Cochrane Library

Cochrane Database of Systematic Reviews

Exercise versus airway clearance techniques for people with cystic fibrosis (Protocol)

Patterson KD, Walsh A, McCormack P, Southern KW

Patterson KD, Walsh A, McCormack P, Southern KW.
Exercise versus airway clearance techniques for people with cystic fibrosis.
Cochrane Database of Systematic Reviews 2019, Issue 3. Art. No.: CD013285.
DOI: 10.1002/14651858.CD013285.

www.cochranelibrary.com

TABLE OF CONTENTS

[Intervention Protocol]

Exercise versus airway clearance techniques for people with cystic fibrosis

Katie D Patterson[1], Adam Walsh[2], Pamela McCormack[3], Kevin W Southern[4]

[1]Department of Respiratory Paediatrics, Royal Liverpool and Broadgreen University Hospitals NHS Trust, Liverpool, UK. [2]Physiotherapy Department, Alder Hey Children's NHS Foundation Trust, Liverpool, UK. [3]Department of Respiratory Physiotherapy, Alder Hey Children's NHS Foundation Trust, Liverpool, UK. [4]Department of Women's and Children's Health, University of Liverpool, Liverpool, UK

Contact address: Katie D Patterson, Department of Respiratory Paediatrics, Royal Liverpool and Broadgreen University Hospitals NHS Trust, Royal Liverpool University Hospital, Prescot Street, Liverpool, L7 8XP, UK. katiepatterson.doctors@gmail.com.

Editorial group: Cochrane Cystic Fibrosis and Genetic Disorders Group.
Publication status and date: New, published in Issue 3, 2019.

Citation: Patterson KD, Walsh A, McCormack P, Southern KW. Exercise versus airway clearance techniques for people with cystic fibrosis. *Cochrane Database of Systematic Reviews* 2019, Issue 3. Art. No.: CD013285. DOI: 10.1002/14651858.CD013285.

ABSTRACT

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

To compare the effect of exercise compared to other ACTs for improving respiratory function and other clinical outcomes in people with CF and to assess the potential adverse effects associated with this method.

BACKGROUND

Description of the condition

Cystic fibrosis (CF) is a genetic condition inherited in an autosomal recessive fashion (when two mutated genes are inherited, one from each parent). It is a multisystem disorder predominantly affecting the respiratory, gastrointestinal, endocrine and reproductive systems. The condition is more prevalent in populations of Northern European descent (Farrell 2018), with an incidence of one in every 2381 live births (Farrell 2008).

CF is the result of a mutation in the cystic fibrosis transmembrane conductance regulator gene (CFTR) which leads to poorly functioning exocrine glands and reduced ion transport across epithelia, resulting in reduced airway surface liquid and a build up of copious mucus. These viscous secretions cause inflammation and irreversible damage to the airway epithelia, which in turn leads to bronchiectasis which then progresses to respiratory failure and is the reason for CF being life-limiting (Koch 1993).

With recent innovations in immunomodulator therapy and potentiators such as ivacaftor, which demonstrated absolute improvement in forced expiratory volume in one second (FEV_1) and decreased number of pulmonary exacerbations in people with the G551D mutation (Skilton 2019), mortality rates have decreased. The current median survival is 52 years in males and 49 years in females (Keogh 2018). As the life expectancy of people with CF continues to rise, disease demographics have changed. Healthcare teams now face the challenge of maintaining health and optimising quality of life (QoL). This highlights the important contribution of exercise and physiotherapy in managing CF.

Description of the intervention

There is evidence from systematic reviews, including Cochrane Reviews, that exercise and airway clearance are important for maintaining respiratory health, even during early stages of the condition (Flume 2009).

There are many established airway clearance techniques (ACTs) that have been evaluated in Cochrane Reviews including manual techniques such as postural drainage and percussion (PD&P) (Main 2005); breathing techniques such as autogenic drainage (AD) (McCormack 2017) and the active cycle of breathing technique (ACBT) (Mckoy 2016); oscillating devices (Morrison 2017) and use of positive expiratory pressure (PEP) devices (McIlwaine 2015). There are other interventions that train respiratory muscles (Hilton 2018; Irons 2016), but since the effects of respiratory muscle training are above the scope of this review these will not be comparator interventions in this review. To date, the evidence surrounding the use of exercise to aid secretion clearance has not been assessed.

It has been shown that habitual physical activity and exercise decrease pulmonary exacerbations, hospitalisations and improve physical function, endurance, energy level and QoL in both children and adults with the disease (Boas 1997; Cerny 2013; LeBlanc 2014; Rand 2012; Radtke 2017; Shoemaker 2008; Wheatley 2011). Increasing levels of exercise and physical activity have also been associated with a slower rate of decline in lung function (Cox 2018; Schneiderman 2014).

Habitual physical activity has been defined as bodily movement produced regularly by the contraction of skeletal muscles that results in a substantial increase over resting energy expenditure (Pescatello 2014). This should be differentiated from exercise which is planned, structured and repetitive bodily movement performed to improve or maintain one or more components of physical fitness (Pescatello 2014). Within exercise there are also different subgroups including aerobic exercise, anaerobic exercise, resistance, strength, balance and flexibility. For the purpose of this review we will be looking to assess the evidence surrounding all types of exercise mentioned as a form of airway clearance for people with CF. This will not be inclusive of respiratory muscle training due to the similarities and overlap between this and traditional ACT.

How the intervention might work

Exercise is thought to promote clearance of mucus in a multimechanistic way including, mechanical vibration, hyperventilation, coughing and changing the viscosity of sputum (Hebestreit 2001; Radtke 2017; Wilson 2019). This increased mucus clearance leads to the removal of infected secretions within the airways, reducing the release of inflammatory cytokines which cause direct effect and damage to the airway epithelia.

In comparison to routine ACTs, exercise has been shown to increase aerobic capacity, the level of activity (Selvadurai 2002) and potentially train the muscles of respiration (Dassios 2013; Hilton 2018). Aerobic capacity is thought to be one of the best predictors of survival for people with CF (Gruber 2014). Exercise capacity and participation in physical training in people with CF have been related to improved posture, bone density (Hind 2008; Sawyer 2004), mental health, QoL (Klijn 2004) and also to a reduction in the number of antibiotic days (Urquhart 2012); and so there are additional benefits to prescribing this form of airway clearance.

Treadmill exercise improves mucus clearance mechanisms in CF by increasing peak expiratory flow (PEF) and reducing sputum mechanical impedance (Dwyer 2011). Theoretically, varying breath volumes during exercise and through vigorous activity produces shearing forces which enhance mucociliary clearance. This facilitates the removal of secretions, improves ventilation and reduces inflammation in the lungs, thus limiting damage to airways.

Why it is important to do this review

Other Cochrane Reviews have been published demonstrating non-superiority between other forms of ACTs such as AD (McCormack 2017), oscillatory devices (Morrison 2017), ACBT (Mckoy 2016), PEP (McIlwaine 2015) and conventional chest physiotherapy (Main 2005). As non-superiority exists, there is no globally agreed definitive treatment strategy for ACTs and their prescription.

Currently, aerobic exercise is recommended for people with CF as an adjunctive therapy for airway clearance (Flume 2009), but not prescribed for this purpose alone. A recent Australian survey, however, showed that 44% of people with CF are using exercise as a substitute for traditional ACTs, suggesting a potential preference for this mode of therapy (Ward 2019). In addition, participants using exercise as a substitute for other ACTs were found to have a significantly higher FEV_1 (% predicted), lower perceived severity of respiratory disease and lower sputum load than other participants (Ward 2019).

A key research question identified from people with CF, their caregivers and clinicians in a priority setting exercise with the James Lind Alliance (JLA), is whether exercise can be used to replace airway clearance in CF (Rowbotham 2018). Adults with CF report spending an average of 108 minutes on treatment and activities each day, the majority of that time performing airway clearance and exercise (Sawicki 2009). It is important that we evaluate the evidence in order to help reduce the large treatment burden imposed on people with CF. It is important to highlight there is a range of evidence available from different sources. In this review, we will be summarising the high-quality evidence available from randomised controlled trials (RCTs) or quasi-RCTs (including cross-over trials) that evaluate ACT and exercise in people with CF.

This review aims to address this gap in the literature. If exercise does prove to be as effective as other ACTs, it is a safe, easily accessible and cost-effective strategy to improve the respiratory health and QoL of people with CF (Williams 2013).

OBJECTIVES

To compare the effect of exercise compared to other ACTs for improving respiratory function and other clinical outcomes in people with CF and to assess the potential adverse effects associated with this method.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs or quasi-RCTs (including cross-over trials) that evaluate ACTs and exercise in people with CF.

We will exclude trials involving a single intervention (i.e. one exercise session). Although inhibition of luminal sodium conductance is thought to increase water content of mucus during exercise in the acute phase (Hebestreit 2001), this review is looking at the long-term effects of exercise on respiratory health and other outcomes for people with CF; therefore, trials where therapy is performed only once, are inappropriate for this review.

Types of participants

We will include children (over four years of age) and adults with CF with a diagnosis based on sweat testing (sweat chloride over 59 mmol/L), genetic testing or a combination of these. We will not have any restrictions based on disease severity or exacerbation status.

Types of interventions

This review will include trials that compare exercise to other recognised ACTs (as described below) either as a single technique or in combination.

Whilst a single exercise session has been reported to inhibit epithelial sodium channels and normalize transepithelial potential difference (Hebestreit 2001), the aim of this review is to establish whether exercise can replace chest physiotherapy, rather than explore the mechanism whereby exercise leads to improved mucociliary clearance. Benefits of exercise for airway clearance and to improve lung function, ventilation and aerobic capacity are likely to be evident after multiple treatment episodes (Cholewa 2012); therefore, only studies using ACT for at least two treatment episodes will be included.

Interventions of variable duration will be considered and separated according to term of intervention (e.g. up to 14 days, 15 days to 12 weeks, over 12 weeks).

Exercise

Exercise is an adjuvant to current methods and is thought to promote mechanical clearance of mucus through increasing minute ventilation and PEF (Dwyer 2011). This helps to slow lung function decline (Schneiderman 2014) and has been associated with improved survival (Hebestreit 2018; Nixon 1992). Various types of exercise can be beneficial including cardiovascular, strength and flexibility training and this review plans to take all types into account. Trials looking at planned, formal, intensity-specific exercise will be included. Those that look at physical activity in a more unstructured way with lower levels of intensity will be considered, but excluded if they are not completed on a regular basis.

PD&P

PD&P was introduced for managing CF in the 1950s and uses positioning, manual vibration and gravity to move mucus within the airways (Main 2005; Wilson 2019).

AD

This is a method of controlled breathing in the expiratory phase which helps move secretions from the smaller to larger airways (McCormack 2017). Secretions are cleared by adjusting the speed and depth of breathing according to where secretions are heard and felt by the individual. This can be performed independently without a device or a trained healthcare professional but requires commitment and training.

ACBT

This is characterised by a combination of relaxation and breathing control, thoracic expansion exercises with forced expiratory techniques (FET) to achieve mucociliary clearance (Mckoy 2016).

PEP

A PEP device is a mask or mouthpiece used to provide a back pressure to the airways during expiration (McIlwaine 2015). There is a valve within the device that increases resistance to expiratory airflow between 10 cm to 20 cm of water (H_2O). This stimulates mucociliary clearance by building up gas behind mucus via collateral ventilation, preventing small airway collapse through stenting of airways and temporarily increasing functional residual capacity (FRC) (Groth 1985). Hi-PEP uses full forced expiration against the PEP mask's expiratory resistor using pressures of between 40 cm to 140 cm of H_2O (Prasad 1993).

Oscillatory devices

There are two main types of oscillatory devices; oscillatory PEP (O-PEP) devices and those using external thoracic high frequency

chest wall oscillation (HFCWO). O-PEP devices include, but are not limited to, the RC-Cornet®, Flutter®, Acapella®, AerobiKA®, Quake® and intrapulmonary percussive ventilation (IPV). The PEP element of these therapies increases FRC and augments collateral ventilation (Groth 1985). These devices also generate intrathoracic oscillation through varying expiratory flow resistance during exhalation. This combined action helps to mobilize secretions by reducing sputum viscosity and creating small bursts of air that move secretions centrally and facilitating expectoration (McIlwaine 2006). HFCWO uses an inflatable garment that covers the chest and is attached to an air pulse-generating compressor, which rapidly inflates and deflates the garment producing oscillations to manipulate the chest wall. It is proposed that HFCWO enhances mucociliary transport by creating a cough-like expiratory flow bias that shears mucus from the airway walls by enhancing ciliary beat frequency (Hansen 1994) and by altering the rheological properties of mucus (Dasgupta 1998).

Types of outcome measures

Primary outcomes

1. Lung function
   i) FEV_1 (per cent (%) predicted) absolute change from baseline values and final value
   ii) FEV_1 (L) absolute change from baseline values and final value
2. 2. Exercise capacity
   i) peak oxygen uptake (VO_2 Peak) in L, mL/kg body weight or fat-free mass or as % predicted (Hebestreit 2015)
   ii) maximal work rate (Wpeak) (Hebestreit 2015)
   iii) any validated field test (e.g. six-minute walk test (m), modified 10-m shuttle test (m))
3. 3. QoL (self-reported)
   i) Cystic Fibrosis Questionnaire-Revised (CFQ-R) (Quittner 2009)
   ii) Cystic Fibrosis Quality of Life Questionnaire (CF-QoL) (Gee 2000)
   iii) Chronic Respiratory Disease Questionnaire (CRQ) (Guyatt 1987)
   iv) any other validated QoL scale (e.g. NHP, SF-36)

Secondary outcomes

1. Adverse effects (related to exercise and exercise testing)
2. Lung Function
   i) forced vital capacity (FVC) % predicted or litres (L)
   ii) mid-forced expiratory flow ($FEF_{25–75}$)
   iii) lung clearance index (LCI)
3. Participant preference
4. Adherence
   i) electronic data capture
   ii) participant diary
5. Sputum weight
   i) wet weight (g)
   ii) dry weight (g)
6. Hospital admissions due to exacerbation as defined by (Rosenfeld 2001)
   i) number of hospital admissions
   ii) duration of hospital admission
7. Need for extra antibiotics (days)
   i) oral
   ii) intravenous (IV)
   iii) inhaled or nebulised

Search methods for identification of studies

We will search for all relevant published and unpublished trials without restrictions on language, year or publication status.

Electronic searches

The Cochrane Cystic Fibrosis and Genetic Disorders Group's Information Specialist will conduct a systematic search of the Group's Cystic Fibrosis Trials Register for relevant trials using the following terms: 'exercise' and 'airway clearance techniques'.
The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the *Cochrane Library*), weekly searches of MEDLINE, a search of Embase to 1995 and the prospective handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching the abstract books of three major CF conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. For full details of all searching activities for the register, please see the relevant section of the Cochrane Cystic Fibrosis and Genetic Disorders Group's website.
We will search the World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch) and ClinicalTrials.gov (www.clinicaltrials.gov). The search strategies for these online databases are presented in the appendices (Appendix 1).

Searching other resources

We will contact experts and organisations in the field to obtain additional information on relevant trials.

Data collection and analysis

Selection of studies

Two authors (KP and AW) will independently review all citations and abstracts retrieved, using the search criteria above to determine which papers are eligible for inclusion. They will then review the full text articles. If any conflict arises, they will consult a third author (PM) to review trials for eligibility.

Data extraction and management

Two authors (KP and AW) will independently extract data using data extraction forms specifically developed for this purpose. The extracted data will include the number of participants, participant characteristics, trial design (type of randomisation, allocation and concealment), details of the intervention (type of exercise, frequency, duration of session, compliance) and outcome measures. If data are incomplete, the review authors will contact trial investigators to collect original data for inclusion.

The authors will use Covidence to manage these data (Covidence) and will compile and analyse the data using the Cochrane software (RevMan 2014). The authors will group the results based on time (i.e. up to 14 days, 15 days to 12 weeks, over 12 weeks), but they will not consider single treatment interventions as it is unlikely that a single treatment will have any long-term effect on any measured outcome. They plan to present results separately for each comparison of the different ACTs, e.g. exercise versus PEP, exercise versus ACBT, etc. They plan to present trials in participants hospitalised as inpatients separately to long-term trials in those who are clinically stable.

Assessment of risk of bias in included studies

Two authors (KP and AW) will independently assess the included trials for risk of bias using the Cochrane risk of bias tool (Higgins 2011a). This tool is a domain-based evaluation in which critical assessments are made separately for six different domains (generation of sequence, concealment of allocation, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting and other potential threats to validity). They will grade each trial as low risk of bias, unclear risk of bias or high risk of bias for each domain. A third author (PM), who is a content expert, will resolve any disagreements.

Measures of treatment effect

For continuous outcomes (FEV_1, exercise capacity, QoL, adherence, FVC, $FEF_{25–75}$, LCI, sputum weight, duration of hospital admissions, number of antibiotic days) the authors will report the mean difference (MD) and 95% confidence intervals (CIs) if trials use the same unit of measurement, otherwise they will use the standardised mean difference (SMD). In the case of binary outcomes or dichotomous data (e.g. participant preference, number of participants admitted to hospital) the authors will combine the data from the studies using risk ratios (RR) and 95% CIs (Deeks 2011).

Unit of analysis issues

The review authors will consider the level at which the randomisation occurred in the trials (Deeks 2011). They will not include cluster RCTs, as they do not consider this design appropriate for exercise as an intervention.

For RCTs with a cross-over design, i.e. where all participants receive all the interventions and act as their own control, the effects of one intervention can often persist into the next treatment period interfering with the effects of the subsequent intervention if there is not a significant washout period. This is known as the 'carry-over effect'. When analysing such trials the authors plan to use the methods suggested by Elbourne (Elbourne 2002). In general, the reporting of data from cross-over trials is variable with limited data published that are required for a paired analysis (Higgins 2011b). If the requisite data are not available, the authors plan to use data from the first arm of the trial and treat it as a parallel trial. However, this is a conservative approach and the CIs are likely to be wider, potentially disguising clinically important information and underestimating the treatment effect (Higgins 2011b).

For trials that have multiple treatment groups, the review authors will combine all relevant control groups into a single control group to create a single pair-wise comparison to decrease the unit-of-analysis error.

Dealing with missing data

In instances of missing data, the review authors will contact the trial authors directly. Where data remain unavailable, the review authors will list the trial under 'Studies awaiting classification' and will include the trial in future updates, should relevant data become available.

Assessment of heterogeneity

For trials with similar interventions and participants, assessing similar outcomes, the review authors will perform a meta-analysis to pool the data and depicted this in a forest plot. They will assess heterogeneity using the Chi^2 test (which assesses whether observed differences in results are compatible with chance alone) and the I^2 statistic (which describes the percentage of total variation across trials due to heterogeneity rather than chance) (Higgins 2003). The values of I^2 lie between 0% and 100%. The authors will categorise heterogeneity according to the *Cochrane Handbook for Systematic Reviews of Interventions* as below (Deeks 2011).

- 0% to 40% as little heterogeneity
- 30% to 60% as moderate heterogeneity
- 50% to 90% as substantial heterogeneity
- over 75% as considerable heterogeneity

Using the null hypothesis of homogeneity, the review authors will deem a P value of 0.1 to be significant.

Assessment of reporting biases

If the authors identify a sufficient number of trials (i.e. 10 trials) of different sizes for the review, they plan on creating funnel plots in RevMan to assess for reporting bias. They will create these by plotting the standard error of the intervention effect, rather than the total sample size, on the y-axis (Sterne 2001). Funnel plots are a visual aid to assess treatment effect against precision. If the trial is highly precise, the points will lie close to the average, if precision is lower, the points will lie either side of the average. If asymmetry or deviation of plot exists, the authors will consider the possibility of publication bias, as well as selection bias, poor methodological quality, true heterogeneity and chance (Egger 1997; Sterne 2000; Sterne 2011).

The review authors will also assess outcome reporting bias. This is when results for outcomes listed in the methodology are not published, giving rise to misleading results (Pocock 1987; Tannock 1996). To reduce this type of bias, for each included trial, the authors will compare the methods section to the results section to ensure all variables are reported. The review authors will also attempt to identify the relevant trial protocols, e.g. from online trial registries.

Data synthesis

The review authors will analyse data using the fixed-effect model (Mantel-Haenszel methods) programmed into RevMan 5.3 (Mantel 1959; Greenland 1985). If at least substantial heterogeneity (I^2 value over 50%) exists between identified trials, they will use the random-effects model for analysis (Deeks 2011).

Subgroup analysis and investigation of heterogeneity

If the review includes sufficient data, they will investigate heterogeneity by performing a separate subgroup analysis based on the participant characteristics:

1. age (four years to 17 years compared with adults);
2. gender;
3. disease severity based on lung function (FEV_1 % predicted, over 90%, 50% to 89%, below 50%).

Sensitivity analysis

If the review authors are able to combine the data from multiple trials, they will test the robustness of the results by performing a sensitivity analysis, presented in the form of a summary table. They will analyse the effect of trial design (parallel versus cross-over), allocation concealment (high risk of bias versus low risk of bias) and loss to follow-up (high risk of bias versus low risk of bias) on the results.

Summary of findings tables

The review authors will determine and rate the quality of evidence for each outcome by using the GRADE approach (Schünemann 2011a; Schünemann 2011b). This will be presented in the summary of findings (SoF) tables (one for each comparison). The outcomes selected for individual comparison are those that the authors feel are patient-important outcomes.

- Pulmonary function - absolute change FEV_1 % predicted
- Exercise capacity - change in VO_2 peak during maximal exercise (mL/min per kg body weight)
- QoL - CFQ-R
- Adverse effects
- Participant preference
- Adherence
- Need for any extra antibiotics (oral, IV, inhaled or nebulised) in days

ACKNOWLEDGEMENTS

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group. 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.

REFERENCES

Additional references

Boas 1997
Boas SR. Exercise recommendations for individuals with cystic fibrosis. *Journal of Sports Medicine* 1997;**24**(1):17–37.

Cerny 2013
Cerny F. Exercise and cystic fibrosis (CF) 2.0. *Pediatric Exercise Science* 2013;**25**(4):616–23.

Cholewa 2012
Cholewa JM, Paolone VJ. Influence of exercise on airway epithelia in cystic fibrosis: a review. *Medicine and Science in Sports and Exercise* 2012;**44**(7):1219–26.

Covidence [Computer program]
Veritas Health Innovation. Covidence. Melbourne, Australia: Veritas Health Innovation, accessed 10 February 2019.

Cox 2018
Cox NS, Alison JA, Button BM, Wilson JW, Morton JM, Holland AE. Accumulating physical activity in at least 10-minute bouts predicts better lung function

after 3-years in adults with cystic fibrosis. *European Respiratory Journal* 2018;**4**(2):00095–2017. DOI: 10.1183/23120541.00095-2017

Dasgupta 1998
Dasgupta B, Brown NE, King M. Effects of sputum oscillations and rhDNase in vitro: a combined approach to treat cystic fibrosis lung disease. *Pediatric Pulmonology* 1998;**26**(4):250–5.

Dassios 2013
Dassios T, Katelari A, Doudounakis S, Dimitriou G. Aerobic exercise and respiratory muscle strength in patients with cystic fibrosis. *Respiratory Medicine* 2013;**107**(5):684–90.

Deeks 2011
Deeks JJ, Higgins JPT, Altman DG on behalf of the Cochrane Statistical Methods Group, editor(s). Chapter 9: Analysing data and undertaking meta-analysis. In: Higgins JPT, Green S editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Dwyer 2011
Dwyer TJ, Alison JA, McKeough ZJ, Daviskas E, Bye PT. Effects of exercise on respiratory flow and sputum properties in patients with cystic fibrosis. *Chest* 2011;**139**(4):870–7.

Egger 1997
Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629–34.

Elbourne 2002
Elbourne DR, Altman DG, Higgins JPT, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;**31**(1):140–9.

Farrell 2008
Farrell PM. The prevalence of cystic fibrosis in the European Union. *Journal of Cystic Fibrosis* 2008;**7**(5):450–3.

Farrell 2018
Farrell P, Férec C, Macek M, Frischer T, Renner S, Riss K, et al. Estimating the age of p.(Phe508del) with family studies of geographically distinct European populations and the early spread of cystic fibrosis. *European Journal of Human Genetics* 2018;**26**(12):1832–9. DOI: 10.1038/s41431-018-0234-z

Flume 2009
Flume PA, Robinson KA, O´ Sullivan BP, Finder JD, Vender RL, Willey-Courand DB, et al. Cystic fibrosis pulmonary guidelines: airway clearance therapies. *Respiratory Care* 2009;**54**(4):522–37.

Gee 2000
Gee L, Abbott J, Conway S, Etherington C, Webb A. Development of a disease specific health related quality of life measure for adults and adolescents with cystic fibrosis. *Thorax* 2000;**55**(11):946–54.

Greenland 1985
Greenland S, Robins JM. Estimation of a common effect parameter from sparse follow-up data. *Biometrics* 1985;**41**(1):55–68.

Groth 1985
Groth S, Stafanger G, Dirksen H, Andersen JB, Falk M, Kelstrup M. Positive expiratory pressure (PEP-mask) physiotherapy improves ventilation and reduces volume of trapped gas in cystic fibrosis. *Bulletin Européen de Physiopathologie Respiratoire* 1995;**21**(4):339–43.

Gruber 2014
Gruber W, Orenstein DM, Braumann KM, Beneke R. Interval exercise training in cystic fibrosis - effects on exercise capacity in severely affected adults. *Journal of Cystic Fibrosis* 2014;**13**(1):86–91.

Guyatt 1987
Guyatt G, Berman L, Townsend M, Pugsley S, Chambers L. A measure of quality of life for clinical trials in chronic lung disease. *Thorax* 1987;**42**(10):773–8.

Hansen 1994
Hansen LG, Warwick WJ, Hansen KL. Mucus transport mechanisms in relation to the effect of high frequency chest compression (HFCC) on mucus clearance. *Pediatric Pulmonology* 1994;**17**(2):113–8.

Hebestreit 2001
Hebestreit A, Kersting U, Basler B, Jeschke R, Hebestreit H. Exercise inhibits epithelial sodium channels in patients with cystic fibrosis. *American Journal of Respiratory Critical Care Medicine* 2001;**164**(3):443–6.

Hebestreit 2015
Hebestreit H, Arets HG, Aurora P, Boas S, Cerny F, Hulzebos EH, et al. Statement on exercise testing in cystic fibrosis. *Respiration* 2015;**90**(4):332–51.

Hebestreit 2018
Hebestreit H, Lands LC, Alarie N, Schaeff J, Karila C, Orenstein DM, et al. Effects of a partially supervised conditioning programme in cystic fibrosis: an international multi-centre randomised controlled trial (ACTIVATE-CF): study protocol. *BMC Pulmonary Medicine* 2018;**18**(1):31.

Higgins 2003
Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557–60.

Higgins 2011a
Higgins JPT, Altman DG, Sterne JAC on behalf of the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group, editor(s). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S editor(s). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2011b
Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins

JPT, Green S editor(s). Cochrane Handbook of Systematic Reviews of Interventions. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hilton 2018
Hilton N, Solis-Moya A. Respiratory muscle training for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2018, Issue 5. DOI: 10.1002/14651858.CD006112.pub4

Hind 2008
Hind K, Truscott JG, Conway SP. Exercise during childhood and adolescence: a prophylaxis against cystic fibrosis-related low bone mineral density? Exercise for bone health in children with cystic fibrosis. *Journal of Cystic Fibrosis* 2008; **7**(4):270–6.

Irons 2016
Irons JY, Petocz P, Kenny DT, Chang AB. Singing as an adjunct therapy for children and adults with cystic fibrosis. *Cochrane Database of Systematic Reviews* 2016, Issue 9. DOI: 10.1002/14651858.CD008036.pub4

Keogh 2018
Keogh RH, Szczesniak R, Taylor-Robinson D, Bilton D. Up-to-date and projected estimates of survival for people with cystic fibrosis using baseline characteristics: A longitudinal study using UK patient registry data. *Journal of Cystic Fibrosis* 2018;**17**(2):218-27.

Klijn 2004
Klijn PH, Oudshoorn A, van der Ent CK, van der Net J, Kimpen JL, Helders PJ. Effects of anaerobic training in children with cystic fibrosis: a randomized controlled study. *Chest* 2004;**125**(4):1299–305.

Koch 1993
Koch C, Høiby N. Pathogenesis of cystic fibrosis. *The Lancet* 1993;**341**(8852):1065–9.

LeBlanc 2014
LeBlanc CM, Lands LC. Can I play?. *Pediatric Annals* 2014;**43**(12):316–24.

Main 2005
Main E, Prasad A, van der Schans CP. Conventional chest physiotherapy compared to other airway clearance techniques for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2005, Issue 1. DOI: 10.1002/14651858.CD002011.pub2

Mantel 1959
Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *Journal of the National Cancer Institute* 1959;**22**(4):719–48.

McCormack 2017
McCormack P, Burnham P, Southern KW. Autogenic drainage for airway clearance in cystic fibrosis. *Cochrane Database of Systematic Reviews* 2017, Issue 10. DOI: 10.1002/14651858.CD009595.pub2

McIlwaine 2006
McIlwaine M. Physiotherapy and airway clearance techniques and devices. *Paediatric Respiratory Reviews* 2006; **7 Suppl 1**:S220–2.

McIlwaine 2015
McIlwaine M, Button B, Dwan K. Positive expiratory pressure physiotherapy for airway clearance in people with cystic fibrosis. *Cochrane Database of Systematic Reviews* 2015, Issue 6. DOI: 10.1002/14651858.CD003147.pub4

Mckoy 2016
Mckoy NA, Wilson LM, Saldanha IJ, Odelola OA, Robinson KA. Active cycle of breathing technique for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2016, Issue 7. DOI: 10.1002/14651858.CD007862.pub3

Morrison 2017
Morrison L, Milroy S. Oscillating devices for airway clearance in people with cystic fibrosis. *Cochrane Database of Systematic Reviews* 2017, Issue 5. DOI: 10.1002/14651858.CD006842.pub4

Nixon 1992
Nixon PA, Orenstein DM, Kelsey SF, Doershuk CF. The prognostic value of exercise testing in patients with cystic fibrosis. *New England Journal of Medicine* 1992;**327**(25): 1785–8.

Pescatello 2014
Pescatello LS, Arena R, Riebe D, Thompson PD. ACSM's guidelines for exercise testing and prescription 9th edition. *Journal of Canadian Chiropractic Association* 2014;**58**(3): 328.

Pocock 1987
Pocock S, Hughes MD, Lee RJ. Statistical problems in the reporting of clinical trials. A survey of three medical journals. *New England Journal of Medicine* 1987;**317**(7): 426–32.

Prasad 1993
Prasad SA. Current concepts in physiotherapy. *Journal of the Royal Society of Medicine* 1993;**86**(20):23–9.

Quittner 2009
Quittner AL, Modi AC, Wainwright C, Otto K, Kirihara J, Montgomery AB. Determination of the minimal clinically important difference scores for the Cystic Fibrosis Questionnaire-Revised respiratory symptom scale in two populations of patients with cystic fibrosis and chronic Pseudomonas aeruginosa airway infection. *Chest* 2009;**135** (6):1610–8.

Radtke 2017
Radtke T, Nevitt SJ, Hebestreit H, Kriemler S. Physical exercise training for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2017, Issue 11. DOI: 10.1002/14651858.CD002768.pub4

Rand 2012
Rand S, Prasad SA. Exercise as part of a cystic fibrosis therapeutic routine. *Expert Review of Respiratory Medicine* 2012;**6**(3):341–52.

RevMan 2014 [Computer program]
Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rosenfeld 2001
Rosenfeld M, Emerson J, Williams-Warren J, Pepe M, Smith A, Montgomery B, et al. Defining a pulmonary exacerbation in cystic fibrosis. *Journal of Pediatrics* 2001; **139**(3):359–65.

Rowbotham 2018
Rowbotham NJ, Smith S, Leighton PA, Rayner O, Gathercole K, Elliott ZC, et al. The top 10 research priorities in cystic fibrosis developed by a partnership between people with CF and healthcare providers. *Thorax* 2018;**73**(4):388–90.

Sawicki 2009
Sawicki GS, Sellers DE, Robinson WM. High treatment burden in adults with cystic fibrosis: challenges to disease self-management. *Journal of Cystic Fibrosis* 2009;**8**(2):91–6.

Sawyer 2004
Sawyer MG, Reynolds KE, Couper JJ, French DJ, Kennedy D, Martin J, et al. Health-related quality of life of children and adolescents with chronic illness - a two year prospective study. *Quality of Life Research* 2004;**13**(7):1309-19.

Schneiderman 2014
Schneiderman JE, Wilkes DL, Atenafu EG, Nguyen T, Wells GD, Alarie N, et al. Longitudinal relationship between physical activity and lung health in patients with cystic fibrosis. *European Respiratory Journal* 2014;**43**(3): 817–23.

Schünemann 2011a
Schünemann HJ, Oxman AD, Higgins JPT, Vist GE, Glasziou P, Guyatt GH on behalf of the Cochrane Applicability and Recommendations Methods Group and the Cochrane Statistical Methods Group. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JPT, Green S editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Schünemann 2011b
Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, et al on behalf of the Cochrane Applicability and Recommendations Methods Group and the Cochrane Statistical Methods Group. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Green S editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Selvadurai 2002
Selvadurai HC, Blimkie CJ, Meyers N, Mellis CM, Cooper PJ, Van Asperen PP. Randomized controlled study of in-hospital exercise training programs in children with cystic fibrosis. *Pediatric Pulmonology* 2002;**33**(3):194–200.

Shoemaker 2008
Shoemaker MJ, Hurt H, Arndt L. The evidence regarding exercise training in the management of cystic fibrosis: a systematic review. *Cardiopulmonary Physical Therapy Journal* 2008;**19**(3):75–83.

Skilton 2019
Skilton M, Krishan A, Patel S, Sinha IP, Southern KW. Potentiators (specific therapies for class III and IV mutations) for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2019, Issue 1. DOI: 10.1002/14651858.CD009841.pub3

Sterne 2000
Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: Power of statistical tests and prevalence in the literature. *Journal of Clinical Epidemiology* 2000;**53**(11):1119–29.

Sterne 2001
Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: Guidelines on choice of axis. *Journal of Clinical Epidemiology* 2001;**54**(10):1046–55.

Sterne 2011
Sterne JAC, Egger M, Moher D on behalf of the Cochrane Bias Methods Group, editor(s). Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Tannock 1996
Tannock IF. False-positive results in clinical trials: multiple significance tests and the problem of unreported comparisons. *Journal of the National Cancer Institute* 1996; **88**(3-4):206–7.

Urquhart 2012
Urquhart D, Sell Z, Dhouieb E, Bell G, Oliver S, Black R, Tallis M. Effects of a supervised, outpatient exercise and physiotherapy programme in children with cystic fibrosis. *Pediatric Pulmonology* 2012;**47**(12):1235–41.

Ward 2019
Ward N, Stiller K, Holland AE, Australian Cystic Fibrosis Exercise Survey Group. Exercise is commonly used as a substitute for traditional airway clearance techniques by adults with cystic fibrosis in Australia: a survey. *Journal of Physiotherapy* 2019;**65**(1):43–50.

Wheatley 2011
Wheatley CM, Wilkins BW, Snyder EM. Exercise is medicine in cystic fibrosis. *Exercise and Sports Sciences Reviews* 2011;**39**(3):155–60.

Williams 2013
Williams CA, Stevens D. Physical activity and exercise training in young people with cystic fibrosis: current recommendations and evidence. *Journal of Sport and Health Science* 2013;**2**(1):39–46.

Wilson 2019
Wilson LM, Morrison L, Robinson KA. Airway clearance techniques for cystic fibrosis: an overview of Cochrane systematic reviews. *Cochrane Database of Systematic Reviews* 2019, Issue 1. DOI: 10.1002/14651858.CD011231.pub2

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Electronic search strategies

ClinicalTrials.gov (www.clinicaltrials.gov/)	RECRUITMENT STATUS: All studies CONDITION OR DISEASE: cystic fibrosis OTHER TERMS: Exercise AND (airway clearance OR oscillating devices OR postural drainage OR percussion OR active cycle OR positive expiratory pressure OR autogenic drainage)
WHO ICTRP (apps.who.int/trialsearch/Default.aspx)	Advanced search Recruitment status: ALL Search 1: Condition: cystic fibrosis AND Intervention: exercise AND airway clearance Search 2: Condition: cystic fibrosis AND Intervention: exercise AND oscillating devices Search 3: Condition: cystic fibrosis AND Intervention: exercise AND postural drainage Search 4 : Condition: cystic fibrosis AND Intervention: exercise AND percussion Search 5 : Condition: cystic fibrosis AND Intervention: exercise AND active cycle Search 6: Condition: cystic fibrosis AND Intervention: exercise AND positive expiratory pressure Search 7: Condition: cystic fibrosis AND Intervention: exercise AND autogenic drainage

CONTRIBUTIONS OF AUTHORS

Roles and responsibilities	
TASK	**WHO WILL UNDERTAKE THE TASK?**
Protocol stage: draft the protocol	**KP**
Review stage: select which trials to include (2 + 1 arbiter)	**KP and AW (PMC)**
Review stage: extract data from trials (2 people)	**KP and AW**
Review stage: enter data into RevMan	**KP**
Review stage: carry out the analysis	**KP, AW, PMC and KS**
Review stage: interpret the analysis	**KP, AW, PMC and KS**
Review stage: draft the final review	**KP**
Update stage: update the review	**KP, AW, PMC and KS**

DECLARATIONS OF INTEREST

All authors: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

This systematic review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group.