Osadnik CR, McDonald VM, Holland AE.

Pulmonary rehabilitation for adults with asthma.
DOI: 10.1002/14651858.CD013485.

www.cochranelibrary.com
Pulmonary rehabilitation for adults with asthma

Christian R Osadnik1,2, Vanessa M McDonald3,4,5, Anne E Holland6,7,8

1Department of Physiotherapy, Monash University, Melbourne, Australia. 2Monash Lung and Sleep, Monash Health, Melbourne, Australia. 3Centre of Excellence in Severe Asthma and Priority Research Centre for Healthy Lungs, The University of Newcastle, Newcastle, Australia. 4School of Nursing and Midwifery, The University of Newcastle, Newcastle, Australia. 5Department of Respiratory and Sleep Medicine, John Hunter Hospital, Newcastle, Australia. 6Physiotherapy, Alfred Health, Melbourne, Australia. 7Discipline of Physiotherapy, School of Allied Health, Human Services and Sport, La Trobe University, Melbourne, Australia. 8Institute for Breathing and Sleep, Melbourne, Australia

Contact address: Christian R Osadnik, Department of Physiotherapy, Monash University, Melbourne, Victoria, Australia. christian.osadnik@monash.edu.

Editorial group: Cochrane Airways Group

Citation: Osadnik CR, McDonald VM, Holland AE. Pulmonary rehabilitation for adults with asthma. Cochrane Database of Systematic Reviews 2019, Issue 11. Art. No.: CD013485. DOI: 10.1002/14651858.CD013485.

Copyright © 2019 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To determine the effects of pulmonary rehabilitation compared to usual care on exercise performance, asthma control and quality of life in adults with asthma.
**BACKGROUND**

**Description of the condition**

Asthma is a respiratory disease characterised by variable airflow limitation and the presence of respiratory symptoms including wheeze, chest tightness, cough or dyspnoea. Symptoms may vary over time in frequency and severity (GINA 2019). Several factors may predispose individuals to the development of asthma, however the common result is a process of chronic airway inflammation that causes bronchoconstriction, airway wall thickening, and increased mucous production (GINA 2019). Precise mechanisms explaining the variability in symptoms are challenging to identify, however intermittent exposure to any number of ‘triggers’ and the degree of airflow reversibility on spirometry may partly contribute to this phenomenon. Asthma is primarily diagnosed on the basis of clinical presentation and symptom history rather than any individual biomarker, which can lead to under- or over-diagnosis. This poses some challenges to accurately appreciate its global impact, however estimates suggest asthma affects over 300 million people worldwide and imposes a large social and financial burden (GAN 2018). Despite the existence of many established pharmacotherapies to manage asthma, morbidity and mortality remains high: the Global Burden of Disease collaboration estimates that 420,000 people died from asthma in 2016 (FIRS 2017).

Asthma severity is assessed according to the degree of treatment required to manage the condition. Compared to people with mild to moderate asthma, those with more severe disease experience poor symptom control (Reddel 2015), impaired quality of life (Foster 2017; McDonald 2018), increased risk of hospitalisation (Eisner 2000; Poulos 2014), and increased risk of death (Ebmeyer 2017). The severe asthma population may therefore represent a specific subgroup in need of high levels of support. Asthma is also associated with several ‘extra-pulmonary’ features (i.e. those occurring outside the lungs); evidence confirms that people with asthma are less active than ‘healthy’ counterparts (Cordova-Rivera 2018), and higher levels of physical activity associates with better measures of lung function (Ritz 2010), disease control (Dogra 2011), health status (Lucas 2005), and healthcare use (Dogra 2009). A proportion of adults with asthma, particularly those of older age, may present with clinical features of chronic obstructive pulmonary disease (COPD) (i.e. asthma-COPD overlap (ACO)) such as significant functional impairment, symptom burden, poor quality of life, co-morbidities, and history of respiratory exacerbations. ACO has been defined as the presence of incompletely reversible airflow obstruction on spirometry in addition to clinical features of asthma, and has been estimated to occur in approximately 20% of people with asthma or COPD (Gibson 2015). Asthma can therefore be challenging to distinguish from COPD, particularly where shared risk factors may be present. Factors such as older age (e.g. older than 50 years) and significant smoking history (e.g. more than 10 to 20 pack years) are common exclusion criteria from pharmacotherapy trials that may result in under-representation of such individuals. This may occur less in studies of rehabilitation. People with asthma are typically encouraged to participate in structured exercise training programmes where possible, and data suggest this to be safe (Cordova-Rivera 2018a), even when performed at high intensity (da Silva 2016; Toennesen 2018). Despite this, many people struggle to achieve this in an independent or unsupervised environment.

Exercise is also a known trigger for asthma in some individuals. Exercise-induced bronchoconstriction (EIB) describes acute airway narrowing that is transient and reversible, that occurs as a result of (i.e. during or after) exercise (Aggarwal 2018; Parsons 2013). Its presence is typically confirmed by a minimum of a 10% decline or greater in FEV1 value between pre-exercise and post-exercise (within 30 minutes of completion) spirometry (Crapo 2000). The precise prevalence of EIB is challenging to identify, however it is reported to occur in up to 90% of people with asthma (Weller 2010), and those with more severe and poorly-controlled asthma are considered more likely to exhibit EIB (Weller 2010). International guidelines indicate EIB can be effectively managed using strategies such as administration of inhaled short-acting beta2-agonist (SABA) medication at least 15 minutes prior to commencing exercise (Parsons 2013). Despite this, the presence of EIB and concerns about the safety of exercise may discourage some people with EIB from participating in exercise programmes or daily physical activity. Strategies to identify and manage EIB may therefore be an important component of exercise training interventions for people with asthma.

**Description of the intervention**

Current leading international guidelines define pulmonary rehabilitation (PR) as "a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, and behaviour change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviours" (Spruit 2013). The precise extent to which specific components should be included within PR programmes is not agreed upon, nor is the number of specific components or the way in which they are implemented. The most widely accepted definition of PR for use in scientific research defines the core criteria of PR as “any inpatient, outpatient, community-based or home-based rehabilitation programme of at least four weeks’ duration that include[s] exercise therapy with or without any form of education and/or psychological support delivered to patients with exercise limitation attributable to “their disease”” (McCarthy 2015). Current literature supports PR as an effective treatment for people with a range of chronic respiratory diseases including chronic obstructive pulmonary disease (COPD), bronchiectasis, interstitial lung disease and pulmonary hypertension. Adults with asthma exhibit similar dysfunction and respiratory symptoms to many of these conditions, yet their circumstances may also differ substantially. For example, people with asthma may be younger, may have concurrent employment or studying commitments, and may be less physically compromised due to ‘ reversibility’ of their airways disease. It is also challenging to determine whether responses to PR would differ in people with ACO compared to those with clearly defined asthma or COPD (or both).

**How the intervention might work**

The cornerstone element underpinning many of the observed benefits from PR is exercise training incorporating aerobic/lower limb endurance exercise. The main benefits are considered to be due to adaptations to the peripheral skeletal muscles, including increased capillary proliferation, improved (local) oxygen uptake, improved mitochondrial function, reduced oxidative stress, and a shift in muscle fibre type composition. Other mechanisms contributing to improvements from exercise may include desensitisation to the discomfort of dyspnoea sensations, reductions in anxiety associated with exercise performance and possible improvements in respi-
A randomised controlled trial (RCT) of people with moderate to severe asthma found aerobic training decreased bronchial hyperresponsiveness and serum pro-inflammatory cytokines (interleukin-6, interleukin-8, monocyte chemoattractant protein-1) (França-Pinto 2015). Benefits were also observed in one RCT conducted in obese people with asthma, where the addition of exercise to a programme of weight loss and psychological therapy increased anti-inflammatory biomarkers and vitamin D levels, and significantly reduced airway and systemic inflammation (fractional concentration of exhaled nitric oxide (FeNO), and serum biomarkers) (Freitas 2017). Improvements in exhaled nitric oxide have even been demonstrated following a single session of moderate-intensity exercise (30 minutes of treadmill walking) in physically inactive adults with asthma (Scott 2015), with this study also suggesting exercise may exert an anti-inflammatory effect that could be attenuated by interleukin-1 receptor antagonists.

There may be plausible reason to exert caution in assuming equal physiological responses to exercise between people with COPD and those with asthma. Ventilatory limitations to exercise are less common in people with asthma compared to those with COPD, meaning the contributory roles of physical inactivity and deconditioning to observed exercise intolerance in these people are likely relevant. This may be due to avoidance behaviours associated with a fear of exacerbations due to exercise. Qualitative research supports this notion, indicating many adolescents with asthma withdraw from exercise as a coping strategy, despite deriving a strong sense of enjoyment from it (Winn 2018). PR programmes also typically involve some form of education or self-management (or both) or psychological support. Whilst the precise extent and nature of these components can vary markedly between programmes, their incorporation distinguishes PR from isolated ‘exercise training’ studies. Evidence regarding the role of education and support in people with asthma is scarce; however it stands to reason that, for a condition that is heavily reliant upon effective self-management, medication technique and adherence, and timely responses in the event of an acute exacerbation, the inclusion of such components would be considered valuable. This may be particularly relevant for the improvement of disease control, which is a common outcome of importance (somewhat uniquely) for people with asthma. Limited data suggest people with poorer levels of asthma control may achieve greater gains in asthma control after PR compared to those who commence with better control, thereby potentially lending support to this notion (Sahin 2019).

Why it is important to do this review

International guidelines recommend PR for the management of chronic lung conditions such as COPD (Alison 2017; Bolton 2013; Spruit 2013), bronchiectasis (Alison 2017; Bolton 2013; Spruit 2013), interstitial lung disease (Alison 2017; Spruit 2013), and pulmonary hypertension (Alison 2017; Spruit 2013). Recommendations for people with asthma are less convincing, and referrals for adults with asthma to PR are not a widespread standard of care in clinical practice. American Thoracic Society/European Respiratory Society PR guidelines advocate for the inclusion of adults with ‘persistent asthma’ in PR (Spruit 2013). British Thoracic Society guidelines advocate that routine referrals for patients with asthma to PR are not recommended (Bolton 2013), however they do suggest discussions regarding the benefits of exercise may be appropriate. Asthma was not included in the Australian and New Zealand PR guidelines (Alison 2017), while current Global Initiative for Asthma (GINA) guidelines suggest advice should be provided about pulmonary rehabilitation for those with “COPD or asthma-COPD overlap” (GINA 2019). It is unclear whether this lack of strong support for PR in people with asthma may reflect an historic predominance of evidence from people with COPD and a need for clearer evidence in people with asthma.

A Cochrane Review of the effects of exercise training specifically for people with asthma demonstrates positive effects on clinically important outcomes such as exercise performance, quality of life, and asthma control (Carson 2013). This evidence, however, offers limited applicability to many adults encountered in clinical respiratory medicine practice. For example, participants included within the review had a mean age of approximately 22 years. Distinct differences are also apparent between the nature of some of the included exercise interventions (e.g. one-hour outdoor running tracks for children, indoor swimming six days per week) and those typically offered by PR programmes in adult clinical respiratory medicine. The findings of this previous Cochrane Review may therefore only apply to younger people with asthma. The training potential of these younger individuals may differ considerably to adults of older age who typically present with increased chronic health comorbidities (McDonald 2019). For example, those who are younger may prefer, and be capable of, independent exercise training at high intensity or duration (or both) at community-based gyms or pools rather than group-based rehabilitation conducted at hospital or healthcare service sites. Such settings also allow flexibility for exercise to be conducted at more convenient times that may fall outside of typical daytime, weekday offerings of many PR programmes, therefore potentially impacting upon training compliance and programme effectiveness. It is also difficult to postulate and identify whether PR may only be suitable for select subgroups (or phenotypes). Little research has been conducted in this area in asthma, however evidence from other diseases such as COPD suggests those with more established disability (e.g. moderate to severe disease severity, worse symptom limitation and exercise intolerance) may benefit more than those with milder disease. It is therefore possible that traditional PR models may better suit people who are more limited by their asthma (e.g. older, more severe disease) than those who are not (e.g. younger, athletes).

The structure and delivery of conventional PR programmes may not ideally suit the needs of adults with asthma. Factors such as concurrent employment or personal preferences to avoid training alongside people with severe respiratory disease (e.g. those on long-term oxygen therapy) may be realistic barriers to attendance. It is not common, or necessarily feasible, to run PR programmes exclusively for people with asthma, hence it is essential to determine whether the ‘typical’ PR model confers clinically worthwhile benefits for this patient group. If the intervention can demonstrate effectiveness, efforts can subsequently be directed towards the overcoming of disease-specific barriers such as competing time demands via flexible class scheduling. At present, we cannot confidently advocate that traditional PR models benefit people with asthma, despite its intuitive likely benefit. In order to therefore help
clarify the precise role of PR for adults with asthma, it is essential we gain clearer insight into the precise effects of PR in people with asthma.

OBJECTIVES

To determine the effects of pulmonary rehabilitation compared to usual care on exercise performance, asthma control and quality of life in adults with asthma.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs), including those that adopt a cluster design. We will include studies reported in full text, those published as an abstract only, and unpublished data. We will not include randomised crossover trials as it is difficult to ensure 'washout' between treatment periods for interventions that possess inherent behavioural interventions, and we wish to explore the impact of interventions upon long-term outcomes that would preclude this type of study design from being appropriate.

Types of participants

We will include adults with a primary clinical diagnosis of asthma (defined by international guidelines or according to study author descriptions). A comorbid principal respiratory condition of COPD will be allowed due to the known significant overlap between asthma and COPD (ACO). We will exclude participants described as having any primary clinical diagnosis other than asthma or COPD/ACO. We will not exclude participants with other comorbidities/characteristics if they were deemed suitable to participate in the rehabilitation intervention within the original study. For studies involving participants of mixed clinical diagnoses, we will include the subgroup of data relating specifically to adults with asthma if this is available. If unavailable, we will only include the data in their entirety if more than 75% of participants are noted as having asthma upon commencement of the intervention.

Types of interventions

We will include studies comparing PR to usual care. PR must involve a minimum of four weeks’ (eight or more sessions) aerobic exercise training (e.g. walking, cycling), including some form of education or self-management strategy. PR may be received as an inpatient or an outpatient at a hospital centre, community-based facility, or home-based environment (including interventions delivered to the home via tele-rehabilitation), but the exercise training component must be supervised by a suitably qualified therapist.

Co-interventions such as other forms of exercise training (e.g. strength, balance, inspiratory muscle training), breathing techniques (e.g. Buteyko method), dietary supplementation, relaxation, or airway clearance techniques will be permitted as these are commonly integrated within PR programmes. Interventions comprising exercise training modalities alone will not be eligible for inclusion. Usual care must not involve participation in a supervised exercise training programme during the study period, but may comprise no formal intervention (e.g. usual medical or self-care management, without rehabilitation), delayed-onset or waitlist-controlled rehabilitation, or provision of generalised self-management advice such as educational materials encouraging general physical activity in daily life.

Types of outcome measures

Primary outcomes

1. Exercise performance: this will be derived from tests of maximal exercise capacity (e.g. incremental cardiopulmonary exercise test (CPET_{inc}), incremental shuttle walk test (ISWT)) and functional exercise capacity (e.g. six-minute walk test (6MWT), constant work rate (CPET_{cwr}), endurance shuttle walk test (ESWT)). The principle metrics of interest for these tests will be peak oxygen uptake (VO_{2peak}) and peak work rate (WR_{max}) for CPET_{inc} tests; distance in metres for ISWT and 6MWT; and time in seconds for CPET_{cwr} and ESWT. All measures will be reported upon completion of the PR intervention and the latest time point up to 12 months after completion of the intervention.

2. Asthma control (e.g. Asthma Control Questionnaire (ACQ) or Asthma Control Test (ACT)): this will be reported upon completion of the PR intervention, and the latest time point up to 12 months after completion of the intervention.

3. Health-related quality of life: this may be measured via disease-specific questionnaires (i.e. Asthma Quality of Life Questionnaire (AQLQ), St. George’s Respiratory Questionnaire (SGRQ), Asthma Impact Survey, Living with Asthma Questionnaire, Chronic Respiratory Disease Questionnaire (CRDQ)) or generic health questionnaires (i.e. Short Form-36 (SF-36), Euro-Qol). Both total scores and symptom-specific subdomain scores will be used but reported separately. Data from disease-specific and generic instruments will also be analysed separately to each other. Disease-specific quality of life total scores will be considered the principal analysis of interest. Data will be reported upon completion of the PR intervention, and the latest time point up to 12 months after completion of the intervention.

Secondary outcomes

1. Severe asthma exacerbations/hospitalisations: measured as the incidence or rate of severe acute asthma exacerbations (episodes requiring oral systemic corticosteroid use) or respiratory-related hospitalisation, or both. Where possible, data from hospitalisations will be analysed separately to those of exacerbations. Data will be reported from the longest time point available up to 12 months after completion of the intervention.

2. Mental health: this will comprise measures of anxiety and depression (e.g. Hospital Anxiety and Depression Scale (HADS), Beck Depression Inventory, Hamilton Anxiety/Depression Rating Scale). Anxiety data will be analysed distinct from depression data. This will be assessed upon completion of the PR intervention, and at the longest time point available up to 12 months after completion of the intervention.

3. Peripheral skeletal muscle force: this may include measures of muscle strength (kilograms), power (Newtons) or torque (Newton.metres). Data from muscle groups of the upper limb will be pooled together, while data from muscle groups of the lower limb will be pooled together. Upper limb muscle force will be analysed separately from lower limb muscle force. This will be assessed upon completion of the exercise training intervention, and the longest time point available up to 12 months after completion of the intervention.
4. Levels of physical activity: this will comprise objectively measured outcomes of movement (e.g. steps, time spent in light/moderate/vigorous activity) but not sedentary behaviour. Subjective recall methods (e.g. surveys) will not be considered for inclusion. This will be assessed upon completion of the PR intervention, and the longest time point available up to 12-months after intervention completion.

5. Inflammatory biomarkers: these will comprise commonly used markers of airway and systemic inflammation. Examples of airway inflammation may include fractional exhaled nitric oxide (FeNO) and eosinophils (sputum and blood samples). Markers of systemic inflammation may include C-reactive protein (CRP), white cell count (WCC), and interleukins (e.g. IL-6).

6. Adverse events/side effects: this will comprise events related to the PR intervention (e.g. within-session incidents), such as respiratory-related hospitalisations, falls and musculoskeletal injuries, as well as incidence of significant exercise-induced bronchoconstriction (where reported in adequate detail). Mortality will not be included within this outcome.

Reporting one or more of the outcomes listed here in the study will not be an inclusion criterion for the review.

Search methods for identification of studies

Electronic searches

We will identify studies from searches of the following databases and trial registries:

1. Cochrane Airways Trials Register (Cochrane Airways 2019), via the Cochrane Register of Studies, all years to date;
2. Cochrane Central Register of Controlled Trials (CENTRAL), via the Cochrane Register of Studies, all years to date;
3. MEDLINE Ovid SP, 1946 to date;
4. Embase Ovid SP, 1974 to date;
5. US National Institutes of Health Ongoing Trials Register, ClinicalTrials.gov (www.clinicaltrials.gov);
6. World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/).

The proposed search strategies and indicative number of search results for MEDLINE and the Airways Register are listed in Appendix 1. These will be adapted for use in the other databases. The search strategies were developed by the Cochrane Airways Information Specialist in collaboration with the authors, and were peer-reviewed by another Cochrane Information Specialist using the PRESS checklist (McGowan 2016).

All databases and trials registries will be searched from their inception to the present, and there will be no restriction on language or type of publication. Handsearched conference abstracts and grey literature will be identified through the Cochrane Airways Trials Register and the CENTRAL database.

Searching other resources

We will check the reference lists of all primary studies and review articles for additional references. We will search relevant manufacturers’ websites for study information. We will search on PubMed for errata or retractions from included studies published in full text, and report the date this was done within the review.

Data collection and analysis

Selection of studies

We plan to use Cochrane’s Screen4Me workflow to help assess the search results. Screen4Me comprises three components:

1. Known assessments, a service that matches records in the search results to records that have already been screened in Cochrane Crowd (Cochrane’s citizen science platform where the Crowd help to identify and describe health evidence) and labelled as ‘RCT’ or ‘not an RCT’;
2. The RCT classifier, a machine-learning model that distinguishes RCTs from non-RCTs; and
3. Cochrane Crowd, if appropriate (crowd.cochrane.org).

More detailed information about the Screen4Me components can be found in the following publications: Marshall 2018, McDonald 2017, Noel-Storr 2018, Thomas 2017.

Following this initial assessment, two review authors (CO, CG (Ciarra Gleeson, who will join at review stage)) will screen the remaining titles and abstracts of the search results independently using Covidence software (Covidence) and classify them as ‘yes’ or ‘maybe’ (eligible or potentially eligible/unclear) or ‘no’ (do not retrieve). We will retrieve the full-text study reports of all potentially eligible studies and two review authors (CO, CG) will independently screen them for inclusion, recording the reasons for exclusion of ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third person/review author (AH). We will identify and exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and ‘Characteristics of excluded studies’ table (Moher 2009).

Data extraction and management

We will use a data collection form for study characteristics and outcome data, which has been piloted on at least one study in the review. One review author (CG) will extract the following study characteristics from included studies, and another review author (VM) will check these for accuracy.

1. 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.
2. Participants: number (recruited and completed), mean age, age range, gender, body mass index, severity of condition, diagnostic criteria, baseline lung function, smoking history, asthma treatment, inclusion criteria and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for studies and notable conflicts of interest of trial authors.

Two review authors (CG, VM) will independently extract outcome data from included studies. We will note in the ‘Characteristics of included studies’ table if outcome data were not reported in a usable way. We will resolve disagreements by consensus or by involving a third person/review author (CO). One review author (CG) will
transfer data into the Review Manager 5 file (RevMan 2014). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (CO) will spot-check study characteristics for accuracy against the study report.

Assessment of risk of bias in included studies

Two review authors (CG, AH) will assess risk of bias independently for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We will resolve any disagreements by discussion or by involving another author (CO). We will assess the risk of bias according to the following domains:

1. Random sequence generation;
2. Allocation concealment;
3. Blinding of participants and personnel;
4. Blinding of outcome assessment;
5. Incomplete outcome data;
6.Selective outcome reporting; and
7. Other bias.

We will judge each study as being at high, low or unclear risk of bias or each domain, and will provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise the 'Risk of bias' judgements across different studies for each of the domains listed. We will consider 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 patient-reported symptom scale). Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and justify any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as risk ratios (RRs), for ease of interpretation, and continuous data as mean difference (MD) or standardised mean difference (SMD) with 95% confidence intervals (95% CIs). We will use SMDs where outcome data are reported via different metrics but deemed clinically homogenous (e.g. data from different field walking tests or different quality-of-life instruments), however they will not be used where such outcome data comprise a combination of both endpoint and change data. Where SMDs are to be used for outcome data expressed as change from baseline (principal unit of interest), we will use the standard deviation (SD) of baseline values as the unit of measurement to calculate the SMD and adjust standard errors to take correlation into account. Where possible, we will use the data closest to the primary time point of interest.

We will use intention-to-treat (ITT) or 'full analysis set' analyses where they are reported (i.e. those where data have been imputed for participants who were randomly assigned but did not complete the study) instead of completer or per-protocol analyses.

Unit of analysis issues

For dichotomous outcomes, we will use participants, rather than events, as the unit of analysis (i.e. number of patients admitted to hospital, rather than number of admissions per individual). However, if rate ratios are reported in a study, we will analyse them on this basis. We will only meta-analyse data from cluster-RCTs if the available data have been adjusted (or can be adjusted), to account for the clustering.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as an abstract only). Where this is not possible, and the missing data are thought to introduce serious bias, we will take this into consideration in the GRADE rating for affected outcomes.

Assessment of heterogeneity

We will use the $I^2$ statistic to measure heterogeneity among the studies in each analysis. If we identify substantial heterogeneity we will report it and explore the possible causes by prespecified subgroup analysis. While we hypothesise treatment effects could differ on the basis of participants’ age, no simple cut-off is appropriate to examine this via traditional subgroup analysis. We will therefore extract information on mean participant age within included studies and consider how between-study heterogeneity may have impacted upon effect estimates. Furthermore, if individual studies present outcomes stratified by age we will extract and report this information.

Assessment of reporting biases

If we are able to pool more than 10 studies we will create and examine a funnel plot to explore possible small-study and publication bi-
ases. This will not be performed for outcomes analysed using SMD, in accordance with the Cochrane Handbook (Higgins 2011).

Data synthesis

We will use a random-effects model for all meta-analyses and perform a sensitivity analysis with a fixed-effect model.

'Summary of findings' table

We will create a 'Summary of findings' table using the following outcomes: exercise tolerance, asthma control, quality of life and adverse events. We will use the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data for the prespecified outcomes. We will use the methods and recommendations described in Section 8.5 and Chapter 12 of the Cochrane Handbook (Higgins 2011), and will create the tables using GRADEpro GDT software (GRADEpro GDT). We will justify all decisions to downgrade the quality of studies using footnotes and we will make comments to aid the reader’s understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses:

1. Programmes that adopt total training durations lasting ≤ 8 weeks versus those that are > 8 weeks;
2. Participants characterised by severe asthma versus those characterised by non-severe asthma (Chung 2014), where identifiable.

We will use the following outcomes in subgroup analyses:

1. Exercise performance (6MWT or ISWT only, considering the predominant use of these tests in clinical practice, measured upon intervention completion);
2. Asthma control, measured upon intervention completion;
3. Health-related quality of life (disease-specific total scores only, measured upon intervention completion).

We will use the formal test for subgroup interactions in Review Manager 5 (RevMan 2014).

Sensitivity analysis

In order to explore whether the effect of PR on the primary outcomes may be moderated by the inclusion of participants with a mixed ACO diagnosis, we plan to carry out a sensitivity analysis involving removal of studies in which more than 50% of participants have ACO (where possible to identify). We will also compare the results from the random-effects model (principal method of analysis) with those using a fixed-effect model.

ACKNOWLEDGEMENTS

The Background and Methods sections of this protocol are based on a standard template used by Cochrane Airways.

The authors and Cochrane Airways editorial team are grateful to the following peer reviewers for their time and comments:

1. Mr Bernard McCarthy, National University of Ireland Galway, Galway, Ireland;
2. Dr Rachael Evans, University of Leicester, Leicester, UK;
3. Louise Lindhardt Toennesen, Bispebjerg University Hospital, Copenhagen, Denmark;
4. Dr Renae McNamara, Prince of Wales Hospital, Randwick, Australia; The University of Sydney, Sydney, Australia; The Woolcock Institute of Medical Research, Sydney, Australia.

The authors and Cochrane Airways editorial team are also grateful to Candida Fenton (Cochrane Vascular, University of Edinburgh, UK) for peer-reviewing the search strategy.

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to Cochrane Airways. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.
Additional references

Aggarwal 2018

Alison 2017

Bolton 2013

Carson 2013

Chung 2014

Cochrane Airways 2019
Cochrane Airways Trials Register. airways.cochrane.org/trials-register (accessed 7 May 2019).

Cordova-Rivera 2018
Cordova-Rivera L, Gibson PG, Gardiner PA, McDonald VM. A systematic review of associations of physical activity and sedentary time with asthma outcomes. Journal of Allergy and Clinical Immunology 2018;6(6):1968-81. e2.

Cordova-Rivera 2018a

Covidence [Computer program]

Crapo 2000

da Silva 2016

Dogra 2009

Dogra 2011

Ebmeier 2017

Eisner 2000

FIRS 2017

Foster 2017
Foster JM, McDonald VM, Guo M, Reddel HK. “I have lost in every facet of my life”: the hidden burden of severe asthma. European Respiratory Journal 2017;50(3):1700765.

França-Pinto 2015

Freitas 2017

GAN 2018
Gibson 2015

GINA 2019

GRADEpro GDT [Computer program]
McMaster University (developed by Evidence Prime). GRADEpro GDT. Version accessed prior to 2 July 2019. Hamilton (ON): McMaster University (developed by Evidence Prime).

Higgins 2011

Lucas 2005

Marshall 2018

McCarthy 2015

McDonald 2017

McDonald 2018

McDonald 2019

McCowan 2016

Moher 2009

Noel-Storr 2018

Osadnik 2019

Parsons 2013

Poulos 2014

Reddel 2015

RevMan 2014 [Computer program]

Ritz 2010

Sahin 2019

Scott 2015

**Thomas 2017**


**Toennesen 2018**


**Weiler 2010**


**Winn 2018**


### APPENDICES

#### Appendix 1. Database search strategies

**Database:** Cochrane Airways Register  
**Platform:** Cochrane Register of Studies

<table>
<thead>
<tr>
<th>Search line</th>
<th>Search term</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>AST:MISC1</td>
<td>22830</td>
</tr>
<tr>
<td>#2</td>
<td>MeSH DESCRIPTOR Asthma EXPLODE ALL</td>
<td>11950</td>
</tr>
<tr>
<td>#3</td>
<td>asthma*:ti,ab</td>
<td>41591</td>
</tr>
<tr>
<td>#4</td>
<td>#1 or #2 or #3</td>
<td>45077</td>
</tr>
<tr>
<td>#5</td>
<td>MESH DESCRIPTOR Physical Therapy Modalities EXPLODE ALL</td>
<td>2228</td>
</tr>
<tr>
<td>#6</td>
<td>MESH DESCRIPTOR Physical Fitness EXPLODE ALL</td>
<td>396</td>
</tr>
<tr>
<td>#7</td>
<td>MESH DESCRIPTOR Physical Endurance EXPLODE ALL</td>
<td>1349</td>
</tr>
<tr>
<td>#8</td>
<td>MESH DESCRIPTOR Rehabilitation</td>
<td>31</td>
</tr>
<tr>
<td>#9</td>
<td>MESH DESCRIPTOR Exercise Therapy EXPLODE ALL</td>
<td>1440</td>
</tr>
<tr>
<td>#10</td>
<td>MESH DESCRIPTOR Physical Exertion</td>
<td>471</td>
</tr>
<tr>
<td>#11</td>
<td>MESH DESCRIPTOR Exercise Test EXPLODE ALL</td>
<td>1617</td>
</tr>
<tr>
<td>#12</td>
<td>((pulmonary* or respiratory*) NEAR rehabilitation*):ti,ab</td>
<td>1672</td>
</tr>
<tr>
<td>#13</td>
<td>exercis*:ti,ab</td>
<td>17878</td>
</tr>
<tr>
<td>#14</td>
<td>#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13</td>
<td>20065</td>
</tr>
<tr>
<td>#15</td>
<td>#4 AND #14</td>
<td>2458</td>
</tr>
<tr>
<td>#16</td>
<td>INREGISTER</td>
<td>41266</td>
</tr>
<tr>
<td>#17</td>
<td>#15 AND #16</td>
<td>1525</td>
</tr>
</tbody>
</table>
### Search line  | Search term                                                                 | Results  |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>exp Asthma/</td>
<td>122606</td>
</tr>
<tr>
<td>2</td>
<td>asthma$.ti,ab.</td>
<td>148172</td>
</tr>
<tr>
<td>3</td>
<td>1 or 2</td>
<td>168766</td>
</tr>
<tr>
<td>4</td>
<td>Physical Therapy Modalities/</td>
<td>34905</td>
</tr>
<tr>
<td>5</td>
<td>exp Physical Fitness/</td>
<td>27266</td>
</tr>
<tr>
<td>6</td>
<td>exp Physical endurance/</td>
<td>31715</td>
</tr>
<tr>
<td>7</td>
<td>exp Exercise Therapy/</td>
<td>45952</td>
</tr>
<tr>
<td>8</td>
<td>Physical Exertion/</td>
<td>55760</td>
</tr>
<tr>
<td>9</td>
<td>exp Exercise Test/</td>
<td>61458</td>
</tr>
<tr>
<td>10</td>
<td>((pulmonary or respiratory) adj3 rehabilitation$).ti,ab.</td>
<td>3726</td>
</tr>
<tr>
<td>11</td>
<td>exercis$.ti,ab.</td>
<td>271789</td>
</tr>
<tr>
<td>12</td>
<td>or/4-11</td>
<td>389346</td>
</tr>
<tr>
<td>13</td>
<td>3 and 12</td>
<td>6413</td>
</tr>
<tr>
<td>14</td>
<td>(controlled clinical trial or randomized controlled trial).pt.</td>
<td>569497</td>
</tr>
<tr>
<td>15</td>
<td>(randomized or randomised).ab,ti.</td>
<td>568250</td>
</tr>
<tr>
<td>16</td>
<td>placebo.ab,ti.</td>
<td>202688</td>
</tr>
<tr>
<td>17</td>
<td>randomly.ab,ti.</td>
<td>310831</td>
</tr>
<tr>
<td>18</td>
<td>trial.ab,ti.</td>
<td>540911</td>
</tr>
<tr>
<td>19</td>
<td>groups.ab,ti.</td>
<td>1932345</td>
</tr>
<tr>
<td>20</td>
<td>or/14-19</td>
<td>2839965</td>
</tr>
<tr>
<td>21</td>
<td>Animals/</td>
<td>6397008</td>
</tr>
<tr>
<td>22</td>
<td>Humans/</td>
<td>17705974</td>
</tr>
<tr>
<td>23</td>
<td>21 not (21 and 22)</td>
<td>4543215</td>
</tr>
<tr>
<td>24</td>
<td>20 not 23</td>
<td>2413463</td>
</tr>
<tr>
<td>25</td>
<td>13 and 24</td>
<td>1840</td>
</tr>
</tbody>
</table>
CONTRIBUTIONS OF AUTHORS

CR Osadnik was responsible for study conception. CR Osadnik, VM McDonald, and AE Holland all contributed equally to the methodological design, preparation and write-up of all aspects of the protocol.

Contributions of editorial team

Rebecca Fortescue (Co-ordinating Editor) edited the protocol; advised on methodology; approved the protocol prior to publication.

Chris Cates (Co-ordinating Editor) checked the planned methods.

Emma Dennett (Managing Editor) co-ordinated the editorial process; advised on content; edited the protocol.

Emma Jackson (Assistant Managing Editor) conducted peer review; edited the references.

Elizabeth Stovold (Information Specialist) designed the search strategy; arranged for peer review of the search strategy.

DECLARATIONS OF INTEREST

CR Osadnik was recipient of a Lung Foundation Australia/Boehringer Ingelheim COPD Research Fellowship during 2016 to 2018 (unrelated to the present work).

VM McDonald has participated in educational symposia funded by GlaxoSmithKline, AstraZeneca and Menarini and has participated on advisory boards for GlaxoSmithKline, Novartis, AstraZeneca and Menarini (unrelated to the present work).

AE Holland has received fees from AstraZeneca and Boehringer Ingelheim for non-promotional speaking engagements (unrelated to the present work).

To the best of all authors’ knowledge, at the time of submitting this work, none of the named entities have any financial interest in the findings of this review and do not manufacture any such intervention or competing product(s).

SOURCES OF SUPPORT

Internal sources

• Monash University, Australia.
  Salary
• La Trobe University and Alfred Health, Australia.
  Salary
• The University of Newcastle, Australia.
  Salary

External sources

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