

We included trials comparing exercise-based rehabilitation with usual care or no exercise-based rehabilitation. Exercise-based

rehabilitation of any frequency and duration was eligible for inclusion, including inpatient, outpatient or home-based settings. We included exercise programmes of any length; however, we only included trials in which exercise training was supervised. We excluded exercise programmes that only provided exercise advice. We included exercise-based programmes prescribing aerobic or strength training, or both.

We planned to analyse exercise-rehabilitation that only included a strength-training programme separately, however no such trials were found. The control group included individuals randomised to a programme of education which had no specific exercise prescription component.

Types of outcome measures

Primary outcomes

- Exercise capacity
 - * Measures of exercise capacity included but were not confined to outcomes such as the six-minute walk distance (6MWD), peak exercise capacity (VO_{2peak}), peak power (W_{peak}) and measures derived during the assessment of exercise capacity such as breathing efficiency (V_E/VCO_2 slope) and anaerobic threshold
- Serious adverse events during the intervention period
 - * We used this measure to assess the short-term safety of exercise training in PH. We defined adverse events as:
 - * mortality;
 - * disease progression, defined according to the investigators' definition;
 - * symptoms precluding training, such as illness, lightheadedness, syncope or presyncope; and
 - * discontinuation of the study
- Health-related quality of life measured by any validated generic or disease-specific quality-of-life measure

Secondary outcomes

- Cardiopulmonary haemodynamics
 - * These included measures made using echocardiographic, right heart catheter or magnetic resonance imaging techniques
 - * Outcome measures included, but were not confined to indices such as mean pulmonary artery pressure (mPAP), mean pulmonary vascular resistance, right ventricular systolic pressure, tricuspid annular plane systolic excursion, ventricular ejection fraction, ventricular end diastolic volume and ventricular end systolic volume
- Functional Class measured by the New York Heart Association (NYHA) Classification/ (NYHA 1994) World Health Organisation (WHO) Functional Classification Rubin 2004
- Clinical worsening during the follow-up period.
 - * The impact of exercise training on clinical worsening was assessed using the investigators definition
 - * Typically clinical worsening is defined using a combination of outcomes including survival, hospitalisation due to PH, transplantation, requirement for additional pharmacological therapy, a reduction in functional class and or a reduction in the six-minute walk test (Frost 2013)

- * For the purpose of this study, we treated mortality during the follow-up period as a separate secondary outcome measure
- Mortality during the follow-up period
 - * We recorded all deaths reported following the exercise intervention
 - * We treated these deaths separately to those that occurred during the exercise training period, which were recorded by the primary outcome measure, serious adverse events
- B-type natriuretic peptide
 - * A commonly used marker of right ventricular dysfunction in PH that is correlated with survival ([Cassery 2009](#))
 - * We examined changes in B-type natriuretic peptide following exercise-based rehabilitation

Reporting one of more of the outcomes listed here was not an inclusion criterion for the review.

Search methods for identification of studies

Electronic searches

We identified trials from searches of the following databases.

- The Cochrane Airways Register of Trials: all years to 23 August 2016
- Cochrane Central Register of Controlled Trials (CENTRAL; 2016, issue 8) (via the Cochrane Register of Studies (CRS-Web): searched 23 August 2016
- MEDLINE (Ovid): 1950 to August week 1 2016
- Embase (Ovid): 1974 to week 33 2016
- Physiotherapy Evidence Database (PEDro): all years to 23 August 2016

The database search strategies are listed in [Appendix 1](#). We searched all databases from their inception to August 2016, with no restriction on language or type of publication. We identified handsearched conference abstracts and grey literature from the CENTRAL database. We also conducted a search of ClinicalTrials.gov (clinicaltrials.gov/) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (apps.who.int/trialsearch/).

Searching other resources

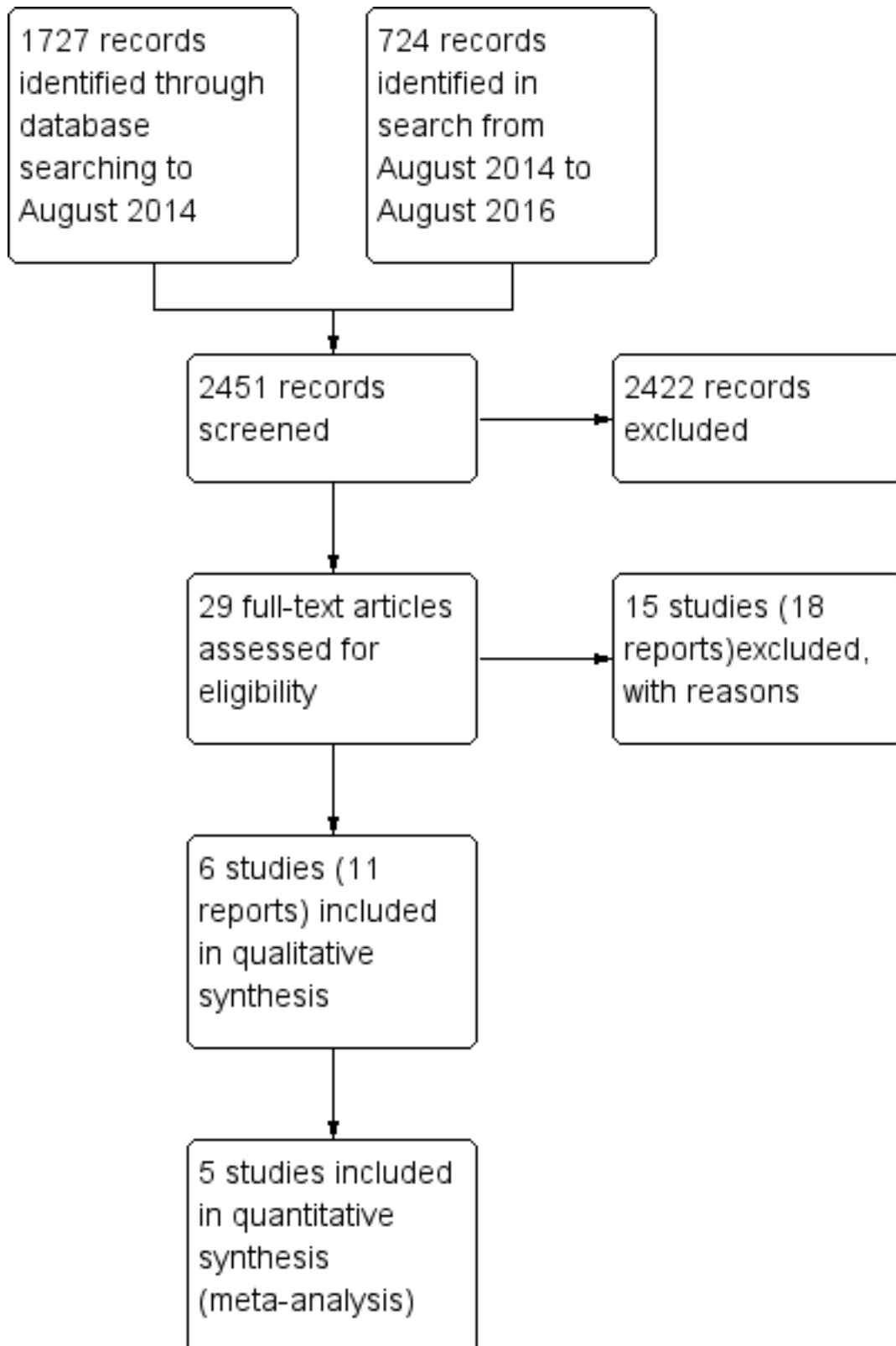
We checked reference lists of all primary studies and review articles for additional references. We searched for errata or retractions from included studies published in full-text on PubMed on 16 August 2016.

Data collection and analysis

Selection of studies

Two review authors (NM and AH) independently screened titles and abstracts for inclusion and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We retrieved the full-text study reports/publication, and two review authors (NM and AH) independently screened the full-text and identified studies for inclusion, and identified and recorded reasons for exclusion of the ineligible studies. We resolved any disagreement through discussion. We identified and excluded duplicates and collated multiple reports of the same study so that each study rather than each report was the unit of interest in the review. We used Covidence ([Covidence 2016](#)) to manage the selection process. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram ([Figure 1](#)) and [Characteristics of excluded studies](#) table.

Figure 1. Study flow diagram



Data extraction and management

We used a data collection form for study characteristics and outcome data which was piloted on one study in the review. Two review authors (NM and AH) extracted study characteristics from included studies in Covidence.

We extracted the following study characteristics.

- **Methods:** study design, total duration of study, details of any 'run in' period, number of study centres and location, study setting, withdrawals, and date of study.
- **Participants:** number enrolled, mean age, age range, gender, severity of condition, diagnostic criteria, baseline echocardiography and right heart catheter data, baseline lung function, inclusion criteria, and exclusion criteria.
- **Interventions:** intervention, training dose (intensity, frequency and duration of exercise training), comparison, concomitant medications, and excluded medications.
- **Outcomes:** primary and secondary outcomes specified and collected, and time points reported.
- **Notes:** funding for trial, and notable conflicts of interest of trial authors.

We noted in the [Characteristics of included studies](#) table if outcome data were not reported in a usable way. We resolved disagreements by consensus. One review author (NM) transferred data into the Cochrane Collaboration's statistical software, Review Manager (RevMan) ([RevMan 2014](#)). We double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (AH) spot-checked study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (NM and AH) independently assessed risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions ([Higgins 2011a](#)). We resolved any disagreements by discussion.

We assessed the risk of bias according to the following domains:

- random sequence generation;
- allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessment;
- incomplete outcome data;
- selective outcome reporting;
- other bias.

We graded each potential source of bias as high, low or unclear and provided a quote from the study report together with a justification for our judgment in a 'Risk of bias' table. We summarised the risk of bias judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a HRQoL scale).

When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.

Assessment of bias in conducting the systematic review

We conducted the review according to the published protocol and reported any deviations from it in the [Differences between protocol and review](#) section of the systematic review.

Measures of treatment effect

We analysed dichotomous data as odds ratios (ORs). For continuous data, we used mean differences (MDs) or standardised mean differences (SMDs). Where it was reported, we used the change from baseline. Where the change from baseline was not reported, we used the adjusted results or final score. We did not combine data expressed as change from baseline with that reported as other metrics. We entered data presented as a scale with a consistent direction of effect.

We undertook meta-analyses only where this was meaningful, that is, if the treatments, participants and the underlying clinical question were similar enough for pooling to make sense.

We narratively described skewed data reported as medians and interquartile ranges.

Where multiple trial arms were reported in a single trial, we planned to include only the relevant arms, however no trials of this nature were identified.

Unit of analysis issues

Where studies randomly allocated the participants to either the exercise-based rehabilitation or control, we considered the participant as the unit of analysis. We excluded cross-over trials due to the potential carry-over effects of exercise training.

Dealing with missing data

We contacted trial investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study was identified as abstract only). Where this was not possible, and the missing data were thought to introduce serious bias, we explored the impact of including such studies in the overall assessment of results by a sensitivity analysis.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis ([Higgins 2003](#)). If we identified substantial heterogeneity, we explored possible causes by prespecified subgroup analysis ([Deeks 2011](#)).

Assessment of reporting biases

If we were able to pool more than 10 trials, we planned to create and examine a funnel plot to explore possible small study and publication biases, however insufficient numbers of trials were identified.

Data synthesis

We performed a pooled quantitative synthesis where the trials were clinically homogeneous. We pooled data using a random-effects model to incorporate between-study heterogeneity into the meta-analysis. Data from an intention-to-treat analysis were used where available. Where the trials were clinically heterogeneous, we performed a narrative synthesis. We used RevMan HAL, developed

by the Cochrane Schizophrenia Group (<http://szg.cochrane.org/revman-hal>), to construct a first draft of the results section.

'Summary of findings' table

We created a 'Summary of findings' table using the following outcomes: exercise capacity, serious adverse events, cardiopulmonary haemodynamics, quality of life, functional class, mortality and clinical worsening during follow-up. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes. We used methods and recommendations described in the Cochrane Handbook for Systematic Reviews of Interventions (Schünemann 2011) using GRADEpro software (GRADEpro GDT 2015). We justified all decisions to downgrade or upgrade the quality of studies in the Footnotes section of [Summary of findings for the main comparison](#), and we made comments to aid readers' understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses.

- Type of PH:
 - * we analysed data separately for people with PAH only (Group 1).
- Severity of PH:
 - * we planned to compare the outcomes of less severe disease classification (NYHA Class I/II) with those with more severe disease classification (NYHA Class III/IV), however insufficient data were available.

We used the following outcomes in subgroup analyses:

- exercise capacity;
- serious adverse events;
- health-related quality of life.

We used the formal test for subgroup interactions in [RevMan 2014](#).

Sensitivity analysis

We performed sensitivity analyses to examine the effects of methodological quality on the pooled estimate by removing studies that were at high or unclear risk of bias for the domains of blinding and incomplete outcome data.

RESULTS

Description of studies

See [Characteristics of included studies](#), [Characteristics of excluded studies](#) and [Characteristics of studies awaiting classification](#) for complete details.

Results of the search

The PRISMA table shows results of our search [Figure 1](#)

In the original search to August 2014, we found 1727 papers that were potentially relevant. We conducted an additional search from August 2014 to August 2016 and identified an additional 724 papers. After removing duplicates and the clearly irrelevant material we selected 29 full-text papers to be further assessed for inclusion. Of these, we excluded 15 studies (18 reports) because they did not meet our inclusion criteria. Finally, after careful scrutiny, we were left with six studies (11 reports).

Included studies

Refer to [Characteristics of included studies](#). The total number of participants from included participants was 206. Sample sizes ranged from 10 to 87 participants. Most participants had PAH (Group 1 PH) or chronic thromboembolic PH. The mean age of participants ranged from 47 to 56 years, and the mPAP on right heart catheterisation ranged from 40 to 52 mmHg. All participants were stable on medical therapy.

Excluded studies

From the 29 full-text papers reviewed, we excluded 15 studies (18 reports). Reasons for exclusion were that studies were not randomised controlled trials (RCTs, n = 8), did not include exercise training (n = 3), was a review (n = 1), included the wrong population (n = 1) or used the wrong intervention (n = 2). Full details of the reasons for exclusion are included in the [Characteristics of excluded studies](#) section.

Risk of bias in included studies

Details on our judgements on the potential risks of bias are summarised in [Figure 2](#) and [Figure 3](#), with full details in the [Characteristics of included studies](#) table.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

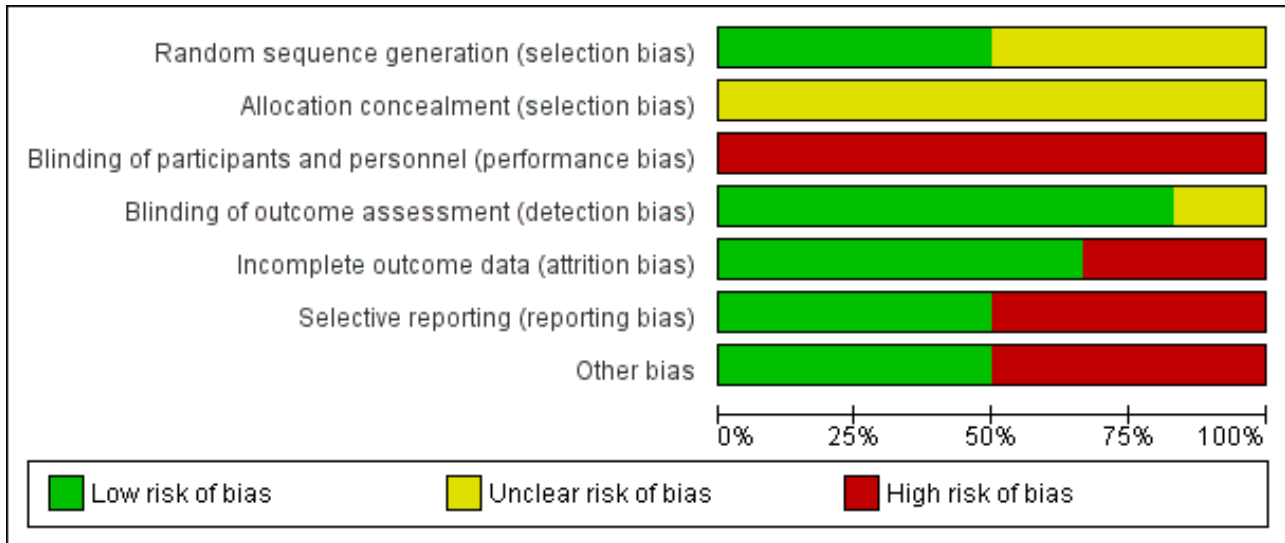


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chan 2013	?	?	-	+	+	-	+
Ehlken 2016	?	?	-	?	-	-	-
Ganderton 2013	+	?	-	+	+	+	+
Ley 2013	+	?	-	+	+	+	+
Mereles 2006	+	?	-	+	+	+	-
Wilkinson 2007	?	?	-	+	-	-	-

Allocation

None of the studies provided details on how allocation was concealed and we therefore judged them to be at unclear risk of bias in this domain. Three of the studies (Mereles 2006; Ganderton 2013; Ley 2013) provided details on how the randomisation sequence was generated and we judged them to be at low risk. For the remaining studies we were unable to ascertain details of random sequence generation.

Blinding

We rated all six of the studies as having a high risk of bias for blinding of participants and personnel. Given the nature of the intervention (exercise training) it was not possible to blind participants or personnel to the intervention. Five out of six studies reported blinding of outcome assessors.

Incomplete outcome data

Based on our review, we rated four of the studies as low risk with regards to attrition bias (Mereles 2006; Chan 2013; Ganderton 2013;

Ley 2013) with each of these studies reporting no or very small numbers of dropouts. We rated the largest study, Ehlken 2016, as high risk as there was a differential rate of attrition with 17% dropout in the intervention group as opposed to 0% dropout in the control.

Selective reporting

We found three studies to have low risk of reporting bias (Mereles 2006; Ganderton 2013; Ley 2013). Two studies did not provide complete results when compared to those provided on the trial registry (Chan 2013; Ehlken 2016). The final study of Wilkinson 2007 was only in abstract form, making it difficult to ascertain if the data reported were complete.

Other potential sources of bias

We found three of the studies to be of low risk with regards to other sources of bias (Chan 2013; Ganderton 2013; Ley 2013). We were unable to rule out some selection bias in the three other studies (Mereles 2006; Wilkinson 2007; Ehlken 2016). Neither of the studies by Mereles 2006 and Wilkinson 2007 provided a CONSORT diagram and hence there is no detail how many participants they screened to achieve the enrolment target (Schulz 2010). The study by Ehlken 2016, whilst providing a CONSORT diagram, did not provide any detail on how many patients were screened and how they applied the inclusion/exclusion criteria to achieve the target enrolment of 95 participants.

Effects of interventions

See: [Summary of findings for the main comparison Exercise compared to control for pulmonary hypertension](#)

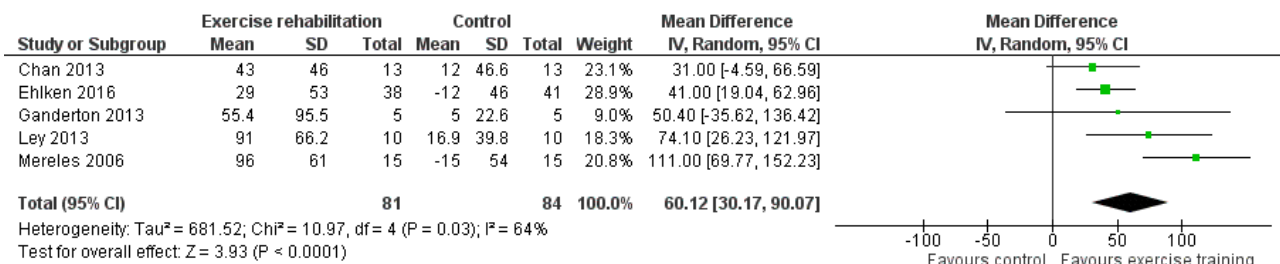
Studies in this review compared exercise-based rehabilitation to no intervention, education alone or usual care. In total there were six relevant randomised studies. We extracted data for meta-analyses from five of the studies (Mereles 2006; Chan 2013; Ganderton 2013; Ley 2013; Ehlken 2016), allowing for comparison between exercise-based intervention and control. We were unable to obtain data for analysis from the study by Wilkinson 2007 (published only as an abstract) despite several attempts to contact the study authors. See [Summary of findings for the main comparison](#) for the main comparisons between the intervention and control groups. In total there were 21 outcomes evaluated including primary outcomes of exercise capacity, adverse events and health-related quality of life.

Primary outcomes

Exercise capacity

Five studies (n = 165 PH participants) reported changes in the 6MWD (Mereles 2006; Chan 2013; Ganderton 2013; Ley 2013; Ehlken 2016) or changes in exercise capacity derived from an incremental exercise test (Mereles 2006; Chan 2013; Ganderton 2013; Ehlken 2016). The mean increase in 6MWD of 60.12 m (MD 30.17 to 90.07 higher, Analysis 1.1, Figure 4) was well in excess of the minimal important difference of 30 metres (Mathai 2012; Holland 2014). However there was marked heterogeneity across studies (I²= 64%).

Figure 4. Forest plot of comparison: 1 Exercise vs control, outcome: 1.1 Exercise capacity: 6MWD



Four studies reported the impact of exercise-based rehabilitation on peak exercise capacity determined from a cardiopulmonary exercise testing (CPET) (Mereles 2006; Chan 2013; Ganderton 2013; Ehlken 2016). There were significant increases in both VO₂peak with exercise-based rehabilitation compared to control (MD 2.4 ml/kg/min, 95% CI 1.4 to 3.4, Analysis 1.2) with no significant heterogeneity across studies (I²= 37%). Similarly, increases in peak power favoured exercise rehabilitation (MD 16.4 W, 95% CI 10.9 to 22.0, Analysis 1.3) with no significant heterogeneity (I²= 0%). Three studies reported changes in the anaerobic threshold, one of which was reported as time to anaerobic threshold (Chan 2013), whilst the other two reported this in ml/min (Mereles 2006; Ganderton 2013). Pooled analysis showed an increase in the standardised mean difference favouring the exercise rehabilitation group (SMD 1.05, 95% CI 0.53 to 1.58, I²= 0%, Analysis 1.4). Whilst there is no reported minimal important difference (MID) for CPET-derived measures of exercise capacity in PH, the increase in peak power is in excess of the MID reported for chronic obstructive pulmonary disease of 5 to 10 W (Sutherland 2005).

To date few studies have examined possible mechanisms for improved exercise capacity following exercise training in PH. In their study Ley 2013 reported improved pulmonary perfusion using magnetic resonance imaging (MRI). These authors suggested that exercise training may improve perfusion of the lungs or contractile function, or both. However it was noted that none of the changes in cardiac function correlated with changes in 6MWD. In their study Ehlken 2016 completed a right heart catheterisation (RHC) in a subgroup of exercise and control subjects. They reported improved pulmonary haemodynamics with a lowering of mean pulmonary artery pressure in the exercise group compared to the control group. For the exercise group there was an improvement in submaximal and maximal cardiac output. The authors hypothesised that exercise training may improve right ventricular (RV) function, however RV function was not directly measured.

Apart from these central changes there is some evidence that exercise training improves skeletal muscle oxidative capacity, similar to what is seen with exercise training in other chronic

lung disease populations. Small observational studies by [Mainguy 2010b](#) (n = 5) and [de Man 2009](#) (n = 19) both reported improvements in skeletal muscle oxidative capacity and capillary density. These preliminary results would suggest that the mechanism for adaptation to exercise training may be the result of improved skeletal muscle oxidative capacity and capillarisation and potentially improved oxygen delivery through improved cardiac function.

Overall the quality of evidence for changes in exercise capacity was rated as low due to imprecision and selective reporting. For details see [Summary of findings for the main comparison](#).

Serious adverse events

Only one study reported any adverse event that precluded a participant from training in a single session ([Ganderton 2013](#)). In this study one subject was reported to have stopped training for a single session due to extreme lightheadedness. No other studies reported any serious adverse events as we defined them in the protocol, that is, mortality, disease progression, symptoms that precluded training or discontinuation of the study.

Health-related quality of life

Quality of life was reported using either the Short-Form 36 (SF-36) questionnaire ([Mereles 2006](#); [Chan 2013](#); [Ganderton 2013](#); [Ehlken 2016](#)) or using the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), a PH-specific questionnaire ([Chan 2013](#); [Ganderton 2013](#)).

We have reported the changes in the physical component scores (PCS) and mental component score (MCS) of the SF-36 in [Summary of findings for the main comparison](#) and [Analysis 1.5](#) and [Analysis 1.6](#) as these provide us with a summary of the global improvement in both physical and emotional aspects of quality of life. Changes in PCS and MCS were reported in two of the smaller studies ([Chan 2013](#); [Ganderton 2013](#)). Analysis showed that exercise-based interventions favoured improved outcomes for PCS (MD 4.63, 95% CI 0.80 to 8.47, [Analysis 1.5](#)) and MCS (MD 4.17, 95% CI 0.01 to 8.34, [Analysis 1.6](#)) with no significant heterogeneity between studies. Both of these studies also examined changes in health-related quality of life using the CAMPHOR and reported greater improvement in the exercise-based rehabilitation group in each of the subscores for activities (MD -1.33, 95% CI -3.56 to 0.90, [Analysis 1.16](#)), symptoms (MD -3.08, 95% CI -7.78 to 1.62, [Analysis 1.17](#)) and overall quality of life (MD -5.42, 95% CI -8.03 to -2.81, [Analysis 1.18](#)), although there was marked heterogeneity for the activities and symptoms domains ($I^2 = 67%$ and $88%$ respectively).

Four of the studies (n = 118 randomised) reported changes in quality of life using the domains of the Short-Form 36 (SF-36) questionnaire ([Mereles 2006](#); [Chan 2013](#); [Ganderton 2013](#); [Ehlken 2016](#)). Exercise-based rehabilitation resulted in a substantial improvement in outcome scores for 'Role physical' (MD 21.8, 95% CI 14.40 to 29.23, [Analysis 1.9](#)), 'Vitality' (MD 13.47, 95% CI 7.55 to 19.40, [Analysis 1.14](#)), and 'Social function' (MD 14.01, 95% CI 9.82 to 18.21, [Analysis 1.15](#)). Pooled analysis found there was no improvement in 'Physical function' (MD 6.13, 95% CI -3.73 to 16.00, [Analysis 1.8](#)), 'Bodily pain' (MD 5.64, 95% CI -3.09 to 14.36, [Analysis 1.10](#)), 'General health' (MD 5.76, 95% CI -0.80 to 12.32, [Analysis 1.11](#)), 'Mental health' (MD 6.21, 95% CI -1.85 to 14.27, [Analysis 1.12](#)) and 'Role emotional' (MD 2.79, 95% CI -7.43 to 13.01, [Analysis 1.13](#)).

Secondary outcomes

Cardiopulmonary haemodynamics

Only the study by [Ehlken 2016](#) reported changes in cardiopulmonary haemodynamics measured using (RHC) following exercise-based rehabilitation. In a subset of the study participants (31 exercise and 28 control) the authors reported a significant decrease ($P < 0.01$) in mPAP following exercise training (MD -9.00, 95% CI -13.60 to -4.40, [Analysis 1.19](#)).

Functional class

Only two studies reported changes in functional class for exercise and control groups [Mereles 2006](#); [Ganderton 2013](#). Improvement in functional class favoured exercise rehabilitation (MD -0.60, 95% CI -0.85 to -0.35, [Analysis 1.20](#)).

Clinical worsening during follow-up period

No data were available for analysis.

Mortality during follow-up period

No data were available for analysis.

B-type natriuretic peptide

Only the study of [Ehlken 2016](#) reported changes in B-type natriuretic peptide for exercise and control groups. These authors reported a non significant ($P = 0.36$) improvement in B-type natriuretic peptide with exercise rehabilitation (MD -236.00, 95% CI -744.48 to 272.48, [Analysis 1.21](#)).

Sensitivity analysis

For our sensitivity analysis we removed studies that did not specify blinding of outcome measurements or had incomplete outcome data (attrition bias). As a result two studies were removed from the analysis of exercise outcomes ([Wilkinson 2007](#); [Ehlken 2016](#)). We did not undertake sensitivity analysis for changes in health-related quality of life as the studies of [Wilkinson 2007](#) and [Ehlken 2016](#) were not included in the original HRQoL analysis. Sensitivity analysis did not change the pattern of findings, with the exercise group showing improvements in 6MWD (MD 67.91 metres, 95% CI 27.12 to 108.69, [Analysis 1.22](#)), VO_2 peak (MD 1.94 ml/kg/m², 95% CI 0.86 to 3.01, [Analysis 1.23](#)), and peak power (MD 15.27 Watts, 95% CI 8.57 to 21.97, [Analysis 1.24](#)) compared to control.

Subgroup analysis

Type of PH

We compared the outcomes for different subgroups of PH using the classification outlined by [Hoeper 2013](#). Three of the studies included a mixed group of PH participants, including both those with PAH (i.e. those from Group 1, [Hoeper 2013](#)) and chronic thromboembolic pulmonary hypertension (i.e. Group 4, CTEPH, [Hoeper 2013](#)) ([Mereles 2006](#); [Ley 2013](#); [Ehlken 2016](#)). We were unable to extract data separately for the subgroups in these studies. We performed a subgroup analysis for the two studies that only included PAH (Group 1) participants ([Chan 2013](#); [Ganderton 2013](#)). The increase in 6MWD, whilst much lower than the group as a whole, still exceeded the MID (MD 33.84 metres, 95% CI 0.95 to 66.73, [Analysis 1.25](#)). Likewise the increases in VO_2 peak (MD 1.28 ml/kg/min, 95% CI -0.19 to 2.75, [Analysis 1.26](#)) and peak power (MD 14.24 Watts, 95% CI 5.78 to 22.70, [Analysis](#)

1.27) were lower in the subgroup of participants with PAH. However these studies also differed in the setting and nature of the exercise rehabilitation programme delivered (see 'Setting of exercise rehabilitation programme' below) and it is therefore not possible to attribute these differences solely to diagnosis.

Severity of PH

Insufficient data were available to perform subgroup analysis according to disease severity.

Setting of exercise rehabilitation programme

We identified an additional source of potential heterogeneity whilst exploring the heterogeneity in 6MWD responses (Analysis 1.1). Three studies used inpatient programmes of three weeks' duration (training seven days per week) (Mereles 2006; Ley 2013; Ehlken 2016), in some cases followed by a 12-week, home-based programme (Mereles 2006; Ehlken 2016), whilst the remaining studies used outpatient training programmes. Because of the observed heterogeneity we chose to examine results for programmes that included inpatient training components in the exercise-based rehabilitation intervention separately to those that only included outpatient programmes, as inpatient programmes may allow closer supervision and greater intensity of exercise prescription. Note for the studies of Mereles 2006 and Ehlken 2016 we reported outcomes following the three-week inpatient plus 12-week home-based programme (i.e. 15 weeks) whereas for Ley 2013 we have reported outcomes following the three-week inpatient programme.

Studies that incorporated an inpatient model of exercise rehabilitation (Mereles 2006; Ley 2013; Ehlken 2016) reported very large improvements in 6MWD, however marked heterogeneity was still present across these three studies (mean improvement 72.79 metres, 95% CI 28.09 to 117.49, $I^2 = 78\%$). The studies that relied totally on outpatient-based exercise programmes (Chan 2013; Ganderton 2013) randomised only 36 people with PH (24% of total subject sample) and reported a smaller mean difference in 6MWD favouring the exercise group of 33.84 metres (0.95 to 66.73 metres higher) but with no evidence of statistical heterogeneity ($I^2 = 0\%$). The test for subgroup differences was not significant ($P = 0.17$, Analysis 1.29). It should be noted that both these studies only included participants with PAH, so these subgroup analyses by setting give rise to the same results as those for the subgroup analysis according to type of PH.

DISCUSSION

Summary of main results

The aim of this review was to examine the efficacy of exercise-based rehabilitation in people with PH. The included studies reported large and clinically significant improvements in exercise capacity, measured using both the 6MWD and CPET. However there was marked heterogeneity across trials for 6MWD; we were unable to determine whether this was due to differences in study populations (PAH versus other), settings (inpatient versus outpatient) or the severity of the disease (where there was insufficient evidence to assess). There were also improvements in quality of life, measured using both PH-specific and non-specific tools, although the magnitude of these changes may not be clinically important. There was only a single reportable adverse event. These results are based on a relatively small number of participants (there were

206 participants in the trials, but data from only 165 in the forest plot with the most data) from only five RCTs. It was not possible to determine the impact of exercise rehabilitation on the secondary outcomes of cardiopulmonary haemodynamics, functional class or B-type natriuretic peptide due to insufficient data. No studies reported on the effects of rehabilitation, time to clinical worsening or mortality. The quality of evidence was generally low, with no studies reporting allocation concealment, and the potential for selection bias, as there were few details provided regarding screening of potential artificialness. All outcomes were short term, measured immediately following the rehabilitation period, so the longer-term effects of exercise rehabilitation remain unknown.

Overall completeness and applicability of evidence

Most participants in the studies had a diagnosis of PAH, so our results should be applied primarily in that group. There was a small number of participants with CTEPH, however their results could not be extracted separately, so it is difficult to be confident regarding the effects of exercise rehabilitation in this group. Of the studies completed to date, none have included groups of participants who had PH associated with connective tissue disease or congenital heart disease, PH due to left heart disease, or PH due to lung disease, so our results cannot be applied to these groups. Few participants in functional class IV were included, so the impact of exercise rehabilitation in those with the most severe disease remains unclear. Importantly, all studies only included participants who were stable on medical therapy (including no recent syncope), so it is in this group that exercise rehabilitation can be applied.

Three of the six studies used an inpatient rehabilitation programme of at least three weeks in duration, with exercise training taking place seven days per week (Mereles 2006; Ley 2013; Ehlken 2016). The magnitude of improvement in exercise outcomes appeared to be greater following these programmes compared to those who used an outpatient exercise-based rehabilitation model, where supervised training took place only two to three times per week (Chan 2013; Ganderton 2013). However we were unable to determine whether the underlying diagnosis of participants also affected the outcomes. The inpatient exercise rehabilitation programmes delivered closer supervision, more sophisticated monitoring and a higher frequency of training than the outpatient programmes, which may contribute to better exercise outcomes. Such inpatient cardiorespiratory rehabilitation programmes are common in some parts of Europe, but are virtually non-existent in other parts of the world such as the UK, Australia and the USA. Such differences in health system organisation may affect the type of exercise rehabilitation model that can be applied in PH. However it should be noted that improvements following outpatient training, although smaller in magnitude, were clinically important.

The exercise rehabilitation protocols tested included lower limb endurance training (walking or cycling), usually with resistance exercises for the upper and lower limbs. These protocols are similar to those recommended for standard pulmonary (Spruit 2013) and cardiac (Piepoli 2014) rehabilitation programmes. Additional components in some studies included stretching, breathing techniques such as pursed lip breathing, body perception, yoga, and strengthening of respiratory muscles (Mereles 2006). Further data is required to identify the contribution of these additional components to rehabilitation outcomes. The similarity of the core rehabilitation components to those delivered in pulmonary and cardiac rehabilitation programmes (lower limb endurance training,

upper and lower limb resistance training) suggests that people with PH could receive their rehabilitation within these existing services, which could improve uptake into practice. However some studies in this review used specialised exercise prescription and monitoring practices that may not occur routinely in existing cardiopulmonary rehabilitation programmes (e.g. low-intensity interval training, continuous monitoring of oxyhaemoglobin saturation and heart rate, restriction of exercise heart rate to less than 120 beats per minute) (Mereles 2006; Ley 2013; Ehlken 2016). Whilst no significant adverse events were documented during supervised exercise training in the studies included in this review, it is clear that exercise is not entirely without risk in PH (Morris 2015) and international guidelines currently suggest that exercise rehabilitation should be undertaken "...by centres experienced in both PH patient care and rehabilitation of compromised patients" (Galie 2015).

Quality of the evidence

It was encouraging that five out of six included studies reported blinding of outcome assessors, which is important for rehabilitation studies where many of the important outcomes (exercise capacity, HRQoL) could be affected by knowledge of group assignment. Random sequence generation and allocation concealment were generally not well reported. However the major source of potential bias related to reporting of participant selection. For three of the six studies it was not clear how many people had been assessed in order to achieve the required sample size. Pulmonary hypertension comprises a diverse group of patients with wide variation in disease severity. In contrast the participants in the included trials were predominantly from Group 1 and tended to have mild to moderate disease. It remains possible that the participants in these studies were a highly selected group who responded well to exercise training. Future studies should carefully report their screening and selection procedures in accordance with CONSORT requirements (Schulz 2010).

Potential biases in the review process

All data were extracted independently by two review authors using Covidence and discrepancies were resolved through discussion (Covidence 2016). Risk of bias ratings were also completed independently by two review authors. We included studies that were published only in abstract form, to ensure that all available trials were included. However, despite attempts to contact the authors of one abstract, additional data were not available (Wilkinson 2007). This may have influenced assessment of trial quality and some estimates of effect. We included an additional subgroup analysis (inpatient versus outpatient rehabilitation setting) that was not included in our protocol. This was because the marked heterogeneity in exercise outcomes prompted us to further explore the differences between studies, but we acknowledge that it is difficult to draw firm conclusions from this analysis due the post hoc nature of the approach.

Agreements and disagreements with other studies or reviews

Currently there are four published systematic reviews on exercise training in PH (Buys 2015; Pandey 2015; Yuan 2015; Babu 2016a), however the included studies, methods of analysis and assessment of study quality differed within these reviews. Like the current review, the systematic review of Buys 2015 examined only controlled trials up to December 2013, not all of which were

randomised. The authors extracted five studies, three of which (Mereles 2006; Chan 2013; Ley 2013) were included in our analyses and used an adapted PEDro scale to rate the quality of these studies. This review also included the studies by Fox 2011 and Martinez-Quintana 2010 both of which were excluded from our analysis as subjects were non-randomly allocated to exercise or control groups. Overall this review generated similar results as the current review with a large increase in 6MWD (5 studies, MD for exercise group 72.5 m, 95% CI: 46.0 to 99.1) and VO₂peak (3 studies, MD for exercise group 2.2 ml/kg⁻¹/min⁻¹, 95% CI 46.0 to 99.1). The other three systematic reviews (Pandey 2015; Yuan 2015; Babu 2016a) included both randomised controlled trials and observational studies and hence analysed a larger number of studies. Babu 2016a reported that exercise training resulted in large changes in exercise capacity, health-related quality of life and very few adverse events in 15 included studies, four of which were classified as randomised controlled trials. These authors did not undertake a meta-analysis of the studies. Yuan 2015 did undertake a meta-analysis, reporting large increases in exercise capacity (6MWD and peak exercise capacity), health-related quality of life (measured using the SF-36) and few adverse events in the 12 studies they classified as being either randomised (n = 2), observational-control (n = 4) or observational (n = 6). The authors undertook a subgroup analysis of randomised trials and whilst producing similar results to our study for exercise capacity (MD for exercise group 62 m, 95% CI: 45.6 to 78.8), these authors included data from Weinstein 2013, which we considered to be a duplicate report of one of the studies included in our review (Chan 2013). Moreover Yuan 2015 included the study by Fox 2011 as an RCT, a study excluded from our analysis. Pandey 2015 included 16 studies, with a subgroup of six parallel-group studies. Similar to Yuan 2015 these authors included the study of Fox 2011 in this analysis. Pandey 2015 also included the study of Martinez-Quintana 2010, in their parallel-group analysis, a study again excluded from our analysis. Like other reviews, Pandey reported large increases in exercise capacity measured using the 6MWD and quality of life. Whilst these systematic reviews overall reported treatment effects of a similar magnitude to the current review, there were differences in the rating of the quality of evidence. Using the Downs and Black Quality Index (Downs and Black 1998), Babu 2016a rated the four included RCTs as providing good-quality evidence (Chan 2013; Weinstein 2013; Ley 2013; Mereles 2006), however issues of possible selection bias were not identified. Pandey 2015 used the Cochrane risk of bias assessment tool to evaluate the quality of the extracted controlled intervention trials. Similar to our findings the authors reported that the majority of studies used random sequence generation and blinded assessment. The authors did not however recognise the potential for selection bias in their analysis. There does not appear to have been any attempt to report on the quality of evidence in the meta-analysis conducted by Yuan 2015.

AUTHORS' CONCLUSIONS

Implications for practice

This review suggests that supervised exercise-based rehabilitation is likely to be safe for people with pulmonary hypertension (PH) who are stable on medical therapy and can lead to meaningful improvements in exercise capacity. Clinical importance of improvements in health-related quality of life (HRQoL) is less clear. Although it is possible that programmes with an inpatient component may confer a greater magnitude of benefits, it must

be acknowledged that these are not available in many parts of the world, and clinically meaningful benefits are still achieved with outpatient programmes. It is possible that people with PH could safely undertake rehabilitation in standard pulmonary or heart failure rehabilitation programmes, although different exercise prescription and monitoring practices appear necessary. These results apply primarily to people with moderate PH (New York Heart Association (NYHA)/World Health Organization (WHO) Functional Class, class II and III); the impact of rehabilitation in class IV is unknown. The duration of benefits for exercise-based rehabilitation in PH is also unknown.

Implications for research

Future randomised controlled trials are needed to inform the application of exercise-based rehabilitation across the spectrum of people with PH, including diagnostic subgroups such as chronic thromboembolic PH, and those with more severe disease. It is essential that future trials provide clarity around participant selection in a CONSORT diagram, so that it is clear to which participants the results can be applied. Additional studies are needed to determine the optimal exercise training strategy for

people with PH, including modality and intensity of training, length of programme, degree of supervision and the optimal setting for delivery of exercise training (e.g. inpatient versus outpatient). Longer-term studies are required to assess the durability of benefits, and to determine the effect of exercise rehabilitation on critical outcomes such as time to clinical worsening and survival.

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CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]
Chan 2013

Methods	Study design: RCT Study grouping: Parallel group
Participants	Baseline characteristics Exercise training <ul style="list-style-type: none"> • Number enrolled: 10 • Gender (male/female): 0/10 • Age (years): 53 (13) • Body Mass Index: 30.2 (7) • Haemodynamics: mPAP (mmHG, RHC): 40.3 (13.8) • Haemodynamics: PVR (Wood Units, RHC): 508 (293) • Height (cm): • Weight (kg): • Medications (mono/dual/triple): 5/1/4 • NYHA, WHO Functional Class (I/II/III/IV): 1/4/4/1 Control <ul style="list-style-type: none"> • Number enrolled: 13 • Gender (male/female): 0/13 • Age (years): 55.5 (8.5) • Body Mass Index: 31.8 (7.4) • Haemodynamics: mPAP (mmHG, RHC): 43.8 (14.2) • Haemodynamics: PVR (Wood Units, RHC): 583 (409) • Height (cm): • Weight (kg): • Medications (mono/dual/triple): 2/5/5 (one had no therapy) • NYHA, WHO Functional Class (I/II/III/IV): 0/208/5/0 <p>Included criteria: Quote "Patients with World Health Organization (WHO) group 1 PH were recruited from local outpatient clinics and enrolled between September 2009 and October 2011. Men and women were eligible if they were between 21 and 82 years of age, had PH diagnosed by a resting mean pulmonary arterial pressure \geq 25 mm Hg as measured by right-sided heart catheterization, were on stable PH therapies for at least 3 months, were sedentary, and had no pulmonary rehabilitation for 6 months prior to enrolment".</p>

Chan 2013 (Continued)

Excluded criteria: Quote "To avoid "ceiling" or "floor" effects, patients were excluded if they were classified as WHO and New York Heart Association (NYHA) functional class I and could walk 400 m during a 6MWT, or classified as functional class IV and could not walk 50 m during a 6MWT. Additional exclusion criteria included FEV1 /FVC ratio \leq 65%; history of ischaemic heart disease; ejection fraction $<$ 40%; documented pulmonary capillary wedge pressure \geq 18 mm Hg; significant hepatic, renal, or mitochondrial dysfunctions; severe psychiatric disease; use of medications that may limit exercise capacity or ability to adapt to exercise training; antiretroviral therapies; illicit drugs; tobacco use; or pregnancy".

Pretreatment: Control group had worse lung function

Interventions	Intervention characteristics
	<p>Exercise training</p> <ul style="list-style-type: none"> • Setting: outpatient programme • Components: exercise training and education • Training dose (frequency number/week): 2-3 times/week (24-30 sessions in total, 10-week programme). Mean number of sessions 28 ± 2 • Training dose (duration - min): 30-45 min • Training dose (intensity): quote: "A target exercise intensity of 70% to 80% of each patient's heart rate (HR) reserve obtained from the baseline CPET was used to guide each exercise session. Target HR range was calculatedin accordance with the method of Karvonen." • Training dose (mode): treadmill walking • Education (total hours): 10, "The education sessions consisted of weekly 1-hour lectures on anatomy and physiology, lung disease processes, medication use, oxygen therapy, sleep disorders, preventing infection, airway clearance, interpreting pulmonary function tests, energy conservation, panic control, relaxation techniques, breathing retraining, community resources, advance directives, social well being, nutrition, and benefits of exercise." <p>Control</p> <ul style="list-style-type: none"> • Education only
Outcomes	<p>6MWD</p> <p>VO₂peak</p> <p>Anaerobic threshold</p> <p>HRQoL (SF-36): Physical functioning</p> <p>HRQoL (SF-36): Role physical</p> <p>HRQoL (SF36): Bodily pain</p> <p>HRQoL (SF-36): General health</p> <p>HRQoL (SF-36): Vitality</p> <p>HRQoL (SF-36): Social function</p> <p>HRQoL (SF-36): Role emotional</p> <p>HRQoL (SF-36): Mental health</p> <p>HRQoL: Physical summary score (SF-36)</p> <p>HRQoL: Mental summary score (SF-36)</p> <p>HRQoL (CAMPHOR): Symptoms</p> <p>HRQoL (CAMPHOR): Activities</p> <p>HRQoL (CAMPHOR): QoL</p>

Chan 2013 (Continued)

NYHA Class

Identification	This work was supported by the US National Institutes of Health (Intramural Funds 1 Z01 CL060068-05 CC)	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients who enrolled in the protocol were sequentially assigned subject numbers that randomly corresponded to a group receiving concurrent patient education plus aerobic exercise training (EXE) or to a group that received only the patient education portion of the regimen (EDU)."
Allocation concealment (selection bias)	Unclear risk	Not specified. Quote " Following the baseline evaluations, patients were informed of the group to which they were randomly assigned"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Study personnel were blind to the randomization of patients during all baseline evaluations."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Investigators administering the CPET, 6MWT, and questionnaires were blind to randomization at baseline."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "criterion (Fig. 1). All 29 of these patients performed baseline testing. Based on their test responses, two of these patients were required to obtain additional medical clearance prior to beginning the intervention. One patient declined further participation while the other patient was cleared for participation and subsequently assigned a new subject number upon re-entry into the protocol. This patient was originally assigned a subject number corresponding to EXE, but at re-entry the randomization procedure resulted re-assignment to EDU. As such, 28 patients in total participated in either the EXE or EDU groups (Fig. 1). Of the 14 patients allocated to the EXE group, two patients withdrew due to changes in medication and one withdrew due to low attendance at the exercise sessions. One patient in the EDU group was withdrawn from the study due to medication changes."
Selective reporting (reporting bias)	High risk	Comment: Trial protocol at clinicaltrials.gov states that they were also going to collect IPAQ, stages of exercise change, exercise self efficacy, profile of mood states and near infrared spectroscopy
Other bias	Low risk	

Ehlken 2016

Methods	Study design: RCT
	Study grouping: Parallel group
Participants	Baseline characteristics
	Exercise

Ehlken 2016 (Continued)

- Number enrolled: 46
- Gender (male/female): 20/26
- Type of PH: CTEPH n = 11, PAH n = 35
- Haemodynamics: PASP (mmHG, Echo):
- Haemodynamics: CI (L/min/m², Echo):
- Haemodynamics: mPAP (mmHG, RHC): 41 (11.7)
- Haemodynamics: PVR (Dyne.s/cm⁵, RHC): 540 (267)
- Age: 55(15)
- Height (cm): 170 (9)
- Weight (kg): 75(18)
- Medications (single/double/triple): 13/20/6
- NYHA, WHO Functional Class (I/II/III/IV): 0/8/36/0
- B-type natriuretic peptide (pg/mL): 1163±2520

Control

- Number enrolled: 41
- Gender (male/female): 20/21
- Type of PH: CTEPH n = 15, PAH n = 26
- Haemodynamics: PASP (mmHG, Echo):
- Haemodynamics: CI (L/min/m², Echo):
- Haemodynamics: mPAP (mmHG, RHC): 37.6(11.8)
- Haemodynamics: PVR (Dyne.s/cm⁵, RHC): 512(338)
- Age: 57(15)
- Height (cm):171 (8)
- Weight (kg): 79 (18)
- Medications (single/double/triple): 14/22/4
- NYHA, WHO Functional Class (I/II/III/IV): 0/6/30/4
- B-type natriuretic peptide (pg/mL): 1114±1386

Included criteria: participants with PAH and inoperable or persistent CTEPH and chronic right heart failure who were stable on disease-targeted medication for at least 2 months prior to inclusion were randomly assigned to a control and a training group. Medication remained unchanged during the study period.

Excluded criteria: not specified

Pretreatment: Nil evident

Interventions
Intervention characteristics
Exercise

- Setting: 3 weeks inpatient training, followed by 12 weeks unsupervised outpatient training at home
- Components: exercise training, mental training, psychological support
- Training frequency: inpatient, walking and cycling 7 d/week, resistance exercises and respiratory training 5 d/week. Outpatient, cycling 5 x/week, walk twice a week, respiratory training and resistance ex second daily.
- Intervention (mode): interval bicycle ergometer training, walking, respiratory training, resistance training
- Training dose: duration: 10-25 min cycle ergometer, 60 min walking, 30 min resistance training, 30 min respiratory training
- Training dose: intensity: cycle ergometer: 60%-80% of HR on CPET. HR maintained < 120 bpm, oxygen saturation > 85%

Control

Ehlken 2016 (Continued)

- Continued usual lifestyle

Outcomes	6MWD VO ₂ peak W _{peak} (peak power) Morbidity - adverse events Disease Progression Precluded from Training HRQoL (SF-36): Physical functioning HRQoL (SF-36): Role physical HRQoL (SF36): Bodily pain HRQoL (SF-36): General health HRQoL (SF-36): Vitality HRQoL (SF-36): Social function HRQoL (SF-36): Role emotional HRQoL (SF-36): Mental health Discontinued training Haemodynamics - mPAP (mmHg), PVR (Dynes), cardiac output (L/min) B-type natriuretic peptide
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Identification	Sponsorship Source: funding to pay the open access publication charges for this article was provided by Centre for Pulmonary Hypertension, Thorax clinic at the University of Heidelberg, Germany Comments Author's contact details Nicola Ehlken University Hospital Heidelberg, nicola.ehlken@med.uni-heidelberg.de Amalienstrasse 5, Heidelberg D-69126, Germany
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Notes	
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Does not specify methods of randomisation
Allocation concealment (selection bias)	Unclear risk	Does not specify whether allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants to intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Assessment of 6MWD, SF-36 and other efficacy parameter were performed by investigators who were blinded to the clinical data"

Ehlken 2016 (Continued)

		Not clear whether assessors were blinded to group allocation, especially for primary outcome
Incomplete outcome data (attrition bias) All outcomes	High risk	Differential attrition - 17% lost to follow-up in exercise group, none lost to follow-up in control group
Selective reporting (reporting bias)	High risk	Not all outcomes specified in the trial protocol are reported
Other bias	High risk	CONSORT diagram does not report how many people were assessed to arrive at the 95 participants enrolled

Ganderton 2013

Methods	Study design: RCT Study grouping: Parallel group
Participants	Baseline characteristics Exercise <ul style="list-style-type: none"> • Number enrolled: 5 • Gender (male/female): 0/5 • Age (years): 51 (40–53) • Body Mass Index: 26 (23–41) • Haemodynamics: mPAP (mmHG, RHC): 23 (19–29) • Haemodynamics: PVR (Dynes, RHC): • FVC (% predicted): 98 (92–102) • NYHA WHO Functional Class (I/II/III/IV): 0/3/2/0 • Medications (single/double/triple): 3/2 • Median sessions 31 of 26 Control <ul style="list-style-type: none"> • Number enrolled: 5 • Gender (male/female): 1/4 • Age (years): 53 (42–57) • Body Mass Index: 28 (26–31) • Haemodynamics: mPAP (mmHG, RHC): 49 (20–65) • Haemodynamics: PVR (Dynes, RHC): • FVC (% predicted): 78 (72–110) • NYHA Functional Class (I/II/III/IV): 0/3/2/0 • Medications (single/double/triple): 3/2 <p>Included criteria: participants were included in the study if they had a confirmed diagnosis of idiopathic PAH, familial PAH or PAH associated with connective tissue disorders, based on elevated pulmonary artery pressures (> 25 mmHg at rest or > 30 mmHg during exercise) measured by right heart catheterisation; were medically stable and had been on PAH-specific pharmaceutical therapy for 3 months prior to enrolment into the study; were in WHO functional class II or III; and were willing to complete the 12-week supervised and 12-week home exercise training programmes.</p> <p>Excluded criteria: participants were excluded if they had:</p> <ul style="list-style-type: none"> • resting hypoxaemia requiring supplemental oxygen therapy;

Ganderton 2013 (Continued)

- significant musculoskeletal disease, claudication pain, neurological or cognitive impairment, psychiatric/psychological or mood disorders that may have affected their ability to undertake exercise testing or training;
- a history of moderate or severe chronic lung disease;
- cardiac disease associated with cardiac failure, poorly controlled angina, unstable cardiac rhythm;
- participated in a supervised exercise training programme within the last 12 months

Pretreatment: nil

Interventions	Intervention characteristics
	<p>Exercise</p> <ul style="list-style-type: none"> • Setting: outpatient • Components: exercise only • Training dose (frequency number per week): 3 times per week, 12 weeks • Training dose (duration - min): 60 min class • Training dose (intensity): 12 weeks. "Intensity for the lower limb endurance exercises will be prescribed with the aim of achieving 60-70% HR max (based on age predicted maximum, $220 - \text{age}$ [37]), while maintaining $\text{SpO}_2 \geq 92\%$ and symptom intensity (Borg CR10 dyspnoea < 4 and RPE < 4). Exercise intensity will be progressed, based on the individual's response to training to maintain HR within the target HR range." • Training dose (mode): lower limb endurance training (walking and cycling). Lower limb functional strength training (step ups and sit to stands) and endurance training of the upper limbs • Education (total hours): 0 <p>Control</p> <ul style="list-style-type: none"> • Training dose (frequency number per week): nil • Training dose (duration - min): nil • Training dose (intensity): nil • Training dose (mode): nil • Education (total hours): 0
<p>Outcomes</p>	<p>6MWD</p> <p>VO_2peak</p> <p>W_{peak}</p> <p>Anaerobic threshold</p> <p>HRQoL (SF-36): Physical functioning</p> <p>HRQoL (Sf-36): Role physical</p> <p>HRQoL (SF36): Bodily pain</p> <p>HRQoL (SF-36): General health</p> <p>HRQoL (SF-36): Vitality</p> <p>HRQoL (SF-36): Social function</p> <p>HRQoL (SF-36): Role emotional</p> <p>HRQoL (SF-36): Mental health</p> <p>HRQoL (CAMPHOR): Symptoms</p> <p>HRQoL (CAMPHOR): Activities</p>

Ganderton 2013 (Continued)

HRQoL (CAMPHOR): QoL

Morbidity

Disease progression

Symptoms precluding training

Discontinued training

NYHA class

HRQoL: Physical summary score (SF-36)

HRQoL: Mental summary score (SF-36)

Assessed at baseline, 12 weeks (post intervention) and 24 weeks (follow-up)

Identification

Sponsorship source: Advanced Lung Disease Unit at Royal Perth Hospital and the Lung Institute of Western Australia

Country: Australia

Setting: Outpatient, hospital

Comments:

Author's name: Louise Ganderton

Institution: Curtin University

Email: louise.ganderton@health.wa.gov.au

Address: School of Physiotherapy, Faculty of Health Sciences, The University of Sydney

Notes

Protocol paper published: Ganderton 2011

Thesis available: http://espace.library.curtin.edu.au:80/R?func=dbin-jump-full&local_base=gen01-era02&object_id=198083

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	From thesis: "Permuted block randomisation with block sizes of four was used to generate a randomisation chart. Fourteen blocks were created in total using a web-based research randomiser."
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants to intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	From thesis: "The primary investigator (LG) carried out all assessments at baseline, 12 weeks and 24 weeks and was blinded to the participants group allocation... The physiotherapists responsible for conducting the exercise training sessions were not involved in any of the formal assessments"
Incomplete outcome data (attrition bias)	Low risk	Data available on all recruited participants for ITT. However planned to enrol 34 and only recruited 10

Ganderton 2013 (Continued)

All outcomes

Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	

Ley 2013

Methods	Study design: RCT Study grouping: Parallel group
Participants	Baseline characteristics Exercise <ul style="list-style-type: none"> • Number enrolled: 10 • Gender (male/female): 2/8 • Age (years): 47 (8) • Type of PH: Group 1 PH n = 9, CTEPH n = 1 • Haemodynamics: mPAP (mmHG, RHC): • Haemodynamics: PVR (Wood Units, RHC): • Height (cm): 168 (12) • Weight (kg): 69 (11) • Medications (mono/dual/triple): 2/6/2 • NYHA, WHO Functional Class (I/II/III/IV): 0/3/7/0 Control <ul style="list-style-type: none"> • Number enrolled: 10 • Gender (male/female): 4/6 • Age (years): 54 (14) • Type of PH: Group 1 PH n = 7, CTEPH n = 3 • Haemodynamics: mPAP (mmHG, RHC): • Haemodynamics: PVR (Wood Units, RHC): • Height (cm): 165 (5) • Weight (kg): 76 (17) • Medications (mono/dual/triple): 3/6/1 • NYHA, WHO Functional Class (I/II/III/IV): 0/1/9/0 <p>Included criteria: adults (≥ 18 years) with confirmed PAH and CTEPH who underwent complete clinical work-up including RHC. All participants were stable under optimised medical therapy (such as endothelin antagonists, iloprost, sildenafil, calcium channel blockers, anticoagulants, diuretics and supplemental oxygen) for at least 3 months before entering the study. Additional inclusion criteria were WHO functional class II to III</p> <p>Excluded criteria: no recent syncope, and no skeletal or muscle abnormalities prohibiting participation in an exercise training programme</p> <p>Pretreatment: nil</p>
Interventions	Intervention characteristics Exercise

Ley 2013 (Continued)

- Setting: inpatient
- Components: "specialized respiratory and exercise training programme"
- Training dose: frequency: cycle ergometry and walking daily, resistance training 5 x/week, 3 weeks
- Training dose: duration: 10-25 min/day cycle ergo, 60 mins walking/day, 30 mins respiratory training, light weights (500-1000 g)
- Training dose: intensity: commence at 60%-80% of HR on CPET, progress as per individual tolerability and improvement
- Intervention (mode): respiratory and exercise training programme as per [Mereles 2006](#) - interval training on cycle ergometer, walking, resistance training, respiratory training (PLB, body perception, yoga, respiratory muscle training)

Control

- "Patients in the control group received a programme without specific exercise training."

Outcomes	Morbidity - adverse events Disease progression Precluded from training 6MWD
Identification	<p>Sponsorship source: this work was supported by the German National Research Agency (DFG): "Image-based V/Q analysis" (FOR 474-2)</p> <p>Country: Germany</p> <p>Setting: inpatient rehabilitation</p> <p>Comments:</p> <p>Author's name: Sebastian Ley</p> <p>Institution: University Hospital Heidelberg</p> <p>Email: ley@gmx.de</p> <p>Address: Department of Diagnostic and Interventional Radiology, University Hospital Heidelberg, Im Neuenheimer Feld 430,69120 Heidelberg, Germany</p>

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomly assigned to either a training or a control group using a permuted block randomization procedure."
Allocation concealment (selection bias)	Unclear risk	The method of allocation was not specified.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unabel to blind participants or personnel due to the to intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Assessment of 6MWD and MR examination were performed by investigators who were blinded to the clinical data and group assignment of the pa-

Ley 2013 (Continued)

tients. Evaluation of the MR data was done blinded to the clinical setting and in random order."

Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients were analysed
Selective reporting (reporting bias)	Low risk	Unclear whether trial was registered but reporting does not appear selective
Other bias	Low risk	

Mereles 2006

Methods	Study design: RCT Study grouping: Parallel group
Participants	Baseline characteristics Exercise <ul style="list-style-type: none"> • Number enrolled: 15 • Gender (male/female): 5/10 • Age (years): 47 (12) • Type of PH: PAH n = 13, CTEPH n = 2 • Haemodynamics: PASP (mmHG, Echo): 61 (18) • Haemodynamics: CI (L/min/m², Echo): • Haemodynamics: mPAP (mmHG, RHC): 49.5 (17.6) • Haemodynamics: PVR (Dyne.s/cm⁵, RHC): 968.7 (444.1) • Height (cm): 171 (11) • Weight (kg): 75 (13) • Medications (single/double/triple): 6/5/4 • NYHA, WHO Functional Class (I/II/III/IV): 0/2/12/1 Control <ul style="list-style-type: none"> • Number enrolled: 15 • Gender (male/female): 5/10 • Age (years) 53 (14) • Type of PH: PAH n = 11, CTEPH n = 4 • Haemodynamics: PASP (mmHG, Echo): 61 (18) • Haemodynamics: CI (L/min/m², Echo): • Haemodynamics: mPAP (mmHG, RHC): 49.6 (12.3) • Haemodynamics: PVR (Dyne.s/cm⁵, RHC): 901.8 (358.0) • Height (cm): 166 (5) • Weight (kg): 78 (18) • Medications (single/double/triple): 7/5/3 • NYHA, WHO Functional Class (I/II/III/IV): 0/4/10/1 <p>Included criteria: people with severe chronic PH who were stable and compensated under optimised medical therapy (such as endothelin antagonists, iloprost, sildenafil, calcium channel blockers, anti-coagulants, diuretics, and supplemental oxygen) for at least 3 months before entering the study were invited to participate. Additional inclusion criteria were age 18-75 years, WHO functional class II to IV.</p>

Mereles 2006 (Continued)

Excluded criteria: no recent syncope, and no skeletal or muscle abnormalities prohibiting participation in an exercise programme

Pretreatment: Nil evident

Interventions	Intervention characteristics
	<p>Exercise</p> <ul style="list-style-type: none"> • Setting: 3 weeks inpatient followed by 12 weeks outpatient, unsupervised training • Components: exercise training (see below), mental training to improve perception of physical abilities and limits to keep physical exercise safe even in demanding situations, dumbbell training of single muscle groups with low weights (500-1000 g) and 30 min of respiratory training, including stretching, breathing techniques such as pursed lip breathing, body perception, yoga, and strengthening of respiratory muscles • Training dose: frequency: inpatient: walking and cycling 7 d/week, resistance ex and respiratory training 5 d/week. Outpatient: cycling 5 x/week, walk twice a week, respiratory training and resistance ex second daily • Intervention (mode): interval bicycle ergometer training, walking, respiratory training, resistance training • Training dose: duration: 10-25 min cycle ergometer, 60 min walking, 30 min resistance training, 30 min respiratory training • Training dose: intensity: cycle ergometer; 60%-80% of HR on CPET. HR maintained < 120 bpm, oxygen saturation > 85% <p>Control</p> <ul style="list-style-type: none"> • Intervention (mode): "Patients in the control group received a common rehabilitation program based on healthy nutrition, physical therapy such as massages, inhalation, counselling, and muscular relaxation without exercise and respiratory training but were allowed to perform daily activity as usual. All patients were advised to avoid heavy exercise" • Training dose: duration: 0 (I) 0 (O) • Training dose: intensity: 0 (I) 0 (O) • 10 of 15 participants entered the exercise training arm at the end of the study
Outcomes	6MWD VO ₂ peak W _{peak} Morbidity - adverse events Disease progression Precluded from training Anaerobic threshold HRQoL (SF-36): Physical functioning HRQoL (SF-36): Role physical HRQoL (SF36): Bodily pain HRQoL (SF-36): General health HRQoL (SF-36): Vitality HRQoL (SF-36): Social function HRQoL (SF-36): Role emotional

Mereles 2006 (Continued)

HRQoL (SF-36): Mental health
 HRQoL:Physical Summary score (SF36)
 HRQoL:Mental Summary score (SF36)
 HRQoL (CAMPHOR): QoL
 NYHA Class
 Discontinued training

Identification

Sponsorship source: this study was funded by a grant from the German Pulmonary Hypertension Group, Pulmonale Hypertonie e.V., Rheinstetten, Germany.

Country: Germany

Setting: inpatient rehabilitation

Comments:

Author's name: Derliz Mereles

Institution: University Hospital Heidelberg

Email: ekkehard_gruenig@med.uni-heidelberg.de

Address: Department of Cardiology and Pneumology, University Hospital Heidelberg, INF 410, D-69120 Heidelberg

Notes

Adverse Outcomes
 Authors report that all participants tolerated training and had no adverse events during training and no progression of the disease as defined by progression of symptoms, PH or right heart failure. Two participants perceived a short episode of dizziness without fainting immediately after bicycle ergometer training. In 1 participant, oxygen saturation dropped from 88% to 74% during exercise, although the training was performed with an oxygen mask.

Continuous Outcomes
 6MWD is reported as a change from baseline at the post-inpatient and post-outpatient time points

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: participants were randomly assigned to either a primary training group or a sedentary control group using a permuted block randomization procedure
Allocation concealment (selection bias)	Unclear risk	Comment: there is no comment regarding allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: unable to blind participants and personnel due to nature of intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The completed questionnaire at baseline was compared with the results after 15 weeks by investigators who were blinded to the patients' clinical data and group assignment. To avoid bias as far as possible in this study, all measurements and/or offline readings were performed by investigators who were blinded to patient data and group assignment."

Mereles 2006 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts reported
Selective reporting (reporting bias)	Low risk	The protocol was not registered or published however the outcome reporting is comprehensive.
Other bias	High risk	Comment: No CONSORT diagram so not possible to tell how many people were assessed in order to recruit the sample.

Wilkinson 2007

Methods	Study design: RCT Study grouping: Parallel group
Participants	Baseline characteristics Exercise <ul style="list-style-type: none"> • Number enrolled: 18 • Age: unclear • Type PH: unclear Control <ul style="list-style-type: none"> • Number enrolled: 18 • Age: unclear • Type of PH: unclear Included criteria: "Clinically stable PH patients in a single centre" Excluded criteria: unclear
Interventions	Intervention characteristics Exercise <ul style="list-style-type: none"> • Setting: outpatient, 3 months, 1 supervised session followed by unsupervised home training, telephone follow-up • "Best practice treatment plus a physiotherapist-led rehabilitation programme (rehabilitation group). Patients in the rehabilitation group attended a single one to one class with a physiotherapist and received a prescribed set of exercises tailored to their needs. They also received telephone support during the 3 month period and were encouraged to continue with their regular exercise regime." Control <ul style="list-style-type: none"> • "Best practice treatment"
Outcomes	Incremental shuttle walk test Endurance shuttle walk test Assessed at baseline and 3 months
Identification	Sponsorship source: Country:

Wilkinson 2007 (Continued)

Setting:
Comments:
Author's name: Anna Wilkinson

Institution: Royal Hallamshire Hospital

Email:
Address:

Notes

Reported as two abstracts

In the Thorax abstract it does not specify the number in each group, only that 40 were randomised. ERS abstract says 18 in each group. Neither specifies age by allocated group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Abstract only, does not specify how sequence was generated
Allocation concealment (selection bias)	Unclear risk	Abstract only, does not specify
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants to intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Blind assessment was undertaken pre intervention and following 3 months"
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts unclear. 2007 abstract specifies 40 participants and 2008 abstract specifies 36 participants.
Selective reporting (reporting bias)	High risk	Abstract only, not all outcomes reported
Other bias	High risk	Abstract only

bpm: beats per minute; CAMPHOR: Cambridge Pulmonary Hypertension Outcome Review; CI: Cardiac Index; CPET: cardiopulmonary exercise test; CTEPH: chronic thromboembolic pulmonary hypertension; Dual: patients on two pharmacotherapies; FEV1: forced expired volume in one second; FVC: forced vital capacity; HR: heart rate; HRQoL: health-related quality of life; ITT: intention-to-treat; Mono: patients on single pharmacotherapy; mPAP: mean pulmonary artery pressure; NYHA: New York Heart Association; PAH: Pulmonary Artery Hypertension; PAsP: Pulmonary Artery Systolic Pressure; PH: Pulmonary Hypertension, PLB: pursed lip breathing; PVR: pulmonary vascular resistance; RCT: randomised controlled trial; SF-36: Short-form 36; 6MWD: six minute walk distance; SPO₂: oxygen saturation; Triple: patients on 3 pharmacotherapies; QoL: quality of life; VO₂peak: peak oxygen uptake; W_{peak}: peak power

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Babu 2013	Review paper

Study	Reason for exclusion
Babu 2014	Not an RCT
Barbosa 2011	No exercise training
Becker Grunig 2013	Not an RCT
Bernheim 2007	Wrong patient population
Ehlken 2014	Not an RCT
Fox 2011	Not an RCT
Grunig 2011	Not an RCT
Grunig 2012	Not an RCT
Kabitz 2014	Not an RCT
Kolesnikova 2011a	Wrong intervention
Kolesnikova 2011b	Wrong intervention
Marvisi 2013	No exercise training
Nagel 2012	Not an RCT
Robalo Cordeiro 2011	No exercise training

RCT: randomised controlled trial

DATA AND ANALYSES

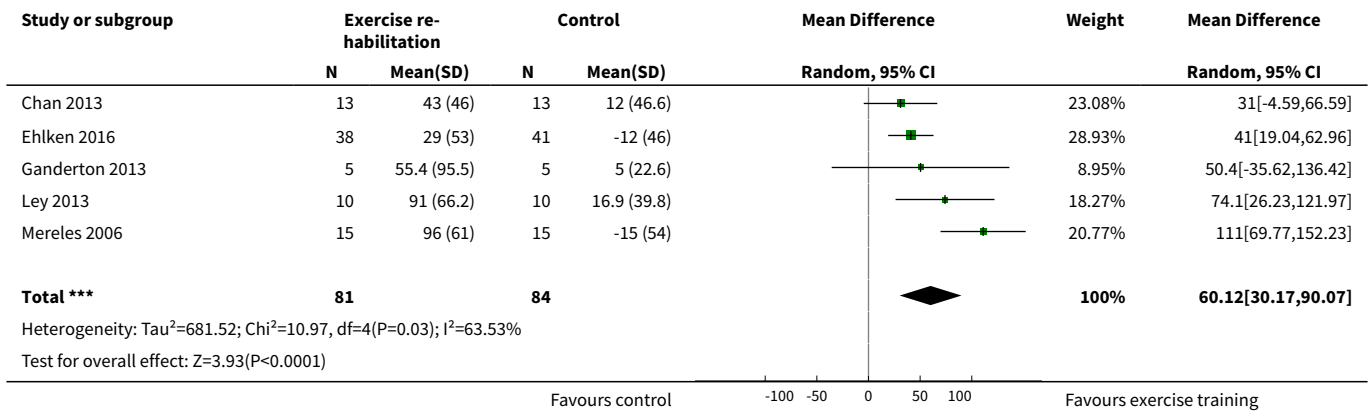
Comparison 1. Exercise vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exercise capacity: 6MWD	5	165	Mean Difference (IV, Random, 95% CI)	60.12 [30.17, 90.07]
2 Exercise capacity: VO ₂ peak	4	145	Mean Difference (IV, Random, 95% CI)	2.41 [1.38, 3.44]
3 Exercise capacity: Peak power	4	145	Mean Difference (IV, Random, 95% CI)	16.44 [10.90, 21.99]
4 Exercisecapacity: Anaerobic threshold	3	66	Std. Mean Difference (IV, Random, 95% CI)	1.05 [0.53, 1.58]
5 HRQoL SF36: Physical component score	2	33	Mean Difference (IV, Random, 95% CI)	4.63 [0.80, 8.47]

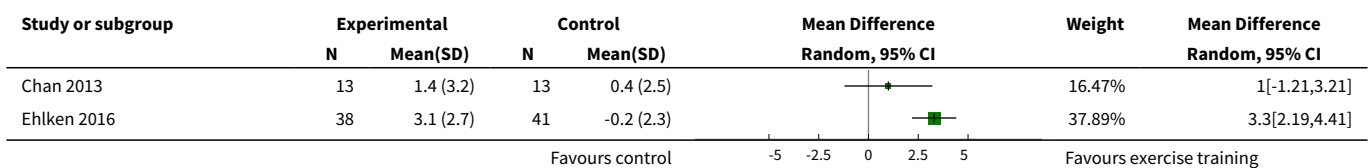
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 HRQoL SF36: Mental component score	2	33	Mean Difference (IV, Random, 95% CI)	4.17 [0.01, 8.34]
7 Adverse events	5	165	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.04, 0.04]
8 HRQoL SF36: Physical function	4	118	Mean Difference (IV, Random, 95% CI)	6.13 [-3.73, 16.00]
9 HRQoL SF36: Role physical	4	116	Mean Difference (IV, Random, 95% CI)	21.81 [14.40, 29.23]
10 HRQoL SF36: Bodily pain	3	88	Mean Difference (IV, Random, 95% CI)	5.64 [-3.09, 14.36]
11 HRQoL SF36: General health	3	84	Mean Difference (IV, Random, 95% CI)	5.76 [-0.80, 12.32]
12 HRQoL SF36: Mental health	3	87	Mean Difference (IV, Random, 95% CI)	6.21 [-1.85, 14.27]
13 HRQoL SF36: Role emotional	3	87	Mean Difference (IV, Random, 95% CI)	2.79 [-7.43, 13.01]
14 HRQoL SF36: Vitality	4	115	Mean Difference (IV, Random, 95% CI)	13.47 [7.55, 19.40]
15 HRQoL SF36: Social function	4	118	Mean Difference (IV, Random, 95% CI)	14.01 [9.82, 18.21]
16 HRQoL: CAMPHOR activities	2	33	Mean Difference (IV, Random, 95% CI)	-1.33 [-3.56, 0.90]
17 HRQoL: CAMPHOR symptoms	2	36	Mean Difference (IV, Random, 95% CI)	-3.08 [-7.78, 1.62]
18 HRQoL: CAMPHOR QoL	2	36	Mean Difference (IV, Random, 95% CI)	-5.42 [-8.03, -2.81]
19 Cardiopulmonary haemodynamics	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
20 Functional class	2	40	Mean Difference (IV, Random, 95% CI)	-0.60 [-0.85, -0.35]
21 B-type natriuretic peptide	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
22 Exercise capacity: 6MWD, sensitivity analysis	4	86	Mean Difference (IV, Random, 95% CI)	67.91 [27.12, 108.69]
23 Exercise capacity: VO ₂ peak, sensitivity analysis	3	66	Mean Difference (IV, Random, 95% CI)	1.94 [0.86, 3.01]

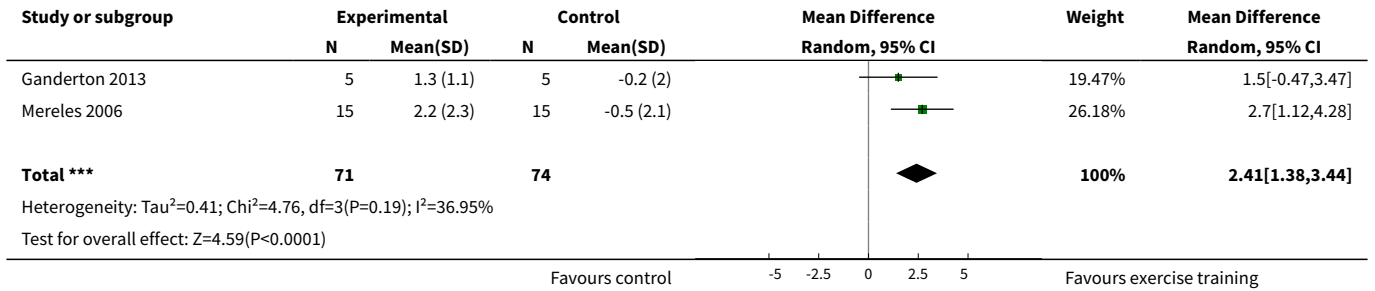
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
24 Exercise capacity: Peak power, sensitivity analysis	3	66	Mean Difference (IV, Random, 95% CI)	15.27 [8.57, 21.97]
25 Exercise capacity 6MWD, PAH subgroup only	2	36	Mean Difference (IV, Random, 95% CI)	33.84 [0.95, 66.73]
26 Exercise capacity: VO ₂ peak, PAH subgroup only	2	36	Mean Difference (IV, Random, 95% CI)	1.28 [-0.19, 2.75]
27 Exercise capacity: Peak power, PAH subgroup only	2	36	Mean Difference (IV, Random, 95% CI)	14.24 [5.78, 22.70]
28 Exercise capacity: Anaerobic threshold, PAH subgroup only	2	36	Mean Difference (IV, Random, 95% CI)	41.31 [-52.05, 134.67]
29 Exercise capacity: 6MWD, subgroup analysis for setting of rehabilitation	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
29.1 Inpatient exercise training	3	129	Mean Difference (IV, Random, 95% CI)	72.79 [28.09, 117.49]
29.2 Outpatient exercise training	2	36	Mean Difference (IV, Random, 95% CI)	33.84 [0.95, 66.73]

Analysis 1.1. Comparison 1 Exercise vs control, Outcome 1 Exercise capacity: 6MWD.

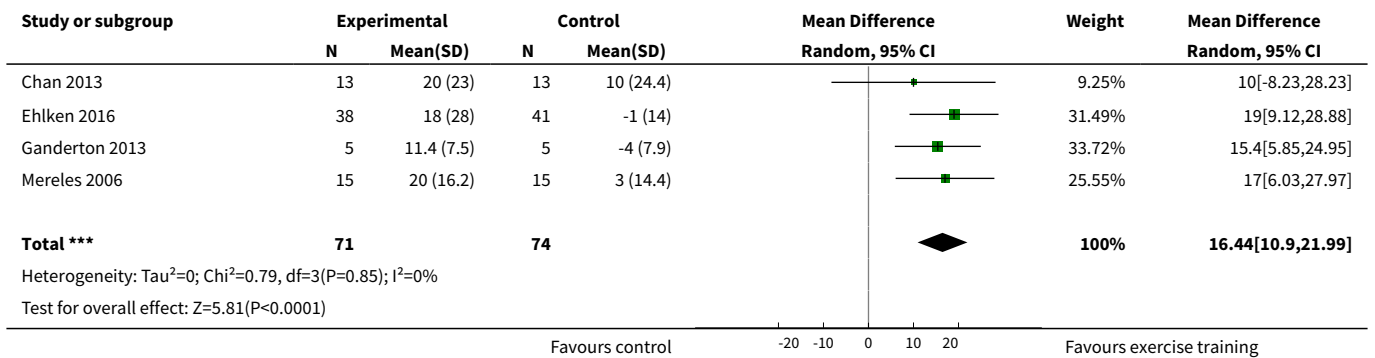


Analysis 1.2. Comparison 1 Exercise vs control, Outcome 2 Exercise capacity: VO₂peak.

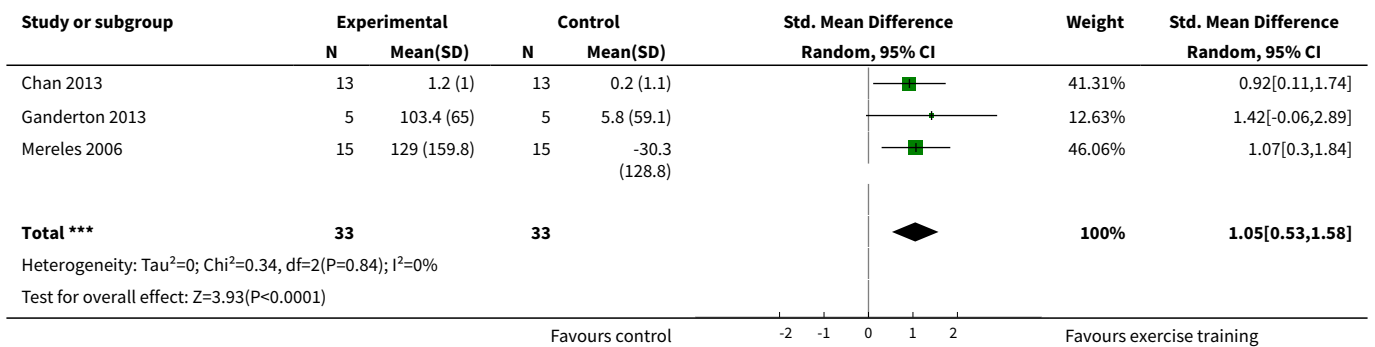




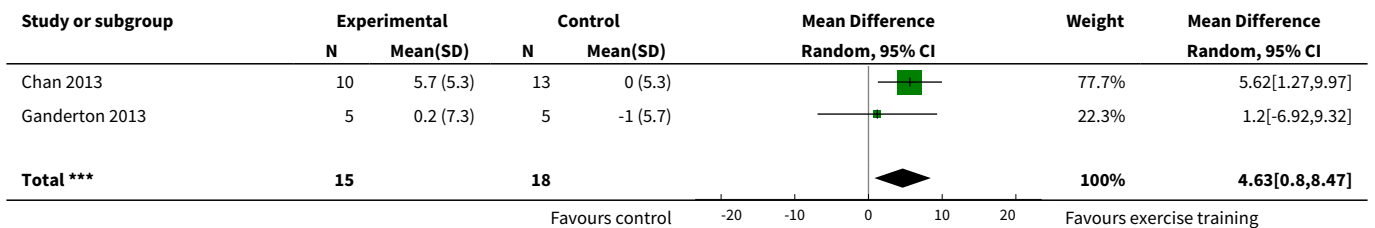
Analysis 1.3. Comparison 1 Exercise vs control, Outcome 3 Exercise capacity: Peak power.

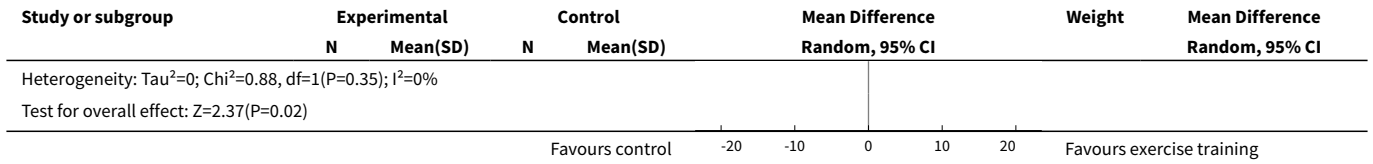


Analysis 1.4. Comparison 1 Exercise vs control, Outcome 4 Exercisecapacity: Anaerobic threshold.

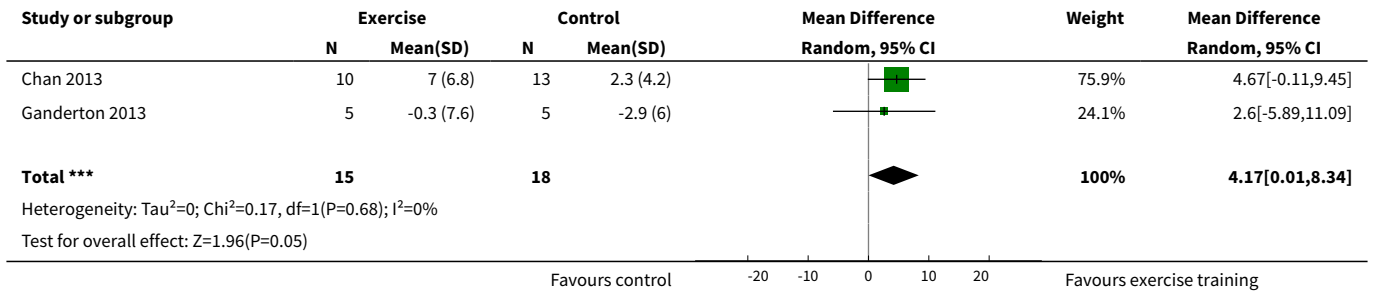


Analysis 1.5. Comparison 1 Exercise vs control, Outcome 5 HRQoL SF36: Physical component score.

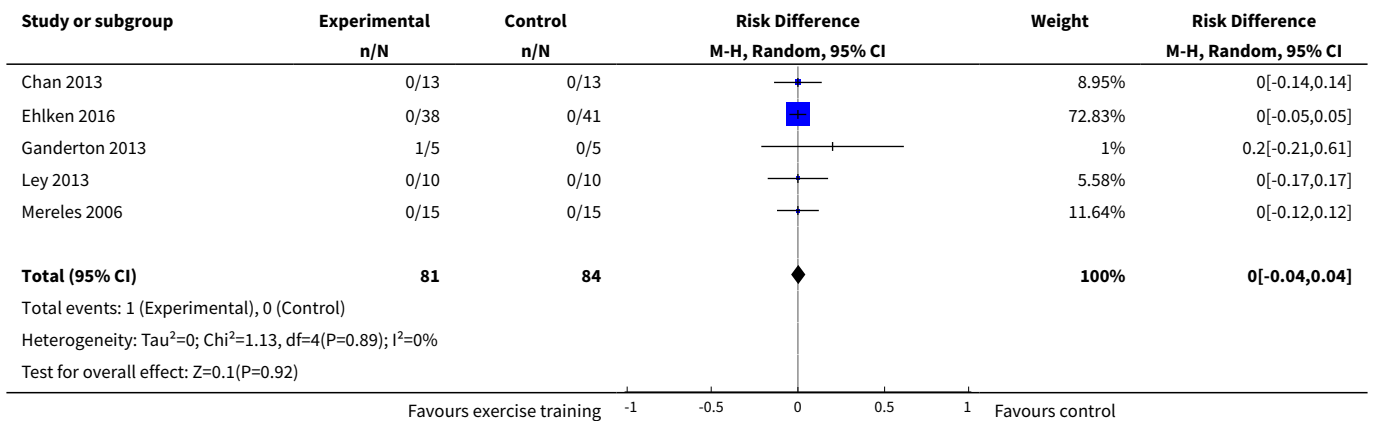




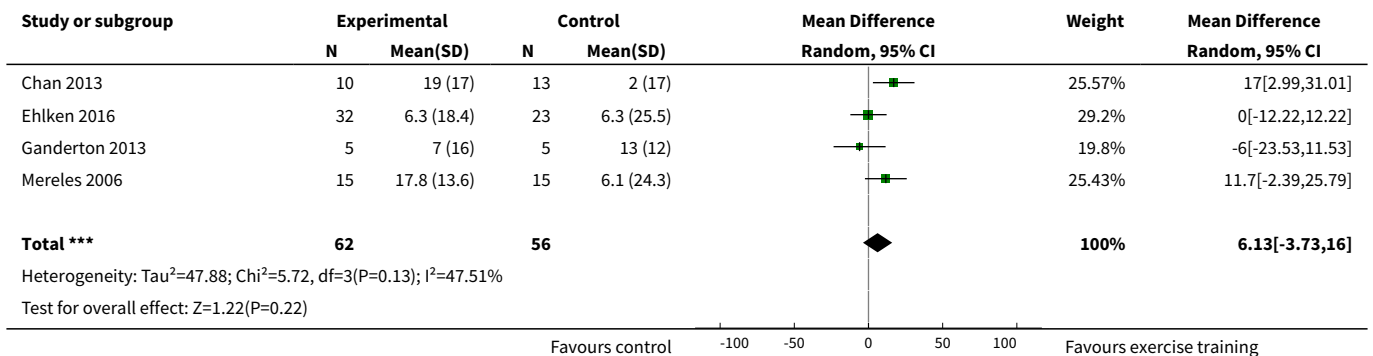
Analysis 1.6. Comparison 1 Exercise vs control, Outcome 6 HRQoL SF36: Mental component score.



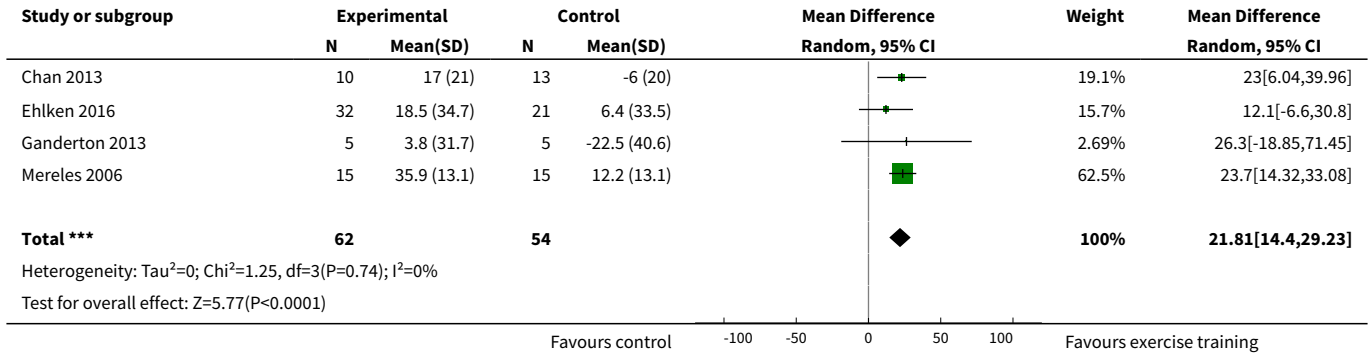
Analysis 1.7. Comparison 1 Exercise vs control, Outcome 7 Adverse events.



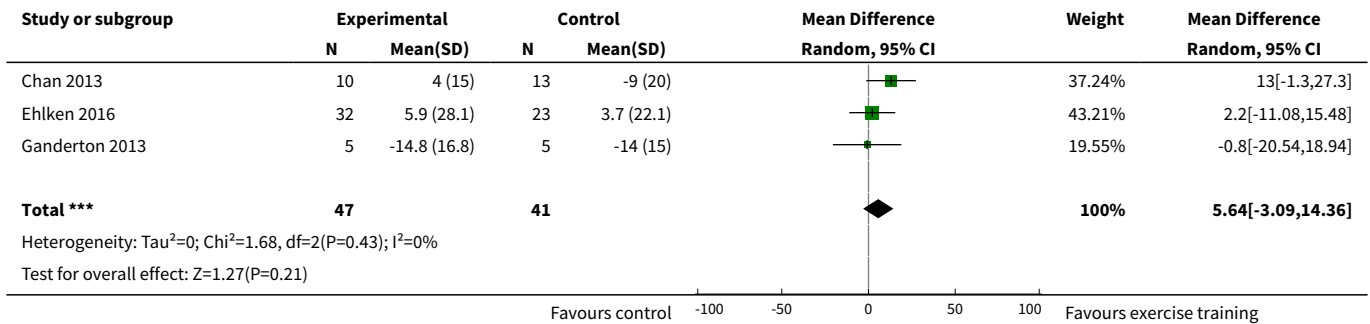
Analysis 1.8. Comparison 1 Exercise vs control, Outcome 8 HRQoL SF36: Physical function.



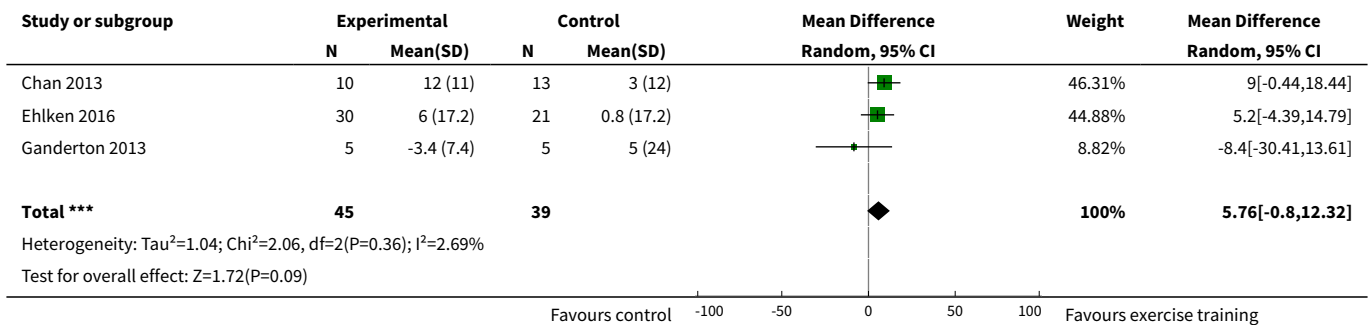
Analysis 1.9. Comparison 1 Exercise vs control, Outcome 9 HRQoL SF36: Role physical.



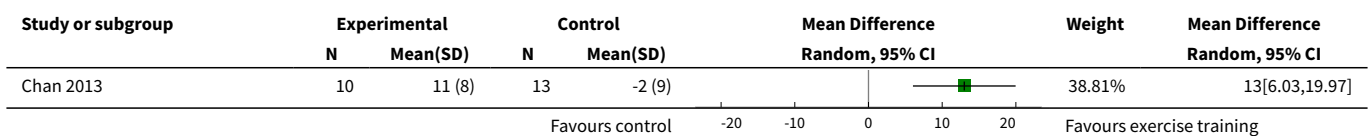
Analysis 1.10. Comparison 1 Exercise vs control, Outcome 10 HRQoL SF36: Bodily pain.

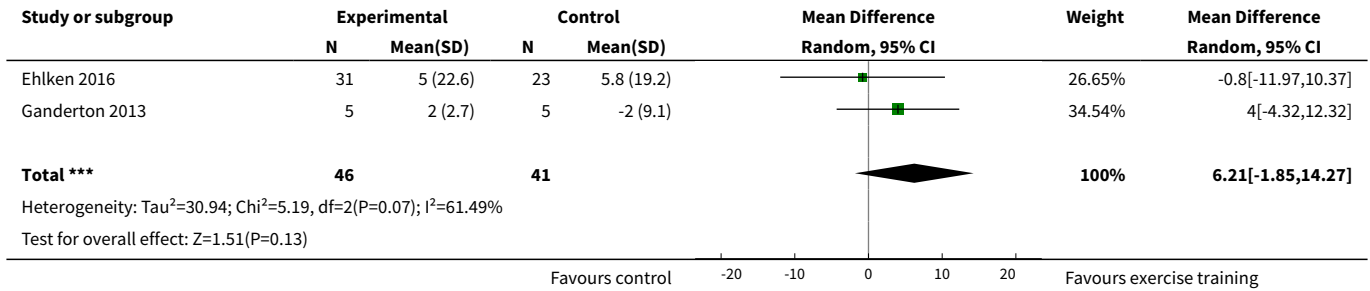


Analysis 1.11. Comparison 1 Exercise vs control, Outcome 11 HRQoL SF36: General health.

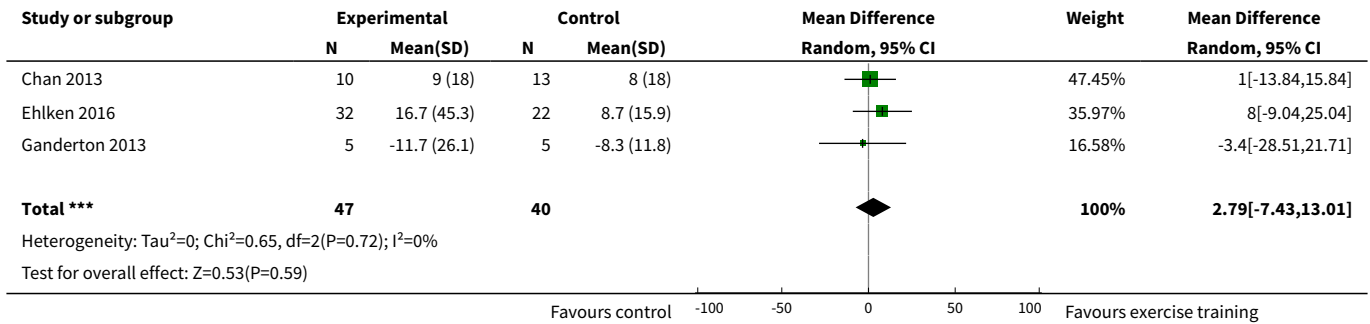


Analysis 1.12. Comparison 1 Exercise vs control, Outcome 12 HRQoL SF36: Mental health.

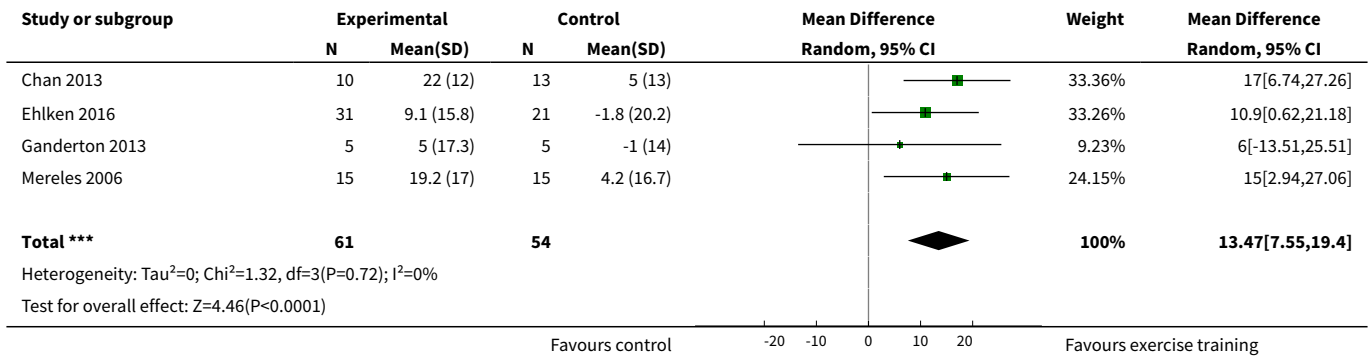




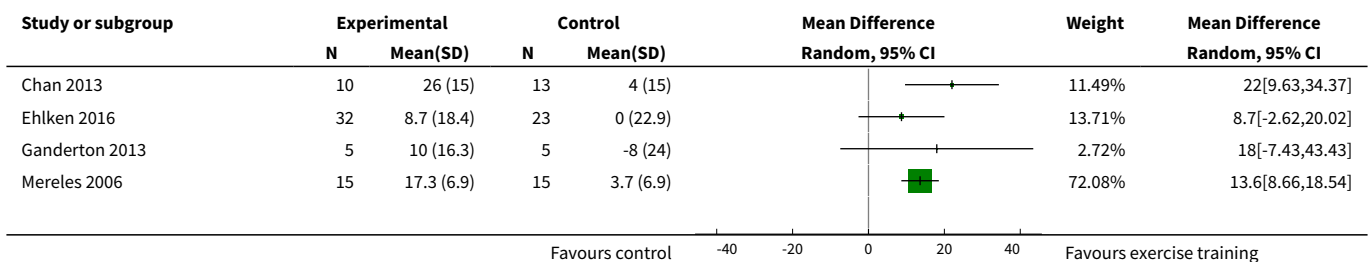
Analysis 1.13. Comparison 1 Exercise vs control, Outcome 13 HRQoL SF36: Role emotional.

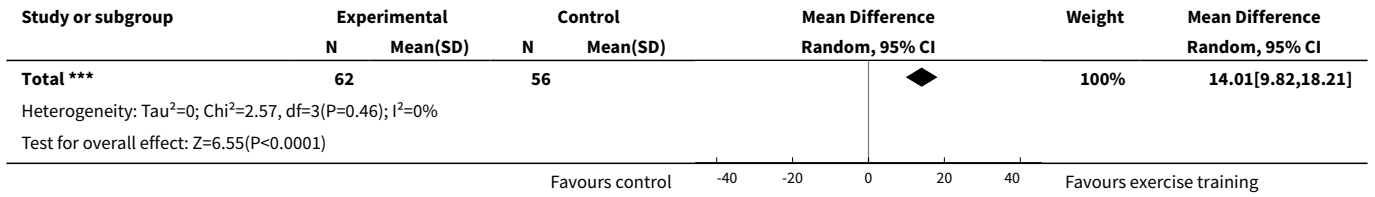


Analysis 1.14. Comparison 1 Exercise vs control, Outcome 14 HRQoL SF36: Vitality.

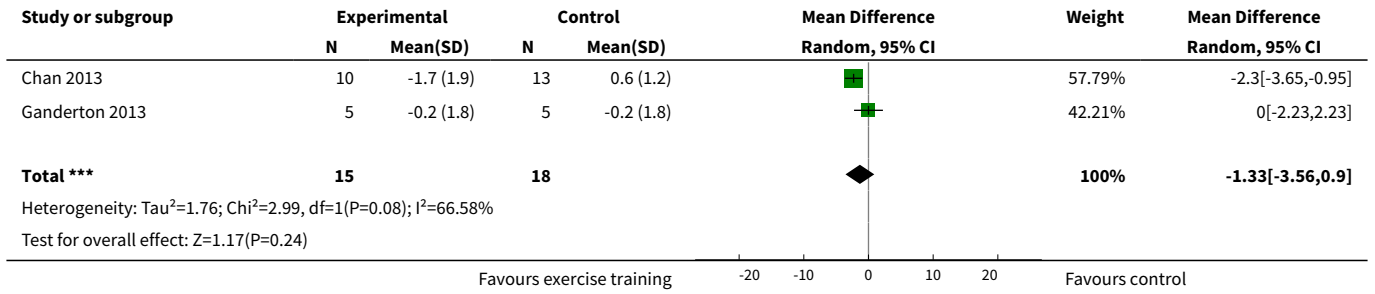


Analysis 1.15. Comparison 1 Exercise vs control, Outcome 15 HRQoL SF36: Social function.

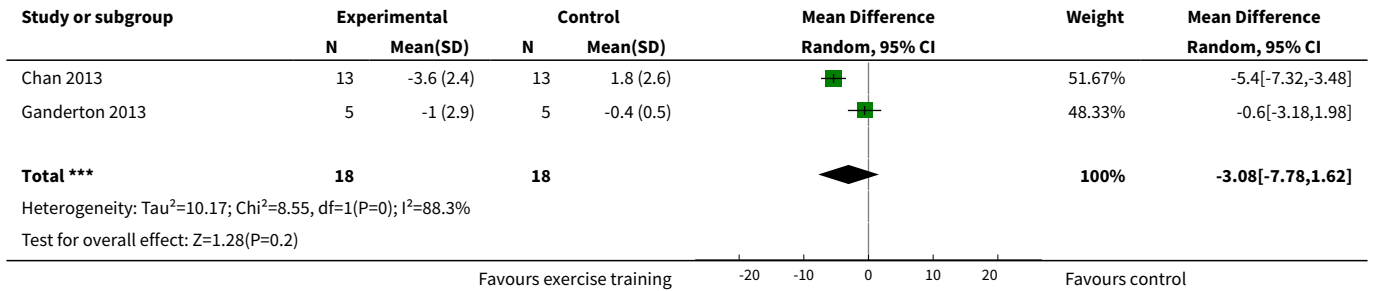




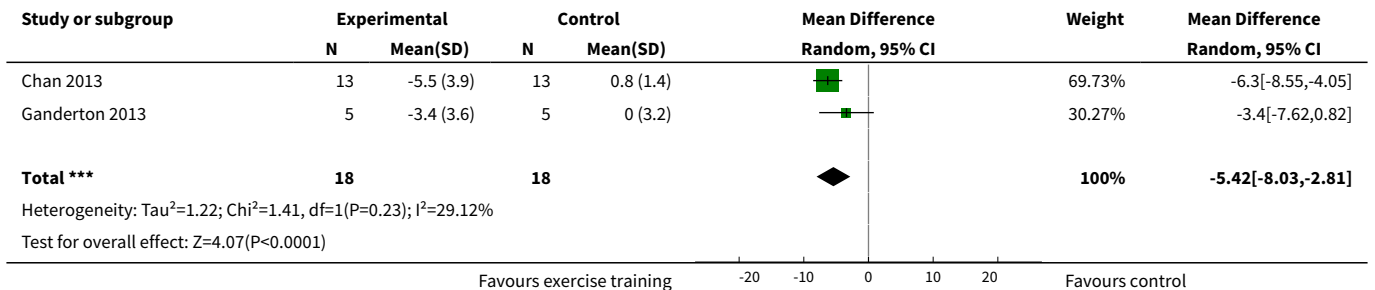
Analysis 1.16. Comparison 1 Exercise vs control, Outcome 16 HRQoL: CAMPHOR activities.



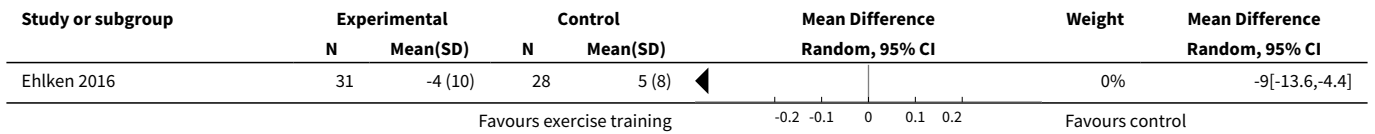
Analysis 1.17. Comparison 1 Exercise vs control, Outcome 17 HRQoL: CAMPHOR symptoms.



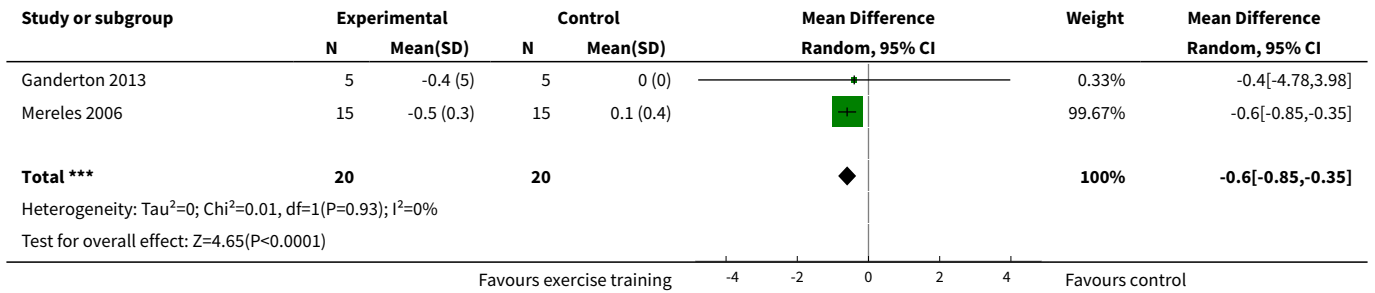
Analysis 1.18. Comparison 1 Exercise vs control, Outcome 18 HRQoL: CAMPHOR QoL.



Analysis 1.19. Comparison 1 Exercise vs control, Outcome 19 Cardiopulmonary haemodynamics.



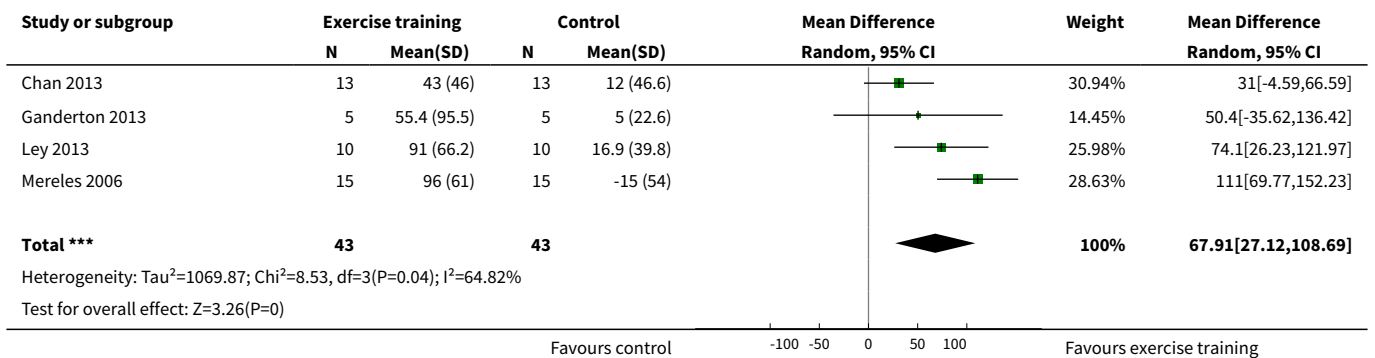
Analysis 1.20. Comparison 1 Exercise vs control, Outcome 20 Functional class.



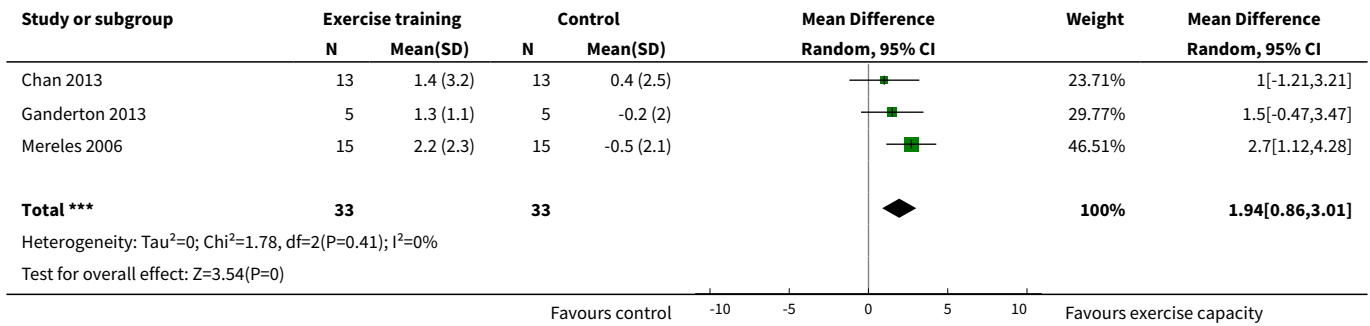
Analysis 1.21. Comparison 1 Exercise vs control, Outcome 21 B-type natriuretic peptide.



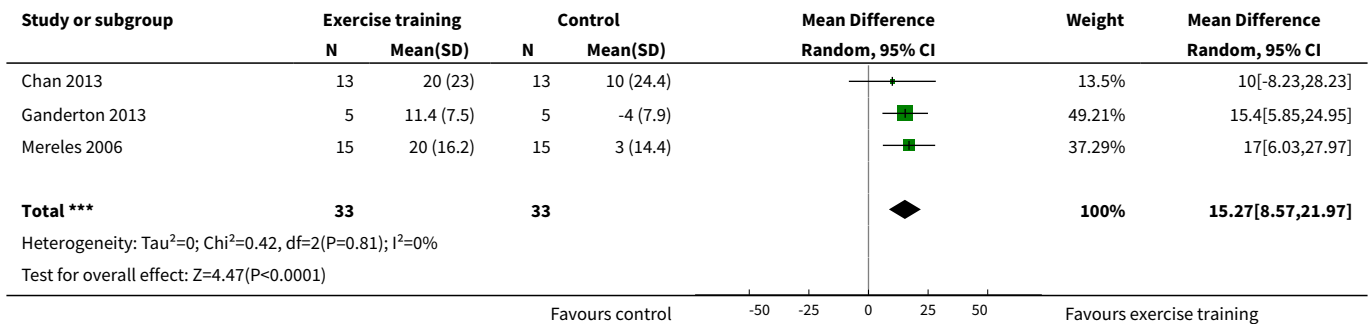
Analysis 1.22. Comparison 1 Exercise vs control, Outcome 22 Exercise capacity: 6MWD, sensitivity analysis.



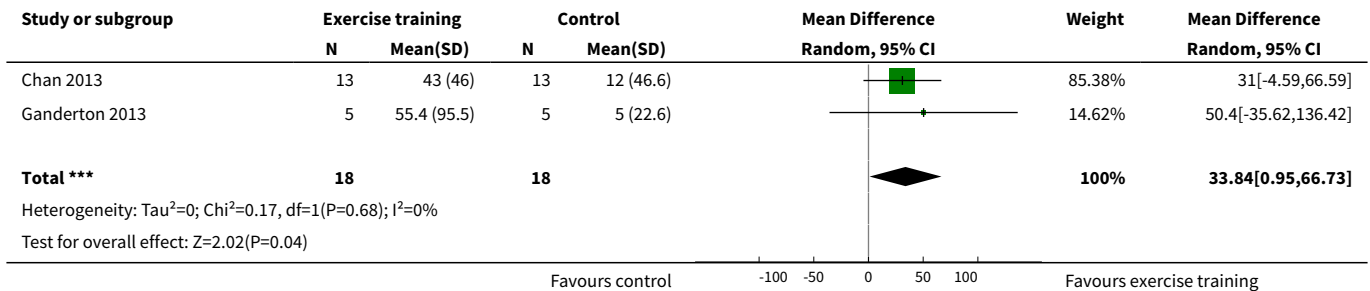
Analysis 1.23. Comparison 1 Exercise vs control, Outcome 23 Exercise capacity: VO₂peak, sensitivity analysis.



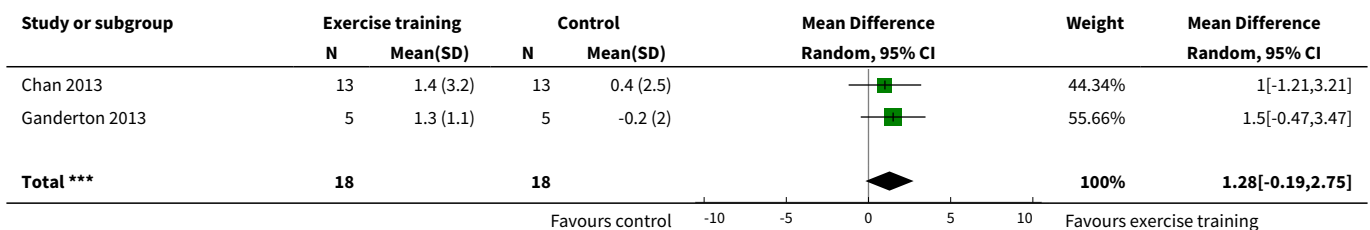
Analysis 1.24. Comparison 1 Exercise vs control, Outcome 24 Exercise capacity: Peak power, sensitivity analysis.

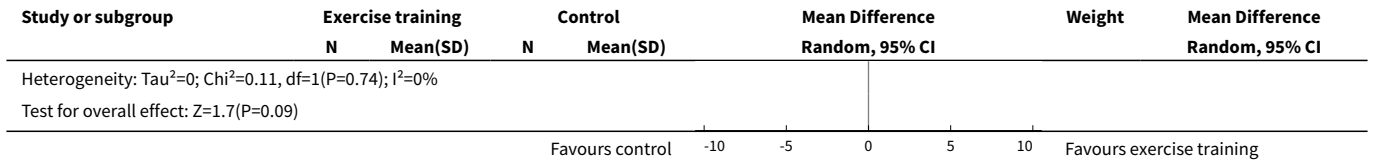


Analysis 1.25. Comparison 1 Exercise vs control, Outcome 25 Exercise capacity 6MWD, PAH subgroup only.

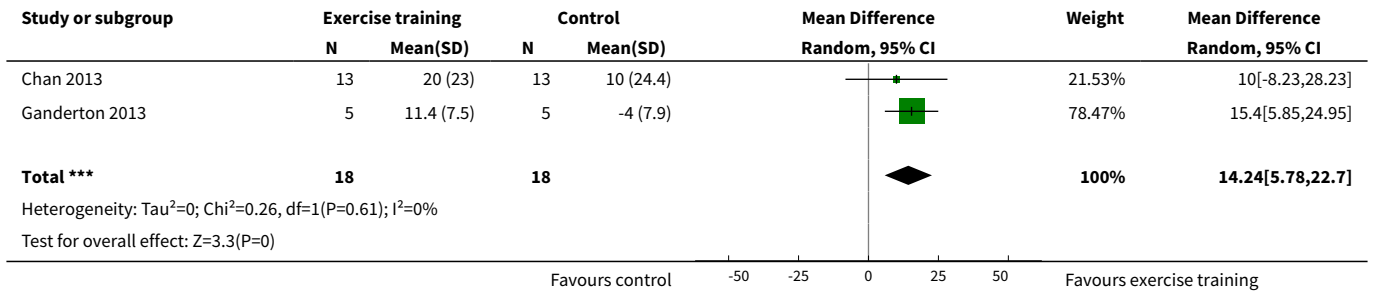


Analysis 1.26. Comparison 1 Exercise vs control, Outcome 26 Exercise capacity: VO₂peak, PAH subgroup only.

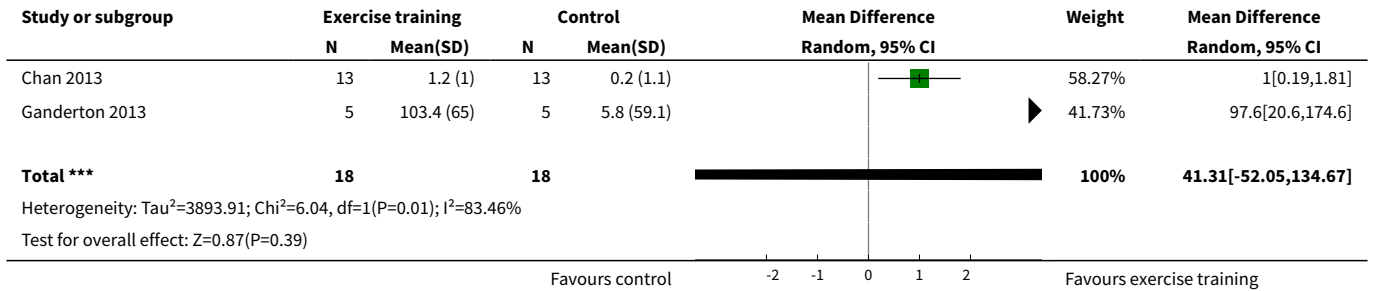




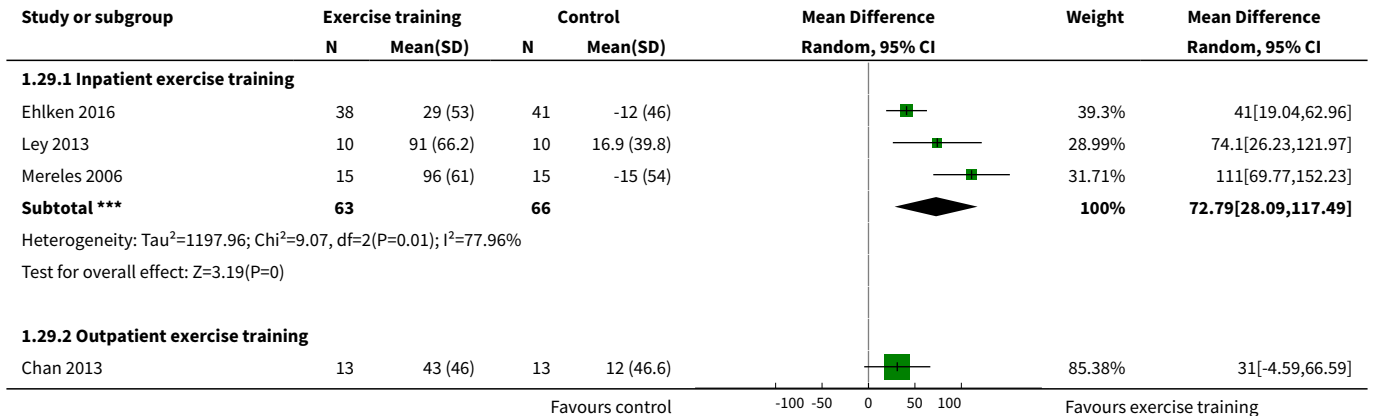
Analysis 1.27. Comparison 1 Exercise vs control, Outcome 27 Exercise capacity: Peak power, PAH subgroup only.

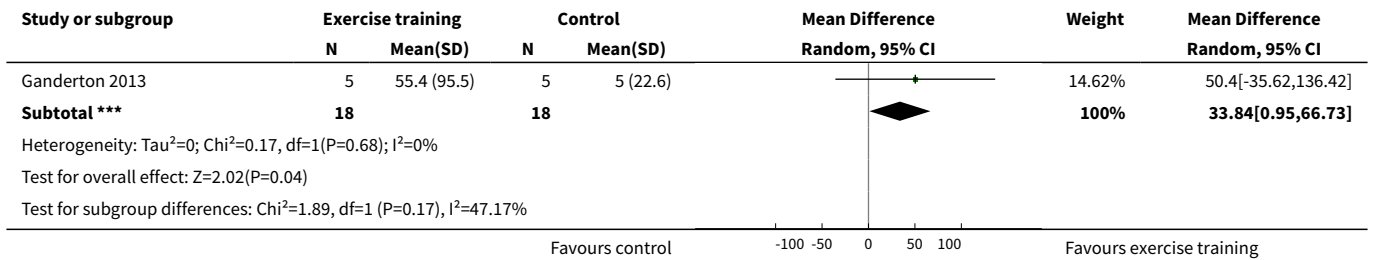


Analysis 1.28. Comparison 1 Exercise vs control, Outcome 28 Exercise capacity: Anaerobic threshold, PAH subgroup only.



Analysis 1.29. Comparison 1 Exercise vs control, Outcome 29 Exercise capacity: 6MWD, subgroup analysis for setting of rehabilitation.





APPENDICES

Appendix 1. Database search strategies

Cochrane Airways Register of Trials

- #1 PULM:MISC1
- #2 MeSH DESCRIPTOR Hypertension, Pulmonary Explode All
- #3 MeSH DESCRIPTOR Pulmonary Heart Disease
- #4 "pulmonary vascular disease":TI,AB
- #5 #1 or #2 or #3 or #4
- #6 MeSH DESCRIPTOR exercise Explode All
- #7 MeSH DESCRIPTOR Exercise Therapy Explode All
- #8 MeSH DESCRIPTOR Exercise Tolerance
- #9 MeSH DESCRIPTOR Physical Fitness
- #10 MeSH DESCRIPTOR Physical Exertion
- #11 MeSH DESCRIPTOR Ergometry
- #12 MeSH DESCRIPTOR Bicycling
- #13 MeSH DESCRIPTOR Weight Lifting
- #14 MeSH DESCRIPTOR Muscle Strength
- #15 exercis*:TI,AB
- #16 conditioning or ergometry or treadmill or endurance or "upper limb" or "lower limb":TI,AB
- #17 walk* or swim* or cycle* or cycling or bicycl* or jog*:TI,AB
- #18 ((strength* or resistance* or weight*) NEAR3 train*):TI,AB
- #19 aerobic*:TI,AB
- #20 rehabilitat*:TI,AB
- #21 #6 OR #7 OR #8 or #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20
- #22 #5 and #21

CENTRAL (CRSO)

- #1MESH DESCRIPTOR Hypertension, Pulmonary EXPLODE ALL TREES
- #2MESH DESCRIPTOR Pulmonary Heart Disease
- #3(pulmonary* NEAR3 hypertens*):TI,AB,KY
- #4("pulmonary vascular disease*"):TI,AB,KY
- #5#1 OR #2 OR #3 OR #4
- #6MESH DESCRIPTOR Exercise EXPLODE ALL TREES
- #7MESH DESCRIPTOR EXERCISE THERAPY EXPLODE ALL TREES
- #8MESH DESCRIPTOR Exercise Tolerance
- #9MESH DESCRIPTOR Physical Fitness
- #10MESH DESCRIPTOR Physical Exertion
- #11MESH DESCRIPTOR Ergometry EXPLODE ALL TREES
- #12MESH DESCRIPTOR Bicycling
- #13MESH DESCRIPTOR Weight Lifting
- #14MESH DESCRIPTOR Muscle Strength EXPLODE ALL TREES
- #15exercis*:TI,AB,KY
- #16(conditioning or ergometry or treadmill or endurance or "upper limb" or "lower limb"):TI,AB,KY
- #17(walk* or swim* or cycle* or cycling or bicycl* or jog*):TI,AB,KY
- #18((strength* or resistance* or weight*) NEAR3 train*):TI,AB,KY

#19aerobic*:TI,AB,KY

#20rehabilitat*:TI,AB,KY

#21#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20

#22#5 AND #21

MEDLINE (Ovid)

1. exp Hypertension, Pulmonary/
2. Pulmonary Heart Disease/
3. (pulmonary adj3 hypertens\$).ti,ab.
4. pulmonary vascular disease.ti,ab.
5. or/1-4
6. exp Exercise/
7. exp Exercise Therapy/
8. Exercise Tolerance/
9. Physical Fitness/
10. Physical Exertion/
11. exp Ergometry/
12. Bicycling/
13. Weight Lifting/
14. Muscle Strength/
15. exercis\$.ti,ab.
16. (conditioning or ergometry or treadmill or endurance or "upper limb" or "lower limb").ti,ab.
17. (walk\$ or swim\$ or cycle\$ or cycling or bicycl\$ or jog\$).ti,ab.
18. ((strength\$ or resistance\$ or weight\$) adj3 train\$).ti,ab.
19. aerobic\$.ti,ab.
20. rehabilitat\$.ti,ab.
21. or/6-20
22. 5 and 21
23. (controlled clinical trial or randomized controlled trial).pt.
24. (randomized or randomised).ab,ti.
25. placebo.ab,ti.
26. randomly.ab,ti.
27. trial.ab,ti.
28. groups.ab,ti.
29. or/23-28
30. Animals/
31. Humans/

32. 30 not (30 and 31)

33. 29 not 32

34. 22 and 33

Embase (Ovid)

1. exp pulmonary hypertension/
2. (pulmonary adj3 hypertens\$).ti,ab.
3. pulmonary vascular disease.ti,ab.
4. or/1-3
5. exp exercise/
6. exp kinesiotherapy/
7. exp ergometry/
8. exp bicycle/
9. exp weight lifting/
10. muscle strength/
11. exercis\$.ti,ab.
12. (conditioning or ergometry or treadmill or endurance or "upper limb" or "lower limb").ti,ab.
13. (walk\$ or swim\$ or cycle\$ or cycling or bicycl\$ or jog\$).ti,ab.
14. ((strength\$ or resistance\$ or weight\$) adj3 train\$).ti,ab.
15. aerobic\$.ti,ab.
16. rehabilitat\$.ti,ab.
17. or/5-16
18. 4 and 17
19. Randomized Controlled Trial/
20. randomization/
21. controlled clinical trial/
22. Double Blind Procedure/
23. Single Blind Procedure/
24. Crossover Procedure/
25. (clinica\$ adj3 trial\$).tw.
26. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (mask\$ or blind\$ or method\$)).tw.
27. exp Placebo/
28. placebo\$.ti,ab.
29. random\$.ti,ab.
30. ((control\$ or prospectiv\$) adj3 (trial\$ or method\$ or stud\$)).tw.
31. (crossover\$ or cross-over\$).ti,ab.
32. or/19-31
33. exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
34. human/ or normal human/ or human cell/
35. 33 and 34
36. 33 not 35
37. 32 not 36
38. 18 and 37

PEDro

Field	Search term
Abstract & Title	pulmonary hypertension
Method	clinical trial

ClinicalTrials.gov

search field	search term
Study type	Interventional
Condition	Pulmonary hypertension
intervention	Exercise

WHAT'S NEW

Date	Event	Description
1 February 2017	Amended	Added the total number of participants

CONTRIBUTIONS OF AUTHORS

NM drafted the protocol with the assistance from AH and FK. NM and AH identified studies for the review, extracted data from the studies and drafted the review. All authors provided critical feedback on the review.

DECLARATIONS OF INTEREST

NM: none known

FK: none known

AH: none known

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- The authors declare that no such external funding was received for this systematic review, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We had intended to perform a subgroup analysis according to severity of PH, but insufficient data were available. We performed an additional subgroup analysis for setting of exercise rehabilitation programme, as there was marked heterogeneity in exercise outcomes that could have been affected by the programme model.

INDEX TERMS

Medical Subject Headings (MeSH)

*Exercise Tolerance; *Oxygen Consumption; *Quality of Life; Exercise Therapy [*methods]; Hemodynamics; Hypertension, Pulmonary [mortality] [physiopathology] [*rehabilitation]; Randomized Controlled Trials as Topic; Selection Bias; Walk Test

MeSH check words

Humans; Middle Aged