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Physical activity and exercise training in cystic fibrosis (Review)

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[Intervention Review]

Physical activity and exercise training in cystic fibrosis

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ABSTRACT

Background

Physical activity (including exercise) may form an important part of regular care for people with cystic fibrosis (CF). This is an update of a previously published review.

Objectives

To assess the effects of physical activity interventions on exercise capacity by peak oxygen uptake, lung function by forced expiratory volume in one second (FEV_1), health-related quality of life (HRQoL) and further important patient-relevant outcomes in people with cystic fibrosis (CF).

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register which comprises references identified from comprehensive electronic database searches and handsearches of relevant journals and abstract books of conference proceedings. The most recent search was on 3 March 2022. We also searched two ongoing trials registers: clinicaltrials.gov, most recently on 4 March 2022; and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), most recently on 16 March 2022.

Selection criteria

We included all randomised controlled trials (RCTs) and quasi-RCTs comparing physical activity interventions of any type and a minimum intervention duration of two weeks with conventional care (no physical activity intervention) in people with CF.

Data collection and analysis

Two review authors independently selected RCTs for inclusion, assessed methodological quality and extracted data. We assessed the certainty of the evidence using GRADE.

Main results

We included 24 parallel RCTs (875 participants). The number of participants in the studies ranged from nine to 117, with a wide range of disease severity. The studies' age demographics varied: in two studies, all participants were adults; in 13 studies, participants were 18 years and younger; in one study, participants were 15 years and older; in one study, participants were 12 years and older; and seven studies included all age ranges. The active training programme lasted up to and including six months in 14 studies, and longer than six months in the remaining 10 studies. Of the 24 included studies, seven implemented a follow-up period (when supervision was withdrawn, but participants were still allowed to exercise) ranging from one to 12 months. Studies employed differing levels of supervision: in 12 studies,

training was supervised; in 11 studies, it was partially supervised; and in one study, training was unsupervised. The quality of the included studies varied widely.

This Cochrane Review shows that, in studies with an active training programme lasting over six months in people with CF, physical activity probably has a positive effect on exercise capacity when compared to no physical activity (usual care) (mean difference (MD) 1.60, 95% confidence interval (CI) 0.16 to 3.05; 6 RCTs, 348 participants; moderate-certainty evidence). The magnitude of improvement in exercise capacity is interpreted as small, although study results were heterogeneous. Physical activity interventions may have no effect on lung function (forced expiratory volume in one second (FEV_1) % predicted) (MD 2.41, 95% CI −0.49 to 5.31; 6 RCTs, 367 participants), HRQoL physical functioning (MD 2.19, 95% CI −3.42 to 7.80; 4 RCTs, 247 participants) and HRQoL respiratory domain (MD −0.05, 95% CI −3.61 to 3.51; 4 RCTs, 251 participants) at six months and longer (low-certainty evidence). One study (117 participants) reported no differences between the physical activity and control groups in the number of participants experiencing a pulmonary exacerbation by six months (incidence rate ratio 1.28, 95% CI 0.85 to 1.94) or in the time to first exacerbation over 12 months (hazard ratio 1.34, 95% CI 0.65 to 2.80) (both high-certainty evidence); and no effects of physical activity on diabetic control (after 1 hour: MD −0.04 mmol/L, 95% CI −1.11 to 1.03; 67 participants; after 2 hours: MD −0.44 mmol/L, 95% CI −1.43 to 0.55; 81 participants; moderate-certainty evidence). We found no difference between groups in the number of adverse events over six months (odds ratio 6.22, 95% CI 0.72 to 53.40; 2 RCTs, 156 participants; low-certainty evidence).

For other time points (up to and including six months and during a follow-up period with no active intervention), the effects of physical activity versus control were similar to those reported for the outcomes above. However, only three out of seven studies adding a follow-up period with no active intervention (ranging between one and 12 months) reported on the primary outcomes of changes in exercise capacity and lung function, and one on HRQoL. These data must be interpreted with caution. Altogether, given the heterogeneity of effects across studies, the wide variation in study quality and lack of information on clinically meaningful changes for several outcome measures, we consider the overall certainty of evidence on the effects of physical activity interventions on exercise capacity, lung function and HRQoL to be low to moderate.

Authors' conclusions

Physical activity interventions for six months and longer likely improve exercise capacity when compared to no training (moderate-certainty evidence). Current evidence shows little or no effect on lung function and HRQoL (low-certainty evidence). Over recent decades, physical activity has gained increasing interest and is already part of multidisciplinary care offered to most people with CF. Adverse effects of physical activity appear rare and there is no reason to actively discourage regular physical activity and exercise. The benefits of including physical activity in an individual's regular care may be influenced by the type and duration of the activity programme as well as individual preferences for and barriers to physical activity. Further high-quality and sufficiently-sized studies are needed to comprehensively assess the benefits of physical activity and exercise in people with CF, particularly in the new era of CF medicine.

PLAIN LANGUAGE SUMMARY

Physical activity to improve exercise capacity in people with cystic fibrosis

Review question

We reviewed the evidence about whether physical activity interventions (including exercise) have any effect on exercise capacity, health-related quality of life and lung function in people with cystic fibrosis (CF). This is an update of a previously published review.

Background

CF affects many systems in the body, but mainly the lungs. It causes shortness of breath and limits the amount of exercise people with CF can tolerate. The progress of lung disease leads to a low ability to exercise and to physical inactivity, which in turn affects health and health-related quality of life. We looked for studies where people with CF engaged in a physical activity intervention (including endurance-type activities such as walking, jogging, swimming and cycling; or resistance training; or combinations of both) compared to a control group with no intervention (usual care).

Search date

The evidence is current to 3 March 2022.

Study characteristics

We included 24 studies (875 participants) in this review. The number of people in each study ranged from nine to 117. Some studies included only children, others only adults, and some both children and adults. The studies included people with a wide range of disease severity. The studies used differing levels of supervision in their active training programmes: in 12 studies, participants were supervised; in 11 studies, participants were partially supervised; and in one study, participants were not supervised at all. The active training programme lasted up to and including six months in 14 studies, and longer than six months in the remaining 10 studies. Of the 24 included studies, seven added on a follow-up period (when all participants reverted to usual care, but were still allowed to exercise if they wished). The quality of the included studies varied widely.

Key results

This systematic review shows that physical activity interventions for longer than six months probably improve exercise capacity in people with CF. When compared with no activity, physical activity interventions may make little or no difference to lung function and health-related quality of life.

The largest study included in this review (117 participants) reported:

- no differences between the physical activity and control groups in the number of pulmonary exacerbations (a flare up of disease) (high-certainty evidence);

- no differences in the time to the first flare up for 12 months (high-certainty evidence);

- no beneficial effects of physical activity on diabetic control after nine months (moderate-certainty evidence).

Two studies (156 participants) found no differences between groups in the number of reported adverse events (low-certainty evidence).

For active training programmes lasting up to and including six months, the effects were similar to the longer programmes.

Only three studies which added a follow-up period (of varying durations) reported data we could analyse on changes in exercise capacity and lung function; and only one reported on quality of life. These results must be interpreted with caution.

Overall and when compared to usual care (no intervention), physical activity and exercise training probably lead to slightly better exercise capacity, while they may have little or no effect on lung function and health-related quality of life in people with CF.

Certainty of the evidence

We included 24 studies. Given the differences in effects across studies, the wide variation in study quality and the lack of information on clinically meaningful changes for several outcome measures, we consider the overall certainty of the evidence on the effects of physical activity interventions on exercise capacity, lung function and health-related quality of life as low to moderate. We are uncertain about the effects we have seen and better-quality studies will likely change these findings.

Factors affecting our certainty included that, in five studies, the characteristics of some of the people taking part were different between groups at the start of the studies, despite people being put into the different treatment groups at random.

Also, when comparing physical activity interventions to no intervention, people will always know which group they are in. However, we do not think the fact that people knew which treatment they were receiving would affect the results for lung function, as long as the assessments were done properly. In contrast, some bias may be introduced when investigators assessing a person's exercise capacity know to which group the person belongs. Investigators tried to prevent the outcome assessors from knowing to which groups the participants belonged in 10 included studies.

Selective reporting of results may also be an issue, especially as most of the included studies were not listed in trial registries, where details of the outcomes are reported.

Summary of findings 1. Physical activity compared with no physical activity for cystic fibrosis

Physical activity compared with no physical activity for cystic fibrosis

Patient or population: adults and children with cystic fibrosis

Settings: at home or in hospital

Intervention: physical activity

Comparison: no physical activity (usual care)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Usual care	Physical activity				
Exercise capacity: change in VO_2 peak (mL/min per kg bodyweight) Active intervention: > 6 months	**VO_2 peak was 1.60 mL/min per kg bodyweight higher** in the physical activity group than in the control group (0.16 mL/min per kg bodyweight higher to 3.05 mL/min per kg bodyweight higher).		—	348 (6)	⊕⊕⊕⊖ **Moderate**[a,b]	P = 0.005 Sensitivity analysis which removed 1 small outlying study did not alter the results. Other time points: **Active intervention ≤ 6 months** 8 studies reported the effect of physical activity for periods of up to and including 6 months (MD 2.10 mL/min per kg bodyweight, 95% CI 0.06 to 4.13; n = 323; P = 0.04). There was a high level of heterogeneity in the results. **Follow-up (no active intervention)** This was reported by 3 out of 9 studies. VO_2 peak was higher in the physical activity versus control groups (MD 3.27 mL/min per kg bodyweight, 95% CI 1.37 to 5.18; n = 125; P < 0.001).

FEV_1 % predicted (change from baseline) Active intervention: > 6 months	**The mean change in FEV_1 % predicted was 2.41% higher** in the physical activity group than in the control group (0.49% lower to 5.31% higher).	—	367 (6)	⊕⊕⊖⊖ **Low**[a,c]	P = 0.1 Sensitivity analysis which removed 1 small outlying study with wide CIs changed the effect slightly towards a beneficial effect of physical activity (MD 1.71 % predicted, 95% CI 0.15 to 3.26; P = 0.02). Other time points: **Active intervention ≤ 6 months** 8 studies found no difference between the physical activity group and control group (MD 1.30 % predicted, 95% CI −3.01 to 5.61; n = 356; P = 0.56). **Follow-up (no active intervention)** 3/9 studies reported this outcome and found no difference between groups (MD 5.68 % predicted, 95% CI −1.88 to 13.23; n = 128; P = 0.14).
HRQoL: change in CFQ-R physical functioning domain score Active intervention: > 6 months	**The mean change in CFQ-R score was 2.19 points higher** in the physical activity group than in the control group (3.42 points lower to 7.80 points higher).	—	247 (4)	⊕⊕⊖⊖ **Low**[d]	P = 0.44 Other time points: **Active intervention ≤ 6 months** 6 studies reported that there was no difference in HRQoL CFQ-R scores between groups (MD 4.67, 95% CI −2.55 to 11.90; n = 217; P = 0.21). **Follow-up (no active intervention)** No studies reported CFQ-R after a period off training.
HRQoL: change in CFQ-R respiratory symptoms domain score Active intervention: > 6 months	**The mean change in CFQ-R score was 0.05 points lower** in the physical activity group than in the control group (3.61 points lower to 3.51 points higher).	—	251 (4)	⊕⊕⊖⊖ **Low**[d]	P = 0.98 Other time points: **Active intervention ≤ 6 months** 5 studies reported that there was no difference in HRQoL CFQ-R scores between groups (MD −1.87, 95% CI −5.66 to 1.92; n = 212; P = 0.33). **Follow-up (no active intervention)** No studies reported CFQ-R after a period off training.

Pulmonary exacerbations: number of exacerbations occurring in the study period Active intervention: 12 months	There was no difference in the number of pulmonary exacerbations between the physical activity and control group. The incidence rate ratio was 1.28 (95% CI 0.85 to 1.94).	—	117 (1)	⊕⊕⊕⊕ **High**	P = 0.24 There was also no difference in the time to first exacerbation between the groups, HR 1.34 (95% CI 0.65 to 2.80). Other time points: **Active intervention ≤ 6 months** 1 study reported no difference in the number of exacerbations between groups at the 6-month time point (incidence rate ratio 1.07, 95% CI 0.60 to 1.90), or in the time to first exacerbation (HR 1.34, 95% CI 0.65 to 2.80). **Follow-up (no active intervention)** No studies reported this outcome after a period off training.
Diabetic control: change in blood glucose levels at rest, at 60 and 120 minutes after a glucose ingestion (mmol/L) Active intervention: 9 months	There were no differences between the physical activity and control groups with regard to blood glucose. At rest: MD −0.16 mmol/L (95% CI −0.44 to 0.12) After 60 minutes: MD −0.04 mmol/L (95% CI −1.11 to 1.03) After 120 minutes: MD −0.44 mmol/L (95% CI −1.43 to 0.55)	—	91 (1)	⊕⊕⊕⊙ **Moderate**[e]	Participants included for this outcome did not have a diagnosis of CFRD on entry to the study. Other time points: **Active intervention ≤ 6 months** 1 study (n = 14, including 2 people with CFRD at study entry) assessed HbA1c, plasma glucose and insulin response to an oral glucose tolerance test. There was no difference in HbA1c (MD −0.00%, 95% CI −0.01 to 0.00). There was no difference in plasma glucose values between groups at any time point apart from at 120 minutes postglucose test when there was a significant difference favouring the exercise group (Beaudoin 2017). **Follow-up (no active intervention)** No studies reported this outcome after a period off training.
Adverse events: number of adverse events Active intervention: 12 months	1 study reported no adverse events in either the physical activity or control group during the 12-month study period (Kriemler 2013). A larger study reported no difference in the number of participants expe-	—	156 (2)	⊕⊕⊙⊙ **Low**[f,g]	Other time points: **Active intervention ≤ 6 months** 2 studies reported adverse events: in the first study there was muscle stiffness (common after active video games) and in the second study there was an ankle in-

riencing an adverse event or serious adverse event related to the intervention between the physical activity and no physical activity group (adverse events: OR 6.22, 95% CI 0.72 to 53.40; serious adverse events: OR 0.95, 95% CI 0.06 to 15.54) (Hebestreit 2022).

jury in the physical activity group and haemoptysis in 1 participant in the control group. 1 further study reported no adverse events during the 6-week intervention period.

Follow-up (no active intervention)

In 1 study it was not clear if the earlier reported muscle stiffness continued in the follow-up period. The study that reported no adverse events in the 6-week intervention period, also observed no adverse events in the follow-up period.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **CFQ-R:** Cystic Fibrosis Questionnaire – Revised; **CFRD:** cystic fibrosis-related diabetes; **FEV_1:** forced expiratory volume in 1 second; **HbA1c:** glycated haemoglobin; **HR:** hazard ratio; **HRQoL:** health-related quality of life; **MD:** mean difference; **n:** number of participants; **OR:** odds ratio; **VO_2 peak:** peak oxygen uptake.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: 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 certainty: we are very uncertain about the estimate.

[a]Downgraded once due to high or unclear risk of bias across many of the domains for the included studies. Two studies contributing data to this outcome were at high risk of bias due to concerns around randomisation and allocation concealment.
[b]There was moderate heterogeneity in the results, but this was due to an outlying study (Kriemler 2013). When this study was removed from the analysis, the result remained significant and therefore we did not downgrade the certainty of evidence due to inconsistency. The outlying study included small numbers and had wide CIs around the effect.
[c]There was moderate heterogeneity in the results due to a small outlying study with wide CIs (Kriemler 2013); downgraded once.
[d]Downgraded twice due to risk of bias across several domains in the studies included in this analysis. There were particular concerns around randomisation and allocation concealment in three of the four included studies.
[e]Downgraded once due to imprecision caused by a small number of participants.
[f]Downgraded once due to risk of bias in one of the two included studies for this outcome.
[g]Downgraded once for imprecision (low event rates and wide CIs).

BACKGROUND

Description of the condition

Cystic fibrosis (CF) is the most common life-limiting, autosomal, recessively inherited disease in populations of Northern European descent. The worldwide incidence of CF has been estimated, on average, at between 1/3000 and 1/6000 live births, with great regional variation (Farrell 2008; Scotet 2020; Southern 2007). Life expectancy of people with CF has increased substantially over recent decades (MacKenzie 2014), with a large proportion of newborns expected to survive into their fifth decade and beyond (Keogh 2018). On the one hand, the changing demographics of CF lung disease and the growing population of older adults (Burgel 2015) with multiple chronic conditions and an increasing number of cardiovascular disease risk factors pose new challenges to healthcare professionals, including those providing and supervising physical activity and exercise training. On the other hand, a substantial proportion of people with CF can now benefit from highly effective drug therapies (Middleton 2019). However, their impact on individuals' daily physical activity and exercise behaviour is currently unknown and remains to be investigated. Reduced exercise capacity is still common among people with CF (Radtke 2018a), and is associated with reduced life expectancy (Hebestreit 2019; Nixon 1992; Pianosi 2005). Thus, healthcare professionals should encourage and support people with CF to live an active lifestyle early on, and, ideally, provide advice and guidance addressing individual barriers and facilitators to long-term participation in physical activity.

Description of the intervention

Physical activity is defined as "any bodily movement produced by skeletal muscles that results in energy expenditure" (Caspersen 1985). Exercise training is a subcomponent of physical activity that is planned, structured and done repetitively, with the objective of improving or maintaining physical fitness (Caspersen 1985). It can be defined as participation in a programme of regular vigorous physical activity designed to improve physical performance, cardiovascular function, muscle strength or any combination of these three (Shephard 1994). There are basically two different types of exercise training: aerobic training or anaerobic training, but neither can be considered purely 'aerobic' or 'anaerobic' with respect to energy supply. Aerobic exercise usually involves periods of continuous and rhythmic training of large muscle groups (e.g. cycling or running) that rely predominantly on aerobic energy metabolism. Anaerobic exercise involves training (e.g. weight or resistance training, sprinting or high-intensity interval training) at a high intensity for a very short duration (ACSM 2017). In this review, we use a broad categorisation of aerobic and anaerobic activities to characterise exercise training studies. However, unlike previous versions of this review, we no longer focus on comparisons between aerobic, anaerobic or a combination of aerobic and anaerobic training regimens versus no training.

Importantly, this review includes both physical activity and exercise training interventions. Exercise training refers to activities that are done for a certain purpose; for example, to improve fitness or to aid the clearance of secretions from the lungs. Since exercise training is a subcomponent of physical activity, we also include randomised controlled trials (RCTs) that focused on improving daily (vigorous) physical activity levels by using wearable technology, such as step counters and fitness trackers, using goal setting and providing motivational feedback throughout their intervention (Nuss 2021), telehealth interventions, or combinations of those. For the rest of this review, we will use the term 'physical activity' inclusive of formal exercise training for ease to the reader.

How the intervention might work

Physical activity has multiple beneficial effects, and is one of the five most important treatments, as rated by people with CF (Davies 2020). Physical activity contributes to the alleviation of exertional dyspnoea and improves exercise tolerance in people with CF (Cerny 2013). Regular physical activity slows the rate of decline in pulmonary function by improving sputum clearance (Cox 2016; Cox 2018; Schneiderman 2014), likely through a combination of hyperventilation, mechanical vibration, coughing and changes in sputum rheology, leading to facilitated and increased sputum expectoration (Dwyer 2011; Dwyer 2017; Hebestreit 2001).

Regular physical activity may also be an important part of the management of diabetes in CF, as it improves glycaemic control in type 1 diabetes mellitus by improving insulin sensitivity and reducing systemic inflammation (Galassetti 2013). Regular physical activity may also delay the onset of osteoporosis by preventing a reduction in bone mineral density (Tejero García 2011). Other postulated benefits of physical activity may be decreased anxiety and depression, and enhanced feelings of well-being and health-related quality of life (HRQoL) (Hebestreit 2014). Non-adherence to prescribed physical activity may contribute to worsening signs and symptoms of respiratory disease, more frequent respiratory infections and a reduced ability to perform activities of daily living, and thus ultimately have a detrimental effect on the individual's prognosis. Side effects of physical activity are rare, so it can be considered safe in CF (Ruf 2010).

Why it is important to do this review

This review aims to provide evidence for the chronic effects of physical activity interventions on physiological, functional and patient-reported outcomes in people with CF. Optimal physical activity programmes (e.g. duration, intensity, type of activity, level of supervision) for people with CF are unknown and have yet to be defined. Doing so would help to support healthcare professionals, who often lack confidence in providing individualised physical activity advice (Denford 2020). This is an update of previous versions of the review (Bradley 2002; Bradley 2008; Radtke 2015; Radtke 2017).

OBJECTIVES

To assess the effects of physical activity interventions on exercise capacity by peak oxygen uptake (VO_2 peak), lung function by forced expiratory volume in one second (FEV_1), HRQoL and further important patient-relevant outcomes in people with CF.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) or quasi-RCTs.

Types of participants

People with CF, of any age, and any degree of disease severity, diagnosed on the basis of clinical criteria and sweat testing or genotype analysis.

Types of interventions

Any type of prescribed physical activity intervention delivered to people with CF compared to usual care. We excluded studies which involved pure respiratory muscle training (exercise training specifically targeting the muscles that drive expansion or contraction of the chest, or both). In a post hoc change, we stipulated that studies must have an intervention duration of at least two weeks.

Types of outcome measures

For the 2022 review update, the review author team decided to reduce the number of secondary outcome measures to those that are most important to people living with CF, clinically relevant and patient-centred. We removed outcomes that are rarely assessed, for which no standardised assessment is available, and outcomes that rely (mostly) on equations that are prone to measurement bias (e.g. fat-free mass based on skinfold thickness). Please see more comprehensive details in the section Differences between protocol and review.

We assessed the following outcome measures at up to and including six months and longer than six months of active interventions and also for a follow-up period where all participants received usual care.

Primary outcomes

1. Exercise capacity (VO_2 peak reported either as L/min, mL/min and per kg bodyweight or kg fat-free mass or as per cent (%) predicted)
2. Lung function measured as FEV_1 (reported either as L or % predicted and as absolute values or change from baseline)
3. HRQoL (measured by generic or disease-specific instruments, or both, using validated instruments or patient reports)
   a. physical functioning
   b. respiratory
   c. other

Secondary outcomes

1. Additional indices of exercise capacity
   a. peak work capacity (reported as either watt (W) absolute values, W per kg bodyweight, W % predicted or change from baseline)
   b. submaximal exercise capacity (e.g. time to the limit of tolerance in constant work rate exercise tests or oxygen uptake or work rate at the anaerobic threshold, or both)
   c. functional exercise capacity (i.e. 6-minute walk test (6MWT) and shuttle tests)
2. Quadriceps muscle strength
   a. isometric muscle strength, measured with strain gauges fixed to a medical bench/chair or using dynamometry (reported as either kg or newtons (N))
   b. isokinetic muscle strength measured by isokinetic dynamometry (reported as newton-metres (N.m))
3. Lung function measured as forced vital capacity (FVC) (reported either as L or % predicted and as absolute values or change from baseline)
4. Physical activity
   a. subjective report (e.g. self-reported diary or validated questionnaires of time spent in moderate-to-vigorous/intense activity)
   b. objective report (e.g. pedometers (i.e. number of steps) or accelerometers (i.e. time spent in moderate-to-vigorous or vigorous physical activity, or both))
5. Body mass index (BMI) (reported as kg/m^2 or z-scores)
6. Pulmonary exacerbations
   a. number of exacerbations
   b. time to first exacerbation
7. Hospitalisation
   a. number of hospitalisations
   b. number of days in hospital
8. Bone health, measured by dual x-ray energy absorptiometry or peripheral quantitative computed tomography
9. Diabetic control, measured by fasting blood glucose levels (mmol/L or mg/dL), insulin levels (mmol/L or mg/dL) or homeostasis model assessment (HOMA) or oral glucose tolerance test (blood glucose in mmol/L or mg/dL)
10. Adverse events related to the physical activity intervention or exercise testing as part of intervention

Search methods for identification of studies

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

Electronic searches

We identified relevant studies from the Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register using the term 'exercise'.

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 through 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 sections of the Cystic Fibrosis and Genetic Disorders Group website (cfgd.cochrane.org/our-specialised-trials-registers). Our most recent search of the Group's Cystic Fibrosis Trials Register was on 3 March 2022.

We also searched the following trials registers:

1. US National Institutes of Health Ongoing Trials Register, ClinicalTrials.gov (www.clinicaltrials.gov; searched 4 March 2022);
2. World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (trialsearch.who.int/; searched 16 March 2022).

For details of our search strategies, please see Appendix 1.

Searching other resources

We searched the reference lists of each RCT and of review articles for additional publications that may contain RCTs. We contacted authors of studies included in this review and other experts in the field to request information on other published and unpublished studies.

Data collection and analysis

We used the following methods where possible.

Selection of studies

Two review authors (for the original review, JB and FM; for the 2015 and 2017 updates, SK and TR; for the 2022 update, TR and SS) independently assessed the titles and abstracts of identified citations and selected the studies to be included in the review. We excluded non-RCTs, studies involving respiratory muscle training exclusively, studies which did not have a physical activity programme and those that did not meet the inclusion criteria, based on screening the abstracts or full-text articles. If disagreement arose on the suitability of a study for inclusion in the review, we reached a consensus through discussion. We recorded any areas of disagreement. We excluded studies that did not fulfil all of the inclusion criteria, and listed their details with the reason for exclusion. A third review author resolved discrepancies where any disagreement or uncertainty between the two review authors persisted.

Data extraction and management

Two review authors (for the 2015 and 2017 updates, SK and TR, or for the included studies where SK and TR were authors, SS and SN; for the 2022 update, TR and SS), independently extracted data using a standard data acquisition form. We collected information about: study design (parallel versus multiarm; single-centre versus multicentre; participants and study characteristics for baseline equality between groups; details on the number of participants screened for eligibility, randomised, analysed, excluded, lost to follow-up and dropped out; method of randomisation and allocation concealment; blinding of personnel and outcome assessors; use of stratification; incomplete outcome data; selective reporting; use of intention-to-treat analysis); the detailed intervention (aerobic training, anaerobic training, or a combination of both training regimens; duration of physical activity intervention (either supervised, partially supervised or unsupervised, i.e. up to and including six months, over six months, and studies with a follow-up period (where all participants received usual care)); and whether the intervention was supervised, partially supervised or not supervised, but still with access to resources for physical activity additional to usual care); and outcome measures (continuous and dichotomous). If disagreement arose about the quality of a study, we attempted to reach a consensus through discussion. If disagreement persisted, a third review author arbitrated. We recorded any areas of disagreement. One review author (for the original review, JB; from the 2015 update onwards, TR) entered the data into the Cochrane software Review Manager 5 (Review Manager 2014), and a second review author (for the 2015 and 2017 update, SK; for the 2021 update, SS) reviewed it. We contacted the authors of the included studies in case of unclear or missing data and information.

We pooled data comparing physical activity versus no activity. For all outcomes in this review, we combined the two active arms of the Kriemler 2013 and Selvadurai 2002 studies. For the meta-analysis of the primary outcomes FEV_1, VO_2 peak and HRQoL, we chose the measurement time points with the longest duration of controlled intervention (i.e. the time point up to which control group participants were asked to maintain their baseline physical activity level).

We reported results from each category of physical activity intervention at the end of that specific category; we reported results from the follow-up periods during which all participants received usual care in a separate category labelled 'Follow-up (no active intervention)'. If a study reported multiple time points for a single category of intervention (supervised, partially supervised or unsupervised) within our predefined training period lengths (i.e. up to and including six months, and longer than six months), we reported the longest time point within the given category. For example, Kriemler 2013 included assessments at three months and six months (fully supervised), 12 months (during the second six months participants were not supervised but still had access to physical activity resources from the study) and 24 months (i.e. 12 months' follow-up with no active intervention or provision of resources)). In this case, we reported the six-month, 12-month and 24-month assessments and discarded the three-month assessment.

Assessment of risk of bias in included studies

For the original review, two review authors judged the methodological quality of the review (JB, FM). For the review updates, two authors (2015 and 2017 update: SK and TR; 2022 update: SS and TR or SS and SN) independently assessed the risk of bias for each included study according to the Cochrane risk of bias tool (Higgins 2017). In particular, we examined details of the randomisation method with sequence generation, allocation concealment, degree of blinding, inclusion and exclusion criteria, dropouts or withdrawals, intention-to-treat and detailed statistical analysis. We also assessed the risk of selective reporting and any other potential sources of bias. For each domain, we judged the risk of bias as low, unclear or high. We considered unexplained dropouts or an unequal number of dropouts across treatment groups as a potential risk of bias. Likewise, we also considered a lack of important information (e.g. on adverse effects, missing data, statistical methods, etc.) as a potential risk of bias.

Measures of treatment effect

We reported continuous outcome data and calculated the mean differences (MDs) with 95% confidence intervals (CIs) where between-group differences in the mean change from baseline were recorded. When data on the standard deviation (SD) for an individual group were not available, but instead standard error (SEM) of the difference was available, we used the calculator within the Review Manager 5 to compute the MD with 95% CIs (Review Manager 2014). Where possible, we used the published standard error of the mean (SEM), or alternatively, we used published CIs to estimate SEM. In this review update, we report the number of acute pulmonary exacerbations as incidence rate ratios (i.e. based on mixed Poisson regression models, as reported in Hebestreit 2022, which is the only included study that reported this outcome). We analysed the outcome of 'time to first pulmonary exacerbation' between the physical activity intervention and control groups as

hazard ratios (HRs) with 95% CIs. We analysed the number of adverse events directly related to physical activity as odds ratios (ORs) with 95% CIs.

In future updates of this review, if trials use different measurement scales for an outcome, we plan to analyse the data using the standardised mean difference (SMD) with 95% CIs.

Unit of analysis issues

We have not included any cross-over studies in this latest version of the review. If future versions of this review include cross-over studies, and if data are presented in published papers from paired statistical analyses or if information is available to allow us to adjust for within-patient correlation using the methods described by Elbourne 2002, we will use the generic inverse variance method for data analysis. If appropriate data are not presented to allow adjustment for within-patient correlation, we will contact study investigators to request these data. If we are unable to make the necessary adjustments, we will describe data from cross-over studies narratively in the review.

Dealing with missing data

We contacted the investigators of studies included in this review for further study details and data. Fourteen investigators responded. The investigators of four studies stated that the requested data were not available (Klijn 2004; Michel 1989; Schneiderman-Walker 2000; Selvadurai 2002). The investigator of a one study confirmed that the extracted data were correct and that no further data were available (Cerny 1989). We also contacted the investigators of the Hebestreit study; additional data were provided and the paper has since been published. One investigator involved in the Phillips study, currently listed under Studies awaiting classification, confirmed that the study has been completed. We updated the information in the table (Phillips 2008). In both publications by Santana-Sosa, the means and SEMs were reported for all variables; we contacted the investigators for additional data, which we received (Santana-Sosa 2012; Santana-Sosa 2014). The investigators of Carr 2018 responded to our initial request to provide additional raw data, but did not respond to further emails. We could not include the additional data.

Finally, investigators of eight studies provided additional raw data for this review update (Beaudoin 2017; Hebestreit 2010; Hebestreit 2022; Kriemler 2013; Rovedder 2014; Santana-Sosa 2012; Santana-Sosa 2014; Sawyer 2020). We received raw data from the corresponding author of Beaudoin 2017 which allowed us to calculate MD and the corresponding SEM for various outcomes. For Hebestreit 2022, we extracted the MDs and their 95% CIs from the adjusted intention-to-treat models with imputation of missing data to compute the relevant SEM using the Review Manager 5 calculator (inverse variance analysis). For Kriemler 2013 study, we extracted mean changes and SDs from the adjusted models for each group and calculated the relevant SEMs (inverse variance analysis). The two studies by Santana-Sosa reported means and SEM at baseline, post-training and 'off training' (i.e. labelled as a 'detraining' period in their original publications and defined as a period during which no supervised exercise was offered to intervention group participants) (Santana-Sosa 2012; Santana-Sosa 2014), and we were unable to calculate the MD. We received incomplete raw data files from the authors. Due to inconsistencies in the data sets provided, we were unable to reproduce all data. Due to our concerns about data quality, we excluded both studies from the formal analysis in the review. Instead, we provided data from these studies in two additional tables (see Table 1; Table 2). Sawyer 2020 reported within-group changes from baseline as medians (interquartile range) for various outcomes. We received raw data from the authors, checked the distribution of the data (and confirmed normal distribution of the majority of outcomes), and calculated MD and SEM for relevant outcomes.

Assessment of heterogeneity

We combined available data (extracted from published papers and calculated as previously stated) and conducted a meta-analysis on the primary outcomes VO_2 peak, FEV_1 and HRQoL. We measured heterogeneity between studies using the Chi^2 test and the I^2 statistic (Higgins 2003). The Chi^2 test measures the deviation of observed effect sizes from the underlying overall effect. A low P value (or a large Chi^2 statistic relative to its degree of freedom) provides evidence of heterogeneity of intervention effects (variation in effect estimates beyond chance). We used a P value of 0.10, rather than the conventional level of 0.05, to determine statistical significance. The I^2 statistic, as defined by Higgins (Higgins 2017), measures heterogeneity as a percentage, where a value:

1. 0% to 40%: might not be important;
2. 30% to 60%: may represent moderate heterogeneity;
3. 50% to 90%: may represent substantial heterogeneity;
4. 75% to 100%: considerable heterogeneity.

The importance of the observed value of I^2 depends on: (i) magnitude and direction of effects; and (ii) strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or a CI for the I^2 statistic).

Assessment of reporting biases

We assessed relevant bias and selective reporting by comparing the 'methods' and 'results' sections from the included papers and trial registries, if available. We documented this information in the risk of bias tables for included studies (see Characteristics of included studies table), and in Figure 1 and Figure 2. If future updates of this review include and combine a sufficient number of studies (10 or more), we will assess publication bias, initially by visual inspection of a funnel plot. However, we are aware that an asymmetrical funnel plot is not necessarily due to publication bias.

Figure 1. Methodological quality summary: review authors' judgments about each methodological quality item for each included study.

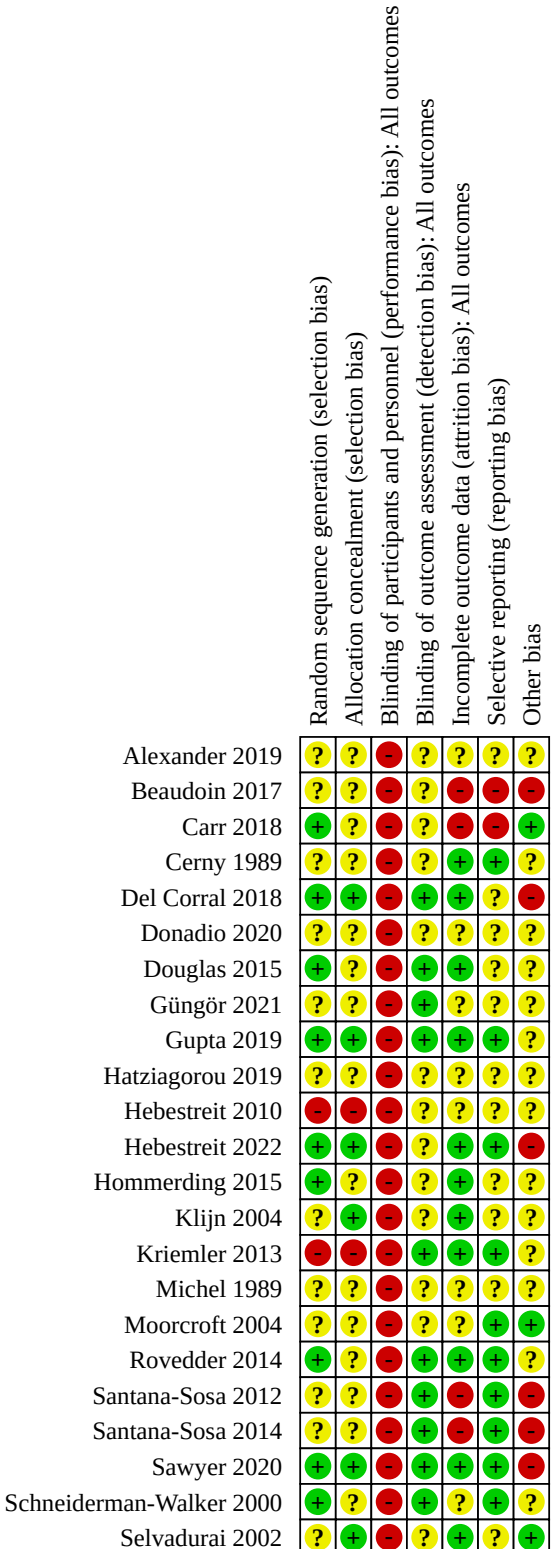


Figure 1. (Continued)

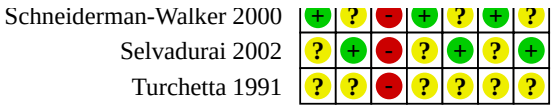
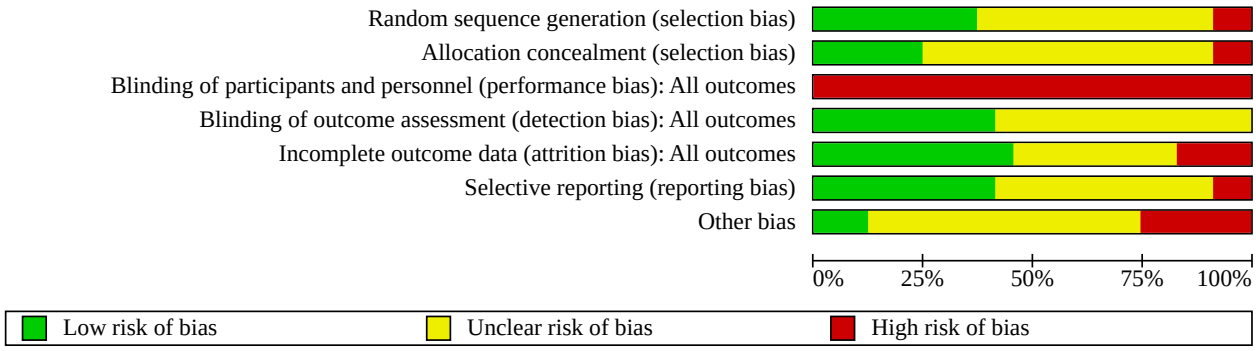


Figure 2. Methodological quality graph: review authors' judgments about each methodological quality item presented as percentages across all included studies.



Data synthesis

We used a fixed-effect model for all outcome parameters using Review Manager 5 (Review Manager 2014). We used a random-effects model for outcomes that were combined, and for which a meta-analysis was performed (i.e. VO_2 peak, FEV_1, HRQoL). The random-effects model incorporates any between-study heterogeneity into a meta-analysis. We selected the MD when we combined data and used forest plots to compare results across studies.

Subgroup analysis and investigation of heterogeneity

For future updates of this review, we plan to undertake subgroup analyses of children versus adults, (partially) supervised versus unsupervised training and according to disease severity, provided there is a sufficient number of studies (about 10) with at least moderate heterogeneity in the pooled analyses. Moreover, in the future, we plan to undertake subgroup analysis comparing studies performed in the 'new' era of CF medicine (i.e. after widespread availability of CF transmembrane conductance regulator modulator therapy) from 2020 onwards to those conducted before 2020.

Sensitivity analysis

We performed sensitivity analysis to investigate whether heterogeneity affected the overall pooled effects estimates by excluding from the pooled analysis individual studies that gave rise to methodological concerns. We restricted sensitivity analysis to primary outcomes. In future updates of this review (i.e. when more studies can be combined for meta-analysis), we plan to perform two additional sensitivity analyses: with and without quasi-randomised studies (not yet possible); and excluding studies with a high risk of bias from the analysis.

Summary of findings and assessment of the certainty of the evidence

We summarised the main findings of this review, including a grading of the certainty of evidence, in Summary of findings 1. We selected the following seven outcomes to report (chosen based on relevance to clinicians and consumers):

1. exercise capacity (VO_2 peak);
2. Lung function measured as FEV_1;
3. HRQoL: Cystic Fibrosis Questionnaire – Revised (CFQ-R) physical functioning domain;
4. HRQoL: CFQ-R respiratory symptoms;
5. pulmonary exacerbations;
6. diabetic control;
7. adverse events.

We determined the certainty of the evidence using the GRADE approach. We downgraded evidence in the presence of a high risk of bias in at least one study, indirectness of the evidence, unexplained heterogeneity or inconsistency, imprecision of results, or high probability of publication bias. We downgraded evidence by one level if we considered the limitation to be serious, and by two levels if very serious.

RESULTS

Description of studies

See Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; and Characteristics of ongoing studies tables.

Results of the search

The combined searches to date have identified 544 individual references. After initial screening to exclude those references which were obviously not eligible, 137 unique studies are listed in the review. We included 24 studies (61 references); excluded 95 studies (147 references; for further details, see Excluded studies); six studies (13 references) are currently awaiting classification; and 12 studies (16 references) are ongoing. Please see the study flow chart for details (Figure 3).

Figure 3. Study flow diagram.

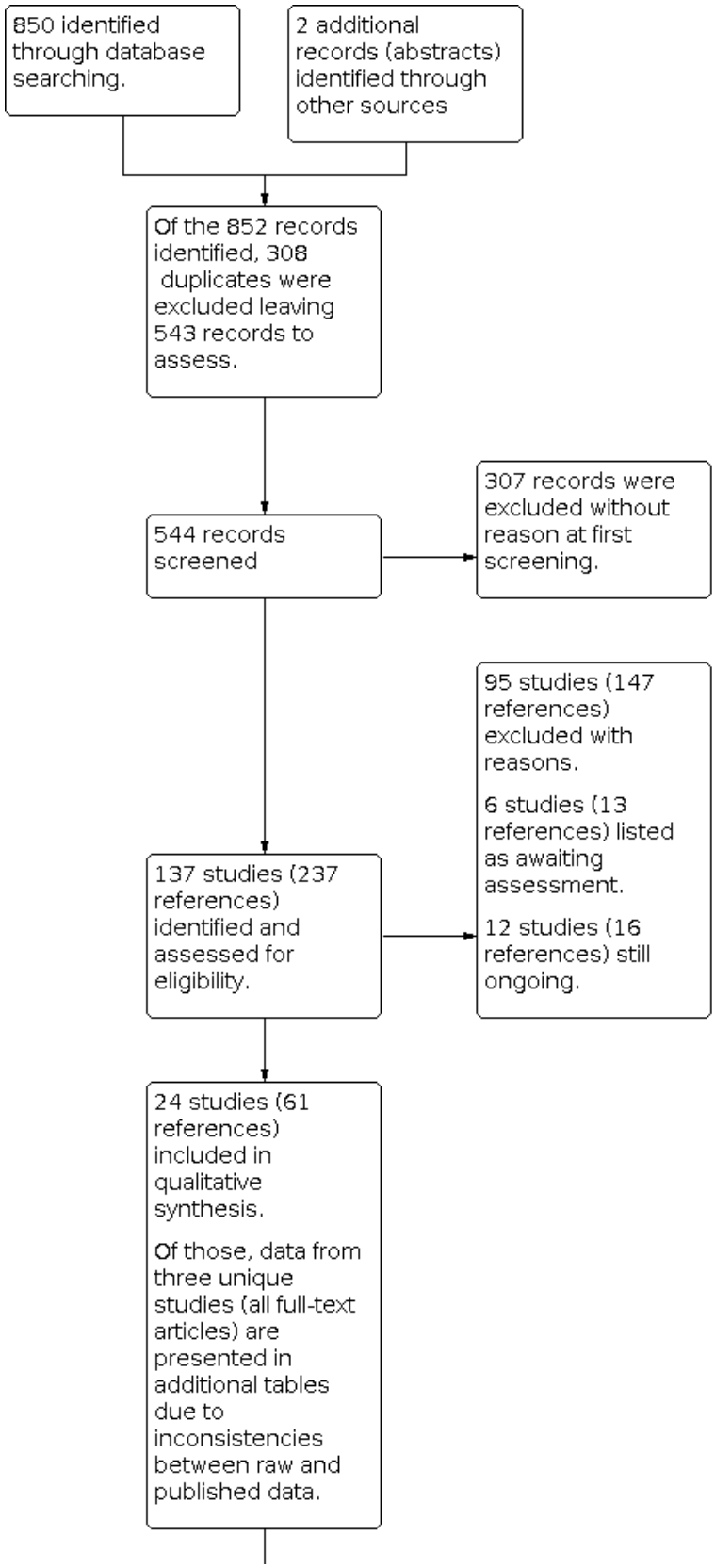
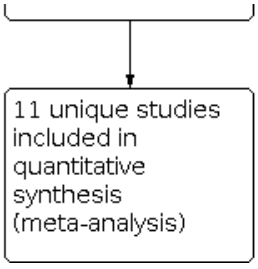


Figure 3. (Continued)



Included studies

A total of 24 studies with 875 participants met the inclusion criteria (Alexander 2019; Beaudoin 2017; Carr 2018; Cerny 1989; Del Corral 2018; Donadio 2020; Douglas 2015; Güngör 2021; Gupta 2019; Hatziagorou 2019; Hebestreit 2010; Hebestreit 2022; Hommerding 2015; Klijn 2004; Kriemler 2013; Michel 1989; Moorcroft 2004; Rovedder 2014; Santana-Sosa 2012; Santana-Sosa 2014; Sawyer 2020; Schneiderman-Walker 2000; Selvadurai 2002; Turchetta 1991).

Three review authors (TR, HH and SK) were lead investigators of the ACTIVATE-CF trial (Principal Investigator Helge Hebestreit), and had full access to the data before the publication of the main manuscript. The data were included in this review, and during the process of preparing this review update, the paper was accepted for publication and is appropriately cited (Hebestreit 2022). Two other review authors (SS and SN) conducted data extraction and management for this study.

Trial characteristics

All included studies were of a randomised parallel-group design. The study by Beaudoin and colleagues was registered as a randomised cross-over study (ClinicalTrials.gov), but results were reported as a randomised parallel-group design in the final publication (Beaudoin 2017). There were 20 single-centre studies (Alexander 2019; Beaudoin 2017; Carr 2018; Cerny 1989; Del Corral 2018; Donadio 2020; Douglas 2015; Güngör 2021; Gupta 2019; Hatziagorou 2019; Hommerding 2015; Klijn 2004; Michel 1989; Moorcroft 2004; Rovedder 2014; Santana-Sosa 2012; Santana-Sosa 2014; Schneiderman-Walker 2000; Selvadurai 2002; Turchetta 1991). Three studies were national, multicentre studies: two were conducted in Germany and Switzerland (Hebestreit 2010; Kriemler 2013), and one in Australia (Sawyer 2020). One study was an international, multicentre study across eight countries in Europe and North America (Hebestreit 2022). The size of trials varied, from a minimum number of nine participants (Michel 1989), to a maximum of 117 participants (Hebestreit 2022). One study did not report the number of participants in each group and the MD between the treatment and control groups could not be calculated (Michel 1989).

There was wide heterogeneity in study designs, with 12 studies using a supervised training approach (Carr 2018; Cerny 1989; Donadio 2020; Douglas 2015; Güngör 2021; Klijn 2004; Michel 1989; Santana-Sosa 2012; Santana-Sosa 2014; Sawyer 2020; Selvadurai 2002; Turchetta 1991); 11 studies using a partially supervised approach (Alexander 2019; Beaudoin 2017; Del Corral 2018; Gupta 2019; Hatziagorou 2019; Hebestreit 2010; Hebestreit 2022; Hommerding 2015; Kriemler 2013; Rovedder 2014; Schneiderman-Walker 2000); and one study using an unsupervised training approach (Moorcroft 2004).

The length of physical activity intervention varied substantially across the 24 studies. In 14 studies, the active intervention (either supervised, partially supervised or unsupervised but with access to study resources) lasted up to and including six months, while in 10 studies, it lasted longer than six months. Seven of the included studies implemented an additional follow-up period (i.e. a period where supervision was withdrawn and participants received usual care and were not specifically discouraged from undertaking physical activity); these lasted from one to 12 months.

Four studies had active interventions of short duration (less than one month) and were carried out during hospitalisations (Cerny 1989; Michel 1989; Selvadurai 2002; Turchetta 1991). In Turchetta 1991, the hospital admission was for routine assessment; in Cerny 1989 and Selvadurai 2002, the hospital admission was due to an acute exacerbation requiring intravenous antibiotic treatment; and in Michel 1989, the reason for and the duration of admission were not reported. Four studies had active intervention periods lasting approximately eight weeks (Donadio 2020; Santana-Sosa 2012; Santana-Sosa 2014; Sawyer 2020). Both Santana-Sosa studies had a two-month active training period, plus a one-month follow-up period 'off training' during which the participants did not engage in supervised physical activity (described in the papers as "detraining") (Santana-Sosa 2012; Santana-Sosa 2014). Donadio 2020 and Sawyer 2020 were both fully supervised physical activity interventions. Five studies had an active intervention period of three months and were either home-based (Alexander 2019; Beaudoin 2017; Hommerding 2015; Rovedder 2014), or performed at the hospital (Klijn 2004). Klijn 2004 also included a three-month follow-up. In the study by Güngör and colleagues, the active intervention lasted for six months. A therapist supervised the first six weeks. Afterwards, the families were encouraged with weekly telephone calls to continue their child's exercise programme until the six-month study visit (Güngör 2021).

In 10 studies, the active interventions lasted longer than six months. Del Corral 2018 was a 12-month study including a six-week, home-based, physical activity intervention with video games. After six weeks, the participants were encouraged to continue video gaming exercise, supervised by their parents or caregivers. Two studies were of 24 months' duration in total with 12 months of active interventions and 12 months of follow-up (Hebestreit 2010; Kriemler 2013). After six months of supervised or partially supervised physical activity, the participants in the intervention groups were no longer supervised but were encouraged to maintain or increase their activity level while retaining access to the study resources, while participants in the control groups were told not to

change their exercise behaviour during the first 12 months. After 12 months, all participants reverted to usual care for a follow-up period (Hebestreit 2010; Kriemler 2013). In Hebestreit 2010, investigators combined the three- and six-month study visits and six- to 12-month follow-up visits. In Kriemler 2013, all study visits were reported separately in the original publication (i.e. three, six, 12 and 24 months). For the purpose of this review, we included the data from six, 12 and 24 months (i.e. after 12 months' follow-up). Carr 2018 was a nine-month intervention study comparing face-to-face versus Internet-delivered Tai Chi lessons. The Internet group started the intervention three months later than the face-to-face group; the Internet group served as the control group in this review and we reported data at the three-month time point only up to which the control group received no active intervention. In four studies, the active intervention lasted 12 months (Gupta 2019; Hatziagorou 2019; Hebestreit 2022; Moorcroft 2004); in one study 24 months (Douglas 2015); and in one study three years (Schneiderman-Walker 2000).

In total, seven studies undertook follow-up periods where all participants reverted to usual care, with these lasting between one and 12 months (Hebestreit 2010; Klijn 2004; Kriemler 2013; Michel 1989; Santana-Sosa 2012; Santana-Sosa 2014; Selvadurai 2002).

Participants

Two studies included adults only (Beaudoin 2017; Moorcroft 2004); 12 studies included children and adolescents only (Del Corral 2018; Donadio 2020; Douglas 2015; Güngör 2021; Gupta 2019; Hatziagorou 2019; Hommerding 2015; Klijn 2004; Santana-Sosa 2012; Santana-Sosa 2014; Selvadurai 2002; Turchetta 1991), eight studies included both adults and children (Carr 2018; Cerny 1989; Hebestreit 2010; Hebestreit 2022; Kriemler 2013; Michel 1989; Rovedder 2014; Schneiderman-Walker 2000); one study included prepubertal children (Alexander 2019); and one study included adolescents (15 years and older) and adults (Sawyer 2020). Overall, the studies included participants with a broad range of disease severity.

Most studies included participants of both sexes (Beaudoin 2017; Carr 2018; Del Corral 2018; Donadio 2020; Douglas 2015; Güngör 2021; Gupta 2019; Hatziagorou 2019; Hebestreit 2010; Hebestreit 2022; Hommerding 2015; Klijn 2004; Kriemler 2013; Moorcroft 2004; Rovedder 2014; Santana-Sosa 2012; Santana-Sosa 2014; Sawyer 2020; Schneiderman-Walker 2000; Selvadurai 2002; Turchetta 1991). However, no information was available for three studies (Alexander 2019; Cerny 1989, Michel 1989). A total of 17 studies provided information about the proportion of male and female participants at baseline (Beaudoin 2017; Carr 2018; Del Corral 2018; Donadio 2020; Güngör 2021; Gupta 2019; Hatziagorou 2019; Hebestreit 2010; Hebestreit 2022; Hommerding 2015; Kriemler 2013; Rovedder 2014; Santana-Sosa 2012; Santana-Sosa 2014; Sawyer 2020; Selvadurai 2002; Turchetta 1991).

In 10/20 studies published as full-text articles, FEV_1 % predicted values were used as exclusion criteria (Beaudoin 2017; Güngör 2021; Gupta 2019; Hebestreit 2010; Hebestreit 2022; Klijn 2004; Kriemler 2013; Santana-Sosa 2012; Santana-Sosa 2014; Schneiderman-Walker 2000); this was also true for the study available only in abstract form and trial register entry on ClinicalTrials.gov (Douglas 2015). The remaining eight studies published as full-text articles did not specify disease severity based on FEV_1 as an exclusion criterion (Carr 2018; Cerny 1989; Del Corral 2018; Hommerding 2015; Moorcroft 2004; Rovedder 2014; Sawyer 2020; Selvadurai 2002). No information was available from the remaining five studies, which were only published as abstracts (Alexander 2019; Donadio 2020; Hatziagorou 2019; Michel 1989; Turchetta 1991).

In four studies, the authors reported differences in baseline characteristics of the participants despite randomisation (Cerny 1989; Rovedder 2014; Santana-Sosa 2012; Santana-Sosa 2014). In Cerny 1989, lung function, measured as FEV_1 and forced mid-expiratory flow 25% to 75% ($FEF_{25–75}$), was significantly lower in the control compared to the physical activity group at admission. In both Santana-Sosa studies, the physical activity groups had a lower aerobic exercise capacity (VO_2 peak) and lower muscle strength (most but not all strength measures) (Santana-Sosa 2012; Santana-Sosa 2014). In Rovedder 2014, there was a significantly lower BMI in the intervention group compared to the control group.

In Kriemler 2013, the control group experienced an unusual deterioration of physical health during the study, and the results should be interpreted with caution. In Del Corral 2018, mean modified shuttle walk test (MSWT) distance in the intervention group was 823.5 (SD 270.6) m and in the control group was 1085.5 (SD 255.6) m. The study did not report differences between groups in MSWT distance. Our own calculations using the Review Manager 5 software revealed a difference between groups at baseline (MD –262 m, 95% CI –425.1 to –98.86; P = 0.003). The authors adjusted for baseline values in their statistical analysis (Del Corral 2018). In Güngör 2021, the physical activity group appeared to have lower HRQoL (respiratory symptoms and physical functioning domain) compared to controls (MD of approximately 15 units to 20 units), but the authors reported that no significant difference existed in baseline characteristics between groups. This might be due to the small sample size and large SDs.

Interventions

As the aim of this review was to assess the efficacy of any type of physical activity intervention versus no physical activity intervention (usual care), we excluded studies which exclusively involved respiratory muscle training. All 24 studies included a control group which did not receive a prescribed physical activity programme.

Three studies had three study arms and compared different types of physical activity programmes (endurance training or resistance training or resistance training with neuromuscular electrical stimulation) with a control group (Donadio 2020; Kriemler 2013; Selvadurai 2002).

Five studies compared a training programme with short bouts of intense activity to a control group (Alexander 2019; Güngör 2021; Gupta 2019; Klijn 2004; Sawyer 2020). Alexander 2019 compared a 12-week whole-body vibration training programme to control; Gupta 2019 compared a 12-month home-based physical activity programme, including strengthening exercises and plyometric jumping exercises, to a control group; and Sawyer 2020 compared an eight-week cycling-based high-intensity interval training programme to a control group (Sawyer 2020). Klijn 2004 compared a 12-week exercise programme including short (20 seconds to 30 seconds) intense exercises to normal daily activities. Güngör 2021 investigated the effects of a six-week pulmonary rehabilitation programme, including active cycle of breathing techniques and

postural exercises, compared with an active cycle of breathing techniques but no additional physical activity programme. After the six-week intervention, children and parents were encouraged with weekly telephone calls to continue with the exercises for the following six months (Güngör 2021).

Five studies compared endurance type activities alone to a control group (Cerny 1989; Hommerding 2015; Michel 1989; Schneiderman-Walker 2000; Turchetta 1991).

In 10 studies, investigators compared the effects of a combined training programme (a mixture of endurance type and resistance training or strengthening activities) to a control group (Beaudoin 2017; Del Corral 2018; Douglas 2015; Hatziagorou 2019; Hebestreit 2010; Hebestreit 2022; Moorcroft 2004; Rovedder 2014; Santana-Sosa 2012; Santana-Sosa 2014). Beaudoin 2017 investigated a 12-week combined endurance and resistance training programme compared to no training. Del Corral 2018 evaluated the efficacy of a six-week video game programme, including a variety of physical activities such as running, squats, lunges and biceps curls; the intervention group participants were encouraged to continue the programme for 12 months. Douglas 2015 and Hatziagorou 2019 investigated individually tailored supervised or partially supervised physical activity programmes in children with CF over 12 months (Douglas 2015) and 24 months (Hatziagorou 2019). Hebestreit 2010 compared an individualised physical activity programme, including endurance-type exercises, strengthening exercises or a combination of both regimens, with a control group over 24 months; the control group was simply encouraged to maintain their level of activity over 12 months. Hebestreit 2022 was a 12-month individualised and partially supervised programme aimed at increasing vigorous activities using a combination of endurance-type and strengthening exercises. Moorcroft and colleagues evaluated the effects of a 12-month individualised, unsupervised physical activity training programme, including a combination of both endurance and resistance activities (Moorcroft 2004). Rovedder 2014 used unsupervised home-based training with endurance and strengthening exercises over 12 weeks. Santana-Sosa 2012, in hospitalised participants, compared supervised endurance and strengthening exercises, three times per week to a control group who were only informed of the benefits of exercise; both groups received the same chest physiotherapy during the entire study period. Santana-Sosa 2014 compared an eight-week combined programme (endurance and strength), including additional inspiratory muscle training, with a control group.

Carr 2018 compared Tai Chi programme to a control group for nine months.

In two studies, all participants additionally received intravenous antibiotic treatment (Cerny 1989; Selvadurai 2002).

Outcomes

The most commonly reported outcome measure was the change in FEV_1, which all reported studies except reported (Alexander 2019; Del Corral 2018; Klijn 2004; Michel 1989). Fourteen studies documented the change in VO_2 peak (Beaudoin 2017; Douglas 2015; Gupta 2019; Hatziagorou 2019; Hebestreit 2010; Hebestreit 2022; Hommerding 2015; Klijn 2004; Kriemler 2013; Santana-Sosa 2012; Santana-Sosa 2014; Sawyer 2020; Schneiderman-Walker 2000; Selvadurai 2002). One study reported changes in VO_2 at the anaerobic threshold following a physical activity intervention (Donadio 2020), and one study reported changes in VO_2 during a submaximal constant work rate exercise test (Sawyer 2020). Sixteen studies reported change in HRQoL (Alexander 2019; Beaudoin 2017; Carr 2018; Del Corral 2018; Güngör 2021; Gupta 2019; Hebestreit 2010; Hebestreit 2022; Hommerding 2015; Klijn 2004; Kriemler 2013; Rovedder 2014; Santana-Sosa 2012; Santana-Sosa 2014; Sawyer 2020; Selvadurai 2002), and 10 studies reported change in muscle strength (Beaudoin 2017; Del Corral 2018; Donadio 2020; Hebestreit 2010; Klijn 2004; Kriemler 2013; Rovedder 2014; Santana-Sosa 2012; Santana-Sosa 2014; Selvadurai 2002). Sixteen studies reported change in body composition (Alexander 2019; Beaudoin 2017; Carr 2018; Del Corral 2018; Hatziagorou 2019; Hebestreit 2010; Hebestreit 2022; Hommerding 2015; Klijn 2004; Kriemler 2013; Michel 1989; Moorcroft 2004; Santana-Sosa 2012; Santana-Sosa 2014; Schneiderman-Walker 2000; Selvadurai 2002). Eight studies reported change in physical activity (Beaudoin 2017; Gupta 2019; Hebestreit 2010; Hebestreit 2022; Hommerding 2015; Kriemler 2013; Schneiderman-Walker 2000; Selvadurai 2002), and five studies reported the change in other indices of exercise capacity (other than cardiopulmonary exercise testing) (Cerny 1989; Güngör 2021; Hommerding 2015; Moorcroft 2004; Rovedder 2014). Two studies reported changes in diabetic control (Beaudoin 2017; Hebestreit 2022), and two studies reported changes in bone health after the intervention (Alexander 2019; Gupta 2019). Six studies reported on adverse events (Del Corral 2018; Güngör 2021; Hebestreit 2022; Kriemler 2013; Sawyer 2020; Selvadurai 2002). Only one study reported the number of pulmonary exacerbations and time to first pulmonary exacerbation (Hebestreit 2022). No study reported hospitalisations.

Excluded studies

We excluded 95 studies for the following reasons.

A total of 24 studies were not RCTs (Andreasson 1987; Asher 1982; Balfour Lynn 1998; Barry 2001; Bongers 2015; Cantin 2005; de Jong 1994; Edlund 1986; Heijerman 1992; Hütler 2002; IRCT20161024030474N4; Moola 2017; NCT02277860; NCT02715921; NCT03117764; Orenstein 1981; Petrovic 2013; Pryor 1979; RBR-34677v; Ruddy 2015; Salh 1989; Stanghelle 1998; Tuzin 1998; White 1997). Thirty-eight studies did not include a physical activity programme according to our protocol (ACTRN12620001237976; Alarie 2012; Albinni 2004; Amelina 2006; Aquino 2006; Balestri 2004; Bellini 2018; Bieli 2017; Bilton 1992; Chang 2015; Chatham 1997; Combret 2018; Combret 2021; Cox 2013; Dwyer 2011; Falk 1988; Giacomodonato 2015; Happ 2013; Haynes 2016; Irons 2012; Kaak 2011; Lannefors 1992; Macleod 2008; Montero-Ruiz 2020; NCT02199340; NCT02821130; NCT02875366; Ozaydin 2010; Patterson 2004; Rand 2012; Reix 2012; Salonini 2015; Spoletini 2020; Vallier 2016; Vivodtzev 2013; Ward 2018; Young 2019; Zeren 2019). There were 19 studies which did not use a control arm with 'no physical activity' (Bass 2019; Calik-Kutukcu 2016; de Marchis 2017; del Corral Nunez-Flores 2014; Gruber 1998; Gruet 2012; Kaltsakas 2021; Kuys 2011; Lang 2019; Lima 2014; Lowman 2012; Martinez Rodriguez 2017; NCT01759342; NCT04888767; NTR2092; Orenstein 2004; RBR-5g9f6w; Reuveny 2020; Shaw 2016). Five studies were acute exercise studies and of insufficient duration (less than 14 days) to be included in this review (Dwyer 2017; Dwyer 2019; Kriemler 2016; Radtke 2018b; Wheatley 2015). Seven studies had a lack of information: the investigators of two studies informed us

that no paper will be published and data were not available (Mandrusiak 2011; NCT00792194); an investigator of one study did not reply to our email request for more information about the study status and planned publication (Oliveira 2010); and for four studies, contact details could not be found online to contact study investigators (Almajan-Guta 2011; Housinger 2015; Johnston 2004; Phillips 2008). Two studies were excluded for other reasons: one study focused on proprioceptive neuromuscular facilitation in children with chronic respiratory diseases (this type of training aims to improve flexibility and range of motion; it is not considered a type of physical activity intervention that is expected to elicit improvements in the outcomes listed in our review and therefore not relevant for this review) (NCT03420209); and for one study, the last status update on ClinicalTrials.gov was posted in 2005 (NCT00129350), and it is unlikely that this study will be published in the future (if published data are found in future literature searches, the study will be considered for inclusion in the review).

Studies awaiting classification

There are six studies awaiting classification (Bishay 2017; Cox 2019; IRCT20190407043190N1; NCT03100214; NCT04293926; Powers 2016).

Trial characteristics

All six studies awaiting classification were of a randomised parallel-group design. Two studies were multicentre (Cox 2019; IRCT20190407043190N1), and four were single-centre studies (Bishay 2017; NCT03100214; NCT04293926; Powers 2016). The study size (i.e. enrolment goal if actual number of participants was not available) ranged from 19 to 80 participants (Bishay 2017; Cox 2019; IRCT20190407043190N1; NCT03100214; NCT04293926; Powers 2016).

All studies reported inclusion and exclusion criteria (Bishay 2017; Cox 2019; IRCT20190407043190N1; NCT03100214; NCT04293926; Powers 2016). One study enrolled adults (aged 18 years and older) (Bishay 2017), two studies enrolled children and adolescents (IRCT20190407043190N1; NCT04293926), and three studies enrolled adolescents and adults (Cox 2019; NCT03100214; Powers 2016).

Interventions

There was great variety between studies with respect to physical activity modalities and approaches. One study employed a combined aerobic and anaerobic home-based training programme (Powers 2016). One study investigated a four-week combined aerobic and anaerobic training programme, but the setting was not entirely clear from the registry entry (IRCT20190407043190N1). One study was conducted with participants hospitalised for treatment of a pulmonary exacerbation (NCT03100214). One study investigated the efficacy of a 12-week web-based application for improving participation in physical activity compared to usual care following hospitalisation for a respiratory exacerbation (Cox 2019). In another study, participants received an activity monitor (Fitbit) to measure physical activity and were followed over one year, completing surveys and exercise tests. Participants in the control group received usual care and were offered Fitbits after the first year (Bishay 2017). One study aimed to assess the effects of an eight-week resistance training programme on the variability in heart rate in children and adolescents with CF versus usual care (i.e. routine recommendations, including lifestyle recommendations) (NCT04293926).

Outcomes

Five studies defined changes in FEV_1 after the physical activity intervention as a secondary study outcome (Bishay 2017; Cox 2019; NCT03100214; NCT04293926; Powers 2016). Four studies reported on functional exercise capacity using a graded exercise test (Bishay 2017), the 6MWT (NCT03100214), or shuttle test (Cox 2019; Powers 2016). Four studies reported changes in HRQoL (Bishay 2017; Cox 2019; IRCT20190407043190N1; Powers 2016). Two studies included physical activity (Cox 2019; Powers 2016).

Ongoing studies

We listed 12 studies as ongoing (Curran 2020; ISRCTN92573472; Monteiro 2019; NCT03273959; NCT03970369; NCT04249999; NCT04543929; NCT04683809; NCT04742049; NCT05147285; NCT05173194; NCT05239611).

Trial characteristics

All 12 ongoing studies are of a randomised parallel-group design and registered with ClinicalTrials.gov or the ISRCTN registry. All but one of the studies are single-centre studies; the exception is a multicentre study conducted across the UK (NCT04249999). The studies range in duration: the shortest being two weeks (NCT03273959), then six weeks (NCT04742049), eight weeks (Monteiro 2019; NCT05147285; NCT05173194), 12 weeks (ISRCTN92573472; NCT04249999; NCT04543929; NCT04683809; NCT05239611), and the longest lasting over six months (Curran 2020; NCT03970369). Three studies included a follow-up period: of eight weeks (Monteiro 2019), three months (NCT03970369), and six months (NCT04249999). All 12 studies have specified their inclusion and exclusion criteria, and all 12 have included both sexes. Five studies focus on children, adolescents or both (Monteiro 2019; NCT03273959; NCT03970369; NCT04683809; NCT05147285), four on adults only (Curran 2020; ISRCTN92573472; NCT04543929; NCT05239611), one on people between 12 and 35 years of age (NCT04249999), and one on people 16 years and older (NCT05173194). In one study, participation in the intervention was not restricted by age (NCT04742049). In four studies, participation in the physical activity trial is restricted to participants with an FEV_1 equal to or greater than 25% predicted (Curran 2020), or equal to or greater than 40% predicted (NCT04742049; NCT05147285; NCT05239611). The target sample size in the studies ranges from 20 to 94 study participants.

Interventions

There is a great variety in interventions with respect to the study designs.

In Curran 2020, participants receive a fitness tracker and personalised feedback via a text message every week about their physical activity levels. A physiotherapist discusses individual short- and long-term goals with each participant. The control group also receives a fitness tracker, but will not receive individualised goals and feedback during the study.

In one study, participants in the partially supervised intervention group receive an exercise manual (hard copy) and access to an online exercise diary for 12 weeks. They also receive a fitness

tracker, to measure daily steps and active minutes. The control group will receive usual care (ISRCTN92573472).

Monteiro 2019 aims to evaluate the effects of anaerobic interval training on glucose tolerance in children and adolescents with CF versus usual care (no exercise training).

In one study, participants receive routine physical therapy plus exercise training (non-supervised) in the form of a booklet and are guided by a health professional during treatment for a pulmonary exacerbation (NCT03273959).

One pilot RCT investigates the effects of an individualised physical activity prescription plus activity monitoring (only intervention group) on retention to the trial, and feasibility and acceptability of activity monitoring in young people with CF (NCT03970369).

One multicentre study is investigating the effects of a physical activity intervention with an online platform to monitor daily activity compared to usual care (NCT04249999).

In one study, the effects of standard of care therapy plus exercise are being compared to standard of care only for improving cardiorespiratory fitness over 12 weeks (NCT04543929).

One study is evaluating the effects of a partially supervised telerehabilitation-based physical activity programme versus usual care (no exercise prescription), including individuals that self-isolated during the 2019 coronavirus pandemic (NCT04742049).

One study aims to assess the effects of rehabilitation sessions, including postural, breathing and high-intensity interval training exercises, through online programmes for rehabilitation. The exercise programme is being applied three days a week for three months (NCT04683809).

One study is assessing the effects of different exercise training modalities on functional exercise capacity (primary outcome). One group takes part in online supervised stabilisation exercises, one group performs online supervised aerobic exercise training and stabilisation exercises, and one group receives physical activity recommendations (control) (NCT05147285).

Another study aims to assess the effects of a remotely supervised resistance exercise programme on lung function, muscle strength, body composition, quality of life and inflammatory markers in adults with CF (NCT05173194).

One study is evaluating the effects of a 12-week home-based telerehabilitation intervention compared to usual care (NCT05239611).

Outcomes

The primary outcome measures of the studies are: changes in (functional) exercise capacity measured with various tests (NCT03273959; ISRCTN92573472; NCT04742049); change in glucose tolerance (Monteiro 2019); change in HRQoL (NCT04683809); and the recruitment rates over a 10-month period, retention to the trial, as well as feasibility and acceptability of physical activity monitoring (NCT03970369). Three registered studies include two different primary outcomes (NCT05147285; NCT05239611), or even four different primary outcomes (NCT05173194); this increases the risk of choosing an outcome with a 'statistically significant' result. Seven studies include FEV_1 as an outcome (Curran 2020; Monteiro 2019; NCT04249999; NCT04543929; NCT05147285; NCT05173194; NCT05239611); two studies report including lung function as an outcome, but do not provide any further details (ISRCTN92573472; NCT03273959). Nine studies include quality of life (QoL) as an outcome (Curran 2020; ISRCTN92573472; Monteiro 2019; NCT04249999; NCT04543929; NCT04683809; NCT05147285; NCT05173194; NCT05239611), and five studies include objectively measured or self-reported physical activity (Curran 2020; NCT03970369; NCT04249999; NCT04742049; NCT05147285). Several other secondary outcomes are being investigated; these are listed in the Characteristics of ongoing studies table.

Risk of bias in included studies

We assessed each study for risk of bias according to the Cochrane risk of bias tool, which categorises risk into low, high or unclear risk of bias (Higgins 2017). The results are displayed graphically in Figure 1 and Figure 2.

Allocation

Sequence generation

Nine studies described the methods used for generation of the randomisation sequence and were judged to have a low risk of bias (Carr 2018; Del Corral 2018; Douglas 2015; Gupta 2019; Hebestreit 2022; Hommerding 2015; Rovedder 2014; Sawyer 2020; Schneiderman-Walker 2000). A total of 13 studies were described as randomised, but gave insufficient details of the randomisation methods used; we deemed these to have an unclear risk of bias (Alexander 2019; Beaudoin 2017; Cerny 1989; Donadio 2020; Güngör 2021; Hatziagorou 2019; Klijn 2004; Michel 1989; Moorcroft 2004; Santana-Sosa 2012; Santana-Sosa 2014; Selvadurai 2002; Turchetta 1991). The abstract for Hatziagorou 2019 states that participants were divided into two groups. We contacted the primary and corresponding author of this study and she confirmed that this is an RCT. However, no details of the method are available and we graded the risk of bias as unclear. In the remaining two studies, information on the generation of the random sequence was provided, but the method used in the studies can potentially introduce selection bias and lacks reproducibility (Hebestreit 2010; Kriemler 2013). We judged these as having a high risk of bias.

Allocation concealment

Only eight studies described how allocation was concealed. We judged six of these studies to have a low risk of bias (Del Corral 2018; Gupta 2019; Hebestreit 2022; Klijn 2004; Sawyer 2020; Selvadurai 2002), and the other two studies to have a high risk of bias (Hebestreit 2010; Kriemler 2013). In these studies, investigators drew lots from a bag to allocate participants. However, allocation concealment is no longer assured when an investigator is aware of the number of lots in the bag and is aware of which have already been drawn; for example, if, for one group, all available lots have already been drawn out. A total of 16 studies (six of which were published as abstracts only) did not give any details of the method of allocation concealment; we assessed these as having an unclear risk of bias (Alexander 2019; Beaudoin 2017; Carr 2018; Cerny 1989; Donadio 2020; Douglas 2015; Güngör 2021; Hatziagorou 2019; Hommerding 2015; Michel 1989; Moorcroft 2004; Rovedder 2014; Santana-Sosa 2012; Santana-Sosa 2014; Schneiderman-Walker 2000; Turchetta 1991).

Blinding

None of the studies was blinded for group assignment, as it is impossible to blind physical activity and exercise training compared to no training.

Blinding of participants and personnel (performance bias)

In two studies, one researcher of the study team was blinded to the participants' group allocation (Klijn 2004; Rovedder 2014). Klijn and colleagues reported that the primary researcher was blinded to group allocation, but their role in the study was not clear (Klijn 2004). In Rovedder 2014, one researcher was blinded for randomisation, the intervention and was responsible for database entries. Furthermore, the study staff who administered the questionnaires and performed the tests to collect outcome data were blinded to the participants' treatment allocations. Nevertheless, we judged all included studies to have a high risk of bias for this domain, as blinding of participants to treatment allocation is not possible in exercise studies.

Blinding of outcome assessment (detection bias)

In 10 studies, outcome assessors were blinded to group allocation; we deemed these studies to have a low risk of bias (Del Corral 2018; Douglas 2015; Gupta 2019; Güngör 2021; Kriemler 2013; Rovedder 2014; Santana-Sosa 2012; Santana-Sosa 2014; Sawyer 2020; Schneiderman-Walker 2000). We deemed 14 studies to have an unclear risk of bias. It is unclear whether outcome measures were assessed by blinded investigators in 13 of the studies (Alexander 2019; Beaudoin 2017; Carr 2018; Cerny 1989; Donadio 2020; Douglas 2015; Hatziagorou 2019; Hebestreit 2010; Hommerding 2015; Michel 1989; Moorcroft 2004; Selvadurai 2002; Turchetta 1991); and one study reported that the primary researcher was blinded, but it is not clear whether this person was responsible for outcome assessment (Klijn 2004). Finally, in one study, the investigators explicitly stated that outcome assessors were not blinded, but we were not certain how this would influence the results for our outcomes (Hebestreit 2022).

Incomplete outcome data

We evaluated risk of bias for incomplete outcome data with respect to the use of an intention-to-treat analysis, including appropriate methods for imputing data and the dropout rate (balanced or unbalanced between groups), including a description of reasons for dropouts.

A total of 19 studies provided information about dropouts (Beaudoin 2017; Cerny 1989; Del Corral 2018; Douglas 2015; Gupta 2019; Güngör 2021; Hebestreit 2010; Hebestreit 2022; Hommerding 2015; Klijn 2004; Kriemler 2013; Moorcroft 2004; Rovedder 2014; Santana-Sosa 2012; Santana-Sosa 2014; Sawyer 2020; Schneiderman-Walker 2000; Selvadurai 2002). Five studies (published only in abstract form) did not give any details about dropouts (Alexander 2019; Donadio 2020; Douglas 2015; Hatziagorou 2019; Michel 1989; Turchetta 1991).

We assessed 11 studies as having a low risk of bias for incomplete outcome data (Cerny 1989; Del Corral 2018; Douglas 2015; Gupta 2019; Hebestreit 2022; Hommerding 2015; Klijn 2004; Kriemler 2013; Rovedder 2014; Sawyer 2020; Selvadurai 2002). Of these, four studies reported no dropouts (Cerny 1989; Gupta 2019; Hommerding 2015; Selvadurai 2002), and in six studies, the dropout rate was balanced among groups and reasons for dropout were reported (Del Corral 2018; Hebestreit 2022; Klijn 2004; Kriemler 2013, Rovedder 2014; Sawyer 2020). Additionally, Hebestreit 2022 and Rovedder 2014 used multiple imputation to account for missing data in their statistical analysis. In one study, there were few dropouts and the reasons were given (two of these withdrew for reasons not related to the intervention) (Douglas 2015).

We judged four studies as having a high risk of bias (Beaudoin 2017; Carr 2018; Santana-Sosa 2012; Santana-Sosa 2014). In Beaudoin 2017, the dropout rate (postrandomisation) was 18% (n = 3) and the group allocation of two study participants was not reported. This study was registered as a randomised cross-over study (NCT02127957), but the results were only reported for the first phase and the original publication described it as a parallel design study (Beaudoin 2017). Carr randomised 51 participants; 21.6% dropped out with reasons that were reported in detail in the CONSORT flow diagram, but investigators did not perform an intention-to-treat analysis (Carr 2018). In the remaining two studies, dropout rates were high and unbalanced between groups (Santana-Sosa 2012; Santana-Sosa 2014). Both studies reported the use of intention-to-treat analysis, while one study used the 'last value carried forward' method (Santana-Sosa 2012). In the other Santana-Sosa study, the method used for data imputation was not reported (Santana-Sosa 2014).

We rated the remaining studies at unclear risk of bias for incomplete outcome data (Alexander 2019; Donadio 2020; Güngör 2021; Hatziagorou 2019; Hebestreit 2010; Michel 1989; Moorcroft 2004; Schneiderman-Walker 2000; Turchetta 1991). Five of these studies were published only in abstract form and did not give any details about dropouts (Alexander 2019; Donadio 2020; Hatziagorou 2019; Michel 1989; Turchetta 1991). In one study lasting longer than six months, dropouts were reported and balanced between groups, but reasons for dropouts were not described and intention-to-treat analysis was not used (Hebestreit 2010). Schneiderman-Walker 2000 reported the reasons for participants dropping out and that an intention-to-treat analysis produced similar results for pulmonary function outcomes; however, data were only reported for 65 participants, excluding dropouts. Another study reported using an intention-to-treat analysis, but missing data were treated by omission rather than imputation and reasons for dropout were not clearly described (Moorcroft 2004). In one study, reasons for dropout were not reported for all individuals (Güngör 2021). Additionally, this study did not use intention-to-treat analysis, and was therefore rated at unclear risk of bias.

Selective reporting

We judged 10 studies to have a low risk of bias since they reported all outcomes detailed in their 'methods' sections for all time points in their 'Results' sections (Cerny 1989; Gupta 2019; Hebestreit 2022; Kriemler 2013; Moorcroft 2004; Rovedder 2014; Santana-Sosa 2012; Santana-Sosa 2014; Sawyer 2020; Schneiderman-Walker 2000). One of these studies mentioned in the original publication that data for HRQoL would be addressed separately (Kriemler 2013). Data from this study were published together with data from another study which used similar methods (Hebestreit 2010); the combined data are presented in a separate paper (Hebestreit 2014). In another study, Hebestreit 2022 reported in the publication that data for substudies are not included in the main report.

A total of 12 studies had an unclear risk of bias for selective outcome reporting (Alexander 2019; Del Corral 2018; Donadio

2020; Douglas 2015; Güngör 2021; Hatziagorou 2019; Hebestreit 2010; Hommerding 2015; Klijn 2004; Michel 1989; Selvadurai 2002; Turchetta 1991). Six studies were only available in abstract format and we could not assess selective reporting (Alexander 2019; Donadio 2020; Douglas 2015; Hatziagorou 2019; Michel 1989; Turchetta 1991). The remaining six studies did not report on all their stated outcomes. Five studies did not report all outcomes for HRQoL (Del Corral 2018; Güngör 2021; Klijn 2004; Hebestreit 2010; Hommerding 2015), and Hebestreit 2010 did not report all anaerobic exercise capacity outcomes. Two studies did not report all variables for cardiopulmonary exercise testing as mentioned in their 'methods' section (Hommerding 2015; Selvadurai 2002).

We judged Beaudoin 2017 at high risk of bias for selective reporting, because the study was registered as a randomised cross-over study, but reported as a parallel-design study. The second part of the study was not reported in the original publication.

Finally, we judged Carr 2018 at high risk of bias for selective reporting because data for HRQoL (primary endpoint) were not presented for all CFQ-R domains for all time points.

Other potential sources of bias

Description of inclusion or exclusion criteria

Six studies were only available in abstract format and did not state inclusion or exclusion criteria (Alexander 2019; Donadio 2020; Douglas 2015; Hatziagorou 2019; Michel 1989; Turchetta 1991). The potential for bias was limited in the 15 studies which clearly stated inclusion and exclusion criteria (Beaudoin 2017; Carr 2018; Del Corral 2018; Gupta 2019; Güngör 2021; Hebestreit 2010; Hebestreit 2022; Hommerding 2015; Kriemler 2013; Moorcroft 2004; Rovedder 2014; Santana-Sosa 2012; Santana-Sosa 2014; Sawyer 2020; Selvadurai 2002). Three studies described the inclusion criteria but not the exclusion criteria, which could be a potential source of bias (Cerny 1989; Klijn 2004; Schneiderman-Walker 2000).

Statistical analysis

A total of 18 studies, published as full-text articles, clearly described the methods of statistical analysis, thus eliminating a potential source of bias (Beaudoin 2017; Carr 2018; Cerny 1989; Del Corral 2018; Güngör 2021; Gupta 2019; Hebestreit 2010; Hebestreit 2022; Hommerding 2015; Klijn 2004; Kriemler 2013; Moorcroft 2004; Rovedder 2014; Santana-Sosa 2012; Santana-Sosa 2014; Sawyer 2020; Schneiderman-Walker 2000; Selvadurai 2002). Of the six studies published as abstracts (Alexander 2019; Donadio 2020; Douglas 2015; Hatziagorou 2019; Michel 1989; Turchetta 1991), one study reported details on the statistical analysis (Donadio 2020).

One study did not report the number of participants in each group so the MD between the treatment and control groups could not be calculated (Michel 1989).

In one study, information on sample size and recruitment goals differed between the information provided on the trial registry and the final publication (Beaudoin 2017). The study aimed to recruit 24 participants (12 in each group) but the recruitment goal was not achieved (18 were recruited and only 17 randomised). According to the power calculation provided in the original publication, 18 participants (nine per group) were required for the analysis. Only 14 participants actually completed the study (Beaudoin 2017). We judged this study to have a high risk of bias.

In two studies, the number of included participants was much lower than the enrolment goal: namely, 117/292 participants in Hebestreit 2022, and 17/32 participants in Sawyer 2020. Consequently, both studies were potentially underpowered for several outcomes. We judged these two studies to have a high risk of bias.

Group characteristics

In five studies, there were significant between-group differences at baseline despite randomisation (Cerny 1989; Kriemler 2013; Rovedder 2014; Santana-Sosa 2012; Santana-Sosa 2014). In one study, FEV_1 and $FEF_{25–75}$ were significantly lower in the control group compared to the training group at admission (Cerny 1989). In a second study, differences in exercise capacity (peak power was higher in the strength training group compared to the control group) and in vigorous physical activity (lower in the aerobic training group compared to controls) were evident at baseline (Kriemler 2013). In both Santana-Sosa studies, the training groups had a lower aerobic exercise capacity (VO_2 peak) and lower muscle strength (most but not all strength measures) (Santana-Sosa 2012; Santana-Sosa 2014). In the fifth study, BMI was significantly lower in the intervention group compared to the control group (Rovedder 2014). In addition, in Güngör 2021, some HRQoL domains were lower in the intervention compared to the control group (Güngör 2021). The authors wrote that no statistically significant differences existed in baseline demographic characteristics between groups. It is uncertain whether these factors could be a potential source of bias so we judged the risk to be unclear for significant between-group differences at baseline.

Ten of the 18 studies published as full-text articles used FEV_1 % predicted values as exclusion criteria (Beaudoin 2017; Güngör 2021; Gupta 2019; Hebestreit 2010; Hebestreit 2022; Klijn 2004; Kriemler 2013; Santana-Sosa 2012; Santana-Sosa 2014; Schneiderman-Walker 2000); this was also true of one study where information on inclusion and exclusion criteria were available from ClinicalTrials.gov (Douglas 2015). The remaining eight studies that were published as full-text articles did not specify disease severity based on FEV_1 as an exclusion criterion (Carr 2018; Cerny 1989; Del Corral 2018; Hommerding 2015; Moorcroft 2004; Rovedder 2014; Sawyer 2020; Selvadurai 2002). There was no information available in the remaining five studies, published as abstracts (Alexander 2019; Donadio 2020; Hatziagorou 2019; Michel 1989; Turchetta 1991). We accept that studies which exclude participants on the basis of one of our outcomes may cause a risk of bias to the review. However, the risk of exercise-induced adverse effects is likely to be higher in people with severe CF lung disease and many researchers tend to exclude those people because of this. In one study, financial support was provided to the physical activity group participants to foster the activity plan; this study was judged at unclear risk of bias (Hebestreit 2010).

Intervention

In the original publication by Beaudoin there was no information on the control intervention (Beaudoin 2017). We noticed discrepancies between the registered trial protocol (clinicaltrials.gov/ct2/show/NCT02127957) and published trial design (cross-over versus parallel-group design) (Beaudoin 2017).

Data discrepancies

We rated three studies as having a high risk of bias (Beaudoin 2017; Santana-Sosa 2012; Santana-Sosa 2014). Two studies for which we received some raw data from the authors were rated as high risk of bias due to inconsistencies between the raw data files and the data reported in the original publications (Santana-Sosa 2012; Santana-Sosa 2014). Furthermore, Beaudoin 2017 reported within-group changes from baseline and not between-group differences, as would be appropriate for an RCT. We calculated between-group differences using raw data provided by the authors and our results suggest no between-group differences for the primary endpoint. When considered alongside the fact that the stated power calculation requiring 18 participants to demonstrate a difference was not achieved (see 'Statistical analysis' above), there is a high risk of bias that the reported effects are not sound.

Effects of interventions

See: **Summary of findings 1** Physical activity compared with no physical activity for cystic fibrosis

We included 24 studies with 875 participants and pooled data comparing any type of physical activity intervention versus no physical activity intervention (Alexander 2019; Beaudoin 2017; Carr 2018; Cerny 1989; Del Corral 2018; Donadio 2020; Douglas 2015; Güngör 2021; Gupta 2019; Hatziagorou 2019; Hebestreit 2010; Hebestreit 2022; Hommerding 2015; Klijn 2004; Kriemler 2013; Michel 1989; Moorcroft 2004; Rovedder 2014; Santana-Sosa 2012; Santana-Sosa 2014; Sawyer 2020; Schneiderman-Walker 2000; Selvadurai 2002; Turchetta 1991). Two studies compared endurance training and resistance training versus no training and for all outcomes in this review, we combined the two active arms of each study (Kriemler 2013; Selvadurai 2002). Six studies were published as abstracts only (Alexander 2019; Donadio 2020; Douglas 2015; Hatziagorou 2019; Michel 1989; Turchetta 1991), and no information on outcomes relevant for this review was available from five of these (Alexander 2019; Donadio 2020; Hatziagorou 2019; Michel 1989; Turchetta 1991). See Summary of findings 1 for explanations of the judgements for the certainty of the evidence.

Where primary studies reported differences between groups but did not provide adequate data (means and SD) that could be presented in Review Manager 5 (Review Manager 2014), we included information from the primary (original) study in the results.

Within the results below, we present the effects of the active interventions (supervised, partially supervised, unsupervised but with access to study resources) at the end of each active intervention period at the time points of up to and including six months and more than six months and for follow-up periods where all participants reverted to usual care. In total, 14 studies had active intervention periods up to and including six months (Alexander 2019; Beaudoin 2017; Cerny 1989; Donadio 2020; Güngör 2021; Hommerding 2015; Klijn 2004; Michel 1989; Rovedder 2014; Santana-Sosa 2012; Santana-Sosa 2014; Sawyer 2020; Selvadurai 2002; Turchetta 1991), and 10 studies had active intervention periods longer than six months (Carr 2018; Del Corral 2018; Douglas 2015; Gupta 2019; Hatziagorou 2019; Hebestreit 2010; Hebestreit 2022; Kriemler 2013; Moorcroft 2004; Schneiderman-Walker 2000). Nine studies implemented an additional follow-up period (Del Corral 2018; Güngör 2021; Hebestreit 2010; Klijn 2004; Kriemler 2013; Michel 1989; Santana-Sosa 2012; Santana-Sosa 2014; Selvadurai 2002).

If a study reported multiple time points for a category of activity (supervised, partially supervised, unsupervised but with access to study resources) within our predefined reporting periods (i.e. up to and including six months, and longer than six months), we reported the longest training period within the given category.

Due to our concerns about data quality from both studies by Santana-Sosa (Santana-Sosa 2012; Santana-Sosa 2014), we excluded these from the formal analysis in the review. We provide their data in two additional tables (Table 1; Table 2).

In one small study (n = 19), data were not normally distributed and within-group changes were reported as median (interquartile range (IQR)) (Güngör 2021). Mean or median differences were not available. We contacted the authors and requested raw data but did not receive feedback. We decided not to compute means (SDs) because of the small group sizes (nine and 10 study participants in the different groups) and skewed data distribution. We presented the data for this study descriptively.

Of note, when interpreting the results presented below, in Kriemler 2013, the control group experienced an unusual deterioration of physical health during the study; the results should be interpreted with caution. In Selvadurai 2002, all participants received intravenous antibiotic therapy during the in-hospital physical activity training programme. In Klijn 2004, the pre-exercise training values for the CFQ-R physical functioning domain were substantially lower in the physical activity group compared to the control group, and the effects were large. For these reasons, we undertook a sensitivity analysis to determine the influence of these single studies to the overall pooled estimate. We evaluated the effect of Kriemler 2013 on the pooled estimate for VO_2 peak; the effect of Kriemler 2013 and Selvadurai 2002 on the pooled effect estimate for FEV_1, and the effect of Klijn 2004 on the pooled estimated for HRQoL.

Primary outcomes

1. Exercise capacity by peak oxygen uptake

Twelve studies reported VO_2 peak (Beaudoin 2017; Douglas 2015; Gupta 2019; Hatziagorou 2019; Hebestreit 2010; Hebestreit 2022; Hommerding 2015; Klijn 2004; Kriemler 2013; Sawyer 2020; Selvadurai 2002; Schneiderman-Walker 2000). See: Analysis 1.1; Analysis 1.2; Analysis 1.3; Analysis 1.4; Analysis 1.5.

Eight studies measured VO_2 peak during an incremental cycling exercise test (Beaudoin 2017; Hatziagorou 2019; Hebestreit 2010; Hebestreit 2022; Klijn 2004; Kriemler 2013; Sawyer 2020; Schneiderman-Walker 2000), and four studies used an incremental treadmill exercise test (Douglas 2015; Gupta 2019; Hommerding 2015; Selvadurai 2002). Data from Hatziagorou 2019 (published as abstract) could not be included in the analysis, and are reported descriptively.

Up to and including six months' active intervention

Eight studies reported VO_2 peak at up to and including six months' active intervention (Beaudoin 2017; Hebestreit 2010; Hebestreit 2022; Hommerding 2015; Klijn 2004; Kriemler 2013; Sawyer 2020; Selvadurai 2002). The combined analyses (n = 323), in which data

from the two active arms of the studies by Kriemler and Selvadurai were combined into a single arm, revealed a difference in VO_2 peak between groups in favour of physical activity (MD 2.10 mL/min per kg bodyweight, 95% CI 0.06 to 4.13; I^2 = 76%; Analysis 1.1). Heterogeneity between these studies was substantial which was most likely due to the unusual deterioration of the control group in Kriemler 2013. In a sensitivity analysis excluding Kriemler 2013, the effect estimate changed towards null and between-study heterogeneity decreased (MD 1.30 mL/min per kg bodyweight, 95% CI −0.17 to 2.78; I^2= 56%; n = 287; Analysis 1.2).

One multicentre study reported changes in VO_2 peak expressed as % predicted after six months of vigorous physical activity versus control (Hebestreit 2022). There was no evidence of a between-group effect on VO_2 peak after six months (MD 0.60% predicted, 95% CI −3.01 to 4.21; Analysis 1.3).

Over six months' active intervention

Six studies reported VO_2 peak at over six months' active intervention (Douglas 2015; Gupta 2019; Hebestreit 2010; Hebestreit 2022; Kriemler 2013; Schneiderman-Walker 2000) (Analysis 1.1). The combined analysis showed an effect on VO_2 peak in favour of physical activity (MD 1.60 mL/min per kg bodyweight, 95% CI 0.16 to 3.05; I^2= 59%; n = 348; Analysis 1.1). Certainty of evidence was moderate (Summary of findings 1). Heterogeneity between studies was substantial, most likely due to the heterogeneous study durations of 12 and 36 months (Analysis 1.1). In a sensitivity analysis (n = 318) excluding the Kriemler 2013 study, the effect estimate changed from 1.60 mL/min per kg bodyweight (95% CI 0.16 to 3.05) to 1.38 mL/min per kg bodyweight (95% CI 0.08 to 2.69), and between-study heterogeneity changed minimally from 59% to 55% (Analysis 1.2).

Hebestreit 2022 reported a higher VO_2 peak (% predicted) in the intervention compared to the control group (MD 4.53, 95% CI 1.07 to 7.99; n = 117; Analysis 1.3).

Hatziagorou 2019 (n = 30) reported an increase in VO_2 peak of 23.8% in the intervention group after 12 months, while there was no change in the control group; however, the authors did not report the MD. At baseline, VO_2 peak was 72.7% predicted in the intervention group, and 89.1% predicted in the control group.

Follow-up (no active intervention)

Three studies reported VO_2 peak at follow-up periods ranging between one and 12 months (Hebestreit 2010; Kriemler 2013; Selvadurai 2002). In this comparison, VO_2 peak was higher in the physical activity intervention versus control group (MD 3.27 mL/min per kg bodyweight, 95% CI 1.37 to 5.18; I^2 = 0%; n = 125; Analysis 1.1). In a sensitivity analysis excluding Kriemler 2013, the overall effect estimate and 95% CIs did not change substantially (MD 3.21 mL/min per kg bodyweight, 95% CI 1.27 to 5.14; I^2 = 0%; n = 99; Analysis 1.2). Between-study heterogeneity remained unchanged.

Total results irrespective of duration of the active intervention

In a combined analysis of 11 studies, VO_2 peak was higher in the physical activity group compared to the control group (MD 1.52 mL/min per kg bodyweight, 95% CI 0.31 to 2.73; I^2 = 60%; n = 496; Analysis 1.4). A sensitivity analysis excluding Kriemler 2013 resulted in a slightly lower effect of physical activity on VO_2 peak, with little effect on between-study heterogeneity (MD 1.38 mL/min per kg bodyweight, 95% CI 0.22 to 2.55; I^2 = 58%; n = 466; Analysis 1.5).

2. Lung function: forced expiratory volume in one second

A total of 18 studies reported FEV_1 (Beaudoin 2017; Carr 2018; Cerny 1989; Donadio 2020; Douglas 2015; Güngör 2021; Gupta 2019; Hatziagorou 2019; Hebestreit 2010; Hebestreit 2022; Hommerding 2015; Klijn 2004; Kriemler 2013; Moorcroft 2004; Rovedder 2014; Sawyer 2020; Schneiderman-Walker 2000; Selvadurai 2002).

We reported six studies descriptively. Three studies, two of which were published as abstracts only, reported on changes in FEV_1 but did not present any data (Carr 2018; Donadio 2020; Hatziagorou 2019). Cerny 1989 reported no difference in the change in FEV_1 % predicted, but data could not be extracted. Klijn 2004 reported that there were no differences between groups in lung function parameters, but no data were available for analysis. Güngör 2021 reported medians and IQRs, which we were unable to analyse in the review.

We analysed data from 12 studies. A total of 11 studies reported data on changes in FEV_1 % predicted (Beaudoin 2017; Douglas 2015; Gupta 2019; Hebestreit 2010; Hebestreit 2022; Hommerding 2015; Kriemler 2013; Rovedder 2014; Sawyer 2020; Schneiderman-Walker 2000; Selvadurai 2002; Analysis 1.6; Analysis 1.7; Analysis 1.10; Analysis 1.11), one study reported in z-score units as well as FEV_1 % predicted (Douglas 2015; Analysis 1.9), and one study reported in mL only (Moorcroft 2004; Analysis 1.8).

Up to and including six months' active intervention

Eight studies reported FEV_1 up to and including six months' active intervention (Beaudoin 2017; Hebestreit 2010; Hebestreit 2022; Hommerding 2015; Kriemler 2013; Rovedder 2014; Sawyer 2020; Selvadurai 2002). In a combined analysis, there was no evidence of a between-group difference for FEV_1, but heterogeneity was substantial (MD 1.30% predicted, 95% CI −3.01 to 5.61; I^2 = 79%; n = 356; Analysis 1.6). A sensitivity analysis excluding Kriemler 2013 and Selvadurai 2002 changed the effect estimate for FEV_1 to a beneficial effect in favour of control (MD −2.16 % predicted, 95% CI −4.14 to −0.17; n = 255; Analysis 1.7). In six of seven studies, the CIs included 0, and the summary estimate appeared to be mainly affected by Hebestreit 2022 (n = 117), as it received much weight in the combined analysis.

Cerny 1989 (n = 17), Carr 2018 (n = 40) and Donadio 2020 (n = 25) reported no differences in FEV_1 after the intervention. Güngör 2021 reported no between-group differences in median FEV_1 % predicted after six weeks (intervention group: 90.5 (IQR 37.75) % predicted; n = 10; control group: 86 (IQR 19) % predicted; n = 9).

In Klijn 2004(n = 20), there were no differences between groups in lung function parameters, but no data were available for analysis.

Over six months' active intervention

Six studies reported FEV_1 at over six months' active intervention (Douglas 2015; Gupta 2019; Hebestreit 2010; Hebestreit 2022; Kriemler 2013; Schneiderman-Walker 2000). The combined analysis showed no between-group differences in FEV_1 % predicted and between-study heterogeneity was moderate to substantial (MD

2.41 % predicted, 95% CI −0.49 to 5.31; I^2 = 52%; n = 367; Analysis 1.6). Certainty of the evidence was low (Summary of findings 1). In a sensitivity analysis excluding Kriemler 2013, FEV_1 % predicted was higher in the physical activity intervention group compared to the control group (but there was an unexpected deterioration of lung health in the control group) (MD 1.71 % predicted, 95% CI 0.15 to 3.26; n = 333; Analysis 1.7). The exclusion of Kriemler 2013 changed the overall effect estimate favouring the physical activity intervention compared to no physical activity intervention, and increased the precision of the effect estimate (narrower 95% CIs). Of note, none of the individual studies included in the combined analysis showed an effect in change in FEV_1 after the intervention (i.e. all 95% CIs included 0).

Moorcroft 2004 found no between physical activity and control on FEV_1 after 12 months (MD 107 mL, 95% CI −73.98 to 287.98; Analysis 1.8). Douglas 2015 found no between-group difference in FEV_1 z-score after 24 months (MD 0.12, 95% CI −0.37 to 0.61; Analysis 1.9).

The 12-month intervention by Hatziagorou 2019 reported unchanged FEV_1 in the physical activity group of 0.88% and no change in the control group (specific MD not reported; n = 30).

Follow-up (no active intervention)

Three studies reported FEV_1 with follow-up periods ranging between one and 12 months (Hebestreit 2010; Kriemler 2013; Selvadurai 2002). There was no difference between physical activity and control groups (MD 5.68 % predicted, 95% CI −1.88 to 13.23; n = 128; Analysis 1.6). When two studies were excluded from this comparison in a sensitivity analysis (Kriemler 2013; Selvadurai 2002), Hebestreit 2010 found no difference between physical activity and no physical activity on FEV_1 % predicted (MD −0.32, 95% CI −11.90 to 11.26; n = 31; Analysis 1.7).

Güngör 2021 reported no between-group differences in FEV_1 % predicted after six months' follow-up (median: intervention group: 88.5 (IQR 8.75) % predicted; n = 10; control group: 95.5 (IQR 49.25) % predicted; n = 9).

Total results irrespective of duration of the active intervention

In a combined analysis of 11 studies, there was no evidence of a difference in FEV_1 % predicted between groups and between-study heterogeneity was moderate (MD 1.37, 95% CI −0.74 to 3.47; I^2 = 43%; n = 536; Analysis 1.10). A sensitivity analysis excluding Kriemler 2013 and Selvadurai 2002 reduced study heterogeneity but the overall effect did not change (MD 1.07, 95% CI −0.36 to 2.49; I^2 = 0%; n = 436; Analysis 1.11).

3. Health-related quality of life

Eight studies reported HRQoL data (Beaudoin 2017; Douglas 2015; Hebestreit 2010; Hebestreit 2022; Klijn 2004; Kriemler 2013; Sawyer 2020; Selvadurai 2002). Seven studies reported on changes in the physical function domain of the CFQ-R questionnaire (Beaudoin 2017; Douglas 2015; Hebestreit 2010; Hebestreit 2022; Klijn 2004; Kriemler 2013; Sawyer 2020), six studies reported on changes in respiratory symptoms (CFQ-R) (Beaudoin 2017; Douglas 2015; Hebestreit 2010; Hebestreit 2022; Kriemler 2013; Sawyer 2020), and one study reported on changes in well-being one month after completion of the study ('off training') (Selvadurai 2002). One study, published only as an abstract, reported no changes in HRQoL (using CFQ-R) between the physical activity and control group after three months, but data were not reported in the abstract (Alexander 2019). Güngör 2021 assessed HRQoL with the CFQ-R but postintervention data were not reported for the physical functioning and respiratory domains.

a. Physical functioning

Up to and including six months' active intervention

Six studies reported physical functioning up to and including six months' active intervention (Beaudoin 2017; Hebestreit 2010; Hebestreit 2022; Klijn 2004; Kriemler 2013; Sawyer 2020) (Analysis 1.12). In a combined analysis, the change in the CFQ-R physical function domain was not different between the physical activity intervention and control groups, but between-study heterogeneity was substantial (MD 4.67, 95% CI −2.55 to 11.90; I^2 = 65%; n = 217; Analysis 1.12). In Klijn 2004, the mean (SD) pre-exercise training values for the CFQ-R physical functioning domain were substantially lower in the physical activity group compared to the control group and the effects were large (70.3 (SD 13.8) with physical activity versus 83.2 (SD 18.5) with control; Analysis 1.12). In a sensitivity analysis excluding Klijn 2004, the effect estimate changed towards null and study heterogeneity decreased substantially (MD 0.10, 95% CI −4.05 to 4.25; I^2 = 0%; n = 197; Analysis 1.13).

In Rovedder 2014, there were no differences in CFQ-R physical function domain between the physical activity and control groups after three months. Data for HRQoL scales were reported in the original publication and presented as medians and IQRs so could not be analysed in the review. Data are presented in Table 3.

Over six months' active intervention

Four studies reported physical functioning at over six months' active intervention (Douglas 2015; Hebestreit 2010; Hebestreit 2022; Kriemler 2013). In a combined analysis, there was no evidence of an effect comparing physical activity versus no physical activity intervention on change in the CFQ-R physical function domain, and between-study heterogeneity was moderate (MD 2.19, 95% CI −3.42 to 7.80; I^2 = 39%; n = 247; Analysis 1.12). Certainty of evidence was low (Summary of findings 1).

Total results irrespective of duration of the active intervention

In a combined analysis of seven studies, there were no between-group effects for changes in the CFQ-R physical functioning domain, and between-study heterogeneity was substantial (MD 4.76, 95% CI −1.09 to 10.61; I^2 = 60%; n = 295; Analysis 1.14). A sensitivity analysis excluding Klijn 2004 changed the effect estimate towards null, and reduced between-study heterogeneity (MD 2.44, 95% CI −1.43 to 6.30; I^2 = 0%; n = 275; I^2 = 0%; Analysis 1.15).

b. Respiratory

Up to and including six months' active intervention

Five studies reported on changes in CFQ-R respiratory symptoms up to and including six months' active intervention (Beaudoin 2017; Hebestreit 2010; Hebestreit 2022; Kriemler 2013; Sawyer 2020). In a combined analysis, there were no between-group differences in CFQ-R respiratory symptoms (MD −1.87, 95% CI −5.66 to 1.92; n = 212; Analysis 1.16).

In Rovedder 2014, there were no differences in CFQ-R respiratory symptoms between the physical activity and control groups after three months. Data for HRQoL scales were reported in the original publication and presented as medians and IQRs so could not be analysed in the review. Data are presented in Table 3.

Over six months' active intervention

Four studies reported on changes in CFQ-R respiratory symptoms at over six months' active intervention (Douglas 2015; Hebestreit 2010; Hebestreit 2022; Kriemler 2013). In a combined analysis, there were no differences in CFQ-R respiratory symptoms between the intervention and control groups (MD −0.05, 95% CI −3.61 to 3.51; n = 251; Analysis 1.16). Certainty of evidence was low (Summary of findings 1).

Total results irrespective of duration of the active intervention

A combined analysis of six studies revealed no differences between physical activity versus no physical activity intervention on CFQ-R respiratory symptoms (MD 0.22, 95% CI −3.15 to 3.58; n = 279; Analysis 1.17).

c. Other

Up to and including six months' active intervention

In Rovedder 2014, there were no differences in the 36-item Short Form Survey (SF-36) (a frequently used self-reported measure of health) between the physical activity and control group after three months. Data for HRQoL scales were reported in the original publication and presented as medians and IQRs so could not be analysed in the review. Data are presented in Table 3.

Follow-up periods (no active intervention)

One study reported on changes in well-being after the intervention had been completed using the Quality of Well-Being questionnaire (Selvadurai 2002). The physical activity group reported higher well-being compared to the control group one month after the study had been completed (MD 0.07, 95% CI 0.01 to 0.13; n = 66; Analysis 1.18).

Secondary outcomes

1. Additional indices of exercise capacity

Eleven studies reported additional indices of exercise capacity (Cerny 1989; Del Corral 2018; Donadio 2020; Douglas 2015; Hebestreit 2010; Hebestreit 2022; Klijn 2004; Kriemler 2013; Rovedder 2014; Sawyer 2020; Schneiderman-Walker 2000).

a. Peak work capacity

Seven studies reported on changes in peak work capacity during maximal exercise, expressed as either watt (W) absolute values, W/kg bodyweight, or W % predicted (Cerny 1989; Hebestreit 2010; Hebestreit 2022; Klijn 2004; Kriemler 2013; Sawyer 2020; Schneiderman-Walker 2000). One study reported on changes in time to symptom limitation (T_{lim}) and VO_2 peak (mL/min per kg bodyweight and % predicted) during a submaximal constant load cycling exercise test (Sawyer 2020), and one study (published as an abstract) reported on changes in VO_2 at the anaerobic threshold (Donadio 2020).

Up to and including six months' active intervention

In a combined analysis of three studies, peak work capacity was higher in the physical activity intervention groups compared to the control groups (MD 0.32 W/kg bodyweight, 95% CI 0.12 to 0.51; I^2 = 69%; n = 164; Analysis 1.19). Between-study heterogeneity was substantial and was likely explained by Kriemler 2013, which showed a large effect, probably due to the deterioration of lung health in the control group.

In Klijn 2004, peak work capacity was higher in the training group compared to the control group after three months (MD 13.00 W, 95% CI 4.11 to 21.89; n = 20; Analysis 1.20).

In a pooled analysis of Hebestreit 2022 and Sawyer 2020, peak work capacity was higher in the physical activity compared to the control groups after two to six months (MD 6.89% predicted, 95% CI 3.94 to 9.83; n = 117; Analysis 1.21).

Cerny 1989 presented results in figures, but raw data were not available. They reported no differences between groups in peak work capacity (W/kg bodyweight).

Over six months' active intervention

In a combined analysis of three studies, peak work capacity was higher in the intervention compared to the control groups (MD 0.18 W/kg bodyweight, 95% CI 0.07 to 0.29; n = 155; Analysis 1.19).

In a combined analysis of Hebestreit 2022 and Schneiderman-Walker 2000, there was no evidence of a difference in peak exercise capacity between the physical activity intervention and control groups (MD 3.59% predicted, 95% CI −2.06 to 9.24; n = 168; Analysis 1.21).

Follow-up (no active intervention)

Two studies reported peak work capacity after a 12-month follow-up (Hebestreit 2010; Kriemler 2013).

In a combined analysis of Hebestreit 2010 and Kriemler 2013, there was no evidence of a difference in peak exercise capacity between the physical activity and control groups were observed (MD 0.26 W/kg bodyweight, 95% CI −0.03 to 0.56; n = 51; Analysis 1.19).

b. Submaximal exercise capacity

Two studies reported on submaximal exercise capacity (Donadio 2020; Sawyer 2020).

Up to and including six months' active intervention

Donadio 2020 (n = 25) reported an increase in VO_2 (% of max) at the anaerobic threshold within the group that was assigned to supervised resistance exercise with neuromuscular electrical stimulation (n = 6) and a decrease in VO_2 (% of max) for the control group (n = 11). The mean values for VO_2 (% of max) at baseline and end of treatment were 59.6 (SD 14.9) versus 68.9 (SD 10.8) (P = 0.05) in the group receiving exercise plus neuromuscular electrical stimulation, and 71.8 (SD 12.3) versus 62.1 (SD 11.6) (P = 0.01) in the control group. The paper did not provide the MD between groups and there was no information for the third group, which received supervised resistance training alone (n = 8) (Donadio 2020).

Sawyer 2020, in which the intervention group performed high-intensity interval training, found improved T_{lim} during a constant work submaximal cycling test in the exercise compared to the control group after two months (MD 211.00 seconds, 95% CI 93.40 to 328.60; Analysis 1.22). However, there were no differences in VO_2

(mL/min per kg bodyweight) or VO_2 (% predicted) during a constant work submaximal exercise test on a cycle ergometer (MD 1.01 mL/min per kg bodyweight, 95% CI −0.89 to 2.91; MD 3.00% predicted, 95% CI −0.92 to 6.92; Analysis 1.23).

c. Functional exercise capacity

Two studies reported on changes in 6MWT distance (Del Corral 2018; Rovedder 2014). Three studies reported changes in MSWT performance (Del Corral 2018; Douglas 2015; Güngör 2021).

Up to and including six months' active intervention

In a combined analysis of two studies (Del Corral 2018; Rovedder 2014), 6MWT distance was higher in the intervention compared to the control groups (MD 25.32 m, 95% CI 11.56 to 39.08; n = 81; Analysis 1.24).

In Del Corral 2018, the physical activity group had better performance in the MSWT compared to controls (MD 78.45 m, 95% CI 18.18 to 138.72; n = 40; Analysis 1.25).

Güngör 2021 reported no between-group differences in MSWT performance after six weeks (median: intervention group: 990 (IQR 377.5) m; n = 10; control group: 760 (IQR 830) m; n = 9) and after six months (median: intervention group; 1235 (IQR 365) m; n = 10; control group: 960 (IQR 705) m; n = 10).

Over six months' active intervention

Two studies reported on changes in MSWT (Del Corral 2018; Douglas 2015); one study reported on changes in 6MWT distance (Del Corral 2018).

After 12 months, Del Corral 2018 found no difference between groups in the changes in 6MWT distance (MD −3.17 m, 95% CI −35.27 to 28.93; Analysis 1.24).

In a combined analysis of two studies, MSWT was higher in the intervention compared to the control group (MD 131.91 m, 95% CI 79.60 to 184.22; n = 107; Analysis 1.25).

2. Quadriceps muscle strength

One study reported quadriceps muscle strength (Selvadurai 2002).

a. Isometric muscle strength

No study reported this outcome.

b. Isokinetic muscle strength

Up to and including six months' active intervention

One study reported isokinetic muscle strength (Selvadurai 2002).

In Selvadurai 2002, the intervention group (n = 44) had higher quadriceps muscle strength compared to the control group (n = 22) at hospital discharge (MD 16.38 newton-metre (N.m), 95% CI 12.34 to 20.42; n = 66; Analysis 1.26).

Follow-up (no active intervention)

After one-month follow-up, Selvadurai 2002 found higher quadriceps muscle strength in the intervention group (n = 44) compared to control group (n = 22) (MD 12.68 N.m, 95% CI 8.88 to 16.48; n = 66; Analysis 1.26).

3. Lung function: forced vital capacity

Fifteen studies reported changes in FVC (Beaudoin 2017; Carr 2018; Cerny 1989; Güngör 2021; Gupta 2019; Hebestreit 2010; Hebestreit 2022; Hommerding 2015; Klijn 2004; Kriemler 2013; Moorcroft 2004; Rovedder 2014; Sawyer 2020; Schneiderman-Walker 2000; Selvadurai 2002).

Up to and including six months' active intervention

Twelve studies FVC at up to and including six months' active intervention (Beaudoin 2017; Carr 2018; Cerny 1989; Güngör 2021; Hebestreit 2010; Hebestreit 2022; Hommerding 2015; Klijn 2004; Kriemler 2013; Rovedder 2014; Sawyer 2020; Selvadurai 2002).

In a combined analysis of eight studies, FVC % predicted there was no difference between groups, but between-study heterogeneity was substantial (MD 1.70% predicted, 95% CI −1.95 to 5.35; I^2 = 80; n = 357; Analysis 1.27) (Beaudoin 2017; Hebestreit 2010; Hebestreit 2022; Hommerding 2015; Kriemler 2013; Rovedder 2014; Sawyer 2020; Selvadurai 2002). This was partly explained by issues with the control group in Kriemler 2013.

Güngör 2021 reported no between-group differences in FVC % predicted after six weeks (median: intervention group 94 (IQR 19) % predicted; n = 10; control group 75.5 (IQR 54) % predicted; n = 9).

The remaining three studies reported this outcome, but did not provide data. Cerny 1989 reported that there was no difference in the change in FVC % predicted among groups; Klijn 2004 reported that there were no significant differences between groups in lung function parameters; and Carr 2018 reported no differences in FVC between groups after three months.

Over six months' active intervention

Five studies reported FVC % predicted at over six months' active intervention (Gupta 2019; Hebestreit 2010; Hebestreit 2022; Kriemler 2013; Schneiderman-Walker 2000), and one study reported on FVC in mL (Moorcroft 2004).

A combined analysis of five studies lasting between 12 months and three years revealed a beneficial effect of physical activity on FVC (MD 2.51% predicted, 95% CI 0.24 to 4.78; n = 199; Analysis 1.27). However, the effect was overestimated due to inclusion of Kriemler 2013, in which the control group experienced a deterioration of lung health. Exclusion of this study changed the effect estimate towards null and reduced between-study variability substantially.

In Moorcroft 2004, the intervention group had better FVC compared to the control group after 12 months (MD 213.00 mL, 95% CI 3.01 to 422.99; Analysis 1.28).

Follow-up (no active intervention)

Three studies reported FVC % predicted at follow-up (Hebestreit 2010; Kriemler 2013; Selvadurai 2002). A combined analysis revealed no between-group difference in FVC following a period 'off training' of between one and 12 months, but between-study heterogeneity was substantial (MD 5.37% predicted, 95% CI −1.69 to 12.43; I^2 = 82%; n = 125; Analysis 1.27).

Güngör 2021 reported no between-group differences in median FVC % predicted after six months' follow-up (intervention group: 93.5 (IQR 14) % predicted; n = 10; control group: 95 (IQR 41.5) % predicted; n = 9).

4. Physical activity

Five studies reported on physical activity, either subjectively measured (self-reported) or objectively measured (Beaudoin 2017; Hebestreit 2010; Hebestreit 2022; Klijn 2004; Kriemler 2013).

a. Subjectively measured

Up to and including six months' active intervention

In a pooled analysis of two studies (Hebestreit 2010; Hebestreit 2022), self-reported vigorous physical activity was higher in the physical activity intervention compared to the control groups after six months (MD 1.36 hours per week, 95% CI 0.86 to 1.86; n = 152; Analysis 1.32).

Klijn 2004 reported for a subgroup of participants (anaerobic group n = 18; controls n = 16) who completed an activity diary; there were no between-group differences.

Over six months' active intervention

In a pooled analysis of two studies (Hebestreit 2010; Hebestreit 2022), self-reported vigorous physical activity was higher in the intervention compared to the control groups after 12 months (MD 1.71 hours per week, 95% CI 1.13 to 2.29; n = 148; Analysis 1.32).

Follow-up (no active intervention)

Hebestreit 2010 found higher self-reported vigorous physical activity in the intervention group compared to the control group after six to 12 months' follow-up (MD 1.63 hours per week, 95% CI 0.02 to 3.24; n = 18; Analysis 1.32).

b. Objectively measured

Up to and including six months' active intervention

Beaudoin 2017 reported no differences in the number of daily steps between the intervention and control groups after three months (MD –110.58 steps per day, 95% CI –2260.72 to 2037.56; n = 14; Analysis 1.29). After six months, Hebestreit 2022 also found no between-group differences in the total daily number of steps (MD 584.00 steps per day, 95% CI –417.10 to 1585.10; 105 participants; Analysis 1.29) and 'aerobic steps' (i.e. steps that were counted when walking more than 60 steps per minute and more than 10 minutes continuously) (MD 330.00 steps per day, 95% CI –195.50 to 855.50; 101 participants; Analysis 1.30). We did not combine data on the number of daily steps from Beaudoin 2017 and Hebestreit 2022. These studies used different devices that were either worn around the hip or around the upper arm, and sensor placement is known to have a substantial impact on the number of daily steps.

Kriemler 2013 reported on objectively measured change in hours of moderate-to-vigorous physical activity per week and found no differences between the intervention (n = 25) and the control group (n = 9) after six months (MD –0.20 hours, 95% CI –1.38 to 1.78; Analysis 1.31).

Klijn 2004 reported for a subgroup of participants (anaerobic group n = 18; controls n = 16) who wore an activity accelerometer; there were no between-group differences.

Over six months' active intervention

Two studies reported objectively measured physical activity at over six months' active intervention (Hebestreit 2022; Kriemler 2013).

Hebestreit 2022 found no between-group differences in the daily number of steps between the physical activity and control group after 12 months (MD 806.00 steps per day, 95% CI –27.10 to 1639.10; n = 105; Analysis 1.29). In addition, there was no difference in total number of daily aerobic steps between groups after 12 months (MD 561.00, 95% CI 191.57 to 930.43; Analysis 1.30).

After 12 months, Kriemler 2013 found no differences in the time spent in moderate-to-vigorous physical activity undertaken each week for the intervention group compared to the control group (MD –0.14 hours per week, 95% CI –1.56 to 1.28; n = 32; Analysis 1.31).

Follow-up (no active intervention)

Kriemler 2013 found no between-group differences in the time spent in moderate-to-vigorous physical activity undertaken per week after 12 months 'off training' (MD 1.16 hours per week, 95% CI –0.57 to 2.89; n = 27; Analysis 1.31).

5. Body mass index

Seven studies reported changes in BMI (Beaudoin 2017; Del Corral 2018; Hebestreit 2010; Hebestreit 2022; Hommerding 2015; Kriemler 2013; Moorcroft 2004).

Up to and including six months' active intervention

In a pooled analysis of four studies (Beaudoin 2017; Hebestreit 2010; Hebestreit 2022; Kriemler 2013), there was no difference in BMI between the intervention and control groups (MD 0.02 kg/m^2,95% CI –0.16 to 0.20; n = 203; Analysis 1.33). Hommerding 2015 reported no differences in BMI z-scores between groups after three months (MD 0.10, 95% CI –0.16 to 0.36; n = 34; Analysis 1.34).

Over six months' active intervention

In a pooled analysis of three studies (Hebestreit 2010; Hebestreit 2022; Moorcroft 2004), there were no differences in BMI between the intervention and control groups (MD 0.29 kg/m^2, 95% CI –0.04 to 0.62; n = 191; Analysis 1.33).

Follow-up (no active intervention)

A pooled analysis of two studies (Hebestreit 2010; Kriemler 2013) revealed no between-group differences in BMI after a period of six to 12 months' follow-up (MD 0.61 kg/m^2, 95% CI –0.03 to 1.26; n = 60; Analysis 1.33).

6. Pulmonary exacerbations

One international multicentre study reported pulmonary exacerbations (Hebestreit 2022).

Up to and including six months' active intervention

In Hebestreit 2022, the number of pulmonary exacerbations, based on a mixed Poisson regression model, was not different between the physical activity and control group at the end of six months' partially supervised active intervention (incidence rate ratio 1.07, 95% CI 0.60 to 1.90; n = 117; Analysis 1.35). The time to first pulmonary exacerbation was calculated covering the entire study period of 12 months and is reported below.

Over six months' active intervention

Hebestreit 2022 reported no between-group differences in the number of pulmonary exacerbations during the 12-month study period (incidence rate ratio 1.28, 95% CI 0.85 to 1.94; n =

117; Analysis 1.35). There was no difference between groups in time to first pulmonary exacerbation, covering the entire study period of 12 months (hazard ratio (HR) 1.34, 95% CI 0.65 to 2.80; Analysis 1.36). Certainty of evidence was high (Summary of findings 1).

7. Hospitalisation

Two studies reported hospitalisation (Hebestreit 2022; Schneiderman-Walker 2000). The principal investigator of a multicentre study provided raw data for this outcome (Hebestreit 2022).

In Hebestreit 2022, there was no difference between the intervention and the control groups in the number of participants being hospitalised over a period of 12 months (odds ratio (OR) 0.93, 95% CI 0.42 to 2.04; n = 117; Analysis 1.37).

Schneiderman-Walker 2000 (n = 65) reported no between-group differences for the mean number of hospitalisations or mean number of days in hospital at years one, two and three.

8. Bone health

Two studies (n = 67) reported changes in bone health after three to 12 months (Alexander 2019; Gupta 2019).

Up to and including six months' active intervention

Alexander 2019 (n = 15, published as an abstract) reported increased bone mineral content (adjusted for height and lean body mass) in the intervention group compared to the control group after 12 weeks of whole body vibration training. The authors reported only P values and no other statistical data. It is unclear if the reported effects reflect between-group comparisons.

Over six months' active intervention

After 12 months, Gupta 2019 found no between-group differences in whole body bone mineral density and lumbar spine bone mineral density (whole body: MD –0.01 g/cm^2, 95% CI –0.04 to 0.03; n = 52; Analysis 1.38; lumbar spine: MD 0.00 g/cm^2, 95% CI –0.02 to 0.02; Analysis 1.39).

9. Diabetic control

Two studies reported on changes in diabetic control after a physical activity intervention (Beaudoin 2017; Hebestreit 2022).

Up to and including six months' active intervention

Beaudoin 2017 reported on this outcome, and the investigators provided additional raw data from the study. The outcomes measured were glycated haemoglobin (HbA1c) and the plasma glucose and insulin response to a two-hour oral glucose tolerance test before and after three months (Beaudoin 2017).

There were no differences in the change in HbA1c between the exercise and control groups (MD –0.00%, 95% CI –0.01 to 0.00; Analysis 1.40). In our analysis, this was also true for area under the curve for plasma glucose (MD –5.59, 95% CI –13.51 to 2.33; Analysis 1.41; in the original publication the authors reported a significant within-group improvement in this outcome for the training group) and area under the curve for plasma insulin (MD –20.02, 95% CI –52.90 to 12.85; Analysis 1.42). However, after three months, the insulin sensitivity index was significantly higher in the exercise compared to the control group (MD 0.02, 95% CI 0.00 to 0.04; Analysis 1.43).

Beaudoin and colleagues also reported data for plasma glucose and plasma insulin at different time points during the oral glucose tolerance test (i.e. at baseline and 30, 60, 90 and 120 minutes after the oral glucose load). The authors presented these data in figures in the original publication (Beaudoin 2017). For this review, we extracted data for the time points 0, 60 and 120 minutes after the oral glucose load.

There was no difference in plasma glucose values between groups at the time points of 0 and 60 minutes (0 minutes: MD 0.44 mmol/L, 95% CI –0.41 to 1.28; 60 minutes: MD –1.86 mmol/L, 95% CI –4.11 to 0.40). However, there was a differences in favour of the intervention group at 120 minutes after ingestion of the glucose solution (MD –3.24 mmol/L, 95% CI –6.41 to –0.06; Analysis 1.44). There was no difference in plasma insulin values between groups at 0 and 120 minutes (0 minutes: MD –2.10 µIU/mL, 95% CI –5.46 to 1.26; 120 minutes: MD 2.23 µIU/mL, 95% CI –13.98 to 18.45). However, there was a difference in plasma insulin in favour of the intervention group 60 minutes after the ingestion of the glucose solution (MD –12.39 µIU/mL, 95% CI –22.14 to –2.65; Analysis 1.45).

The results presented here are different from the results reported in the original Beaudoin 2017 publication. Beaudoin and colleagues reported within-group changes for plasma glucose and plasma insulin at different time points (Figure 1 A–D in the original publication) during the oral glucose tolerance test for the intervention and control groups separately (Beaudoin 2017). The results presented here should be interpreted with caution due to the low sample size and high chance of a type II error (failing to conclude there was an effect when there actually was).

Over six months' active intervention

Hebestreit 2022 (n = 91) reported changes in blood glucose during an oral glucose tolerance test in participants without a diagnosis of CF-related diabetes at study entry. After nine months, there were no between-group differences in blood glucose levels at rest, 60 or 120 minutes after glucose ingestion (at rest: MD –0.16 mmol/L, 95% CI –0.44 to 0.12; 60 minutes: MD –0.04 mmol/L, 95% CI –1.11 to 1.03; 120 minutes: MD –0.44 mmol/L, 95% CI –1.43 to 0.55; Analysis 1.46). Certainty of evidence was moderate (Summary of findings 1).

10. Adverse events

Six studies reported adverse events (Del Corral 2018; Güngör 2021; Hebestreit 2022; Kriemler 2013; Sawyer 2020; Selvadurai 2002). Hebestreit 2022 provided additional data on adverse events. In the original publication, they reported the total number of adverse events per group; here, we focused on the number of people experiencing an adverse event.

Up to and including six months' active intervention

Del Corral 2018 reported that muscle stiffness was common during or after playing active video games and that no further adverse events occurred. They provided no further details.

Güngör 2021 reported that none of the study participants complained about pain before or during the intervention, and that there were no adverse events in either group during the supervised six-week intervention.

The high-intensity interval training study by Sawyer 2020 reported that no minor or major adverse event occurred during the two-month study.

In Selvadurai 2002, one participant in the "aerobic" training group injured her ankle and missed two days of training. One participant from the control group developed haemoptysis and withdrew from the study.

Over six months' active intervention

Kriemler 2013, after 12 months (six months of partially supervised and six months of unsupervised training with access to resources but excluding the follow-up period), reported that no adverse effects (e.g. injuries, pneumothorax, asthma attacks, hypoglycaemia) occurred.

Hebestreit 2022 reported adverse and serious adverse events for the intervention and control groups during the 12-month active intervention period (six months of partially supervised and six months of unsupervised training with access to resources). There was no difference in the number of participants experiencing an adverse event directly related to physical activity between the physical activity intervention group and the control group (OR 6.22, 95% CI 0.72 to 53.40; n =117; Analysis 1.47). There was also no difference in the number of participants experiencing a serious adverse event directly related to physical activity between the physical activity intervention group and the control group (OR 0.95, 95% CI 0.06 to 15.54; Analysis 1.47). Reported adverse events were contusion of the right foot during football (n = 1, control group), knee pain (n = 2, intervention group), asthma attack while walking uphill (n = 1, intervention group), soft tissue injury to neck after a fall from the trampoline (n = 1 intervention group), pain in the foot (n = 2, intervention group). Serious adverse events were patella dislocation during football (n = 1, intervention group) and cruciate ligament fracture during skiing (n = 1, control group).

Certainty of evidence based on the results of Hebestreit 2022 and Kriemler 2013 was low (Summary of findings 1).

Follow-up (no active intervention)

Kriemler 2013 and Selvadurai 2002 reported on adverse events during their active intervention periods but not during their follow-up periods.

Del Corral 2018 reported that muscle stiffness was common during or after playing active video games, and that no further adverse events occurred. No further details were provided, and it is unclear if this was also true for the 12-month follow-up period.

Güngör 2021 reported that none of the study participants complained of pain before or during the intervention and that there were no adverse events during the follow-up period.

DISCUSSION

Summary of main results

In this systematic review, moderate-certainty evidence indicates that physical activity interventions of longer than six months probably have a positive effect on aerobic exercise capacity in people with CF compared to no intervention. Low-certainty evidence suggests that physical activity interventions may have no effect on lung function (specifically FEV_1) and HRQoL. The effects were similar across studies of different durations of active intervention (i.e. up to and including six months and over six months) and during follow-up periods where all participants reverted to usual care. The results for our primary outcomes during a follow-up period should be interpreted with caution because only three studies with varying duration of follow-up (ranging from one to 12 months) reported on the primary outcomes of VO_2 peak and FEV_1.

Primary outcomes

1. Exercise capacity

We considered this outcome in terms of VO_2 peak. The improvement of VO_2 peak may be considered clinically relevant as physical activity interventions address low aerobic exercise capacity, which is an important risk factor and strong predictor of mortality in CF (Hebestreit 2019; Nixon 1992; Pianosi 2005). In a meta-analysis, we found moderate-certainty evidence for an improvement in VO_2 peak (mL/min per kg bodyweight) in favour of physical activity intervention compared to no intervention, irrespective of the duration of active intervention or follow-up. The MD for the improvement in VO_2 peak was approximately 2.10 mL/min per kg bodyweight for studies with an active intervention lasting up to and including six months; 1.60 mL/min per kg bodyweight for longer than six months; and 3.27 mL/min per kg bodyweight in studies after follow-up (Analysis 1.1). Nevertheless, the effects were not consistent across all studies, and between-study heterogeneity was substantial for studies with an active intervention lasting up to and including six months and over six months. The magnitude of improvement in VO_2 peak was rather small but may still be considered clinically relevant (Saynor 2013; Wilkinson 2019); however, robust estimates for a meaningful change in VO_2 peak over time in people with CF are yet to be determined. One study in adults with chronic kidney disease estimated a change in VO_2 peak of 1.5 mL/min per kg bodyweight as clinically relevant (Wilkinson 2019). Pianosi and colleagues reported an annual decline in VO_2 peak of 1.9 mL/min per kg bodyweight in children and adolescents with CF over five years (Pianosi 2005). In another longitudinal study in adolescents with CF, there was a mean annual decline in VO_2 peak of 3.23% predicted (van de Weert-Van Leeuwen 2012). Given the fact that VO_2 peak is an independent predictor of mortality in CF (Hebestreit 2019; Nixon 1992; Pianosi 2005), regular physical activity (including structured exercise) should be promoted to maintain the highest possible aerobic fitness (VO_2 peak).

2. Lung function: forced expiratory volume in one second

We found low-certainty evidence that a physical activity intervention compared to control has little or no effect on FEV_1 % predicted (MD 2.41 % predicted, 95% CI –0.49 to 5.31). These findings were based on a combined analysis of six studies (n = 367) with moderate to substantial between-study heterogeneity (Analysis 1.6). In a sensitivity analysis of five studies lasting 12 to 24 months, FEV_1 % predicted was higher in the physical activity intervention group compared to the control group (MD 1.71 % predicted, 95% CI 0.15 to 3.26; n = 333). This is in line with observational studies showing a slower annual rate of decline in FEV_1 over time in physically active versus less active children and adults with CF (Cox 2016; Cox 2018; Elce 2018; Schneiderman 2014). It may well be the case that a physical activity programme needs to be performed over longer time periods to observe beneficial effects on lung function.

The largest international multicentre study to date (ACTIVATE-CF; n = 117) provided data on the effects of vigorous physical activity, which we included in a meta-analysis; results showed a beneficial effect in favour of the control group after six months (Hebestreit 2022). The effect was predominantly driven by an improvement in FEV_1 in the control group, while FEV_1 remained relatively unchanged in the intervention group. It was postulated that control group participants also started to do more physical activity, although less intensively (Hebestreit 2022). Interestingly, in a sensitivity analysis of six studies (excluding Kriemler 2013 and Selvadurai 2002) with physical activity interventions lasting up to and including six months, the MD in FEV_1 between the intervention and control groups was –2.16 % predicted (95% CI –4.14 to –0.17; n = 255; Analysis 1.7). We can only speculate on the underlying reasons for these counterintuitive results. It may be that participants in the physical activity group perceived the intervention as an added stress on top of an already high treatment burden (Davies 2020), or that the interventions were too intensive with inadequate recovery time. It may also be the case that the physical activity programme induced inflammatory responses or increased infection susceptibility, or a combination of these (van de Weert-Van Leeuwen 2013). Further studies are needed to better understand the immunological and physiological adaptations in response to repetitive bouts of acute physical activity on lung function in people with CF. This includes studying dose–response relationships on the effects of regular physical activity on lung function.

3. Health-related quality of life

This review found that physical activity may make little or no difference to HRQoL measured with the CFQ-R, which is a validated and responsive instrument to assess changes in HRQoL in people with CF (low-certainty evidence) (Quittner 2009). However, the analysis was limited to four studies with physical activity interventions lasting longer than six months.

Secondary outcomes

With regard to the review's secondary outcomes presented in Summary of findings 1, one study with an active intervention period lasting longer than six months reported data on the number of pulmonary exacerbations and diabetic control (Hebestreit 2022), and two studies with active interventions lasting longer than six months reported data on adverse events (Hebestreit 2022; Kriemler 2013). In the multicentre Hebestreit 2022 study (n = 117), there were no differences in the number of pulmonary exacerbations between the physical activity and control group after 12 months (incidence rate ratio was 1.28, 95% CI 0.85 to 1.94; high-certainty evidence; Summary of findings 1). This study also found no between-group differences in diabetic control after nine months (moderate-certainty evidence) (Summary of findings 1). During the 12-month active intervention period in Kriemler 2013, investigators reported no adverse events in either the physical activity or control group, while low-certainty evidence from Hebestreit 2022 suggests physical activity may or may not make a difference in the number of participants experiencing an adverse event (OR 6.22, 95% CI 0.72 to 53.40) or serious adverse event (OR 0.95, 95% CI 0.06 to 15.54) related to the intervention. Future studies are likely to change our confidence on the impact of regular physical activity and exercise on adverse events in people with CF. In Hebestreit 2022 the odds of experiencing an adverse event was six times higher in the intervention compared to the control group, but the lower CI was relatively close to one (statistically, if the CI crosses one, this implies there is no difference between arms of the study).

Overall completeness and applicability of evidence

In this review update, we included nine new studies, which almost doubled the number of included participants in comparison to the previous version (Radtke 2017). For the first time, we were able to perform meta-analyses for the primary outcomes VO_2 peak, FEV_1 and HRQoL.

The studies included in this review were heterogeneous in terms of study quality, selection of study participants, sample size and intervention duration. The studies recruited mixed populations with regard to age, gender and disease severity, and may have some applicability to the general population of people living with CF. One important issue is participant selection based on predefined inclusion and exclusion criteria in the original studies. In a large number of the included full-text articles (where inclusion and exclusion criteria were reported), participants were excluded based on disease severity expressed by FEV_1, which is one of our primary outcome measures. We acknowledge that study investigators are ethically bound to keep potential exercise-induced adverse reactions to a minimum; however, this limits the generalisability of the review's findings to people with mild-to-moderate CF lung disease. Moreover, it is important to note that most studies were conducted before the widespread availability of highly effective CFTR modulator therapies (Middleton 2019; Wainwright 2015), which clearly limits the generalisability of our findings to the current population of people living with CF. Moreover, this review includes a substantial number of small studies, known to overestimate effects of interventions compared to larger trials (Ioannidis 1998).

We choose aerobic exercise capacity (VO_2 peak) and lung function (FEV_1) as objectively measurable outcomes, and HRQoL as an important patient-reported outcome. Overall out of 24 studies, 11 reported on changes in VO_2 peak, 16 reported on changes in FEV_1 and eight reported on changes in HRQoL. It may well be that the studies included in the meta-analysis represented a selection of studies that did not cover the full spectrum of possible intervention effects that would have been observed if more of the included studies reported these outcomes.

With regard to changes in lung function, the sensitivity of FEV_1 to detect change in response to a physical activity intervention needs to be discussed. This is particularly important in times of highly effective CFTR modulators (Middleton 2019), and in a population in which lung function is better than ever (Stanojevic 2016). There may be measurement methods more sensitive than FEV_1 to document subtle, but clinically relevant, effects of regular physical activity on pulmonary function (Stanojevic 2016).

Since only a third of included studies reported on changes in HRQoL, the current evidence on the effects of physical activity interventions on changes in HRQoL is limited.

Quality of the evidence

Overall, there is moderate-certainty evidence that physical activity interventions of longer than six months have a beneficial effect on VO_2 peak, while there is low-certainty evidence that physical

activity interventions have no positive effect on FEV_1 and HRQoL. Moreover, with regard to secondary outcomes, there were no differences in the risk for pulmonary exacerbations (high-certainty evidence), change in diabetic control (blood glucose levels) (moderate-certainty evidence) and adverse events (low-certainty evidence) between physical activity interventions and usual care (no physical activity).

In general, several studies included in this review showed considerable methodological shortcomings based on the Cochrane risk of bias tool used to assess them (Higgins 2017). This may also reflect the inappropriate methodology of the current literature (i.e. insufficient power), in general. Most studies had small sample sizes, which puts them at risk of imprecision and lack of power, which can work in two ways: that is, underestimation or overestimation of intervention effects (Ellis 2010). This phenomenon might be explained by publication bias, as small studies are less likely be published if they present negative results (Hopewell 2009). Moreover, there were differences in baseline characteristics in five small studies (Cerny 1989; Del Corral 2018; Rovedder 2014; Santana-Sosa 2012; Santana-Sosa 2014). Although testing for between-group differences is not recommended in RCTs, some authors reported differences in participant characteristics at baseline. It is important to note that none of the studies reporting between-group differences in baseline characteristics contributed data for the pooled analysis of the primary outcomes, which could have introduced bias.

In addition to interindividual differences in the course of CF lung disease and differences among studies in type, duration, level of supervision and implementation of the intervention, methodological differences in outcome measures may have contributed to the observed between-study heterogeneity in the primary outcomes VO_2 peak, FEV_1 and HRQoL. Among the studies in the pooled analysis investigating change in VO_2 peak, nine studies used a cycle ergometer, and three studies used a treadmill as testing modality. Different testing modalities (treadmill testing elicits higher VO_2 peak values compared to cycle ergometry), testing protocols (e.g. ramp protocol versus minute-by-minute protocol versus three-minute stages protocol), type of metabolic carts, and quality control procedures (e.g. calibration and verification methods, criteria to define a maximal effort) have likely contributed to the observed variability. Similar methodological challenges were recently addressed in an RCT investigating the effects of CFTR modulator treatment on VO_2 peak (primary outcome) in children and adolescents with CF (Wilson 2021). This study highlighted several methodological challenges using cardiopulmonary exercise testing in a multicentre setting. However, several of those challenges can be addressed at design stage; for example, by implementing standard operating procedures and by using study-specific equipment. The latter is often not possible in investigator-initiated trials due to limited financial resources. Further, although the measurement of FEV_1 is less complex than the measurement of VO_2 peak, and all people with CF are used to performing spirometry measurements early in their lives, the same quality and standardisation principles apply. We noticed moderate-to-substantial between-study heterogeneity in FEV_1 that may partly be explained by several of the aforementioned factors, as well as by pretesting conditions, including withdrawal of beta 2-mimetics or not. In addition, for this review update, we restricted HRQoL measurements with the CFQ-R questionnaire to respiratory symptoms and the physical function domain of the CFQ-R questionnaire. The pooled analysis revealed no effect of physical activity (versus usual care) on changes in respiratory symptoms and physical functioning. Between-study heterogeneity was small to substantial, and the CIs of the effect estimates were wide. The large variability might be partly explained by inclusion of different groups of study participants (i.e. children, adolescents, adults), time and mode of administration, possible differences in languages and versions, few studies in the pooled analysis, and different study durations of 12 and 24 months covering a large observational period during which lung disease can substantially deteriorate.

Further research will likely have an important impact on our confidence in the estimate of effects of physical activity versus no physical activity intervention on the primary outcomes VO_2 peak, FEV_1 and HRQoL, and is (very) likely to change those estimates. We downgraded the certainty of evidence for studies with active interventions lasting longer than six months due to unclear or high risk of bias across several domains; in particular, due to concerns around randomisation and allocation concealment, and an outlying study.

A limited number of studies reported on secondary outcomes, such as bone health and diabetic control, suggesting that additional research will very likely add to the existing evidence and very likely change the estimate of effects. In general, a lack of efficacy does not necessarily mean that the intervention was ineffective: especially in longer-term studies, poor adherence to physical activity, which requires precise monitoring, could be a reason for lack of intervention effects. Although the included studies used standard outcome measures to assess efficacy of physical activity and exercise training, robust estimates for a minimal clinically important difference of these outcome measures are often not available, thus limiting the interpretation of the magnitude of observed effects (e.g. VO_2 peak).

RCTs are a powerful study design to assess interventional efficacy, assuming high-quality standards for the randomisation and allocation concealment process aim to minimise confounding and selection bias. In this review, only nine studies had a low risk of bias due to clearly describing their randomisation procedures and six studies a low risk of bias for describing their allocation concealment. Two studies included in the meta-analysis had a high risk of bias in both domains, leading us to downgrade the certainty of evidence. Research has shown that inadequate or unclear allocation concealment – compared to adequately reported concealment of random allocation – is associated with larger effects, introducing bias (Schulz 1995). The extent to which lack of methodological rigour has had an impact on our effects estimates is difficult to ascertain; the possibility cannot be ruled out.

In summary, this review includes a substantial number of small studies of low to moderate quality and predominantly unclear risk of bias.

Potential biases in the review process

Despite extensive searches, it is theoretically possible that we failed to identify studies. However, since the field of researchers publishing on physical activity interventions in CF is relatively small

and close-knit, we are quite confident that we did not miss any potentially relevant studies.

Two authors of this review (HH and SK) were Principal Investigators of three included studies (Hebestreit 2010; Hebestreit 2022; Kriemler 2013). Moreover, one review author (HH) was the Principal Investigator of the ACTIVATE-CF trial, and two other authors (SK, TR) were core team members of the study (Hebestreit 2022). It is important to note that other review authors (SJN, SS) who were not members of the ACTIVATE-CF study team performed the risk of bias assessment and data extraction for those studies.

Agreements and disagreements with other studies or reviews

To the best of our knowledge, there are no other published systematic reviews on physical activity and exercise training interventions versus usual care in people with CF; in particular, reviews with a focus on RCTs.

Two systematic reviews focused on subjectively reported or objectively measured physical activity levels (or a combination of both) in children and adolescents with CF (Puppo 2020), or adults with CF (Shelley 2019). Both reviews included different types of study designs and were not restricted to RCTs.

We are aware of a study protocol for a systematic literature review that aims to summarise the effects of RCTs comparing physical activity and exercise interventions versus usual care, and which will assess fitness, physical activity, lung health, inflammation, body composition, glycaemic control, patient-reported outcomes, adverse events and healthcare utilisation (Tomlinson 2021). In the study protocol, we noticed overlap with outcomes included in this review, but the planned review by Tomlinson and colleagues may extend the findings of this review, as the authors planned to include additional outcomes, such as inflammation and healthcare utilisation (Tomlinson 2021).

For the first time, since the original review in 2002 (Bradley 2002), we were able to combine data and perform a meta-analysis. Despite a larger number of studies included in the current version of the review, the conclusions have not substantially changed compared to previous versions (Bradley 2002; Bradley 2008; Radtke 2015; Radtke 2017), but we extended our knowledge on clinically relevant and patient-centred outcomes. Moreover, our certainty in the beneficial effects of regular physical activity and exercise training on aerobic exercise capacity has strengthened, while there were no beneficial effects on lung function and HRQoL (Bradley 2002; Bradley 2008; Radtke 2015; Radtke 2017).

AUTHORS' CONCLUSIONS

Implications for practice

This review found moderate-certainty evidence that physical activity interventions probably improve aerobic exercise capacity in people with cystic fibrosis (CF). From the evidence we have identified, physical activity interventions may have little or no effect on lung function or health-related quality of life (HRQoL) at any time point (low-certainty evidence). Between-study heterogeneity ranged from low to substantial for the primary outcomes. Most studies included in this review are limited by their small size, insufficient duration and incomplete reporting.

Overall, the benefits obtained from including physical activity in a package of care may be influenced by the type and duration of training programme. Physical activity is already part of the regular care offered to most people with CF and there is no evidence to actively discourage this.

Implications for research

Further research is needed to comprehensively assess the benefits of physical activity programmes in people with CF. There is a clear need for high-quality studies with sufficient numbers of study participants and well-chosen, objectively measurable, reproducible and sensitive primary outcome measures. Unfortunately, a substantial number of ongoing studies and those listed as awaiting classification in this review are of short duration and include a small sample size. We would argue that further small studies of short duration are unlikely to make a meaningful contribution, and we call for greater collaboration in designing studies in order to advance the field.

Below, we suggest how future study designs could be improved, including in terms of outcomes. Future well-designed and well-executed studies are very likely to change our confidence in the estimates for several outcomes included in this review.

The conduct of physical activity trials in a rare disease such as CF is extremely challenging for several reasons. First, participation rates in physical activity studies are often substantially lower than expected (Hebestreit 2022; Sawyer 2020), and researchers in the field should be encouraged to form study collaborations to achieve meaningful participation rates and statistical power. Second, contamination of control groups is a common issue in randomised controlled trials (RCTs), and could be overcome by offering control group participants an attractive alternative programme unrelated to the intervention, in order to avoid contamination and excess dropout rates. Third, participation rates and adherence to physical activity interventions have been shown to be suboptimal (Douglas 2015), and could potentially be improved by considering individual facilitators and barriers towards physical activity in order to build positive, long-term physical activity behaviour (Gruet 2022). Fourth, training components (type, intensity, duration and frequency of physical activity) should be sufficient to elicit beneficial adaptations, but should also be tailored to an individual. In that context, a progressive increase in volume and intensity of physical activity over time should be considered and adapted to the individual participant. Finally, future studies should focus on clinically relevant outcomes such as bone health, diabetic control, exacerbations and HRQoL. Using forced expiratory volume in one second (FEV_1) as a marker of lung disease severity may lack sensitivity to detect any changes within a given study period. Additional lung function parameters, such as the Lung Clearance Index, which is based on multiple washout techniques, might be considered.

Life expectancy for people with CF has substantially increased over recent decades (MacKenzie 2014), and new drug therapies have had a huge impact on the clinical course of people living with CF (Middleton 2019; Wainwright 2015). Changing demographics and increased life expectancy impact the clinical course of young people with CF, who are healthier than ever (Burgel 2015). This offers new opportunities for physical activity and exercise. It is expected that physical activity and exercise will gain more attention because of the health effects of cystic

fibrosis transmembrane conductance regulator (CFTR) modulator therapies (e.g. substantially reduced sputum production), now available for the vast majority of people living with CF. A substantial proportion of people with CF already use exercise as a supplement to traditional chest physiotherapy (Rowbotham 2020), and one of the top 10 research priorities in CF lung disease is to investigate the effectiveness of exercise as a replacement airway clearance technique (Rowbotham 2018). Conversely, people with CF are getting older and experience multiple comorbidities, which may affect their physical activity levels and their ability to take part in structured physical activity programmes. The CF and exercise community should be open to developing and testing new training strategies to optimise the outcomes of physical activity interventions aimed at building positive long-term physical activity behaviour (Gruet 2022). Future interventions should be targeted towards groups of individuals (e.g. children versus adults, mild versus severe CF lung disease and following lung transplantation) by considering different training modalities to maximise the benefit for these specific groups (Gruet 2022). This includes studies on dose–response relationships between physical activity and exercise stimuli and changes in lung function over time. Future studies should develop their intervention to incorporate elements of behaviour change theory. Wearable technology, such as fitness trackers and step counters to measure and monitor individual physical activity levels, in combination with motivational feedback and goal setting might be a promising approach for future physical activity interventions (Curran 2020).

Of note, RCTs are a powerful study design to establish causal relationships between an exposure and outcome. However, the successful conduct of RCTs in people with a rare disease is challenging. Healthcare professionals should think of alternatives such as the design of longitudinal multicentre studies using harmonised measurement techniques to study the role of a physically active lifestyle on health-related and patient-centred outcome measures. In this context, assessment of and control for confounders is of critical importance and should be carefully considered at the design stage. Ideally, such an effort is made with a multidisciplinary team involving clinicians, exercise scientists, physiotherapists, epidemiologists, methodologists and people with CF to cover their needs.

Finally, study investigators should carefully select the number and type of study outcomes. A high number of outcomes requiring time-consuming assessments may decrease participants' adherence as well as increase the risk of false-positive results by chance. Besides selecting clinically relevant and patient-centred outcomes, testing of the inter-relationships of outcome measures would ascertain whether, for instance, changes in HRQoL correlate with changes in exercise capacity (Hebestreit 2014).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Alexander 2019

Study characteristics

Methods	**Design:** single-centre, parallel RCT
	Location: no details given on hospital, city or country

Alexander 2019 *(Continued)*

	Inclusion criteria: not specified **Exclusion criteria:** not specified **Duration:** 12 weeks
Participants	15 prepubertal children with CF, mean age 7.94 (SD 1.35) years **Intervention group** (n = 9): no further details available **Control group** (n = 6): no further details available
Interventions	12-week, home-based, whole body vibration exercise training programme **Intervention group:** 12-week, home-based, whole body vibration training programme (5 times per week for 20 min) combined with their regular airway clearance therapy regimen. **Control group:** usual airway clearance therapy regimen.
Outcomes	**Primary outcome** 1. Change in total body lean body mass (DEXA) from baseline to 12 weeks **Secondary outcomes** 1. Change in quality of life from baseline to 12 weeks 2. Change in bone parameters from baseline to 12 weeks 3. Change in spirometry indices from baseline to 12 weeks
Notes	Study reported as an abstract and, therefore, the information was limited.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but no details given for sequence generation.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants to intervention. Unclear whether personnel blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear whether outcomes assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details of dropouts or whether intention-to-treat analysis was used.
Selective reporting (reporting bias)	Unclear risk	Abstract so unable to assess if all outcomes used in methods were reported in results.
Other bias	Unclear risk	Did not state inclusion or exclusion criteria, neither did they describe the methods of statistical analysis used.

Beaudoin 2017

Study characteristics	
Methods	**Design:** single-centre, open-label, parallel RCT (the record on clinicaltrials.gov states cross-over design, but this is not evident from published paper) **Location:** Institut de Recherches Cliniques de Montreal, Canada **Inclusion criteria:** participants with CF; aged > 18 years; sedentary (< 100 min/week of structured exercise assessed by physical activity questionnaire and telephone interview; FEV_1 > 40 % predicted; clinically stable for the last 6 weeks; IGT; CFRD without pharmacological treatment or elevated 1-hour plasma glucose concentration during an OGTT (indeterminate 1-hour glucose concentration > 11.0 but 2-hour plasma glucose concentration < 7.8 mmol/L) **Exclusion criteria:** current pulmonary exacerbation; use of oral or IV corticosteroids; low SaO_2 during exercise; history of haemoptysis in last 6 weeks **Duration:** 13 weeks
Participants	14 participants with CF *Group demographics* **Intervention group** (n = 8): mean age 31.9 (range 24–41) years **Control group** (n = 6): mean age 35.5 (range 22–57) years
Interventions	12-week combined aerobic and resistance training study **Intervention group:** aerobic and resistance training exercises 3 times per week for about 20–40 min with a day off between the training sessions (in total 36 training sessions). Exercise intensity and volume were progressively increased. Participants recorded their training sessions in a diary. Once every 4 weeks, participants received a supervised training session and a telephone call on a weekly basis. 1. Aerobic training consisted of walking, jogging, cycling and elliptic trainer. Training intensity progressively increased throughout the study, starting at 60% of VO_2 peak during the first 4 weeks. Thereafter, intensity was increased to 70% (weeks 5–8) and 80% (weeks 9–12) of VO_2 peak. 2. Resistance training consisted of 5–7 exercises for large muscle groups using own BW, free weights and elastic bands (goal 8–12 repetitions with a weight of 30–50% of 1 repetition maximum). Exercise intensity and volume were progressively increased. **Control group:** no information reported in the original publication. Detailed information on control intervention was available on ClinicalTrials.gov (NCT02127957). See 'Notes' below for further information.
Outcomes	**Primary outcome** 1. Change in plasma glucose at 2 hours during OGTT **Secondary outcomes** 1. Change in metabolic parameters (HbA1c, plasma glucose area under the curve, insulin sensitivity index, plasma insulin area under the curve (0–120 min) 2. Change in lung function (FVC, FEV_1) 3. Change in exercise capacity measured by a cycle CPET (VO_2 peak and VE at VO_2 peak) 4. Change in muscle strength (leg press, chest press, lat pulldown, biceps curl) 5. Change in muscle endurance (push-up, sit-up, flexibility, handgrip strength) 6. Change in body composition (bodyweight, BMI, body fat and fat-free mass) 7. Change in HRQoL

Beaudoin 2017 *(Continued)*

8. Change in objectively measured physical activity (steps per days; energy expenditure) assessed by questionnaire

Outcomes measured at baseline and week 13.

Further, inflammatory markers were measured in this study but inflammatory biomarkers are not outcomes relevant for this review.

Notes

Study registration

The study was registered as a cross-over trial (ClinicalTrials.gov NCT02127957; clinicaltrials.gov/ct2/show/NCT02127957) but results were reported as parallel-design study. The authors confirmed that they had to stop the study due to recruitment problems. The authors presented only results from the first study phase (12 weeks).

Information provided on ClinicalTrials.gov

"Intervention Model: Crossover Assignment"

"Following the visit #6, patients in the control group will be invited to participate in a second study phase to participate in supervised exercise program. This participation will involve an additional 12 weeks of follow-up, which included the same visit as Group 1 with exercises. In this case, to simplify participation and reduce the volume of blood collected, the final visit (#5) of the project will also be the first visit of exercises phase. This part of study involves 2 supervised training sessions and 8 follow up phone call. The exercises program will be performed three times per week for about one hour."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned open-label study with 2 parallel arms. Randomisation was conducted in blocks by gender with a ratio of 2:2. No details given for generation of sequence.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
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	Unclear whether outcome assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	At screening, 1 participant could not be randomised due to an adverse event during CPET. 3 dropouts **postrandomisation** (18%). 1. 2 due to a pulmonary exacerbation; group allocation for these 2 participants was not reported. 2. 1 participant was excluded due to non-compliance with the exercise programme, but the criteria for the decision of "non-compliance" were not reported in the publication. The study was registered as a cross-over study but results for the second study part were not presented.

Beaudoin 2017 *(Continued)*

Selective reporting (reporting bias)	High risk	Heart rate and SaO_2 were measured during CPET, but results were not reported. The second study phase was not reported in the original publication.
Other bias	High risk	*Sample size* Information on sample size and recruitment goals differed between the information provided under ClinicalTrials.gov and the final publication. This study aimed to recruit 24 participants (12 exercise group, 12 control group), see Clinicaltrials.gov, NCT02127957. The recruitment goal was not achieved (18 were recruited **but only 17 randomised**), but no information was provided in the final paper. According to the power calculation provided in the original publication, 18 participants (9 per group) were required for the analysis. Finally, 14 participants completed the study so the study is likely to be underpowered. *Statistical analyses* The authors reported pre–post within-group changes and no between-group differences as would be appropriate for an RCT. We received raw data from the authors and calculated between-group differences for plasma glucose and plasma insulin values during the OGTT. Our results differed compared to the results reported in the original publication. The initial power analysis, aiming to demonstrate a difference of 1.5 mmol/L in plasma glucose levels 120 min after ingestion of the glucose solution after exercise training, required a study sample of 18 participants (9 per group). Finally, only 14 participants completed the study, reducing the statistical power to observe a difference between the interventions in the study. *Control intervention* In the original publication, there was no information on the control intervention. We noticed discrepancies between the registered (ClinicalTrials.gov) and published trial design (cross-over versus parallel-group design).

Carr 2018

Study characteristics	
Methods	**Design:** parallel RCT; single-centre comparative effectiveness Phase 2 trial **Location:** Royal Brompton Hospital, London, UK **Inclusion criteria:** participants with CF aged ≥ 6 years; no prior experience practicing Tai Chi; required to have the time to complete the study and be within reasonable distance of the centre for teachers to travel to lessons; have Internet access **Exclusion criteria:** taking part in any other interventional study or had participated in the pilot study **Duration:** 9 months
Participants	40 participants with CF *Group demographics* **Intervention group** (n = 22): median age 22.8 (range 7.1–45.7) years, mean FEV_1 69 (SD 21.6) % predicted **Control group** (n = 18): median age 22.8 (range 6.1–51.5) years, mean FEV_1 77 (SD 21.8) % predicted
Interventions	Phase 2 study

Carr 2018 *(Continued)*

	Intervention group: 8 × face-to-face Tai Chi sessions then given a DVD and a handout to use at home for 9 months and encouraged to practice up to 5 times per week **Control group:** no treatment (standard care) for the first 3 months (this is the control), then 8 × online Tai Chi sessions (e.g. via Skype) and given a DVD and a handout to use at home for 6 months and again encouraged to practice up to 5 times per week Programme evaluated at baseline and after 3, 6 and 9 months
Outcomes	**Primary endpoint** 1. Change in HRQoL (CFQ-R) **Secondary endpoints** 1. Change in BMI 2. Change in lung function (FEV_1 and FVC) 3. Change in SaO_2 4. Change in dyspnoea (modified 0–10 Borg scale) 5. Number of oral and IV antibiotic course 6. Questionnaire including questions about breathlessness (modified Borg dyspnoea scale), change in medication, exacerbations, antibiotic use, frequency and timing of practice, the feasibility of learning and practising Tai Chi, engagement with the process, levels of concentration and perceived health (5 questions on a 1–4 Likert scale: never, sometimes, often, always), as well as feedback on participation in the study. A more general health question was recorded on a 0–100 VAS (0 = "as bad as it can be" and 100 "as good as it can be"). 7. Change in PSQI 8. FFMS for adults aged > 16 years and the CAMM for children Outcomes measured at baseline and after 3, 6 and 9 months. The outcomes for PSQI, FFMS and CAMM were not of interest for this review.
Notes	We contacted the corresponding author for additional raw data. The initial response was positive, but ultimately, we did not receive additional raw data. For the purpose of this review (i.e. comparison of exercise versus no exercise), we included changes from baseline to 3 months between the face-to-face Tai Chi group and the control group (i.e. starting with the Internet-delivered intervention 3 months later).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The authors used random number tables to generate random sequencing for blocks of 6 participants in 3 groups according to participants' age (6–11 years; 12–16 years; > 16 years).
Allocation concealment (selection bias)	Unclear risk	Not discussed.
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	Unclear whether outcome assessors blinded.
Incomplete outcome data (attrition bias)	High risk	51 participants were randomised (27 in the face-to-face Tai Chi group and 24 in the Internet-delivered Tai Chi group), of which 40 completed the study (22 in

Carr 2018 *(Continued)*

All outcomes		the face-to-face Tai Chi group and 18 in the Internet-delivered Tai Chi group). Dropout rate was 21.6%. Reasons for study withdrawal were reported in detail in the CONSORT flow diagram. Intention-to-treat analysis was not performed.
Selective reporting (reporting bias)	High risk	The trial was registered with ClinicalTrials.gov (identifier: NCT02054377) and a study protocol was published (Lorenc et al. *Chinese Journal of Integrative Medicine* 2015 May 26. [Epub ahead of print]). HRQoL assessed with the CFQ-R (9 quality-of-life domains) was defined as primary endpoint; i.e. change from baseline at 3 months, change from baseline at 6 months and change from baseline at 9 months. HRQoL was reported for 2/9 CFQ-R domains (i.e. respiratory domain and digestion) at baseline (Table 1 in original publication). Individual responses to the CFQ-R respiratory domain were visualised for all time points (Figure 2 in the original publication). Data for all other domains for the different time points were not reported. The authors noted that questionnaire returns at 9 months were low and no further analyses of the difference at this time were performed. Numbers (percentages) of available questionnaires were not reported.
Other bias	Low risk	Clearly stated inclusion and exclusion criteria and described method of statistical analysis used.

Cerny 1989

Study characteristics	
Methods	**Design:** single-centre, parallel RCT during hospital admission for acute exacerbation **Location:** no details given on hospital, city or country **Inclusion criteria:** participants with CF admitted to hospital for treatment of an acute exacerbation; able to perform a pulmonary function test and provided written informed consent (assumed patient or parental, depending on age) were included **Exclusion criteria:** not described **Duration:** mean 13 days
Participants	17 participants with CF *Group demographics* **Intervention group** (n = 9): mean age 15.4 (SD 4.9) years **Control group** (n = 8): mean age 15.9 (SD 4.9) years
Interventions	Short-term aerobic study **Intervention group:** 2 cycle ergometer sessions and 1 bronchial hygiene session per day during admission: mean 13 (SD 3) days **Control group:** 3 bronchial hygiene sessions per day during admission: mean 13 (SD 2.6) days
Outcomes	1. Pulmonary function (FVC, ERV, IC, FEV_1, $FEF_{25–75}$, RV, FRC, TLC, Raw, sGAW, SaO_2 and PFS) 2. Exercise performance during cycle ergometry with load increased by 0.3 W/kg every 2 min until participant could continue no longer (SaO_2, peak load, electromyography activity, peak heart rate, peak VE to peak load ratio, peak heart rate to peak load ratio) 3. Cough (15 min post-treatment session) 4. Sputum (wet and dry weight, volume)

Cerny 1989 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised but no details of the method.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants to intervention. Unclear whether personnel were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear whether outcome assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no dropouts.
Selective reporting (reporting bias)	Low risk	All outcomes detailed in methods were reported in results. Data reported for all time points.
Other bias	Unclear risk	Stated the inclusion criteria but not the exclusion criteria. Pulmonary function values FEV_1 and $FEF_{25–75}$ were lower in the control compared to the training group at admission. Clearly described statistical analysis methods.

Del Corral 2018

Study characteristics

Methods	**Design:** single-centre, parallel RCT; simple randomisation (1:1 ratio); home-based exercise training programme using active video games; blinding (outcome assessor) **Location:** Universidad Autónoma de Madrid, Madrid, Spain **Inclusion criteria:** diagnosis of CF; aged 7–18 years; clinically stable without exacerbation in the past 6 weeks prior to study start **Exclusion criteria:** evidence of cardiovascular, neuromuscular or osteoarticular comorbidities; lung transplant candidates; participation in a rehabilitation programme within the past 12 months prior to study start **Duration:** 12 months (6-week intervention and 12-month follow-up period)
Participants	40 participants with CF *Group demographics* **Intervention group** (n = 20): mean age 12.6 (SD 3.4) years; mean FEV_1 82.7 (SD 21.7) % predicted

Del Corral 2018 *(Continued)*

	Control group (n = 20): mean age 11 (SD 3) years; mean FEV_1 86.2 (SD 20.5) % predicted
Interventions	Home-based exercise training programme using active video games **Intervention group:** 6-week, home-based exercise training using the Nintendo Wii platform with the game EA SPORTS TM ACTIVE 2. The game involved exercises such as running, squats, lunges and biceps curls. Participants were instructed to exercise 5 times per week for 30–60 min per session and the training load was progressively increased over time. Participants were advised to perform all exercise at a fitness level of 3. A physiotherapist contacted the training group participants via telephone on a weekly basis. After the first 3-month training period, the participants were instructed to continue with the exercise programme (minimum 2 days per week; 20 min duration). **Control group:** no exercise training programme (usual care)
Outcomes	**Primary outcome** 1. Change in MSWT distance (m)[a] **Secondary outcomes** 1. Change in 6MWT distance (m) 2. Change in horizontal jump performance (cm) 3. Change in medicine ball throw performance (cm) 4. Change in handgrip strength (kg) 5. Change in HRQoL (CFQ-R – 3 different versions: CFQ-R 6–11 years; CFQ-R 14+; CFQ-R Parents) Outcomes were measured at baseline, after 6 weeks of training and at 12-month follow-up. [a]See comment in the risk of bias table
Notes	HRQoL data were not included in this review. See detailed comment in risk of bias table ("domain selective reporting").

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers (GraphPad Software); simple randomisation (1:1) ratio. The randomisation sequence was generated by a person not involved in the study.
Allocation concealment (selection bias)	Low risk	Adequately sealed envelopes were used. An external person not involved in the study allocated participants to each group.
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	Study staff who administered the questionnaires and collected outcome data were blinded to participants' group allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Clear description and details about dropouts and loss to follow-up: 1 participant in the intervention group did not finish the programme due to lack of time; 4 participants were lost to follow-up (10%): 2 participants in the intervention group (1 = no response; 1 = died); 2 participants in the control group (no response). Intention-to-treat and per-protocol analysis were performed. Intention-to-treat analysis was performed post hoc.

Del Corral 2018 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	The trial was registered with ClinicalTrials.gov (registration number: NCT02552043; clinicaltrials.gov/ct2/show/NCT02552043) and all outcomes were reported. Intention-to-treat analysis was performed post hoc. **HRQoL data** Data for HRQoL (CFQ-R) for 3 different groups (children aged 6–11 years; parents of children aged 6–13 years; adolescents/adults aged > 14 years) were provided in 2 tables in the online supplements. The tables (1 for the per-protocol analysis and 1 for the intention-to-treat analysis) contain mean (SD) values for all CFQ-R domains, but mean differences and their 95% CIs and effect sizes were not reported, as the authors did for the other outcomes in their main publication (i.e. tables 2 and 3). The tables in the online supplement contained information on within-group differences in HRQoL domains between baseline and end of intervention (i.e. 6 weeks) and baseline and follow-up. Between-group differences were only reported for the comparison between baseline and follow-up values, not for baseline versus 6 weeks. It is not clear what type of statistical analysis was conducted and the numbers of participants in each group were not reported. Questionnaire response rates and potential missing data could not be evaluated. We decided not to use HRQoL data from the original publication. Data were not reported as change from baseline and we were not sufficiently confident to rely on final HRQoL scores for the analyses. This would assume that the different groups are comparable in their pre-intervention HRQoL scores. However, this is not the case and we noticed some differences in pre-intervention HRQoL domains between groups, e.g. respiratory symptom scale (mean values between 66 and 82 between the control groups).
Other bias	High risk	**Primary outcome** The trial was registered with ClinicalTrials.gov (registration number: NCT02552043) and the 6MWT and MSWT were both listed as primary outcome measures. In the original publication, the MSWT was reported as a primary outcome measure and the 6MWT was reported as a secondary outcome measure. The sample size for this study was calculated to detect between-group differences in 6MWT distance (see pages 3 and 4 in the original publication). In the intention-to-treat analysis (posthoc), effects of exercise training on 6MWT distance and MSWT distance were significant (based on $P < 0.05$) for the comparison between baseline versus 6 weeks, but not for the comparison between baseline and 12-month follow-up. In comparison, in the per-protocol analysis, intervention effects were "significant" for the MSWT for the comparison between both measurement time points (i.e. baseline versus 6 weeks and baseline versus 12 months); whereas effects on 6MWT distance were "only" significant when baseline values were compared to the end of the training programme (i.e. 6 weeks). It appeared to the authors of this review that Del Corral and colleagues selected their primary outcome measure based on the results of the final statistical analysis, i.e. the outcome with the "more positive" result.

Donadio 2020

Study characteristics	
Methods	**Design:** single-centre, parallel RCT **Location:** Universidad Europea de Madrid, Madrid, Spain **Inclusion criteria:** diagnosis of CF; aged 6–18 years; signature of informed consent of legal guardian and patient

Donadio 2020 *(Continued)*

	Exclusion criteria: being a smoker; having had an exacerbation in last 3 months; having undergone gastric surgery; having enteral nutrition at present; attending the Hospital Infantil Universitario Niño Jesús of Madrid; currently taking CFTR modulators **Duration:** 8 weeks
Participants	25 participants with CF (20 boys); mean age 12.7 (SD 2.9) years; mean FEV_1 z-score −1.5 (SD 1.5) **Intervention group1** (n = 8): no additional information **Intervention group2** (n = 6): no additional information **Control group** (n = 11): no additional information
Interventions	Study participants were randomised to 1 of 3 groups. **Intervention group1:** supervised resistance exercise training programme performed 3 times per week over 8 weeks. **Intervention group2:** supervised resistance exercise training programme using electrical stimulation of the lower limbs and posterior trunk muscles performed 3 times per week over 8 weeks. **Control group:** participants received standard exercise recommendations from the CF care team.
Outcomes	**Primary outcome** 1. Change from baseline in strength at 8 weeks **Secondary outcomes** 1. Change from baseline in cardiorespiratory fitness measured using CPET at 8 weeks 2. Changes from baseline in pulmonary function at 8 weeks 3. Changes in physical activity levels (at 2 assessment points throughout the study: baseline and 8 weeks after the intervention) 4. Changes from baseline in physical activity levels measured using Physical Activity Questionnaire for Children and Adolescents at 8 weeks 5. Change from baseline in quality of life measured using the CFQ-R at 8 weeks 6. Change from baseline in food consumption frequency measured using food frequency questionnaire at 8 weeks **Outcomes reported in abstract** 1. BW (change from baseline to 8 weeks) 2. Lung function (change from baseline to 8 weeks) 3. VO_2 anaerobic threshold (change from baseline to 8 weeks) 4. Leg press (change from baseline to 8 weeks) 5. Bench press (change from baseline to 8 weeks) 6. Seated row (change from baseline to 8 weeks)
Notes	The full paper to this study was published during the process of finalising this review, i.e. after the last systematic literature search on 3 March 2022 (www.resmedjournal.com/article/S0954-6111(22)00063-4/fulltext). The results presented in the current review were drawn from a single abstract and therefore the information is currently limited. We will include results from this full paper at the next update.

Risk of bias

Bias	Authors' judgement	Support for judgement

Donadio 2020 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Described as randomised, but no details given for sequence generation.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants to intervention. Unclear if personnel blinded .
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear whether outcomes assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details of dropouts or whether intention-to-treat analysis was used.
Selective reporting (reporting bias)	Unclear risk	Did not state inclusion or exclusion criteria.
Other bias	Unclear risk	Did not state primary endpoint. No information on inclusion or exclusion criteria available.

Douglas 2015

Study characteristics	
Methods	**Design:** single-centre RCT (INSPIRE-CF). Powered to show changes in primary outcome measure of FEV_1 z-score after 24 months (66 participants needed) **Location:** Great Ormond Street Hospital CF Unit, London, UK **Inclusion criteria:** participants with a documented diagnosis of CF; male or female aged 6 years or older at baseline and < 17 years old at the end of the 2-year study; currently under the primary care of the Great Ormond Street Hospital CF Unit; able to perform spirometry with a baseline FEV_1 percentage predicted of ≥ 40%, as measured on ≥ 3 occasions in the previous year, during times of clinical stability (i.e. not during an exacerbation, and not during or within 2 weeks of IV antibiotics); the participant's parent or legal guardian must have given informed consent; assent sought from all children. **Exclusion criteria:** people who had had lung transplantation or listed for lung transplantation; clinically significant disease or medical condition other than CF or CF-related conditions that, in the opinion of the multidisciplinary clinical team, would compromise the safety of the individual; orthopaedic impairment that compromises exercise performance; mental impairment leading to inability to co-operate; unable to understand verbal or written (or both) instructions in English; children unable to understand exactly what the physiotherapists were instructing them to do, for safe and effective exercise training sessions; unable to read information sheets and questionnaires available in English; participants, parents or legal guardians who are unwilling to sign consent to participate in the study. Quote: "The following criteria will not exclude a child from participating in the study, but based on the hospital's exercise laboratory's infection control protocol, may preclude the participant from Cardiopulmonary Exercise Testing. • Patients with Methicillin-Resistant *Staphylococcus aureus*; • Patients with *Burkholderia cepacia*."

Douglas 2015 *(Continued)*

	Duration: 24 months
Participants	71 participants with CF. Data from 67/71 participants available: mean age 10 (SD 3; range 6–15) years; mean FEV_1 86.6 (SD 15.3) % predicted; mean FEV_1 z-score –1.10 (SD 1.23) *Group demographics* **Intervention group** (n = 34): mean FEV_1 89.2% predicted; FEV_1 z-score –0.89; LCI 8.6; VO_2 peak 36.1 mL/min per kg BW **Control group** (n = 33): mean FEV_1 83.8% predicted; FEV_1 z-score –1.32; LCI 9.6; VO_2 peak 36.9 mL/min per kg BW 67 participants completed study (4 dropouts: 1 from control; 3 from intervention).
Interventions	**Intervention group:** standard specialist care including weekly exercise training **Control group:** standard specialist care without weekly exercise training
Outcomes	1. Average and individual exercise training attendance rates (%) and reason for non-attendance to the exercise training programme. At baseline, 12 and 24 months, measured the following outcomes. 1. LCI by multiple-breath washout 2. FEV_1, FVC, FEV_1/FVC measured in L and converted to z-scores 3. Growth parameters (height; weight; BMI (measured in kg/cm^2 and converted to z-scores) 4. Exercise capacity by CPET (Bruce protocol): at peak and anaerobic threshold (VO_2 peak; work rate (power); V_E/VCO_2; RER; HRmax; SaO_2) 5. Exercise capacity by 10-m MSWT (25-level version) (distance in m; level achieved); HRmax; SaO_2 6. CFQ UK version Assessments at 6-month study visit 1. Spirometry 2. 10-m MSWT
Notes	INSPIRE-CF is a 24-month exercise training study that investigates the effects of an individually tailored and supervised exercise training programme on lung function, exercise capacity and HRQoL for children with CF. The study has been completed. 5 abstracts have been published, but a full-text article is not yet available. Data were extracted from the latest published abstract, presented at the 2017 World Confederation for Physical Activity Conference (Ledger et al. 2017; see under Douglas 2015) Study was powered to show changes after 24 months in primary outcome measure of FEV_1 z-score; required 66 participants

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Described as randomised but no details of the method. Randomised by minimisation to 1 of the 2 groups (after baseline testing) by an independent blinded medical statistician using the SiMin software package (Wade 2006).

Douglas 2015 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not discussed.
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	Investigators confirmed blinded outcome assessment for lung function (spirometry and multiple inert gas washout) and CPET.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 participants dropped out: 1 from the control group at 6 months (social concerns); 3 from the intervention group at 12 months (1 due to moving to a new area and changing hospitals; 2 because they no longer wished to exercise).
Selective reporting (reporting bias)	Unclear risk	Data published in abstract from, so unable to assess if all outcomes in methods were reported in results. Unable to assess if data were reported for all time points.
Other bias	Unclear risk	None identified based on limited information available.

Güngör 2021

Study characteristics	
Methods	**Design:** parallel RCT; single-centre study, triple blinding (study participant, care provider, outcome assessor) **Location:** Marmara University School of Medicine, Department of Physical Medicine and Rehabilitation, Istanbul, Turkey **Duration:** 6 weeks, including 3- and 6-month follow-up assessments
Participants	22 participants with CF **Inclusion criteria:** boys and girls aged 6–14 years; ability to understand study aims **Exclusion criteria:** FEV_1 < 30% predicted; cor pulmonale; advanced gastro-oesophageal reflux; current hospital admission due to lung infection; neuromuscular disease
Interventions	**Intervention group:** pulmonary rehabilitation programme including active cycle of breathing techniques (breathing control, chest expansion exercise, huff coughing) plus postural exercise programme, including thoracic vertebral mobilisation, pectoral stretching, scapular and thoracic extensor strengthening and core stability exercises. Breathing techniques and exercises performed once a week for 6 weeks **Control group:** pulmonary rehabilitation programme including active cycle of breathing techniques (once per week)
Outcomes	**Primary outcome** 1. Exercise tolerance (m) measured with the MSWT and assessed at baseline, 6 weeks, 3 months and 6 months **Secondary outcomes** 1. HRQoL measured with the CFQ-R at baseline, 6 weeks, 3 months and 6 months

Güngör 2021 *(Continued)*

2. FEV_1 measured at baseline, 6 weeks, 3 months and 6 months
3. Postural stability measured with the Balance Master Device – Limits of Stability Test at baseline, 6 weeks, 3 months and 6 months
4. Spinal deformity – Cobb Angle (done by 2 independent researchers), at baseline and 6 months
5. Spinal deformity – Modified Cobb Angle (done by 2 independent researchers), at baseline and 6 months

Notes	Trial status: completed (last update 26 October 2018)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Authors stated that the study was randomised but generation of the code was not described. The only information they gave was that they used a sealed opaque envelope system with blocking.
Allocation concealment (selection bias)	Unclear risk	Used sealed opaque envelopes but there was little information to explain whether this meant that the allocation was concealed and from whom.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The paper stated that the trial was single-blind (outcome assessors). However, the trial registration document (NCT03295201) stated that the trial was triple-blind (participant, care provider, outcome assessor). Given that the participants had to do postural exercises if they were in the intervention arm, it is unclear to the review authors how they could be blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All outcomes detailed in methods were reported in results. Data for HRQoL were not reported in detail; i.e. only for 2 selected subdomains. Data reported for all time points. 3 participants were lost to follow-up. Reasons were reported for 1 participant (i.e. hospitalisation of control group participant). Intention-to-treat analysis was not performed. The study was registered with ClinicalTrials.gov (identifier: NCT03295201).
Selective reporting (reporting bias)	Unclear risk	HRQoL was assessed postintervention but data were only presented for the subdomains emotional function and treatment difficulties. Changes in emotional function and treatment difficulties improved in the intervention group, not in controls. Between-group differences were not statistically significant.
Other bias	Unclear risk	It is not clear if the study participants were familiar with the MWST and if a practice test was done because of well-known learning effects. Small sample size and lack of statistical power Remarkable differences in HRQoL domains at baseline (i.e. physical functioning and respiratory domain values were substantially lower in the intervention compared to the control group).

Gupta 2019

Study characteristics	
Methods	**Design:** single-centre, parallel RCT; stratified block randomisation, allocation concealed using sequentially numbered, sealed, opaque envelopes, open-label **Location:** outpatient department of a tertiary care hospital in northern India **Inclusion criteria:** confirmed diagnosis of CF; aged 6–18 years; not having required IV antibiotics in the 1 month prior to enrolment into study; $FEV_1 \geq 20\%$ predicted **Exclusion criteria:** prior diagnosis of musculoskeletal disorder (e.g. rheumatoid arthritis, muscular dystrophy) or chronic renal failure **Duration:** 1 year
Participants	52 participants with CF were included (30 males; 22 females). *Group demographics* **Intervention group** (n = 25): 15 females (60%); mean age 147.16 (SD 33.96) months; mean FEV_1 61.44 (SD 24.72) % predicted; median BMI z-score −2.46 (IQR −3.79 to −1.48) **Control group** (n = 27): 15 females (56%); mean age 152.22 (SD 40.01) months; mean FEV_1 60.93 (SD 24.87) % predicted; median BMI z-score −1.93 (IQR −3.59 to −0.91)
Interventions	**Intervention group:** home-based exercise programme consisting of resistance exercises (e.g. squats, push-ups, forward lunges) performed 3 times per week and plyometric jumping exercises (i.e. 3 types of jumps), each performed on a daily basis (20 times per day) over 1 year. Intensity of exercises was progressively increased over time. Intervention participants received a CD with animated demonstrations of exercises; they kept a diary and were contacted via telephone every 2 weeks. **Control group:** no exercise programme, continue with regular physical activity for 1 year.
Outcomes	**Primary outcomes** 1. Change in whole body and lumbar spine bone mineral density (g/cm^2) between baseline and 1 year 2. Change in whole body and lumbar spine bone mineral apparent density (g/cm^3) between baseline and 1 year **Secondary outcomes** 1. Change in lung function (FEV_1 and FVC) at baseline; 3, 6 and 9 months; and end of 1 year 2. Change in exercise capacity measured by a treadmill CPET (VO_2 peak, exercise duration) at baseline and at the end of 1 year 3. Change in other exercise testing outcomes (VE peak; maximum heart rate; minimum SaO_2) at baseline and end of 1 year 4. Change in HRQoL (CFQ-R) assessed at baseline and 1 year 5. Change in physical activity (HAES) assessed at baseline and 1 year
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stratified block randomisation used to randomly allocate participants to intervention and control groups using computer software. A person not involved in the study generated the list of random numbers. Stratification was based on pubertal status (prepubertal versus peri-/postpubertal): children of both strata

Gupta 2019 *(Continued)*

		were further stratified based on their lung function (i.e. FEV_1 ≥ 20% and ≤ 50% predicted versus > 50% predicted.
Allocation concealment (selection bias)	Low risk	Concealment of random allocation was done by enclosing assignments in sequentially numbered opaque, sealed envelopes for the 4 strata.
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	Personnel performing dual-energy absorptiometry (primary outcome) scans and laboratory assays were blinded for group allocation. Personnel performing spirometry and exercise testing, etc. (secondary outcomes) were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Study was retrospectively registered with Clinical Trials Registry-India (Trial No: REF/2013/01/004447). All participants completed the trial. There were no reported dropouts during the study.
Selective reporting (reporting bias)	Low risk	No indication for selective reporting.
Other bias	Unclear risk	The primary outcome measure was defined as mean bone mineral density and not further specified. CPET: (quote): "Effort was considered to be at a maximal level when the participant showed clinical signs of intense effort or saturation fell below 90%". Arterial oxygen desaturation is common in people with CF lung disease during exercise testing. Oxygen saturation at peak exercise is independently related to FEV_1 (Ruf 2009). Therefore, stopping an exercise test when SpO_2 drops < 90% may significantly underestimate maximal exercise capacity. This is supported by the rather low end-test heart rates achieved at maximal exercise on the treadmill (mean values about 160–167 bpm).

Hatziagorou 2019

Study characteristics	
Methods	**Design:** single-centre, partially supervised, parallel-group RCT **Location:** Aristotle University of Thessaloniki, Greece **Inclusion criteria:** not stated **Exclusion criteria:** not stated **Duration:** 12 months
Participants	30 participants with CF (50% male) Mean age 16.2 years; mean FEV_1 91.2 (SD 20.1) % predicted; mean VO_2 peak 80.9 (SD 17.6) % predicted *Group demographics* **Intervention group** (n = 15): mean FEV_1 90.1% predicted; mean VO_2 peak 72.7% predicted

Hatziagorou 2019 *(Continued)*

	Control group (n = 15): mean FEV_1 92.2% predicted; VO_2 peak 89.1% predicted
Interventions	**Intervention group:** individualised exercise training programme; supervised using accelerometry **Control group:** no exercise training
Outcomes	1. FEV_1 (% predicted) 2. VO_2 peak (% predicted)
Notes	Limited information as published as abstract only. The abstract stated that participants were divided into 2 groups. We contacted the authors to clarify the study design. The first author of the abstract and principal investigator (Elpis Hatziagorou) confirmed that the study was an RCT. The Principal Investigator confirmed that the trial is a partially supervised intervention, in which a physiotherapist provides instructions and feedback regarding exercise training at outpatient follow-up visits. Assessments were performed at 1, 3, 6 and 12 months after baseline assessments.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not discussed.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants to intervention. Unclear whether personnel were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details of dropouts or whether it used an intention-to-treat analysis.
Selective reporting (reporting bias)	Unclear risk	Abstract, so unable to assess if all outcomes used in methods were reported in results.
Other bias	Unclear risk	Did not state inclusion or exclusion criteria, neither did they describe the methods of statistical analysis used.

Hebestreit 2010

Study characteristics

Methods	**Design:** multicentre parallel-group RCT **Location:** different study sites (Frankfurt, Hanover, Würzburg) in Germany **Inclusion criteria:** participants with CF; aged ≥ 12 years; FEV_1 ≥ 35% predicted; ability to perform physical activities

Hebestreit 2010 *(Continued)*

	Exclusion criteria: non CF-related chronic diseases and CF-related conditions posing an increased risk to the participant when exercising (e.g. oesophageal varicosis, pulmonary bullae, < 80% drop in SaO_2 with exercise and signs of pulmonary hypertension on electrocardiogram or echocardiogram, or both). **Duration:** 24 months (6-month intervention and long-term, open follow-up period)
Participants	38 participants with CF *Group demographics* **Intervention group** (n = 23): mean age 19.5 (SD 6.4) years **Control group** (n = 15): mean age 19.4 (SD 5.3) years
Interventions	Long-term, partially supervised conditioning programme **Intervention group:** exercise intervention with endurance-type and strengthening exercises. Participants agreed to increase their vigorous physical activities by a minimum of 3 × 60 min per week in the first 6 months of the study. An individual exercise plan was devised for participants; activity counselling was stopped after the first 6 months and participants were encouraged to maintain or further increase their physical activity level. **Control group:** participants were kept their activity level constant during the first 12 months of study. During the second year (period from 12 to 24 months), they were free to change their activity behaviour.
Outcomes	**Primary outcome** 1. Change in VO_2 peak, 12–18 months after end of 6-month intervention **Secondary outcomes** 1. Change in peak workload 2. Change in anaerobic performance; Wingate Anaerobic Test (PP, MP) 3. Change in pulmonary function (FEV_1, FVC, RV/TLC) 4. Change in vigorous physical activity 5. Change in body composition (skinfold thickness, body fat, fat-free mass) 6. Change in HRQoL Outcomes measured at baseline and after 3, 6, 12, 18 and 24 months
Notes	Study is a full-text article of the Hebestreit 2003 abstract (see under Hebestreit 2010). The author provided additional raw data for this review (e.g. data for RV/TLC, bodyweight, BMI, body fat, fat-free mass and HRQoL) that were not reported in detail in the original paper. The control group in this study was also used in Kriemler 2013. Data from this control group were not used for any analysis in this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	40 folded paper tickets were put into a bag with a 3:2 ratio, i.e. 24 tickets for the intervention group and 16 for the control group. Participants drew a ticket at random and the drawn ticket was then destroyed. Principal Investigator was aware of the number of lots in the bag.
Allocation concealment (selection bias)	High risk	Participants drew a folded paper ticket from an opaque bag with closed eyes. If all lots were drawn out by 1 study group, allocation concealment would no longer exist.

Hebestreit 2010 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants to intervention. Unclear whether personnel were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcome assessors were not blinded with respect to the participants' group allocation for VO_2 peak and skinfold measurements.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5 participants dropped out during the first 12 months of the study: 3 gave no reason, 1 joined another study and 1 moved away. At 18 months dropout rate was 13% and at 24 months it was 26%. Dropouts were balanced between groups. Reasons for dropout were not recorded. Intervention group participants received financial support (maximum EUR 200) to foster the realisation of the exercise training plan, which potentially introduced bias. There was no indication for differential loss to follow-up between the intervention and control group participants suggesting that the financial support did not influence attrition rates. Intention-to-treat was not performed.
Selective reporting (reporting bias)	Unclear risk	Anaerobic capacity (PP, MP) was only reported for 18–24 months' follow-up (non-significant) and results for HRQoL were only presented for the scale 'physical functioning'. There were no effects for all other HRQoL scales.
Other bias	Unclear risk	Financial support (maximum EUR 200) was offered for intervention group participants to foster the realisation of the exercise training plan. It is unclear if paying intervention group participants had an impact on attrition. Dropouts were balanced between groups suggesting that the financial incentive had no influence on attrition rates.

Hebestreit 2022

Study characteristics	
Methods	**Design:** parallel-group design; block randomisation stratified by FEV_1 (< 70% predicted, ≥ 70% predicted) and country; computer-generated list of random numbers; randomisation within the REDCap database at each study centre to allow complete allocation concealment **Location:** international multicentre RCT conducted in 27 centres across Europe and North America **Inclusioncriteria:** males and females aged 12 years and older with a confirmed diagnosis of CF; FEV_1 ≥ 35% predicted and access to Internet **Exclusioncriteria:** participation in another clinical trial up to 4 weeks prior to the first baseline visit; pregnant or breastfeeding; inability to exercise; > 4 hours of reported vigorous physical activities per week currently or up to 3 months prior to baseline measurements and not already planned within the coming 6 months; unstable condition precluding exercise (major haemoptysis or pneumothorax within the last 3 months, acute exacerbation and IV antibiotics during the last 4 weeks, planned surgery, listed for lung transplantation, major musculoskeletal injuries such as fractures or sprains during the last 2 months, others according to the impression of the treating physician); cardiac arrhythmias with exercise; requiring additional oxygen with exercise; recent diagnosis of CF-related diabetes 3 months prior to screening or at screening; recent changes in medication ≤ 1 month prior to screening (systemic steroids, ibuprofen, inhaled antibiotics, mannitol, dornase alfa, hypertonic saline); ≥ 1 G551D mutation and not on ivacaftor (VX770) yet but planned start or planned stop of ivacaftor during the trial and colonisation with *Burkholderia cenocepacia*.

Hebestreit 2022 *(Continued)*

	Duration: 12 months
Participants	117 participants with CF *Group demographics* **Intervention group** (n = 60): 65 (56%) female; mean age 25.3 (SD 11.4) years; FEV_1 74 (SD 22) % predicted; BMI 22.0 (SD 4.1) kg/m^2; VO_2 peak 71 (SD 17) % predicted **Control group** (n = 57): 52 (56%) female; mean age 22.8 (SD 10.8) years; FEV_1 74 (SD 21) % predicted; BMI 20.8 (SD 3.5) kg/m^2; VO_2 peak 69 (SD 15) % predicted
Interventions	**Interventiongroup:** participants were advised to add 3 hours of vigorous physical activities per week to baseline activities. Weekly exercises included ≥ 30 min of strength-building activities and ≥ 2 hours of aerobic activities. Exercise bouts lasting ≥ 20 min were counted with respect to total weekly training time. Participants were given exercise counselling to boost motivation towards an active lifestyle, strategies included face-to-face information, motivational interviewing, goal setting, a written "activity contract" with specific information on which activities were scheduled for which day and for how long, a pedometer, a web-based activity diary (www.activate-cf.org) providing feedback on missing time in vigorous activities to reach the weekly goal, and repeated counselling via telephone contacts and during clinic visits. A full manual describing the intervention and all intervention materials including the website was available in 4 languages: Dutch, English, French and German. **Controlgroup:** usual care. Group was advised to keep their physical activity level constant during the 12-month study.
Outcomes	**Primary outcome** 1. Change in FEV_1 (% predicted) from baseline to 6 months **Secondary outcomes** 1. Change in VO_2 peak (% predicted) from baseline to 6 months and baseline to 12 months 2. Change in maximal aerobic power (% predicted change from baseline to 6 months and baseline to 12 months) 3. Change in daily steps from baseline to 6 months and baseline to 12 months 4. Change in daily exercise steps from baseline to 6 months and baseline to 12 months 5. Change in self-reported physical (hours) activity from baseline to 6 months and baseline to 12 months 6. Change in FEV_1 (% predicted) from 6 months to 12 months and baseline to 12 months 7. Change in FVC (% predicted) from baseline to 6 months and baseline to 12 months 8. Change in RV (% of TLC) from baseline to 6 months and baseline to 12 months 9. Time to first exacerbation from baseline to 6 months and baseline to 12 months 10. Number of upper respiratory tract infections (diary) from baseline to 6 months and baseline to 12 months 11. Days on additional oral or IV antibiotics (questionnaire) from baseline to 6 months and baseline to 12 months 12. Change in BMI from baseline to 6 months and baseline to 12 months 13. Change in muscle mass (estimated from skinfold thickness) from baseline to 6 months and baseline to 12 months 14. Change in body fat (estimated from skinfold thickness) from baseline to 6 months and baseline to 12 months 15. Change in HRQoL (CFQ-R) from baseline to 6 months and baseline to 12 months 16. Change in depression, anxiety and stress (Depression Anxiety Stress Scales) from baseline to 6 months and baseline to 12 months 17. Change in plasma glucose concentrations 1 and 2 hours after a standardised glucose load (standardised OGTT only for participants without CFRD from baseline to 9 months 18. Adverse events possibly or likely related to exercise (causality as judged by investigator, from baseline to 6 months and baseline to 12 months)

Hebestreit 2022 *(Continued)*

19. Severe adverse events and serious adverse events from baseline to 6 months and baseline to 12 months

Other outcomes

1. Compliance with the exercise goal based on questionnaire and diary entries from baseline to 6 months and baseline to 12 months
2. Substudy: change in time spent in moderate-to-vigorous physical activity (accelerometry, in selected centres only) from baseline to 6 months and baseline to 12 months
3. Substudy: change in LCI based on nitrogen multiple breath washout (in selected centres only) from baseline to 6 months and baseline to 12 months
4. Substudy: change in bone mineral density and body composition based on dual energy x-ray absorptiometry (in selected centres only) from baseline to 6 months and baseline to 12 months
5. Substudy: change in mucociliary clearance with exercise based on nuclear medicine scans (US centres only) from baseline to 6 months

Notes

The review authors Thomas Radtke, Helge Hebestreit and Susi Kriemler were lead investigators of the ACTIVATE-CF trial and had full access to the data before the publication of the main manuscript. The data were included in this review, and during the process of preparing the review update, the paper was accepted for publication and appropriately cited.

Author Sherie Smith and Sarah Nevitt performed data extraction and risk of bias assessment for this study.

Data from substudies were not published in the main manuscript. The substudy on bone health and body composition using dual energy x-ray absorptiometry was stopped due to insufficient recruitment.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified block randomisation (1:1 ratio) within REDCap database, computer-generated randomisation list generated by a statistician. Randomisation was stratified by country and lung disease severity (i.e. moderate-to-severe lung disease (FEV_1 value < 70% predicted) or mild lung disease (FEV_1 ≥ 70% predicted)).
Allocation concealment (selection bias)	Low risk	Randomisation within each study site conducted centrally via a database. Study investigators had no access to the randomisation list.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants to intervention. Unclear whether personnel were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcome assessors were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes detailed in methods were reported in results. Data reported for all time points. All randomised participants who received allocated intervention were included in a (modified) intention-to-treat analysis. Losses to follow-up were reported with reasons. Data from substudies were not reported in the main publication (see comment in original report).

Hebestreit 2022 *(Continued)*

		The study was registered with ClinicalTrials.gov (identifier: NCT01744561) and a study protocol was published (Hebestreit et al. *BMC Pulmonary Medicine* 2018;18(1):31).
Selective reporting (reporting bias)	Low risk	No indication of selective reporting.
Other bias	High risk	The estimated sample size of 292 participants was not achieved; 155 individuals were assessed for eligibility, and 117 individuals were randomised. Consequently, the analysis of the primary endpoint (i.e. change in FEV_1 % predicted from baseline to 6 months) was underpowered and the unexpected finding of a significant difference favouring the control group might be due to chance.

Hommerding 2015

Study characteristics	
Methods	**Design:** single-centre parallel RCT **Location:** Centro Universitario Franciscano (UNIFRA), Santa Maria, Rio Grande do Sul, Brazil **Inclusion criteria:** participants with CF aged 7–20 years; stable disease, no signs of exacerbation of respiratory symptoms in last 15 days **Exclusion criteria:** cognitive impairment, non CF-related bone and muscle abnormalities, heart disease with haemodynamic instability **Duration:** 3 months
Participants	34 participants with CF (20 males, 14 females) *Group demographics* **Intervention group** (n = 17): mean age 13.4 (SD 2.8) years **Control group** (n = 17): mean age 12.7 (SD 3.3) years
Interventions	Aerobic exercise programme based on verbal and written guidelines. **Intervention group:** 3-month aerobic exercise training programme based on verbal and written guidelines. Programme included exercises such as jogging, swimming, walking, ball games and stretching exercises. Participants were told to practice the exercises ≥ 2 × per week for ≥ 20 min. No recommendations provided regarding exercise intensity. Participants received telephone calls every 2 weeks and instructions were provided by 1 of the authors. **Control group:** participants were instructed about aerobic exercises once at baseline according to the CF centre routine.
Outcomes	1. Change in VO_2 peak 2. Change in lung function (FVC; FEV_1; FEV_1/FVC; $FEF_{25–75}$) 3. Change in HRQoL (CRQ) 4. Change in self-reported physical activity 5. Change in body composition (BW; BMI z-score; triceps skinfold thickness; arm muscle circumference) 6. Change in SaO_2 at rest, peak exercise and recovery 7. Change in treadmill time and treadmill speed 8. Change in heart rate at rest and peak exercise 9. Change in Borg breathlessness and fatigue at peak exercise and during recovery

Hommerding 2015 *(Continued)*

	Outcomes measured at baseline and after 3 months.
Notes	Sample size estimated based on a mean change of 18.1 (SD 13.8) points in the physical score of the HRQoL questionnaire. Estimated sample size 15 participants in each group (95% power at a 5% level of significance). 2 more participants were included in each group to account for potential dropouts. Another study from the same group using the same aerobic exercise programme was published in 2015 (Schindel et al. *Journal of Pediatrics* 2015;166(3):710-6). The responsible author of this publication confirmed that the most included participants were the same as in the Hommerding 2015. There were only marginal differences in lung function (FEV_1, FVC and $FEF_{25–75}$) compared to Hommerding 2015, for which reason we decided not to include lung function data in this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were allocated to the intervention or control group in blocks of 6. Used a computer-based programme for randomisation.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants to intervention. Unclear whether personnel were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear whether outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts were reported during the study.
Selective reporting (reporting bias)	Unclear risk	Blood pressure was measured prior to and after CPET but not reported. Heart rate at rest and SaO_2 at peak exercise were measured but results were not reported at baseline.
Other bias	Unclear risk	No validity criteria for maximal performance during CPET were reported in the methods. The mean peak heart rate reached during the exercise test was 157.1 (SD 38.5) bpm in the training group and 167.7 (SD 20.8) bpm in the control group, indicative of a submaximal effort. This likely underestimates the true VO_2 peak of the study participants.

Klijn 2004

Study characteristics

Methods	**Design:** single-centre, parallel RCT **Location:** Cystic Fibrosis Center at University Medical Center, Utrecht, Netherlands **Inclusion criteria:** participants with CF aged 9–18 years; stable clinical condition (i.e. no need for oral or IV antibiotic treatment in the 3 months prior to testing); absence of musculoskeletal disorders; and FEV_1 > 30% predicted **Exclusion criteria:** not specified

Klijn 2004 *(Continued)*

	Duration: 12 weeks
Participants	20 participants with CF (stable disease) completed study *Group demographics* **Intervention group:** (n = 11): mean age 13.6 (SD 1.3) years **Control group:** (n = 9): mean age 14.2 (SD 2.1) years 3 participants dropped out: 1 withdrew from the training group for practical reasons, and 2 from the control group as they did not complete assessments due to pulmonary exacerbations.
Interventions	Long-term anaerobic study (12 weeks) **Intervention group:** anaerobic exercise (2 days per week for 30–45 min) **Control group:** normal daily activities
Outcomes	1. Change in anaerobic performance measured by Wingate Anerobic Test (PP, MP) 2. Change in body composition (BMI, fat-free mass) 3. Change in lung function (FEV_1; FVC; FEF_{25-75}; RV/TLC) 4. Change in aerobic capacity (VO_2 peak; peak working capacity; VCO_2; VE; RER; lactate) 5. Change in HAES 6. Change in HRQoL (CFQ) Outcomes were measured at baseline and after 12 weeks.
Notes	To achieve a difference in PP per kg BW of 10% with an SD of 0.8 W/kg and a statistical power of 80%, it was calculated that 8 participants had to be included in each study group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but no details of the method.
Allocation concealment (selection bias)	Low risk	Allocation concealed in opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants to intervention. Primary researcher was blinded but their role in the study was unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Primary researcher was blinded, but it was unclear whether this researcher was responsible for outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Clear description and details about dropouts. 3 participants dropped out: 1 participant from the training group withdrew for practical reasons; 2 from the control group did not complete assessments due to pulmonary exacerbations. Intention-to-treat analysis was not performed.
Selective reporting (reporting bias)	Unclear risk	Results for HRQoL are only presented for the scale 'physical functioning', which was significantly higher in the training group after the 12-week training period. There were no change in this HRQoL scale in the control group after 12

Klijn 2004 *(Continued)*

		weeks. There were no significant effects for any other HRQoL scales. Data were not reported in detail.
Other bias	Unclear risk	Clearly stated inclusion criteria but exclusion criteria were not reported. Described statistical methods used in analysis.

Kriemler 2013

Study characteristics	
Methods	**Design:** multicentre, parallel RCT with 3 arms **Location:** different study sites in Switzerland **Inclusion criteria:** diagnosis of CF; aged ≥ 12 years; FEV_1 % predicted ≥ 35%; ability to perform physical activity without harm **Exclusion criteria:** non-CF-related chronic diseases and conditions posing an increased risk to the participant when exercising **Duration:** 24 months (6-month intervention and long-term, open follow-up period)
Participants	39 participants with CF split into 3 groups *Group demographics* **Intervention group 1:** (aerobic training) (n = 17): mean age 23.8 (95% CI 21.5 to 26.5) years **Intervention group 2:** (strength training) (n = 12): mean age 19.0 (95% CI 16.0 to 22.0) years **Control group:** (n = 10): mean age 20.3 (95% CI 17.0 to 23.6) years A separate control group from a parallel study (Hebestreit 2010) was added due to an unusual deterioration of physical health in the control group in this study (n = 15), mean age 19.5 (95% CI 16.8 to 22.2) years. Data from this control group were not used in this review.
Interventions	Long-term exercise study **Intervention group 1:** participants consented to perform 3 aerobic training sessions per week of 30–45 min duration for the first 6 months and received support which was stopped thereafter. **Intervention group 2:** participants consented to perform 3 strength training sessions per week of 30–45 min duration for the first 6 months and received support which was stopped thereafter. **Control group:** participants in the control group were told to keep their activity level constant. Free access to a fitness centre for 1 year was offered after the first study year.
Outcomes	**Primary outcome** 1. Change in FEV_1 from baseline to 6 months **Secondary outcomes** 1. Change in lung function (FVC; RV/TLC) 2. Change in aerobic exercise capacity measured by CPET (VO_2 peak; peak workload) 3. Change in anaerobic exercise capacity measured by Wingate anaerobic test (PP, MP) 4. Change in objectively measured physical activity 5. Change in body composition (body fat; fat-free mass)

Kriemler 2013 *(Continued)*

	Outcomes were measured at baseline and after 3, 6, 12 and 24 months.
Notes	Study was a full-text article of the Kriemler 2001 and Hebestreit 2003 abstracts (see under Kriemler 2013 and Hebestreit 2010). Control group experienced a deterioration of physical health during the study. In the original paper, a second control group from a German study with similar design and methods (Hebestreit 2010) was used for comparisons. Data from this control group were not used in this review. The author provided additional raw data for this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Participants were randomly assigned by a lot that was drawn with their eyes closed from an opaque bag. Investigator was aware of the number of lots in the bag.
Allocation concealment (selection bias)	High risk	Participants with their eyes closed drew a lot from an opaque bag. If all lots for 1 study group have been drawn out, allocation concealment would no longer exist.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants to intervention. Unclear whether personnel were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded for pulmonary function testing (primary outcome FEV_1). Outcome assessors were not involved in supervision and delivery of the intervention.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Clear description and details about excluded participants and dropouts. 3 participants were excluded at baseline due to FEV_1 < 35% predicted. 8 participants dropped out at different time points (exacerbation n = 1; non-compliance n = 2; death n = 2; unclear reasons n = 3). 2 participants who dropped out for unclear reasons were in the control group and 1 was in the aerobic training group. Dropout rate was 21%. Intention-to-treat analysis not performed.
Selective reporting (reporting bias)	Low risk	All outcome detailed in methods were reported in results except HRQoL (secondary outcome), which was mentioned to be reported separately. In the meantime, study was published as Hebestreit et al. *BMC Pulmonary Medicine* 2014;14:26. HRQoL data were pooled from 2 intervention studies (Hebestreit 2010; Kriemler 2013), and results were presented for baseline and 6-month follow-up.
Other bias	Unclear risk	Clearly stated inclusion and exclusion criteria and described statistical methods used in analysis. Due to the deterioration of physical health in the control group, the results of this study should be interpreted with caution.

Michel 1989

Study characteristics

Michel 1989 *(Continued)*

Methods	**Design:** single-centre, parallel RCT during hospital admission **Location:** no details given on hospital, city or country **Inclusion criteria:** not specified **Exclusion criteria:** not specified **Duration:** duration of hospital admission
Participants	9 participants with CF; not stated how many allocated to each group *Group demographics* **Intervention group:** mean age 25.5 (SD 10.5) years **Control group:** mean age 21.5 (SD 3.2) years
Interventions	Short-term aerobic study **Intervention group:** exercise and standardised CF protocol **Control group:** standardised CF protocol
Outcomes	1. Skin folds 2. Mid-arm circumference 3. Grip strength 4. Respiratory muscle strength 5. Ideal BW Outcomes were measured at 1-month postdischarge.
Notes	Limited information as published as abstract only.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but no details of method.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants to intervention. Unclear whether personnel were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear whether outcome assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details of dropouts or whether intention-to-treat analysis was used.
Selective reporting (reporting bias)	Unclear risk	This was an abstract so unable to assess if all outcome used in methods were reported in results. Unable to assess if data were reported for all time points.

Michel 1989 *(Continued)*

Other bias	Unclear risk	Did not state inclusion or exclusion criteria, neither did they describe the methods of statistical analysis used.

Moorcroft 2004

Study characteristics

Methods	**Design:** single-centre, parallel RCT **Location:** adult CF centre in Manchester, UK **Inclusion criteria:** people with CF who were willing to participate were recruited from 150 people attending the adult CF centre in Manchester at time of study; all had documented CF based on clinical history plus either an increased sweat chloride or abnormal genetic testing **Exclusion criteria:** participation in another clinical trial, pregnancy, transplant listing, clinical cor pulmonale **Duration:** 1 year
Participants	51 participants with CF were randomised; 42 completed the study *Group demographics* **Intervention group** (n = 30): mean age 23.5 (SD 6.4) years **Control group** (n = 18): 23.6 (SD 5.5) years 3 participants dropped out at the start of the programme: 1 from training group due to failure to attend on initial assessment; and 2 in the control group were withdrawn due to ill health. A further 6 participants dropped out during the 1-year period
Interventions	Long-term aerobic and anaerobic study over 1 year **Intervention group:** unsupervised exercise (based on individual preferences, general aerobic exercises for lower body and weight training for upper body) 3 times per week **Control group:** continue with usual activities
Outcomes	1. Change in lung function (FEV_1; FVC) 2. Change in BMI 3. Change in whole blood lactate; RER; heart rate; Borg breathlessness and muscle effort; VE, RR peak for arm and bicycle ergometry at 55% maximal workload Outcome were measured at baseline and after 1 year
Notes	Study was a full-text article of Dodd 1998 and Moorcroft 2000 abstracts (see under Moorcroft 2004).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised to either active or control groups in a ratio of 3:2. A stratified randomisation in blocks (block size not stated) was used to balance the groups for FEV_1, sputum colonisation by *Burkholderia cepacia* and gender. No details of method reported.

Moorcroft 2004 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants to intervention. Unclear whether personnel were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear whether outcome assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3 participants dropped out at start of programme: 1 from training group due to failure to attend on initial assessment; and 2 in control group were withdrawn due to ill health. A further 6 participants dropped out during the 1-year period. Reasons for dropout were not clearly reported. After 1 year, overall dropout rate was 18% and balanced between the groups (19% in the intervention and 15% in the control group). Intention-to-treat analysis was not performed. Missing data were treated by omission and only data for those who completed study presented.
Selective reporting (reporting bias)	Low risk	All outcomes detailed in methods were reported in results. Data reported for all time points.
Other bias	Low risk	Clearly stated inclusion and exclusion criteria and described method of statistical analysis used.

Rovedder 2014

Study characteristics	
Methods	**Design:** single-centre, parallel RCT of a home-based exercise programme **Location:** Porto Alegre Clinical Hospital, Porto Alegre, Brazil **Inclusion criteria:** participants diagnosed with CF in accordance with the criteria of the CF adult care consensus conference report by Yankaskas 2004; aged ≥ 16 years; ≥ 30 days of clinical respiratory disease stability **Exclusion criteria:** participants who refused to take part in the study; pregnant women; people with heart disease, orthopaedic or traumatological problems **Duration:** 3 months
Participants	41 participants with CF *Group demographics* **Intervention group** (n = 22): mean age 23.8 (SD 8.3) years **Control group** (n = 19): mean age 25.4 (SD 6.9) years 2 study participants in the exercise group could not be assessed at the 3-month follow-up due to lung transplant assessment.

Rovedder 2014 *(Continued)*

Interventions	3-month home-based exercise programme **Intervention group:** participants received printed guidance for aerobic and muscle strengthening exercises and were advised to perform the programme on a daily basis. Weekly telephone contacts were performed during the 3-month period. **Control group:** participants received standard programme without any specific exercise instructions.
Outcomes	1. Change in lung function (FEV_1; FVC) 2. Change in HRQoL (CFQ) and Medical Outcomes Study 36-item Short-Form Health Survey (SF-36). 3. Change in functional exercise capacity (distance covered during a 6MWT) 4. Change in SaO_2 at rest and peak exercise; RR at peak exercise; peak exercise heart rate; dyspnoea and fatigue scores at rest and peak exercise during 6MWT 5. Change in upper and lower body muscle strength Outcomes were measured at baseline and after 3 months
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants randomly allocated in blocks of 6 to exercise or control group. A computer programme was used to generate the randomisation sequence.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants to intervention. 1 researcher was blinded to the randomisation and intervention and was responsible for database entries.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants in the exercise group could not be assessed at the 3-month visit due to submission to the lung transplant programme. Intention-to-treat analysis was used and imputations for missing data were performed for these 2 participants.
Selective reporting (reporting bias)	Low risk	All outcomes detailed in methods were reported in results. Data reported for all time points
Other bias	Unclear risk	Clearly stated inclusion and exclusion criteria and described method of statistical analysis used. Baseline between-group differences existed in BMI which could possibly impact on HRQoL (primary outcome).

Santana-Sosa 2012

Study characteristics

Methods	**Design:** single-centre, parallel RCT

Santana-Sosa 2012 *(Continued)*

	Location: Children's Hospital Infantil Universitario Niño Jesús in Madrid, Spain **Inclusion criteria:** potential participants included 111 children previously diagnosed using a genetic test for CF and treated at the Children's Hospital Niño Jesús in Madrid. Boys or girls aged 5–15 years and living in the Madrid area (able to attend training sessions) **Exclusion criteria:** severe lung deterioration, as defined by an FEV_1 < 50% predicted; unstable clinical condition (i.e. hospitalisation within the previous 3 months); *Burkholderia cepacia* infection; musculoskeletal disease or any other disorder impairing exercise **Duration:** 3 months (8 weeks' training, 4 weeks' 'detraining')
Participants	22 participants with CF *Group demographics* **Intervention group** (n = 11): mean age 11 (SEM 3) years; range 5–15 years **Control group** (n = 11): mean age 10.0 (SEM 2) years; range 6–14 years
Interventions	8-week intrahospital programme followed by a 4-week detraining period. All participants received the same chest physiotherapy during the entire study period. **Intervention group:** supervised endurance and strengthening exercises, 3 times per week **Control group:** continue with standard therapy and instructed on the positive effects of regular physical activity
Outcomes	**Primary outcomes** 1. Change in cardiorespiratory fitness (VO_2 peak) measured by treadmill CPET 2. Change in dynamic muscle strength (upper and lower body strength (bench press, leg press, seated row) **Secondary outcomes** 1. Change in lung function (FEV_1; FVC; PI_{max}) 2. Change in body composition (BW; BMI; fat-free mass; body fat) 3. Change in HRQoL (CFQ-R) 4. Change in functional mobility measured by Timed Up and Go test; Timed Up and Down Stairs test **Other outcomes** 1. Adherence to exercise training 2. Adverse effects of exercise training Outcomes were measured at baseline, after 8 weeks of training and after 4 weeks of detraining.
Notes	Additional raw data for all included outcomes provided by the authors. The study authors used the term 'detraining', which is a time period during which no supervised exercise training was provided. The meaning of 'detraining' is consistent with our term 'off training', which also describes a period during which no (partially) supervised physical activity took place, but study participants were not explicitly discouraged from undertaking physical activity.

Risk of bias

Bias	Authors' judgement	Support for judgement

Santana-Sosa 2012 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Participants were randomly assigned to exercise or control group (quote) "with a block on gender on the basis of a randomization sequence". No details about how randomisation sequence was generated.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants to intervention. Personnel involved in training not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded to participants' group assignment.
Incomplete outcome data (attrition bias) All outcomes	High risk	Clear description of missing outcome data. 5 participants could not be assessed at different time points (1 postintervention and 4 after detraining) due to hospitalisations (n = 3), relocation (n = 1) and parents who declined further evaluation (n = 1). Dropout rate was unbalanced with 28% in the control group and 9% in the intervention group after the detraining period. Intention-to-treat analysis was used and missing outcome data (at post-training or detraining visit) were replaced by baseline data.
Selective reporting (reporting bias)	Low risk	All outcomes detailed in methods were reported in results. Data reported for all time points
Other bias	High risk	Some raw data were made available, but there were inconsistencies between raw data and data reported in the original publication. There were significant between-group differences in primary (VO_2 peak) and secondary (strength measures) outcome measures at baseline.

Santana-Sosa 2014

Study characteristics	
Methods	**Design:** single-centre, parallel RCT **Location:** Children's Hospital Infantil Universitario Niño Jesús in Madrid, Spain **Inclusion criteria:** potential participants included 95 outpatient children previously diagnosed with CF by genetic testing and treated at the Children's Hospital Niño Jesús in Madrid. Males or females aged 6 to 17 years and living in the Madrid area (able to attend training sessions) **Exclusion criteria:** severe lung deterioration (FEV_1 < 50% predicted); unstable clinical condition (i.e. hospitalisation within the previous 3 months); *Burkholderia cepacia* infection or any disorder (e.g. musculoskeletal) impairing exercise **Duration:** 3-month study (8 weeks' training, 4 weeks' 'detraining')
Participants	20 participants with CF *Group demographics* **Intervention group** (n = 10): mean age 11.1 (SEM 1.1) years

Santana-Sosa 2014 *(Continued)*

	Control group (n = 10): mean age 10.1 (SEM 1.1) years
Interventions	8-week programme followed by a 4-week detraining period. All participants received the same standard chest physiotherapy **Intervention group:** whole body aerobic and weight training 3 times per week, plus 2 daily inspiratory muscle training sessions **Control group:** inspiratory muscle training only at a low intensity.
Outcomes	**Primary outcomes** 1. Change in lung function (FEV_1; FVC; PI_{max}) 2. Change in VO_2 peak measured by treadmill CPET **Secondary outcomes** 1. Change in dynamic muscle strength (upper and lower body strength (bench press, leg press, seated row)) 2. Change in body composition (BW; fat-free mass; body fat) 3. Change in HRQoL (CFQ-R) **Other outcomes** 1. Adherence to exercise training 2. Adverse effects of exercise training Outcomes were measured at baseline, after 8 weeks of training and after 4 weeks of detraining.
Notes	Additional raw data for all included outcomes provided by the authors. Study authors used the term 'detraining', which is a time period during which no supervised exercise training was provided. The meaning of 'detraining' is consistent with our term 'off training', which also describes a period during which no (partially) supervised physical activity took place, but study participants were not explicitly discouraged from undertaking physical activity.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation to intervention or control group "with block on gender". No details given for sequence generation.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants to intervention. Personnel involved in training not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded to participants' group assignment.
Incomplete outcome data (attrition bias) All outcomes	High risk	Clear description of missing outcome data. 3 participants from control group could not be assessed at different time points (1 at postintervention and detraining phase and 2 after detraining phase) due to hospitalisation for lung transplantation preparation (n = 1), infection with *Burkholderia cepacia* (n = 1) and refusal (n = 1).

Santana-Sosa 2014 *(Continued)*

		Unbalanced distribution of dropouts. Dropout rate in control group was 30% versus 0% in intervention group. Intention-to-treat analysis was reported, but it was not clear how missing data were handled.
Selective reporting (reporting bias)	Low risk	All outcomes detailed in methods were reported in results. Data reported for all time points.
Other bias	High risk	Some raw data were made available, but there were inconsistencies between raw data and data reported in the original publication. Significant between-group differences in primary outcomes (VO_2 peak and strength measures) existed at baseline.

Sawyer 2020

Study characteristics	
Methods	**Design:** parallel-design RCT (2 arms). Central randomisation (1:1 ratio); minimisation algorithm with stratification for study site, FEV_1 (≥ 70% predicted, 40–69% predicted, ≤ 39% predicted) and ivacaftor treatment **Location:** Sir Charles Gairdner Hospital (adult service) and Perth Children's Hospital (paediatric service), Perth, Australia **Inclusion criteria:** males and females aged ≥ 15 years with BMI > 16 kg/m^2 **Exclusion criteria:** recent (within previous 4 weeks) pulmonary exacerbation requiring oral or IV antibiotics; comorbidity that would impact on the ability to undertake a maximal exercise test; poorly controlled diabetes; previous lung transplant or current listing for lung transplantation; participation in moderate-intensity structured exercise ≥ 2 times per week for the previous 3 months, and inability to provide written informed consent **Duration:** 8 weeks
Participants	14 participants with CF *Group demographics* **Intervention group** (n = 7): 4 females and 3 males; median age 31 (IQR 29–31) years; FEV_1 66% predicted (IQR 45–83); BMI 23.2 (IQR 21.4–34.5) kg/m^2 **Control group** (n = 7): 5 females and 2 males; median age 31 (IQR 26–39) years; FEV_1 57% predicted (IQR 39–80); BMI 24.6 (IQR 20.5–28.5) kg/m^2
Interventions	**Intervention group:** 8-week low-volume, high-intensity interval training programme on a bicycle ergometer. 22 sessions were planned over 8 weeks. Each training session was composed of a 2-min warm-up phase (15–20 W), followed by a 30-second work phase and 30-second rest period, repeated 6 times. Total duration of each session was about 10 min. The training intensity increased progressively: first session at 60% of peak workload, aiming to achieve a training intensity of 80% of peak workload during the fourth training session. Thereafter, training intensity was increased as rapidly as symptoms of breathlessness and muscle fatigue permit. Each session was individually supervised by a physiotherapist. All sessions were audio recorded. **Control group:** usual care; no specific exercise programme; participants were contacted once per week (telephone calls, text messages or email) to monitor changes in symptoms, healthcare utilisation and participation in exercise over the preceding week.
Outcomes	**Primary outcome**

Sawyer 2020 *(Continued)*

1. Exercise tolerance, i.e. time during a constant work rate test performed at 80% of peak after 8 weeks

Secondary outcomes

1. Change in HRQoL (CFQ-R questionnaire) from baseline to 8 weeks
2. Change in Awe-Score CF from baseline to 8 weeks
3. Change in HADS from baseline to 8 weeks
4. Change in PACES from baseline to 8 weeks
5. Lung function: change in FEV_1 and FVC (in L and % predicted), and FEV_1/FVC ratio from baseline to 8 weeks

Other outcomes (intervention group only)

1. Change in postexercise quadriceps femoris muscle soreness (24 hours after first training session following a sit-to-stand task)
2. Attendance and completion of training sessions for 8 weeks
3. Cardiorespiratory and symptom responses, e.g. VO_2, VCO_2, heart rate, oxygen saturation, breathlessness and leg muscle fatigue (Borg scale) during high-intensity interval training sessions in the laboratory (weeks 1, 4 and 8 during training period)
4. Behaviour change techniques such as reinforcement, feedback and goal setting during the exercise training programme

Notes	Author provided raw data for this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were allocated on a 1:1 ratio via a central randomisation service (the National Health and Medical Research Council randomisation service). Used a minimisation algorithm to stratify for site of recruitment, lung disease severity (i.e. mild ($FEV_1 \geq 70\%$ predicted), moderate (FEV_1 40–69% predicted) or severe ($FEV_1 \leq 39\%$ predicted)) and the use (or not) of ivacaftor.
Allocation concealment (selection bias)	Low risk	Central randomisation service (the National Health and Medical Research Council randomisation service).
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants to intervention. Unclear whether personnel were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded to group allocation for follow-up assessments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes were reported as planned. All participants completed the trial. No dropouts were reported during the study. Maximal exercise testing was completed by 10/14 participants and submaximal exercise testing by 11/14 participants at the 8-week follow-up assessment. Study was registered with the Australian and New Zealand Clinical Trials Registry (12617001271392) and a study protocol was published (Sawyer et al. *BMC Sports Science, Medicine and Rehabilitation*, 2018;10:19).
Selective reporting (reporting bias)	Low risk	No indication of selective reporting.

Sawyer 2020 *(Continued)*

Other bias	High risk	The authors were able to include 14 participants. The sample size calculation defined a target sample size of 40 participants including a 20% loss to follow-up (n = 32). The planned statistical analyses (i.e. linear models with adjustment for baseline values as covariates and group allocation as fixed effect) could not be realised. Non-parametric test statistics were applied. Due to the small sample size, some variables of interest were not balanced between groups (e.g. sex, VO_2 peak).

Schneiderman-Walker 2000

Study characteristics	
Methods	**Design:** single-centre, parallel RCT **Location:** Hospital for Sick Children, Toronto, Canada **Inclusion criteria:** people with CF aged 7–19 years with a FEV_1 > 40% predicted **Exclusion criteria:** not specified **Duration:** 3 years
Participants	65 participants with CF; 2 groups similar at baseline. 7 dropouts Group demographics **Intervention group** (n = 30): mean age 13.4 (SD 3.9 years) **Control group** (n = 35): mean age 13.3 (SD 3.6) years
Interventions	Long-term aerobic study **Intervention group:** minimum of 20 min aerobic activity plus 5 min warm up and cool down 3 times per week **Control group:** maintained regular activity (control)
Outcomes	**Primary outcome** 1. Rate of decline in FEV_1 **Secondary outcomes** 1. Annual rate of change in lung function (FVC; $FEF_{25–75}$; PEFR) 2. Annual rate of decline in exercise capacity (VO_2 peak, peak workload, peak exercise heart rate; peak exercise VE; VE peak/MVV) 3. Annual rate of change in per cent of ideal weight for height 4. Changes in chest x-ray and Schwachman scores 5. Compliance with conventional physiotherapy 6. Sense of well-being 7. Feasibility of exercise 8. Mean number of hospital stays and number of days in hospital
Notes	
Risk of bias	

Schneiderman-Walker 2000 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants to intervention. Unclear whether personnel blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Pulmonary function assessors were blinded to group assignment (primary outcome measure).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Clear description and details of 7 dropouts were recorded. Intention-to-treat analysis was reported to yield similar results for pulmonary function. Results were only reported for 65 participants who completed the 2-year follow-up.
Selective reporting (reporting bias)	Low risk	All outcome detailed in methods were reported in results. Data reported for all time points.
Other bias	Unclear risk	Groups similar at baseline. Stated the inclusion criteria but not the exclusion criteria. Described statistical methods used in analysis.

Selvadurai 2002

Study characteristics	
Methods	**Design:** single-centre, parallel RCT; hospital admission for recurrent chest infections **Location:** Royal Alexandra Hospital for Children, Sydney, Australia **Inclusion criteria:** children with CF, aged 8–16 years who were admitted to the Royal Alexandra Hospital for Children for the treatment of an infectious pulmonary exacerbation **Exclusion criteria:** children with known pulmonary hypertension, or who required daytime oxygen prior to the pulmonary exacerbation that led to the hospital admission
Participants	66 children with CF (28 boys, 38 girls). No dropouts *Group demographics* **Intervention group 1:** aerobic exercise training (n = 22): mean age 13.2 (SD 2.0) years, 9 boys and 13 girls **Intervention group 2:** resistance exercise training (n = 22): mean age 13.1 (SD 2.1) years, 10 boys and 12 girls

Selvadurai 2002 *(Continued)*

	Control group (n = 22): mean age 13.2 (SD 2.0) years, 9 boys and 1 girl
Interventions	Short-term aerobic and anaerobic/strength training study during hospital admission (mean duration 18.7 days, range 14–36 days). **Intervention group 1:** 30-min supervised aerobic exercise training 5 times per week **Intervention group 2:** 30-min supervised resistance training 5 times per week **Control group:** no specific training
Outcomes	1. VO_2 peak 2. VE peak 3. VCO_2 4. Peak heart rate 5. HRQoL 6. FEV_1 7. FVC 8. Weight 9. Lower limb strength 10. Fat-free mass Reported at hospital discharge and 1 month after hospital discharge.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random allocation in sets of 6. No details given for generation of sequence.
Allocation concealment (selection bias)	Low risk	Concealed information inside opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants to intervention. Unclear whether personnel blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear whether outcome assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Stated no dropouts.
Selective reporting (reporting bias)	Unclear risk	Did not report on all secondary outcomes detailed in methods (e.g. VE, VCO_2, respiratory quotient) in results. Data reported for all time points.
Other bias	Low risk	Clearly stated inclusion and exclusion criteria. Described statistical methods used to analyse data.

Turchetta 1991

Study characteristics	
Methods	**Design:** single-centre, parallel RCT, hospital admission for routine assessment of clinical condition **Location:** Ospedale Pediatrico Bambino Gesu, Rome, Italy **Inclusion criteria:** not specified **Exclusion criteria:** not specified **Duration:** 2 weeks
Participants	12 children with CF, 8 boys, mean age 12.3 years No group demographics available
Interventions	Short-term aerobic study **Intervention group:** 20 min running or treadmill per day for 2 weeks **Control group:** normal hospital treatment
Outcomes	1. Lung function (FEV_1 and FVC)
Notes	This study was only reported in a single abstract and, therefore, information was limited.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but no details given for sequence generation.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants to intervention. Unclear whether personnel blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear whether outcome assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details of dropouts or whether intention-to-treat analysis was used.
Selective reporting (reporting bias)	Unclear risk	This is an abstract so unable to assess if all outcome used in methods were reported in results. Data were reported for all time points.
Other bias	Unclear risk	Did not state inclusion or exclusion criteria, neither do they describe the methods of statistical analysis used.

6MWT: 6-minute walk test; Awe-Score CF: Alfred Wellness Score for CF; BMI: body mass index; bpm: beats per minute; BW: bodyweight; CAMM: Child and Adolescent Mindfulness Measure; CF: cystic fibrosis; CFRD: cystic fibrosis-related diabetes; CFTR: cystic fibrosis transmembrane conductance regulator; CFQ-R: Cystic Fibrosis Questionnaire – Revised; CPET: cardiopulmonary exercise test; ERV: expiratory reserve volume; $FEF_{25–75}$: forced mid-expiratory flow between 25% and 75% of vital capacity; FEV_1: forced expiratory volume

in 1 second; FFMS: Five Facet Mindfulness Scale; FRC: functional residual capacity; FVC: forced vital capacity; HADS: Hospital Anxiety and Depression Scale; HAES: Habitual Activity Estimation Scale; HbA1c: glycated haemoglobin; HRQoL: health-related quality of life; IC: inspiratory capacity; IGT: impaired glucose tolerance; IV: intravenous; LCI: Lung Clearance Index; min: minute; MP: mean power; MSWT: modified shuttle walk test; MVV: maximal voluntary ventilation; OGTT: oral glucose tolerance test; PACES: Physical Activity Enjoyment Scale; PEFR: peak expiratory flow rate; PFS: progression-free survival; PI_{max}: maximum inspiratory mouth pressure; PP: peak power; PSQI: Pittsburgh Sleep Quality Index; Raw: airways resistance; RCT: randomised controlled trial; RER: respiratory exchange ratio; RR: respiratory rate; RV: residual volume; SaO_2: arterial oxygen saturation; SpO_2: peripheral blood oxygen saturation; SD: standard deviation; SEM: standard error of the mean; sGAW: specific airways conductance; TLC: total lung capacity; VAS: Visual Analogue Scale; VE: minute ventilation; VE peak: peak minute ventilation; VO_2 peak: peak oxygen uptake; VCO_2: carbon dioxide production; VO_2: oxygen uptake; W: watt; WAnT: Wingate Anaerobic Test.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ACTRN12620001237976	No control group with no physical activity.
Alarie 2012	Study compared acute cardiovascular response in participants playing different active video games. No control group included.
Albinni 2004	Study designed with the exercise group as the control group; therefore, we could not compare data with baseline; no physical exercise training according to our protocol.
Almajan-Guta 2011	No information available about whether a publication is planned for this study. We could not find contact details of the authors to get more information about the study status.
Amelina 2006	IMT training and not physical exercise training according to our protocol.
Andreasson 1987	Not a randomised controlled study.
Aquino 2006	Study was designed to compare the effectiveness of a single treatment session of exercise and PEP on sputum clearance. Participants in this study did not undertake a programme of physical training.
Asher 1982	IMT training and not physical exercise training according to our protocol.
Balestri 2004	Study designed to compare the effectiveness of a single treatment session of exercise and PEP on sputum clearance. Participants in this study did not undertake a programme of physical training.
Balfour Lynn 1998	Not a physical exercise training study; comparison of different tests for assessing exercise capacity.
Barry 2001	Not a randomised controlled study.
Bass 2019	No control group with no physical exercise training.
Bellini 2018	Not a physical exercise training study.
Bieli 2017	Study of respiratory muscle endurance training; not a physical exercise training study.
Bilton 1992	Study designed to compare the effectiveness of a single treatment session of exercise or physiotherapy or exercise and physiotherapy on sputum clearance and lung function. Participants in this study did not undertake a programme of physical training.
Bongers 2015	Study evaluating the clinical usefulness of the steep ramp test. Not a physical exercise training study.
Calik-Kutukcu 2016	No control group with no physical exercise training.

Study	Reason for exclusion
Cantin 2005	Not a physical exercise training study.
Chang 2015	Study of methods for evaluating muscle function and not a physical exercise training study.
Chatham 1997	Study involved respiratory muscle training exclusively. This intervention did not constitute physical training as defined within our protocol.
Combret 2018	Not a physical exercise training study.
Combret 2021	Not a physical activity intervention.
Cox 2013	Not a physical exercise training study.
de Jong 1994	Not a randomised controlled study.
del Corral Nunez-Flores 2014	No control group with no physical training.
de Marchis 2017	No control group with no physical exercise training.
Dwyer 2011	Study duration insufficient.
Dwyer 2017	Acute exercise study. Study duration insufficient.
Dwyer 2019	This randomised cross-over study evaluated the acute effects of airway clearance techniques and exercise on mucociliary clearance. Insufficient study duration.
Edlund 1986	Not a randomised controlled study.
Falk 1988	Study designed to compare the effectiveness of a single treatment session of exercise or PEP on lung function. Participants in this study did not undertake a programme of physical training.
Giacomodonato 2015	Study of respiratory muscle endurance training and not a physical exercise training study.
Gruber 1998	No control group with no physical exercise training.
Gruet 2012	No control group with no physical exercise training.
Happ 2013	Qualitative descriptive study nested within a randomised controlled trial of a self-regulated, home-based exercise programme. Outcomes of this study were not relevant for this review.
Haynes 2016	Evaluation of the incremental step test, not a study of physical training.
Heijerman 1992	Not a randomised controlled study.
Housinger 2015	No contact details available online. Very unlikely that this study will be published.
Hütler 2002	Not a physical exercise training study.
IRCT20161024030474N4	Not a randomised controlled study.
Irons 2012	Not a physical exercise training study; examined effect of a singing programme compared to no singing.
Johnston 2004	No information available about whether a publication is planned for this study. We could not find contact details of the authors to obtain more information about the study status.

Study	Reason for exclusion
Kaak 2011	Not a physical exercise training study.
Kaltsakas 2021	Study compared interval versus continuous exercise training. No control group with no physical exercise training.
Kriemler 2016	Study duration insufficient: only 3 single-day interventions on non-consecutive days of 1 week.
Kuys 2011	Compared Nintendo Wii exercise training to an existing exercise programme; no control group with no physical training.
Lang 2019	No control group with no physical exercise training. Study evaluated the efficacy of a telehealth physiotherapy intervention. Control group participants engaged in a home exercise programme and recorded their activities in a self-reported paper-based exercise diary.
Lannefors 1992	Study designed to compare the effectiveness of a single treatment session of exercise and FET or PEP and FET or postural drainage, thoracic expansion exercises and FET on mucous clearance. Participants in this study did not undertake a programme of physical training.
Lima 2014	No physical exercise training study; study looked at effect of non-invasive ventilation on exercise capacity and lung function.
Lowman 2012	No control group with no physical training.
Macleod 2008	Not a physical exercise training study.
Mandrusiak 2011	The first author of this study confirmed that the study will not be published.
Martinez Rodriguez 2017	No control group with no physical training.
Montero-Ruiz 2020	Not a physical exercise training study.
Moola 2017	Study assessed the feasibility of a parent-mediated physical activity counselling programme for children with CF. The programme did not include supervised or partially supervised exercise sessions.
NCT00129350	Study is unlikely to be published (last status update 2005). If study publications are identified in future searches, it will be considered for inclusion in this review.
NCT00792194	The investigator informed us that the trial has been terminated prematurely due to recruitment problems and that no paper will be published.
NCT01759342	No control group with no physical exercise training.
NCT02199340	Not a physical exercise training study.
NCT02277860	Not a randomised controlled study; single arm trial of physical exercise.
NCT02715921	Not a randomised controlled study; single arm trial of physical exercise.
NCT02821130	Study of CFTR potentiator therapy and effects on exercise capacity.
NCT02875366	Study of CFTR potentiator therapy and effects on exercise capacity.
NCT03117764	Not a randomised controlled study; study of the effect of antibiotics on muscular strength and not physical training.

Study	Reason for exclusion
NCT03420209	Study focused on proprioceptive neuromuscular facilitation in children with chronic respiratory diseases. This type of training aims to improve flexibility and range of motion. It is not a classical exercise or physical intervention study according to our protocol.
NCT04888767	No control group with no exercise training. Study compared high-intensity interval training with moderate-intensity continuous exercise training.
NTR2092	IMT study. Not a physical exercise training study with a control group with no exercise.
Oliveira 2010	We contacted 1 author to request more information about this study and discover whether a publication is planned. No response received.
Orenstein 1981	Not a randomised controlled study.
Orenstein 2004	Compared aerobic training to upper-body strength training; no control group with no physical training.
Ozaydin 2010	IMT training and not physical exercise training according to our protocol.
Patterson 2004	Study evaluated the efficacy of the test of incremental respiratory endurance; not a physical training study.
Petrovic 2013	Not a randomised controlled study.
Phillips 2008	No contact details available online. Very unlikely that this study will be published.
Pryor 1979	Not a physical exercise training study.
Radtke 2018b	Not a physical exercise training study.
Rand 2012	Not a physical exercise training study. Study was designed to develop an incremental field exercise test for children with CF.
RBR-34677v	Not a randomised controlled study.
RBR-5g9f6w	No control group with no physical exercise training.
Reix 2012	Acute study comparing exercise with expiratory breathing manoeuvres to breathing techniques for airway clearance.
Reuveny 2020	No control group with no physical exercise training.
Ruddy 2015	Study registered as a randomised controlled trial but study results were published without a control group.
Salh 1989	Not a randomised controlled study.
Salonini 2015	Comparison of 2 exercise interventions (Xbox Kinect versus stationary cycle). No control group with no physical training.
Shaw 2016	No control group with no physical exercise training.
Spoletini 2020	Not a physical exercise training study.
Stanghelle 1998	Not a randomised controlled study.

Study	Reason for exclusion
Tuzin 1998	Not a randomised controlled study.
Vallier 2016	Study to evaluate MSWT and not a study of physical training.
Vivodtzev 2013	Study evaluated neuromuscular electrical stimulation prior to endurance training in people with CF. No control group with no physical training.
Ward 2018	Study investigated the use of exercise as a stand-alone form of airway clearance in adults with CF. No control group with no physical exercise training.
Wheatley 2015	Intervention only given on 3 single days; comparison of physical training and albuterol for airway clearance.
White 1997	Not a physical exercise training study.
Young 2019	Not a physical exercise training study.
Zeren 2019	IMT training and not physical exercise training according to our protocol.

CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; FET: forced expiration technique; IMT: inspiratory muscle training; MSWT: modified shuttle walk test; PEP: positive expiratory pressure.

Characteristics of studies awaiting classification *[ordered by study ID]*

Bishay 2017

Methods	**Design:** parallel RCT, single-centre study **Location:** Boston Children's Hospital, Boston, Massachusetts, USA **Duration:** 24 months
Participants	**Enrolment goal:** 80 participants with CF **Inclusioncriteria:** men and women aged ≥ 18 years with confirmed diagnosis of CF; able to complete at least level 1 of the baseline exercise fitness test; participants must not have required IV antibiotics for a CF exacerbation within 30 days of starting the study **Exclusioncriteria:** pregnancy at enrolment; history of CF exacerbation requiring IV antibiotics within the last month; use of a fitness tracker or similar product within 6 months of enrolment
Interventions	Study evaluates whether use of a Fitbit device and an exercise prescription is associated with increased daily activity and, in turn, increased exercise tolerance in young adults with CF. **Interventiongroup:** given a Fitbit and followed for 1 year, completing surveys and exercise tests **Controlgroup:** usual care for 1 year, then offered a Fitbit in the 2nd year. Followed to assess use of Fitbit and health outcomes
Outcomes	**Primary outcome** 1. Submaximal exercise capacity (graded exercise test: 2 years at enrolment, and 6, 12 and 24 months) **Secondary outcomes** 1. Fitbit activity data (2 years) 2. Self-reported physical activity (HAES, 2 years)

Bishay 2017 *(Continued)*

3. FEV_1 relative change (% predicted, 2 years); FEV_1 from before study (baseline, to each data collection time point, and from 1 data collection time point to the next)
4. FVC relative change (% predicted, 2 years); FVC from before study (baseline, to each data collection time point, and from 1 data collection time point to the next)
5. $FEF_{25–75}$ relative change (% predicted, 2 years); $FEF_{25–75}$ from before study (baseline, to each data collection time point, and from 1 data collection time point to the next
6. Incidence of exacerbations requiring IV antibiotics (2 years)
7. Body mass index (2 years)
8. HRQoL (CFQ-R, 2 years)
9. Overall qualitative assessment of participant's satisfaction with the Fitbit (2 years; 6-month time point)
10. Overall qualitative assessment of participant's potential barriers to Fitbit use (2 years, 6-month time point)
11. Qualitative data obtained by open-ended interview
12. Depression (Patient Health Questionnaire-9, 2 years: enrolment, and 6, 12, 18 and 24 months)
13. Anxiety (General Anxiety Disorder-7, 2 years: enrolment, and 6, 12, 18 and 24 months)

Notes	

Cox 2019

Methods	**Design:** multicentre, parallel-design RCT. Blinding: outcome assessor **Location:** 8 Australian sites (Alfred Health, Monash Health and Royal Children's Hospital, Victoria; Royal Hobart Hospital, Tasmania; Royal Prince Alfred Hospital, Westmead Hospital and Children's Hospital at Westmead, New South Wales; Royal Adelaide Hospital, South Australia) **Duration:** 12 weeks (with 3-month and 12-month follow-up for different outcomes)
Participants	**Enrolment goal:** 75 participants with CF **Inclusion criteria:** confirmed diagnosis of CF; age 12–35 years (inclusive); hospital inpatient admission (including hospital in the home) for IV antibiotic therapy for a respiratory cause; able to provide informed consent; able to access the Internet via computer or mobile device **Exclusion criteria:** severe comorbidity limiting mobilisation or physical activity participation (e.g. orthopaedic, cardiac or neurological condition); lung transplant recipients; pregnancy; participants (or parents) are unable to provide informed consent
Interventions	This trial investigates whether an Internet-based application to improve physical activity participation is more effective than usual care in the period following hospitalisation for a respiratory exacerbation. All participants in both groups will be provided with standardised information regarding general physical activity recommendations for adolescents and young adults. **Intervention group:** in addition to usual care (see information for control group), participants will have access to an Internet-based physical activity platform (ActivOnline: www.activonline.com.au) for the 12-week intervention period. ActivOnline allows users to track their physical activity, set goals, and self-monitor progress. When logging into ActivOnline, participants will be prompted to set weekly exercise and physical activity goals, as well as to record details of their physical activity or exercise sessions, including total time and step count. To support recording of daily step count, participants may use their own activity tracker or mobile telephone. A pedometer (Yamaxdigiwalker SW500, Yamasa Tokei Keiki Co, Ltd, Tokyo, Japan) will be provided to participants on request. Data entered into ActivOnline are displayed in numerical and graphical form to allow visualisation of progress over time. Participants can choose the frequency of use of ActivOnline, as data can be entered retrospectively. If no activity has been logged for 3 days, a standardised alert message will

Cox 2019 *(Continued)*

	be issued by the ActivOnline program and emailed to the participant. Participants in the intervention group will also be able to communicate with research clinicians directly via the messaging system contained within ActivOnline about the trial or their clinical status, should they require (Cox et al. *BMC Pulmonary Medicine* 2019;19:253) **Control group:** usual care. Participants will be provided with age-appropriate information regarding recommended guidelines for physical activity participation. Participants will be referred to a free online resource (www.nhs.uk/Livewell/fitness/Pages/physical-activity-guidelines-for-young-people.aspx) containing guidelines and information regarding amount and intensity of daily physical activity participation.
Outcomes	**Primary outcome** 1. Change in time spent in moderate-to-vigorous physical activity as measured objectively using accelerometry (Actigraph) at baseline and after 12 weeks **Secondary outcomes** 1. Change in exercise capacity as measured by the MSWT at baseline, 12 weeks and 3 months' postintervention 2. Change in self-reported physical activity assessed with the HAES at baseline, 12 weeks and 3 months' postintervention 3. Change in FEV_1 and FVC measured at baseline, 12 weeks and 3 months' postintervention 4. Change in HRQoL assessed with the CFQ-R at baseline, 12 weeks and 3 months' postintervention 5. Change in HADS assessed at baseline, 12 weeks and 3 months' postintervention 6. Change in the Pittsburgh Sleep Quality Index, assessed at baseline, 12 weeks and 3 months' postintervention 7. Change in the Centre for Epidemiological Studies – Depression scale, assessed at baseline, 12 weeks and 3 months' postintervention 8. Change in reasons for participating in physical activity (BREQ-2), assessed at baseline and 3 months' postintervention 9. Healthcare utilisation: number of hospital inpatient days by medical record review and time to first hospital admission, 12 months' postintervention
Notes	Study characteristics were extracted from the information provided in the Australian New Zealand Clinical Trials Registry (ANZCTR) and the published protocol paper (Cox et al. *BMC Pulmonary Medicine* 2019;19:253).

IRCT20190407043190N1

Methods	**Design:** multicentre, parallel-design, RCT **Location:** University of Medical Sciences, Ahvaz, Khouzestan, Iran and Aboozar Hospital, Ahvaz, Khouzestan, Iran **Duration:** 4 weeks
Participants	**Enrolment:** 70 participants with CF **Inclusion criteria:** willingness to participate in the study (informed consent); understanding of Persian language; no acute and chronic psychological and physical illnesses; moderate disease severity based on physician's diagnosis (not further specified); ability to perform physical activity; absence of concomitant disease (not further specified) **Exclusion criteria:** age < 8 years and > 12 years; acute and chronic mental and physical disease
Interventions	**Intervention group:** participants will receive, regularly according to their interest, aerobic physical exercises, such as cycling, swimming, walking, dancing, playing ball, rope skipping, jumping, and

IRCT20190407043190N1 *(Continued)*

	stretching guidelines for upper limbs, body and lower limbs (gymnastics) in 4 sessions of physical activity **Control group:** no training
Outcomes	**Primaryoutcome** 1. HRQoL assessed with the Pediatric Quality Of Life Inventory (4 weeks after the intervention) **Secondary outcomes:** none
Notes	Description of study was unclear. Study was retrospectively registered.

NCT03100214

Methods	**Design:** parallel single-centre RCT; outcome assessor (exercise supervisor) blinded **Location:** Hospital de Clínicas de Porto Alegre, Brazil **Duration:** up to 14 days
Participants	**Estimated enrolment:** 68 participants with CF **Inclusioncriteria:** males and females age 16–50 years; diagnosed with CF according to consensus criteria (Yankaskas 2004) and regularly followed up in the Hospital de Clínicas de Porto Alegre Programme for Adolescents and Adults with CF; admitted to hospital (for ≥ 24 hours) due to exacerbation of lung disease **Exclusioncriteria:** cardiac, orthopaedic or trauma complications that make it impossible to perform the proposed exercises; pregnancy; haemodynamic instability, massive haemoptysis, pneumothorax and continuous use of non-invasive ventilation
Interventions	**Interventiongroup:** aerobic and anaerobic exercise 5 times a week during the hospitalisation period, with sessions lasting about 1 hour; programme beginning within 48 hours of admission **Controlgroup:** physiotherapeutic follow-up (including respiratory physiotherapy, inhalation therapy and techniques for removal of secretions) performed by the physiotherapist of the programme for adults with CF during the hospitalisation period
Outcomes	**Primary outcome** 1. 6MWT distance **Secondary outcomes** 1. FEV_1 2. HRQoL (CFQ-R) 3. C-reactive protein 4. Interleukin-6 and interleukin-8 5. Tumour necrosis factor
Notes	Study aims to evaluate the effects of an early rehabilitation programme based on aerobic training and muscle strength training in adolescents and adults with CF hospitalised at Hospital de Clinicas de Porto Alegre for exacerbation of lung disease.

NCT04293926

Methods	**Design:** single-centre, parallel-design, RCT **Location:** Universidad Europea de Madrid, Madrid, Spain **Inclusion criteria:** diagnosis of CF, age 6–18 years, mild-to-moderate lung function levels; written informed consent form by legal guardian and patient **Exclusion criteria:** active smoking, exacerbation in last 3 months, presence of gastrostomy, use of beta-blocker drugs, diagnosed heart disease, alterations in the locomotor system **Duration:** 8 weeks
Participants	19 participants were enrolled in this study (status: completed)
Interventions	Study aimed to assess the effects of a resistance exercise training programme on heart rate variability in children and adolescents with CF. **Intervention group:** 8-week individualised and guided resistance exercise training programme (3 sessions per week, 60 min per session). Training prescription was individualised and based on the 5 repetition maximum test (60–80%). Upper- and lower-limb exercises were performed, including seated bench press, seated lateral row and leg press. **Control group:** routine recommendations by the paediatrician, including specific lifestyle advice. No exercise training programme
Outcomes	**Primary outcomes** 1. Change in the SD of R-R intervals expressed in milliseconds, measured with an Ambit 3 Sport watch at baseline and after 8 weeks 2. Change in the root mean square SD expressed in milliseconds, measured with an Ambit 3 Sport watch at baseline and after 8 weeks 3. Change in the percentage of differences between R-R intervals > 50 ms expressed in percentage, measured with an Ambit 3 Sport watch at baseline and after 8 weeks 4. Change in the low-frequency band expressed in normalised units, measured with an Ambit 3 Sport watch at baseline and after 8 weeks 5. Change in the high frequency band expressed in normalised units, measured with an Ambit 3 Sport watch at baseline and after 8 weeks 6. Change in the quotient (low frequency/high frequency) between the low-frequency band and the high-frequency band expressed as a ratio, measured with an Ambit 3 Sport watch at baseline and after 8 weeks **Secondary outcomes** 1. Lung function: change in FEV_1 and FVC expressed as z-scores, measured at baseline and after 8 weeks
Notes	6 primary outcomes were defined in this study, all of which are not relevant for this review.

Powers 2016

Methods	**Design:** parallel RCT ("Do More, B'More, Live Fit"), single-centre study **Location:** Johns Hopkins University, Baltimore, Maryland, USA **Duration:** 6 months
Participants	**Enrolment goal:** 60 participants with CF

Powers 2016 *(Continued)*

	Inclusioncriteria: males and females aged 12–21 years with CF and cared for at Johns Hopkins; participants must have a smartphone or computer (or both) with universal serial bus (USB) to set-up Fitbit Flex **Exclusioncriteria:** FEV_1 < 40% predicted; individuals already participating in vigorous physical activity (as assessed by the study team) in year-round organised sports or aerobic exercise for longer than 30 min more than 5 times per week (or organised sports and aerobic exercise) may or may not be included in this study at the discretion of the principal investigator and study team
Interventions	**Interventiongroup:** at baseline assessment, participants given individualised exercise prescriptions with the aim of achieving 30 min of an endurance-style exercise (team sports, walking, jump roping, stair climbing or more complex Tabata-style workouts) 5 times per week for 6 months. At 4–6 weeks and 8–10 weeks after enrolment, participants attend a follow-up 30-min session which will vary based on initial assessment and previous exercise prescription success, but will include strength training for major muscles groups or flexibility exercises with yoga (or both), as well as reinforcement of previously learned techniques with additional individualised recommendations. Participants will also receive motivational messages starting 14 days after enrolment via preferred contact method (SMS, telephone call, email) every 3–4 days over the 6-month study period. Participants also given access to "Do More, B'More, Live Fit" web page, which includes spotlighted exercises, instructional exercise photos and videos; also invited to join the "Do More, B'More, Live Fit" Activity Group via the Fitbit Dashboard and to friend the study team members and other exercise-intervention participants in order to take part in Fitbit step-goal challenges. **Controlgroup:** at baseline assessment, the Fitbit daily step goal is set at the manufacturer standard 10,000 steps. At routine clinic visits, baseline and follow-up assessments (3- and 6-month clinic visits) participants given generic, non-personalised encouragement and recommendations (if requested by the participant) for physical activity. At the 3- and 6-month visits, exercise is reinforced with generic encouragement, Fitbit data are exported and reviewed for any missing data due to equipment failure or user error.
Outcomes	**Primaryoutcomes** 1. LCI (LCI 2.5 and LCI 5.0) 2. Daily activity via Fitbit step count and daily step count (mean, median and highest daily) recorded through participant Fitbit Flex **Secondaryoutcomes** 1. FEV_1 % predicted 2. Self-reported physical activity (HAES) 3. HRQoL (CFQ-R) 4. Exercise capacity (MWST) 5. Acceptability and feasibility of the programme using semi-structured interviews
Notes	This study evaluates the "Do More, B'More, Live Fit", a 6-month fitness programme designed to optimise exercise habits of people with CF through structured exercises with personalised coaching, exercise equipment including the Fitbit Flex, online support and motivational messages delivered electronically. The intervention incorporates fitness preferences and encompasses endurance, strength and flexibility exercises while adjusting to physical fitness needs. The hypothesis is that intervention participants will have increased and sustained engagement and better health outcomes compared to control group participants.

6MWT: 6-minute walk test; BREQ-2: Behavioral Regulation in Exercise Questionnaire-2; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire – Revised; $FEF_{25–75}$: forced mid-expiratory flow between 25% and 75% of vital capacity; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; HADS: Hospital Anxiety and Depression Scale; HAES: Habitual Activity Estimation Scale; HRQoL: health-related quality of life; IV: intravenous; LCI: Lung Clearance Index; min: minute; MSWT: modified shuttle walk test; RCT: randomised controlled trial; R-R intervals: intervals between successive heartbeats; SD: standard deviation.

Characteristics of ongoing studies *[ordered by study ID]*

Curran 2020

Study name	Steps Ahead: optimising physical activity in adults with cystic fibrosis: study protocol for a pilot randomised trial using wearable technology, goal setting and text message feedback ClinicalTrials.gov identifier: NCT03672058 Study protocol (version 3, 16 June 2021): hrbopenresearch.org/articles/3-21
Methods	**Design:** pilot, parallel-design RCT; single centre **Location:** adult CF Unit, University Hospital Limerick, Ireland **Duration:** 24 weeks (12-week intervention; 12-week follow-up)
Participants	**Enrolment goal:** 50 participants with CF **Inclusion criteria:** age ≥ 18 years; confirmed diagnosis of CF (based on CF-causing mutations or a sweat chloride concentration during 2 tests of > 60 mmol/L, or both); clinically stable individuals with CF attending University Hospital Limerick, determined by those who are not experiencing a pulmonary exacerbation. Pulmonary exacerbation is defined as acute or subacute worsening of respiratory symptoms which warrant change in treatment (i.e. new oral or intravenous antibiotics); access to a smartphone/tablet to access, and ability to upload, Fitbit application; capacity and willingness to give explicit informed consent **Exclusion criteria:** FEV_1 < 25% predicted; on the waiting list for lung transplantation and have undergone lung transplantation; exacerbation in the 4 weeks prior to the study. Patients can undergo testing once they are finished their antibiotics and deemed clinically stable by the Respiratory Consultant; dependent on supplemental oxygen for exercise; pregnancy; any cardiac, neurological or musculoskeletal impairment that may impact on their ability to participate in the study; participation in another clinical trial up to 4 weeks prior to the first baseline visit
Interventions	The intervention consists of wearable technology, text message feedback and goal setting. **Intervention group:** participants are provided with wearable technology (Fitbit Charge 2), and educated on how to use it. It will be linked to an online monitoring system (Fitabase). Fitabase, the online monitoring system, enables the physiotherapists to access step count data remotely. The physiotherapist discusses the participant's physical activity levels (as measured at baseline by an accelerometer) and individual, patient-centred physical activity goals are set with each participant. Participants are encouraged to write a minimum of 3 goals. Participants are asked to set a step count target for weeks 4, 8 and 12. Goals will be individualised to the participant, taking into account their preferences. Participants receive a weekly 1-way personalised text message by their physiotherapist for 12 weeks. The text messages in this study are texts with positive reinforcement on step count attained by the participant. **Control group:** participants are provided with a Fitbit Charge 2 and educated on how to use it. It will be linked to "Fitabase" for data collection purposes. Participants receive no feedback on their physical activity levels throughout the study period. **Follow-up:** at week 12, both groups will have outcome measures reassessed. Both groups will continue with the Fitbit Charge 2 only for the following 12 weeks. At the end of the 24 weeks, participants will have all outcome measures repeated.
Outcomes	**Primary outcome** 1. Step counts measured with Fitbit Charge 2 (measured during first 2 weeks, and week 6 and 12 during intervention, and at weeks 18 and 24) **Secondary outcomes** 1. CPET outcomes

Curran 2020 *(Continued)*

	a. VO_2 max, test duration; peak workload b. VE, respiratory exchange ratio, ventilatory equivalents for oxygen and for carbon dioxide (not relevant for this review) 2. Spirometry: FEV_1, FVC; $FEF_{25–75}$ 3. Physical activity assessed with the International Physical Activity Questionnaire 4. Body composition assessed with bioelectrical impedance 5. Quality of life assessed with CFQ-R 6. Sleep quality assessed with PSQI (not relevant for this review) 7. Dyspnoea during activities of daily living assessed with the University of California San Diego Shortness of Breath Questionnaire (not relevant for this review) 8. State of wellness assessed with Awescore questionnaire (not relevant for this review)
Starting date	Recruitment began in January 2019
Contact information	Contact: Roisin Cahalan, PhD: telephone +353 61 202959 ext +35361202959; Email: roisin.cahalan@ul.ie Maire Curran, BSc: telephone +353 61 482151 ext +35361202959; Email: maire.curran@ul.ie
Notes	

ISRCTN92573472

Study name	The evaluation of a 12-week partially supervised, self-regulated exercise intervention in patients with cystic fibrosis (CF-Ex)
Methods	**Design:** single-centre RCT **Location:** Dublin City University, Glasnevin, Dublin, UK **Duration:** 12 weeks
Participants	**Enrolment goal:** 30 participants with CF **Inclusion criteria:** established diagnosis of CF (positive sweat chloride or genetic identification test); residing in Ireland; age ≥ 18 years; lung function ≥ 50% predicted **Exclusion criteria:** undergone lung transplantation; culturing MRSA, NTM or *Burkholderia cepacia*
Interventions	12-week partially supervised and self-regulated exercise intervention **Intervention group:** exercise manual (hard copy) and access to an online exercise diary for a 12-week period. Over this period, the exercise group will receive a Fitbit device to track daily steps and active min. **Control group:** usual care.
Outcomes	**Primary outcome** 1. Cardiorespiratory fitness measured using CPET with monitoring of ventilatory gases, heart rate (ECG), blood pressure and oxygen saturation at baseline and 12 weeks (no specific fitness end-point was specified, i.e. VO_2 peak or Wpeak) **Secondary outcomes** 1. Anthropometry measured using a stadiometer, electronic scales, bioelectrical impedance and waist-to-hip ratio conducted using tape-measurements at baseline and 12 weeks

ISRCTN92573472 *(Continued)*

	2. Muscle strength measured using sit-to-stand and Biodex isokinetic dynamometry for lower extremity strength and hand-grip dynamometry for upper body strength at baseline and 12 weeks 3. Pulmonary function assessed using spirometry (EasyOne Air device) at baseline and 12 weeks 4. Physical activity assessed using accelerometry (ActivPAL) at baseline and 12 weeks 5. Quality of life evaluated using a CF-specific questionnaire (CFQ-R) at baseline and 12 weeks
Starting date	9 September 2019 Trial end date: 9 July 2020
Contact information	Miss Nicola Hurley: XB26, Dublin City University, Dublin 9, Ireland; telephone: +353 017008470; Email: nicola.hurley5@mail.dcu.ie
Notes	Study retrospectively registered

Monteiro 2019

Study name	Effects of aerobic interval training on glucose tolerance in children and adolescents with cystic fibrosis: a randomized trial protocol
Methods	**Design:** parallel design, RCT. Double blinded (investigator and outcome assessors) **Location:** 2 hospitals in the Brazilian states of Rio Grande do Norte and Paraíba **Duration:** 8-week intervention with 8-week follow-up
Participants	**Enrolment goal:** 20 participants with CF **Inclusion criteria:** diagnosis of CF, according to the Brazilian Guidelines for diagnosis and treatment of CF; age 6–18 years; boys males and females **Exclusion criteria:** inability to follow the study protocol (not further specified); exacerbation of the disease, with hospitalisation required during the intervention period; pregnancy
Interventions	The intervention aims to evaluate the effects of anaerobic interval training on glucose tolerance in children and adolescents with CF. **Intervention group:** participants will take part in an aerobic interval training programme conducted at home, 3 times a week on alternating days, and using a cycle ergometer for lower limbs (Altmayer Sport). Each session will start with 5 min warm-up and end with 5 min cool-down at 30–40% of the maximum heart rate. The training in the initial 2 weeks will be carried out in 6 sessions of 20 seconds, reaching 70–80% of maximum heart rate, interspersed by 2 min of active rest, and reaching 50–60% of maximum heart rate. Progression will be carried out every 2 weeks by adjusting the time and the number of exercise sessions. Participants will be given a diary before the start of the programme to record information about the disease exacerbation, training heart rates, modified Borg scale, and signs and symptoms observed during training. The diary will be returned to the research team after completion of the study for evaluation of adherence to the proposed intervention. 1 member of the research team will maintain weekly contact via mobile phone with the parent/guardian to stimulate the intervention and minimise possible deviations from the protocol. **Control group:** participants and their parents/caregivers will receive an educational intervention, which will be administered through an interactive presentation lasting 20 min. The presentation will address physiopathology, complications, treatments (medical and physiotherapeutic), physical exercises and prevention of exacerbation. Practical demonstrations of routine care such as the use of inhalation devices, bronchial hygiene techniques and medication intake will be performed.
Outcomes	**Primary outcome**

Monteiro 2019 *(Continued)*

	1. Change in glucose tolerance during an oral glucose tolerance test, measured at baseline, after 8 and 16 weeks **Secondary outcomes** 1. Change in quality of life assessed with the CFQ (at baseline, after 8 and 16 weeks). 4 questionnaire versions will be used: age 6–11 years (35 questions); age 12–13 years (35 questions); age ≥ 14 years and older (50 questions) and parents of children aged 6–11 years (44 questions) 2. Change in lung function, i.e. FEV_1 and FVC, FEV_1/FVC ratio, $FEF_{25–75}$, measured at baseline and after 8 and 16 weeks 3. Exacerbations using Fuchs criteria, assessed at baseline, after 8 and 16 weeks
Starting date	4 February 2019
Contact information	Karolinne Monteiro, MSc: telephone: +5584996387722; Email: karolsm@outlook.com.br Thayla Santino, MSc: telephone: +5583999424386; Email: thaylaamorim@gmail.com
Notes	Trial registration: ClinicalTrials.gov (NCT03653949) Outcomes that are not relevant for this review: change in functional exercise capacity measured with the 3-min step test at baseline, after 8 and 16 weeks; and change in respiratory muscle strength (i.e. maximum expiratory pressure), measured at baseline, after 8 and 16 weeks.

NCT03273959

Study name	Program of exercises during the hospitalization of children and adolescents with cystic fibrosis
Methods	**Design:** parallel, single-centre RCT; single blinded (outcome assessor) **Location:** Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil **Duration:** 14 days
Participants	**Estimated enrolment:** 50 participants hospitalised for treatment of a pulmonary exacerbation **Inclusion criteria:** males and females with CF; age 6–18 years and followed by the Pediatric Pulmonology Team at Hospital de Clínicas de Porto Alegre; hospital admission defined as "a stay of 24 hours or more in any Hospital de Clinicas de Porto Alegre unit"; exacerbation of lung disease defined as the presence of ≥ 1 of the following: change in sputum volume and colour, new or enlarged haemoptysis, increased cough, increased dyspnoea, malaise, fatigue, lethargy, fever, anorexia or weight loss, headache or pain in the sinuses, alteration of the pulmonary auscultation, non-FEV_1 decrease of > 10%, radiological [sic], eradication of new bacteria **Exclusion criteria:** cardiac, orthopaedic or trauma complications that make it impossible to perform the proposed exercises; haemodynamic instability, massive haemoptysis, pneumothorax; continuous use of non-invasive ventilation; pregnancy
Interventions	**Intervention group:** routine physical therapy plus exercise programme in the form of a booklet and guided by a health professional. Programme includes exercises such as punching, climbing and descending stairs, sit and stand, push-up on the wall, cycling and others, performed 5 times per week. Participants record their training in a diary. The programme is not supervised. **Control group:** routine physical therapy during hospitalisation
Outcomes	**Primary outcome** 1. Change in 6-min walk test distance from baseline to hospital discharge (14 days)

NCT03273959 *(Continued)*

	Secondary outcomes 1. Change in spirometry (outcome variables not defined) from baseline to hospital discharge (14 days) 2. Change in physical fitness and health score (score and instrument not defined) from baseline to hospital discharge (14 days) 3. Change in BMI from baseline to hospital discharge (14 days) 4. Change in clinical Shwachman-Kulczycki score from baseline to hospital discharge (14 days)
Starting date	28 August 2017
Contact information	Hospital de Clínicas de Porto Alegre, Brazil, 90035-903 Bruna Ziegler: telephone: +55 51991221192; E-mail: brunaziegler@yahoo.com.br Taiane Feiten: telephone: +55 51991539788; E-mail: taifeiten@gmail.com
Notes	Recruitment status: unknown (latest update 6 September 2017); estimated study completion date: 28 March 2019 Contacted Ms Ziegler for more information about the status of the study (30 June 2021).

NCT03970369

Study name	Motivated to move: a study to determine the feasibility of self-monitoring physical activity in youth
Methods	**Design:** pilot parallel, single-centre RCT, no blinding **Location:** Exercise Medicine Clinic at McMaster Children's Hospital, Hamilton, Ontario, Canada **Duration:** 6 months (3 study visits over 6 months)
Participants	**Estimated enrolment:** 30 participants **Inclusion criteria:** male and females with CF; aged 7–18 years; newly referred to the Exercise Medicine Clinic (i.e. either 1st or 2nd visit) **Exclusion criteria:** inability to communicate in English
Interventions	Participants at the Exercise Medicine Clinic receive individualised physical activity prescriptions to follow for the next 3 months. **Intervention group:** participants ("Monitor group") wear a step counter and receive personalised goals including feedback. **Control group:** participants receive the activity prescription including personalised goals ("Usual care"), but will not receive a step counter. Physical activity monitoring will be performed in all participants using an accelerometer which is worn around the waist for 7 days at baseline, 3- and 6-month study visits.
Outcomes	**Primary outcomes** 1. Recruitment rates determined by calculating the proportion of eligible children who enrol in the study over the estimated 10-month recruitment period. 2. Retention to the trial at 3-month follow-up visit. Proportion of participants who remained enrolled in the study (regardless of data completeness) at 3 months. 3. Retention to the trial at 6-month follow-up visit. Proportion of participants who remained enrolled in the study (regardless of data completeness) at 6 months.

NCT03970369 *(Continued)*

4. Feasibility of activity monitoring over the first 3 months. Participants' compliance wearing the activity monitor will be measured by determining the % of days participants wore the monitor over the first 3 months.
5. Feasibility of activity monitoring over 6 months. Participants' compliance wearing the activity monitor will be measured by determining the % of days participants wore the monitor over 6 months.
6. Acceptability of activity monitoring. A brief survey will be used at the final visit (6 months) to assess the acceptability of activity monitoring.

Secondary outcomes

1. Change in self-regulation and motivation (at baseline, 3 and 6 months) measured using BREQ-3, which includes 4 items (responses 0–4) for each of the following 6 dimensions: amotivation, external regulation, introjected regulation, identified regulation, integrated regulation, intrinsic regulation. Dimensions are calculated by the mean score on the 4 corresponding items.
2. Change in perceived competence in physical activity (at baseline, 3 and 6 months) measured using the Self-Perceived Competence in Physical Education Scale. Mean responses (1–7) of 4 items. Higher score indicates greater perceived competence.
3. Change in autonomy (supportive versus controlling) at baseline, 3 and 6 months). Participants' perceptions of the degree to which their healthcare providers are autonomy-supportive versus controlling. Measured using the Health Care Climate questionnaire. Mean responses (1–7) on 6 items. A higher score indicates higher perception of supportive autonomy.
4. Change in physical activity at baseline, 3 and 6 months.

Starting date	20 June 2019
Contact information	McMaster University Exercise Medicine Clinic at McMaster Children's Hospital, Hamilton, Ontario, Canada Principal Investigator: Joyce Obeid, PhD; Contact: Clinical Research Co-ordinator: telephone: 905-521-2100 ext 75620; E-mail: proudfna@mcmaster.ca
Notes	

NCT04249999

Study name	ActivOnline: Physical Activity in Cystic Fibrosis Trial UK (ActiOnPACTUK)
Methods	**Design:** parallel-design, open-label, RCT. Follow-up assessments by blinded outcome assessors **Location:** University of Exeter, UK **Duration:** 12-week intervention and 24-week follow-up
Participants	**Enrolment goal:** 94 participants with CF **Inclusion criteria:** confirmed diagnosis of CF; aged 12–35 years (inclusive); able to provide informed consent/assent; able to access the Internet via computer or mobile device **Exclusion criteria:** presence of severe comorbidity limiting mobilisation or physical activity participation (e.g. orthopaedic, cardiac or neurological condition); previous lung transplantation; pregnancy; unable to provide informed consent/assent
Interventions	Physical activity intervention with an online platform to monitor daily activity **Intervention group:** access to online physical activity platform (www.activonline.com.au) in addition to usual care

NCT04249999 *(Continued)*

	Control group: no access to online physical activity platform. Continue with usual care
Outcomes	**Primary outcomes** 1. Change in objectively measured physical activity (ActiGraph GT9X Link accelerometer) at baseline and 12 and 24 weeks postintervention. Time spent in sedentary, light, moderate and vigorous physical activity domains will be assessed over 1 week. Accelerometer to be worn on non-dominant wrist. 2. Change in subjectively assessed physical activity (HAES), at baseline and 12 and 24 weeks postintervention. Questionnaire determines time spent being inactive, somewhat inactive, somewhat active and very active, each reported as a percentage of the day. **Secondary outcomes** 1. Change in FEV_1 in L and % predicted), and FVC in L and % predicted measured at baseline and 12 and 24 weeks postintervention. 2. Change in FVC in L and % predicted measured at baseline and 12 and 24 weeks postintervention. 3. Change in exercise attitudes, measured using the Behavioural Regulation in Exercise Questionnaire at baseline and 12 and 24 weeks postintervention. Assessment of reasons underlying people's decision to engage, or not engage, in exercise. Scores range from –24 to +20, where a higher score indicates greater exercise autonomy (better outcome). 4. Change in quality of life, measured using age-specific CFQ-R at baseline and 12 and 24 weeks postintervention. Subjective assessment of HRQoL, scored from 0 to 100 where a higher score indicates higher quality of life (better outcome). 5. Change in anxiety, measured using HADS at baseline, 12 weeks, and 24 weeks post-intervention. Subjective report of anxiety, scored from 0 to 21, where a higher score indicates higher anxiety (worse outcome). 6. Change in depression, measured using HADS at baseline and 12 and 24 weeks postintervention. Subjective report of depression, scored from 0 to 21, where a higher score indicates higher depression (worse outcome). 7. Change in depression, measured using CES-D scale at baseline and 12 and 24 weeks postintervention. Subjective reports of anxiety and depression, scored from 0 to 60 where a higher score indicates greater depressive symptoms (worse outcome). 8. Change in sleep quality, measured using PSQI at baseline and 12 and 24 weeks postintervention. Subjective report of sleep quality, scored from 0 to 21 where a higher score indicates worse sleep quality (worse outcome) **Other outcomes** 1. Qualitative assessment of barriers and facilitators to physical activity at 24 weeks postintervention. Semi-structured, 10-item interview for participants in both intervention and control group. 2. Qualitative assessment of ActivOnline programme at 24 weeks postintervention. Semi-structured interview question for participants assigned to intervention group. 3. Usage of ActivOnline programme at 12 weeks postintervention. Frequency of access and logging of physical activity data. 4. Changes in physical activity, measured by Sport England Short Active Lives Survey at baseline, and 12, 24 and 36 weeks postintervention. Subjective assessment of physical activity. 5. Changes in physical activity, measured by Sport England Engagement in Sport Questions at baseline, and 12, 24 and 36 weeks postintervention. Subjective assessment of physical activity.
Starting date	7 May 2020 Recruitment status: active, not recruiting (30 June 2021)
Contact information	Professor Craig Williams: Director: Children's Health & Exercise Research Centre (CHERC) Sport and Health Sciences, University of Exeter, Exeter, UK; telephone: +44 (0)1392 724890; Email: C.A.Williams@exeter.ac.uk

NCT04249999 *(Continued)*

Notes	The study team informed us about the following changes in the study design on 3 July 2021: in light of the ongoing COVID-19 pandemic, the study team plans to perform the research activities online (including recruitment and consent), with data capture/measurements being performed by participants in their home, with questionnaires and monitors delivered by post (according to the original protocol). The intervention itself, and timelines for participation, remain the same as before. This has a 2-fold objective, in that these changes will 1) minimise exposure risk to the target population (people with CF) who are still being advised to 'shield' at home, by removing visits to hospital; and 2) reduce burden on NHS staff and sites by removing the need to assist with recruiting/consenting participants and performing measures. These proposed changes will not adversely affect anyone already on the trial, as the COVID-19 pandemic prevented recruitment throughout 2020 and therefore this project has yet to recruit its first participant.

NCT04543929

Study name	Effects of innovative aerobic exercise training in cystic fibrosis
Methods	**Design:** single-centre, open-label, parallel-design RCT; no blinding **Location:** University of Kansas Medical Center, USA **Duration:** 12 weeks
Participants	**Enrolment goal:** 9 participants with CF **Inclusion criteria:** diagnosis of CF; prescribed and taking for 28 days ivacaftor-tezacaftor-elexacaftor (Trikafta); aged ≥ 18 years **Exclusion criteria:** aged ≤ 17 years; not eligible for ivacaftor-tezacaftor-elexacaftor (Trikafta); inability to exercise; pregnancy; status after lung transplantation; already participating in > 150 min of aerobic exercise per week
Interventions	This study evaluates the effectiveness of standard of care therapy plus exercise compared to standard of care only for improving cardiorespiratory fitness. **Intervention group:** partially supervised and home-based exercise training (exercise prescription plus standard of care) **Control group:** standard of care (no exercise prescription)
Outcomes	**Primary outcome** 1. Change in aerobic exercise capacity at the anaerobic threshold via submaximal CPET, measured at baseline and after 12 weeks **Secondary outcomes** 1. Change in FEV_1, measured at baseline and after 12 weeks 2. Change in quality of life (CFQ-R), measured at baseline and after 12 weeks 3. Change in sweat chloride concentration, measured at baseline and after 12 weeks 4. Change in HbA1c concentration, measured at baseline and after 12 weeks
Starting date	11 February 2020
Contact information	University of Kansas Medical Center, Kansas City, Kansas, USA Christine Morgan: telephone: 00 1 913-588-1572; Email: cmorgan6@kumc.edu Larry Scott: telephone: 00 1 913-588-1572; Email: lscott2@kumc.edu

NCT04543929 *(Continued)*

Notes	The primary outcome is broadly defined and not clear to the authors of this review.

NCT04683809

Study name	The effects of telerehabilitation on quality of life, anxiety and depression levels in children with cystic fibrosis and their caregivers
Methods	**Design:** parallel RCT **Location:** Marmara University, Turkey **Duration:** 3 months
Participants	**Estimated sample size:** 30 participants **Inclusion criteria:** diagnosed with CF; aged 6–13 years **Exclusion criteria:** current pulmonary exacerbation; musculoskeletal problems that hinder exercising; no Internet access; participants and parents do not consent to intervention
Interventions	**Intervention:** rehabilitation sessions including postural, breathing and high-intensity interval training exercises through online programmes for rehabilitation. Exercise programme will be applied 3 days a week for 3 months **Control:** routine follow-up
Outcomes	**Primary outcome** 1. CFQ-R
Starting date	January 2021 (estimated completion May 2021)
Contact information	Ozge Kenis-Coskun: Email: ozgekenis@gmail.com
Notes	Sponsors and collaborators: Marmara University

NCT04742049

Study name	The effects of telerehabilitation on muscle function, physical activity and sleep in cystic fibrosis during pandemic
Methods	**Design:** single-centre, parallel-design, RCT **Location:** Hacettepe University, Ankara, Turkey **Duration:** 6 weeks
Participants	**Enrolment goal:** 30 participants with CF **Inclusion criteria:** people diagnosed with CF; volunteering to participate in the study; in social isolation due to COVID-19 pandemic; FEV_1 > 40% at last pulmonary function test **Exclusion criteria:** acute pulmonary exacerbation at the time of study or within the last month (or both); diagnosis of COVID-19 before or during study; being physically or perceptually competent to

NCT04742049 *(Continued)*

	exercise [sic]; ABPA treated with systemic steroid therapy; inability to complete the exercise training; FEV_1 < 40% predicted
Interventions	This study evaluates the effects of a telerehabilitation-based exercise programme versus usual care in participants who are at home during the self-isolation process due to the COVID-19 pandemic. **Intervention group:** an online 6-week training programme includes 30 min of exercise performed 3 days per week, supervised by a physiotherapist. Training will start with warm-up and finish with cool-down exercises. **Control group:** receives same exercise document including the same exercise protocol. Participants will be called by the physiotherapist once a week for follow-up.
Outcomes	**Primary outcomes** 1. 1-min sit to stand test repetitions, measured at baseline and after 4 and 6 weeks 2. Crunch repetitions, measured at baseline and after 4 and 6 weeks 3. Squat repetitions, measured at baseline and after 4 and 6 weeks 4. Push-up repetitions, measured at baseline and after 4 and 6 weeks 5. Plank duration, measured at baseline and after 4 and 6 weeks **Secondary outcomes** 1. Sleep quality will be evaluated by Epworth Sleepiness Scale and Pediatric Sleep Questionnaire, measured at baseline and after 6 weeks 2. Physical activity level assessed with the Physical Activity Questionnaire at baseline and after 6 weeks
Starting date	28 December 2020
Contact information	Kubra Kilic, PhD Student: Hacettepe University, Ankara, Turkey; telephone: +903123051576 (+903123051576 University); Email: fztktas@gmail.com
Notes	5 different outcome measures were defined as primary endpoints. Single blinding of participants is mentioned on ClinicalTrials.gov. It is not clear to the review authors how participants can be blinded to exercise training/no exercise training in this study setting.

NCT05147285

Study name	The effect of different exercise modalities applied by tele rehabilitation on functional capacity, oxidative stress and respiratory parameters in cystic fibrosis children
Methods	**Design:** parallel RCT **Location:** Hacettepe University, Turkey **Duration:** 8 weeks
Participants	**Estimated sample size:** 39 participants **Inclusion criteria:** aged 8–18 years with a diagnosis of CF; access to online exercise training; % predicted FEV_1 > 40% **Exclusion criteria:** diagnosed with acute pulmonary exacerbation at the time of study or within the last month (or both); physically or perceptually competent to exercise [sic]; ABPA treated with systemic steroid therapy; FEV_1 % < 40%

NCT05147285 *(Continued)*

Interventions	**Intervention 1:** online supervised stabilisation exercises 3 times a week for 8 weeks **Intervention 2:** online supervised aerobic exercise training and stabilisation exercises. Aerobic exercises will be performed for 8 weeks, for 30–45 min, at 65–75% of maximum heart rate, 3 days a week, on the days when stabilisation exercises are not performed. **Control:** the importance of physical activity will be explained to the participants and appropriate physical activity recommendations will be made.
Outcomes	**Primary outcomes** 1. 6-min walk test distance 2. MSWT distance **Secondary outcomes** 1. Respiratory muscle strength evaluated using mouth pressure device 2. Respiratory muscle endurance evaluated using constant load test 3. Spirometry (FVC, FEV_1, PEF) 4. Oxidative stress levels of the following in blood samples: malondialdehyde; carbonyl protein; superoxide dismutase; catalase; total oxidant status; and total antioxidant status 5. Peripheral muscle strength evaluated using dynamometer 6. Crunch repetitions in 2 min 7. Squat repetitions in 2 min 8. Push-up repetitions in 2 min 9. Plank duration 10. Sit-to-stand test repetitions in 1 min 11. Myokine assessment assessed by irisin levels in blood samples 12. Posture evaluated using Corbin Postural Assessment scale (lateral and posterior views will be assessed) 13. Posture evaluated using thoracic kyphosis and lumbar lordosis angles in the sagittal plane with spinal mouse device 14. Balance evaluated using paediatric Berg balance scale (14 parts) 15. Static balance evaluated using functional reach test 16. Dynamic balance evaluated using one-legged standing test 17. Functional mobility evaluated using timed up and go test 18. McGill core endurance test – trunk muscles evaluated: trunk flexor, trunk extensor and side plank test 19. Quality of life assessment using the CFQ-R 20. Physical activity assessment assessed by the Physical Activity Questionnaire
Starting date	22 October 2021 (estimated completion May 2022)
Contact information	Principal Investigator: Professor Deniz Dogru-Ersoz, Hacettepe University; Contact: Kubra Kilic, MSc: telephone: +903123051576; Email: fztktas@gmail.com
Notes	Sponsors and collaborators: Hacettepe University

NCT05173194

Study name	Effects of a remotely supervised exercise program on inflammatory markers, muscle strength and lung function in adult patients with cystic fibrosis
Methods	**Design:** parallel RCT

NCT05173194 *(Continued)*

	Location: Universidad Europea de Madrid, Madrid, Spain **Duration:** 8 weeks
Participants	**Estimated sample size:** 48 participants **Inclusion criteria:** confirmed clinical and genetic diagnosis for CF; aged ≥ 16 years **Exclusion criteria:** musculoskeletal disorders that do not allow the performance of physical exercise; pregnancy; absence of registration of clinical required [sic]
Interventions	**Intervention:** remotely supervised resistance exercise, 3 sessions of 60 min each per week. Training programme consisted of warm-up and joint mobility, strength exercises for different muscle groups and cool down (stretching and breathing exercises) **Control:** routine recommendations from the multidisciplinary CF team
Outcomes	**Primary outcomes** 1. Change from baseline in peripheral muscle strength – upper and lower limb muscle strength will be evaluated using the 5 maximum repetition test in specific strength machines; handgrip strength will be measured with a dynamometer 2. Change from baseline in body composition (muscle mass and skeletal mass index in kg/m^2) measured through DEXA 3. Change from baseline in plasmatic levels of Klotho 4. Change from baseline in plasmatic levels of IL-8 and IL-10 **Secondary outcomes** 1. Change from baseline in lung function 2. Change from baseline in quality of life evaluated using the CFQ-R +14 3. Change from baseline in inspiratory muscle strength 4. Change from baseline in functional capacity (30 seconds sit-to-stand test)
Starting date	26 October 2021 (estimated completion December 2021)
Contact information	Margarita Perez Ruiz, PhD: telephone: +34912115200 ext 3010; Email: pruizmarga@gmail.com Rosa María Girón Moreno, PhD: telephone: +34915202200; Email: rmgiron@gmail.com
Notes	Sponsor and collaborator: Universidad Europea de Madrid

NCT05239611

Study name	Feasibility of home-based exercise program for adults with cystic fibrosis to improve patient-centered outcomes, including a novel measure of ventilation
Methods	**Design:** parallel RCT **Location:** University of Kansas Medical Center, Kansas City, USA **Duration:** 3 months
Participants	**Estimated sample size:** 30 participants **Inclusion criteria:** people with a confirmed diagnosis of CF (2 CF mutations or sweat chloride > 60 mmol/L); aged ≥ 18 years; stable while either on/off CFTR modulator therapy and no plan to start/discontinue CFTR modulator therapy; clearance from their CF physician to participate in exercise;

NCT05239611 *(Continued)*

	access to the Internet; not involved in an exercise intervention in the previous 6 months, and not performing structured exercise > 150 min per week **Exclusion criteria:** pregnancy; history of solid organ transplant; active treatment for mycobacterial infections; significant untreated hypoxaemia, oxygen dependent at rest or with exercise; FEV_1 < 40% of predicted or clinical evidence of cor pulmonale; untreated arterial hypertension (resting systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg); systolic blood pressure > 90 mmHg while standing; congestive heart failure; active treatment for ABPA; acute upper or lower respiratory infection or pulmonary exacerbation within 4 weeks prior to day 1; changes in therapy (including antibiotics) for pulmonary disease within 4 weeks prior to day 1; significant haemoptysis within 4 weeks prior to day 1 (≥ 5 mL of blood in 1 coughing episode or > 30 mL of blood in a 24-hour period; ongoing participation in an investigational drug study within 60 days prior to day 1
Interventions	**Intervention:** each participant will be assigned a pulmonary rehabilitation coach[a] and receive a weekly exercise consulting session delivered by that coach during the 12-week intervention **Control:** standard of care [a]Including a registered respiratory therapist and clinical registered dietitian who have been trained in exercise training as recommended by the American Association of Cardiovascular and Pulmonary Rehabilitation and American College of Sports Medicine
Outcomes	**Primary outcomes** 1. Cardiorespiratory fitness assessment using MSWT 2. Ventilation defect percentage as detected by 129Xenon MRI **Secondary outcomes** 1. FEV_1 2. Quality of life assessment using the CFQ-R 3. Exercise time assessed as weekly adherence to prescribed exercise as % prescribed exercise time completed
Starting date	14 February 2022 (estimated completion April 2023)
Contact information	Contact: Joel Mermis, MD: telephone: 9135886045; Email: jmermis@kumc.edu Contact: Dave Burnett, PhD: telephone: 913-588-9499; Email: dburnett@kumc.edu
Notes	Sponsors and Collaborators: University of Kansas Medical Center

ABPA: allergic bronchopulmonary aspergillosis; BMI: body mass index; BREQ-3: Behavioral Regulation in Exercise Questionnaire-3; CES-D scale: Centre for Epidemiological Studies – Depression scale; CF: cystic fibrosis; CFQ: Cystic Fibrosis Questionnaire; CFQ-R: Cystic Fibrosis Questionnaire – Revised; CFTR: cystic fibrosis transmembrane conductance regulator; CPET: cardiopulmonary exercise test; DEXA: dual-energy x-ray absorptiometry; ECG: electrocardiogram; $FEF_{25–75}$: forced mid-expiratory flow between 25% and 75% of vital capacity; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; HADS: Hospital Anxiety and Depression Scale; HAES: Habitual Activity Estimation Scale; HbA1c: glycated haemoglobin; HRQoL: health-related quality of life; IL: interleukin; min: minute; MRI: magnetic resonance imaging; MRSA: methicillin-resistant *Staphylococcus aureus*; MSWT: modified shuttle walk test; NHS: National Health Service; NTM: non-tuberculous mycobacteria; PEF: peak expiratory flow; PSQI: Pittsburgh Sleep Quality Index; RCT: randomised controlled trial; VE: minute ventilation; VO_2 peak: peak oxygen uptake; VO_2 max: maximum oxygen uptake; VO_2 peak: peak oxygen uptake; Wpeak: peak work rate.

DATA AND ANALYSES

Comparison 1. Physical activity versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Change in VO_2 peak (mL/min per kg bodyweight)	11		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1.1 End of active intervention ≤ 6 months	8	323	Mean Difference (IV, Random, 95% CI)	2.10 [0.06, 4.13]
1.1.2 End of active intervention > 6 months	6	348	Mean Difference (IV, Random, 95% CI)	1.60 [0.16, 3.05]
1.1.3 Follow-up (no active intervention)	3	125	Mean Difference (IV, Random, 95% CI)	3.27 [1.37, 5.18]
1.2 Change in VO_2 peak (mL/min per kg bodyweight): sensitivity analysis	10		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.2.1 End of active intervention ≤ 6 months	7	287	Mean Difference (IV, Random, 95% CI)	1.30 [-0.17, 2.78]
1.2.2 End of active intervention > 6 months	5	318	Mean Difference (IV, Random, 95% CI)	1.38 [0.08, 2.69]
1.2.3 Follow-up (no active intervention)	2	99	Mean Difference (IV, Random, 95% CI)	3.21 [1.27, 5.14]
1.3 Change in VO_2 peak (% predicted)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.3.1 End of active intervention ≤ 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.4 Change in VO_2 peak (mL/min per kg bodyweight): combined subgroups	11	496	Mean Difference (IV, Random, 95% CI)	1.52 [0.31, 2.73]
1.5 Change in VO_2 peak (mL/min per kg bodyweight): combined subgroups – sensitivity analysis	10	466	Mean Difference (IV, Random, 95% CI)	1.38 [0.22, 2.55]
1.6 Change in FEV_1 (% predicted)	11		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.6.1 End of active intervention ≤ 6 months	8	356	Mean Difference (IV, Random, 95% CI)	1.30 [-3.01, 5.61]
1.6.2 End of active intervention > 6 months	6	367	Mean Difference (IV, Random, 95% CI)	2.41 [-0.49, 5.31]
1.6.3 Follow-up (no active intervention)	3	128	Mean Difference (IV, Random, 95% CI)	5.68 [-1.88, 13.23]
1.7 Change in FEV_1 (% predicted): sensitivity analysis	9		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.7.1 End of active intervention ≤ 6 months	6	255	Mean Difference (IV, Random, 95% CI)	-2.16 [-4.14, -0.17]
1.7.2 End of active intervention > 6 months	5	333	Mean Difference (IV, Random, 95% CI)	1.71 [0.15, 3.26]
1.7.3 Follow-up (no active intervention)	1	31	Mean Difference (IV, Random, 95% CI)	-0.32 [-11.90, 11.26]
1.8 Change in FEV_1 (mL)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.8.1 End of active intervention > 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.9 Change in FEV_1 (z-score)	1	67	Mean Difference (IV, Fixed, 95% CI)	0.12 [-0.37, 0.61]
1.9.1 End of active intervention > 6 months	1	67	Mean Difference (IV, Fixed, 95% CI)	0.12 [-0.37, 0.61]
1.10 Change in FEV_1 (% predicted): combined subgroups	11	536	Mean Difference (IV, Random, 95% CI)	1.37 [-0.74, 3.47]
1.11 Change in FEV_1 (% predicted): sensitivity analysis	9	436	Mean Difference (IV, Random, 95% CI)	1.07 [-0.36, 2.49]
1.12 Change in HRQoL: CFQ-R physical functioning domain	7	464	Mean Difference (IV, Random, 95% CI)	3.57 [-0.81, 7.95]
1.12.1 End of active intervention ≤ 6 months	6	217	Mean Difference (IV, Random, 95% CI)	4.67 [-2.55, 11.90]
1.12.2 End of active intervention > 6 months	4	247	Mean Difference (IV, Random, 95% CI)	2.19 [-3.42, 7.80]
1.13 Change in HRQoL: CFQ-R physical functioning domain: sensitivity analysis	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.13.1 End of active intervention ≤ 6 months	5	197	Mean Difference (IV, Random, 95% CI)	0.10 [-4.05, 4.25]
1.14 Change in HRQoL: CFQ-R physical functioning domain: combined subgroups	7	295	Mean Difference (IV, Random, 95% CI)	4.76 [-1.09, 10.61]
1.15 Change in HRQoL: CFQ-R physical functioning domain: combined subgroups – sensitivity analysis	6	275	Mean Difference (IV, Random, 95% CI)	2.44 [-1.43, 6.30]
1.16 Change in HRQoL: CFQ-R respiratory symptoms	6	463	Mean Difference (IV, Random, 95% CI)	-0.90 [-3.50, 1.69]
1.16.1 End of active intervention ≤ 6 months	5	212	Mean Difference (IV, Random, 95% CI)	-1.87 [-5.66, 1.92]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.16.2 End of active intervention > 6 months	4	251	Mean Difference (IV, Random, 95% CI)	-0.05 [-3.61, 3.51]
1.17 Change in HRQoL: CFQ-R respiratory symptoms: combined subgroups	6	279	Mean Difference (IV, Random, 95% CI)	0.22 [-3.15, 3.58]
1.18 Change in HRQoL: Quality of Well-Being scale	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.18.1 Follow-up (no active intervention)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.19 Change in peak work capacity (W/kg bodyweight) during maximal exercise	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.19.1 End of active intervention ≤ 6 months	3	164	Mean Difference (IV, Random, 95% CI)	0.32 [0.12, 0.51]
1.19.2 End of active intervention > 6 months	3	155	Mean Difference (IV, Random, 95% CI)	0.18 [0.07, 0.29]
1.19.3 Follow-up (no active intervention)	2	51	Mean Difference (IV, Random, 95% CI)	0.26 [-0.03, 0.56]
1.20 Change in peak work capacity (W) during maximal exercise	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.20.1 End of active intervention ≤ 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.21 Change in peak work capacity (% predicted) during maximal exercise	3	285	Mean Difference (IV, Random, 95% CI)	5.12 [1.63, 8.61]
1.21.1 End of active intervention ≤ 6 months	2	117	Mean Difference (IV, Random, 95% CI)	6.89 [3.94, 9.83]
1.21.2 End of active intervention > 6 months	2	168	Mean Difference (IV, Random, 95% CI)	3.59 [-2.06, 9.24]
1.22 Change in time to symptom limitation (T_{lim} in sec) during constant work submaximal exercise	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.22.1 End of active intervention ≤ 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.23 Change in VO_2 (mL/min per kg bodyweight and % predicted) during constant work submaximal exercise	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.23.1 End of active intervention ≤ 6 months - VO_2 peakexpressed as mL/min per kg bodyweight	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.23.2 Active intervention ≤ 6 months - VO_2 peakexpressed as % predicted	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.24 Change in 6MWT distance (m)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.24.1 End of active intervention ≤ 6 months	2	81	Mean Difference (IV, Fixed, 95% CI)	25.32 [11.56, 39.08]
1.24.2 End of active intervention > 6 months	1	40	Mean Difference (IV, Fixed, 95% CI)	-3.17 [-35.27, 28.93]
1.25 Change in modified shuttle walk distance (m)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.25.1 End of active intervention ≤ 6 months	1	40	Mean Difference (IV, Fixed, 95% CI)	78.45 [18.18, 138.72]
1.25.2 End of active intervention > 6 months	2	107	Mean Difference (IV, Fixed, 95% CI)	131.91 [79.60, 184.22]
1.26 Change in quadriceps muscle strength (Nm)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.26.1 End of active intervention ≤ 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.26.2 Follow-up (no active intervention)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.27 Change in FVC (% predicted)	10		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.27.1 End of active intervention ≤ 6 months	8	357	Mean Difference (IV, Random, 95% CI)	1.70 [-1.95, 5.35]
1.27.2 End of active intervention > 6 months	5	299	Mean Difference (IV, Random, 95% CI)	2.51 [0.24, 4.78]
1.27.3 Follow-up (no active intervention)	3	125	Mean Difference (IV, Random, 95% CI)	5.37 [-1.69, 12.43]
1.28 Change in FVC (mL)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.28.1 End of active intervention > 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.29 Change in objectively measured physical activity (steps per day)	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.29.1 End of active intervention ≤ 6 months	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

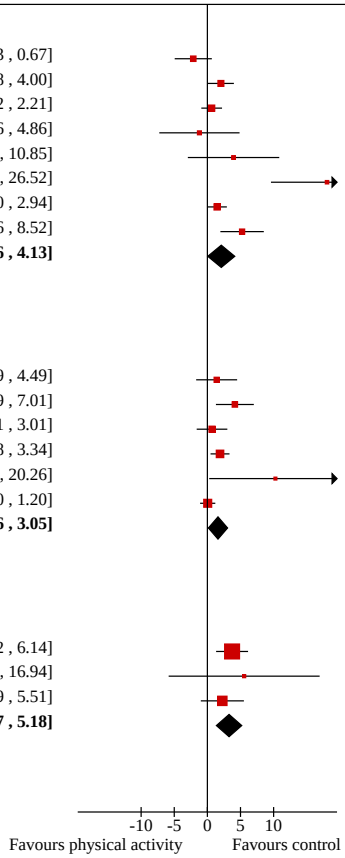
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.29.2 End of active intervention > 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.30 Change in objectively measured physical activity (aerobic steps per day)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.30.1 End of active intervention ≤ 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.30.2 End of active intervention > 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.31 Change in objectively measured moderate-to-vigorous physical activity (hours per week)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.31.1 End of active intervention ≤ 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.31.2 End of active intervention > 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.31.3 Follow-up (no active intervention)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.32 Change in self-reported vigorous physical activity (hours per week)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.32.1 End of active intervention ≤ 6 months	2	152	Mean Difference (IV, Fixed, 95% CI)	1.36 [0.86, 1.86]
1.32.2 End of active intervention > 6 months	2	148	Mean Difference (IV, Fixed, 95% CI)	1.71 [1.13, 2.29]
1.32.3 Follow-up (no active intervention)	1	18	Mean Difference (IV, Fixed, 95% CI)	1.63 [0.02, 3.24]
1.33 Change in BMI (kg/m^2)	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.33.1 End of active intervention ≤ 6 months	4	203	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.16, 0.20]
1.33.2 End of active intervention > 6 months	3	191	Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.04, 0.62]
1.33.3 Follow-up (no active intervention)	2	60	Mean Difference (IV, Fixed, 95% CI)	0.61 [-0.03, 1.26]
1.34 Change in BMI (z-score)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.34.1 End of active intervention ≤ 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.35 Number of pulmonary exacerbations	1		Other data	No numeric data
1.35.1 Number of exacerbations at end of 6 months' partially supervised active intervention (mixed Poisson regression model)	1		Other data	No numeric data
1.35.2 Number of exacerbations after 12 months: 6 months' partially supervised activity followed by 6 months unsupervised activity with access to study resources (mixed Poisson regression model)	1		Other data	No numeric data
1.36 Time to first pulmonary exacerbation	1		Other data	No numeric data
1.37 Number of hospitalisations	1		Odds Ratio (IV, Fixed, 95% CI)	Totals not selected
1.37.1 Hospitalisations during 12 months of active intervention	1		Odds Ratio (IV, Fixed, 95% CI)	Totals not selected
1.38 Change in whole body bone mineral density (g/cm^2)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.38.1 End of active intervention > 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.39 Change in lumbar spine bone mineral density (g/cm^2)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.39.1 End of active intervention > 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.40 Change in metabolic parameters (HbA1c (%))	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.40.1 End of active intervention ≤ 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.41 Change in metabolic parameters (glucose AUC)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.41.1 End of active intervention ≤ 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.42 Change in metabolic parameters (total insulin AUC)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.42.1 End of active intervention ≤ 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.43 Change in metabolic parameters (insulin sensitivity index)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.43.1 End of active intervention ≤ 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.44 Change in plasma glucose (mmol/L) during an oral glucose tolerance test: end of active intervention ≤ 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.44.1 Change in fasting plasma glucose (mmol/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.44.2 Change in 1-hour plasma glucose (mmol/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.44.3 Change in 2-hour plasma glucose (mmol/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.45 Change in plasma insulin (µIU/mL) during an oral glucose tolerance test: end of active intervention ≤ 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.45.1 Pretest measurement	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.45.2 After 60 minutes	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.45.3 After 120 minutes	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.46 Change in blood glucose (mmol/L) during an oral glucose tolerance test: end of active intervention > 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.46.1 Change in fasting blood glucose (mmol/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.46.2 Change in blood glucose level (mmol/L) at 60 minutes	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.46.3 Change in blood glucose level (mmol/L) at 120 minutes	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.47 Adverse events and serious adverse events	2		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
1.47.1 Adverse events related to physical activity: end of active intervention > 6 months	2	156	Odds Ratio (IV, Fixed, 95% CI)	6.22 [0.72, 53.40]
1.47.2 Serious adverse events related to physical activity: end of active intervention > 6 months	1	117	Odds Ratio (IV, Fixed, 95% CI)	0.95 [0.06, 15.54]

Analysis 1.1. Comparison 1: Physical activity versus control, Outcome 1: Change in VO_2 peak (mL/min per kg bodyweight)

Study or Subgroup	MD	SE	Physical activity Total	No physical activity Total	Weight	Mean Difference IV, Random, 95% CI
1.1.1 End of active intervention ≤ 6 months						
Beaudoin 2017 (1)	-2.13	1.43	8	6	14.7%	-2.13 [-4.93 , 0.67]
Hebestreit 2010 (2)	2.04	1	20	14	17.2%	2.04 [0.08 , 4.00]
Hebestreit 2022 (3)	0.649	0.798179	55	50	18.3%	0.65 [-0.92 , 2.21]
Hommerding 2015 (1)	-1.2	3.09	17	17	7.3%	-1.20 [-7.26 , 4.86]
Klijn 2004 (4)	3.95	3.52	11	9	6.1%	3.95 [-2.95 , 10.85]
Kriemler 2013 (3)	18.06	4.316525	26	10	4.5%	18.06 [9.60 , 26.52]
Sawyer 2020 (5)	1.47	0.75	7	7	18.5%	1.47 [0.00 , 2.94]
Selvadurai 2002 (6)	5.24	1.671821	44	22	13.4%	5.24 [1.96 , 8.52]
Subtotal (95% CI)			**188**	**135**	**100.0%**	**2.10 [0.06 , 4.13]**
Heterogeneity: Tau² = 5.26; Chi² = 28.80, df = 7 (P = 0.0002); I² = 76%						
Test for overall effect: Z = 2.02 (P = 0.04)						
1.1.2 End of active intervention > 6 months						
Douglas 2015 (7)	1.4	1.577257	34	33	13.2%	1.40 [-1.69 , 4.49]
Gupta 2019 (8)	4.15	1.458757	27	25	14.4%	4.15 [1.29 , 7.01]
Hebestreit 2010 (9)	0.7	1.18	17	12	17.9%	0.70 [-1.61 , 3.01]
Hebestreit 2022 (9)	1.909	0.729857	55	50	25.1%	1.91 [0.48 , 3.34]
Kriemler 2013 (9)	10.27	5.097359	22	8	2.0%	10.27 [0.28 , 20.26]
Schneiderman-Walker 2000 (10)	0.05	0.585497	30	35	27.5%	0.05 [-1.10 , 1.20]
Subtotal (95% CI)			**185**	**163**	**100.0%**	**1.60 [0.16 , 3.05]**
Heterogeneity: Tau² = 1.63; Chi² = 12.20, df = 5 (P = 0.03); I² = 59%						
Test for overall effect: Z = 2.18 (P = 0.03)						
1.1.3 Follow-up (no active intervention)						
Hebestreit 2010 (11)	3.73	1.23	20	13	62.7%	3.73 [1.32 , 6.14]
Kriemler 2013 (12)	5.55	5.813434	19	7	2.8%	5.55 [-5.84 , 16.94]
Selvadurai 2002 (13)	2.26	1.658735	44	22	34.5%	2.26 [-0.99 , 5.51]
Subtotal (95% CI)			**83**	**42**	**100.0%**	**3.27 [1.37 , 5.18]**
Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 2 (P = 0.72); I² = 0%						
Test for overall effect: Z = 3.36 (P = 0.0008)						
Test for subgroup differences: Chi² = 1.88, df = 2 (P = 0.39), I² = 0%						

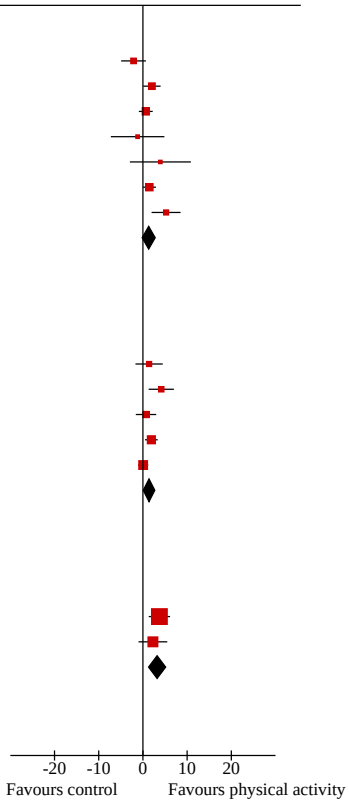


Footnotes

(1) After 3 months (partially supervised activity)
(2) After 3–6 months (partially supervised activity)
(3) After 6 months (partially supervised activity)
(4) After 3 months (supervised activity)
(5) After 2 months (supervised activity)
(6) At hospital discharge (supervised activity)
(7) After 24 months (supervised activity)
(8) After 12 months (partially supervised activity)
(9) After 12 months (6 months' partially supervised activity followed by 6 months' unsupervised activity with access to study resources)
(10) Annual rate of change over 36 months (partially supervised activity)
(11) 8–12 months (usual care for all participants following end of active intervention periods)
(12) 12 months (usual care for all participants following end of active intervention periods)
(13) 1 month after hospital discharge (usual care for all participants following end of active intervention periods)

Analysis 1.2. Comparison 1: Physical activity versus control, Outcome 2: Change in VO_2 peak (mL/min per kg bodyweight): sensitivity analysis

Study or Subgroup	MD	SE	Physical activity Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.2.1 End of active intervention ≤ 6 months						
Beaudoin 2017 (1)	-2.13	1.43	8	6	14.3%	-2.13 [-4.93 , 0.67]
Hebestreit 2010 (2)	2.04	1	20	14	19.5%	2.04 [0.08 , 4.00]
Hebestreit 2022 (3)	0.649	0.798179	55	50	22.3%	0.65 [-0.92 , 2.21]
Hommerding 2015 (1)	-1.2	3.09	17	17	4.9%	-1.20 [-7.26 , 4.86]
Klijn 2004 (4)	3.95	3.52	11	9	4.0%	3.95 [-2.95 , 10.85]
Sawyer 2020 (5)	1.47	0.75	7	7	22.9%	1.47 [0.00 , 2.94]
Selvadurai 2002 (6)	5.24	1.671821	44	22	12.1%	5.24 [1.96 , 8.52]
Subtotal (95% CI)			**162**	**125**	**100.0%**	**1.30 [-0.17 , 2.78]**
Heterogeneity: Tau² = 1.91; Chi² = 13.78, df = 6 (P = 0.03); I² = 56%						
Test for overall effect: Z = 1.73 (P = 0.08)						
1.2.2 End of active intervention > 6 months						
Douglas 2015 (7)	1.4	1.577257	34	33	12.2%	1.40 [-1.69 , 4.49]
Gupta 2019 (8)	4.15	1.458757	27	25	13.6%	4.15 [1.29 , 7.01]
Hebestreit 2010 (9)	0.7	1.18	17	12	17.6%	0.70 [-1.61 , 3.01]
Hebestreit 2022 (9)	1.909	0.729857	55	50	26.6%	1.91 [0.48 , 3.34]
Schneiderman-Walker 2000 (10)	0.05	0.585497	30	35	30.0%	0.05 [-1.10 , 1.20]
Subtotal (95% CI)			**163**	**155**	**100.0%**	**1.38 [0.08 , 2.69]**
Heterogeneity: Tau² = 1.14; Chi² = 8.96, df = 4 (P = 0.06); I² = 55%						
Test for overall effect: Z = 2.07 (P = 0.04)						
1.2.3 Follow-up (no active intervention)						
Hebestreit 2010 (11)	3.73	1.23	20	13	64.5%	3.73 [1.32 , 6.14]
Selvadurai 2002 (12)	2.26	1.658735	44	22	35.5%	2.26 [-0.99 , 5.51]
Subtotal (95% CI)			**64**	**35**	**100.0%**	**3.21 [1.27 , 5.14]**
Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 1 (P = 0.48); I² = 0%						
Test for overall effect: Z = 3.25 (P = 0.001)						
Test for subgroup differences: Chi² = 2.84, df = 2 (P = 0.24), I² = 29.5%						

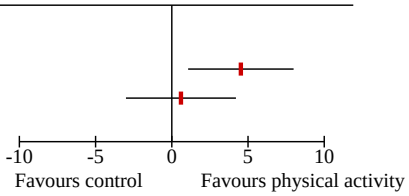


Footnotes

(1) After 3 months (partially supervised activity)
(2) After 3–6 months (partially supervised activity)
(3) After 6 months (partially supervised activity)
(4) After 3 months (supervised activity)
(5) After 2 months (supervised activity)
(6) At hospital discharge (supervised activity)
(7) After 24 months (supervised activity)
(8) After 12 months (partially supervised activity)
(9) After 12 months (6 months' partially supervised activity followed by 6 months' unsupervised activity with access to study resources)
(10) Annual rate of change over 36 months (partially supervised activity)
(11) 8–12 months (usual care for all participants following end of active intervention periods)
(12) 1 months (usual care for all participants following end of active intervention periods)

Analysis 1.3. Comparison 1: Physical activity versus control, Outcome 3: Change in VO_2 peak (% predicted)

Study or Subgroup	MD	SE	Physical activity Total	Control Total	Mean Difference IV, Fixed, 95% CI
1.3.1 End of active intervention ≤ 6 months					
Hebestreit 2022 (1)	4.53	1.764767	55	50	4.53 [1.07 , 7.99]
Hebestreit 2022 (2)	0.6	1.8404	55	50	0.60 [-3.01 , 4.21]



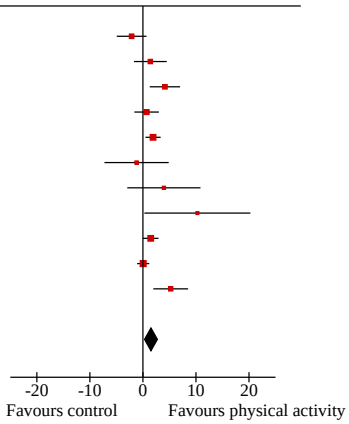
Footnotes

(1) After 12 months (6 months' partially supervised activity followed by 6 months' unsupervised activity with access to study resources)
(2) After 6 months (partially supervised activity)

Analysis 1.4. Comparison 1: Physical activity versus control, Outcome 4: Change in VO_2 peak (mL/min per kg bodyweight): combined subgroups

Study or Subgroup	MD	SE	Physical activity Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
Beaudoin 2017 (1)	-2.13	1.43	8	6	9.4%	-2.13 [-4.93 , 0.67]
Douglas 2015 (2)	1.4	1.577257	34	33	8.5%	1.40 [-1.69 , 4.49]
Gupta 2019 (3)	4.15	1.458757	27	25	9.2%	4.15 [1.29 , 7.01]
Hebestreit 2010 (4)	0.7	1.18	17	12	11.3%	0.70 [-1.61 , 3.01]
Hebestreit 2022 (5)	1.909	0.729857	55	50	15.1%	1.91 [0.48 , 3.34]
Hommerding 2015 (1)	-1.2	3.09	17	17	3.3%	-1.20 [-7.26 , 4.86]
Klijn 2004 (6)	3.95	3.52	11	9	2.6%	3.95 [-2.95 , 10.85]
Kriemler 2013 (4)	10.27	5.097359	22	8	1.4%	10.27 [0.28 , 20.26]
Sawyer 2020 (7)	1.47	0.75	7	7	14.9%	1.47 [0.00 , 2.94]
Schneiderman-Walker 2000 (8)	0.05	0.585497	30	35	16.3%	0.05 [-1.10 , 1.20]
Selvadurai 2002 (9)	5.24	1.671821	44	22	8.0%	5.24 [1.96 , 8.52]
Total (95% CI)			**272**	**224**	**100.0%**	**1.52 [0.31 , 2.73]**

Heterogeneity: Tau² = 1.99; Chi² = 24.85, df = 10 (P = 0.006); I² = 60%
Test for overall effect: Z = 2.46 (P = 0.01)
Test for subgroup differences: Not applicable



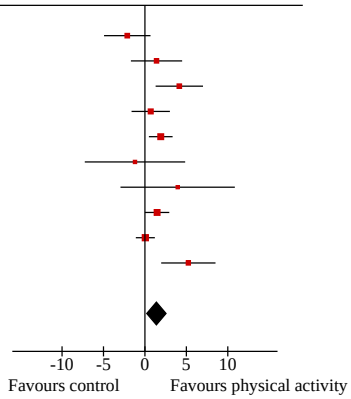
Footnotes

(1) After 3 months (partially supervised activity)
(2) After 24 months (supervised activity)
(3) After 12 months (partially supervised activity)
(4) After 12 months (6 months' partially supervised activity followed by 6 months' unsupervised activity with access to study resources)
(5) After 12 months (6 months partially supervised activity followed by 6 months unsupervised activity with access to study resources)
(6) After 3 months (supervised activity)
(7) After 2 months (supervised activity)
(8) Annual rate of change over 36 months (partially supervised activity)
(9) At hospital discharge (supervised activity)

Analysis 1.5. Comparison 1: Physical activity versus control, Outcome 5: Change in VO_2 peak (mL/min per kg bodyweight): combined subgroups – sensitivity analysis

Study or Subgroup	MD	SE	Physical activity Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
Beaudoin 2017 (1)	-2.13	1.43	8	6	9.4%	-2.13 [-4.93 , 0.67]
Douglas 2015 (2)	1.4	1.577257	34	33	8.4%	1.40 [-1.69 , 4.49]
Gupta 2019 (3)	4.15	1.458757	27	25	9.2%	4.15 [1.29 , 7.01]
Hebestreit 2010 (4)	0.7	1.18	17	12	11.3%	0.70 [-1.61 , 3.01]
Hebestreit 2022 (4)	1.909	0.729857	55	50	15.7%	1.91 [0.48 , 3.34]
Hommerding 2015 (1)	-1.2	3.09	17	17	3.1%	-1.20 [-7.26 , 4.86]
Klijn 2004 (5)	3.95	3.52	11	9	2.5%	3.95 [-2.95 , 10.85]
Sawyer 2020 (6)	1.47	0.75	7	7	15.5%	1.47 [0.00 , 2.94]
Schneiderman-Walker 2000 (7)	0.05	0.585497	30	35	17.1%	0.05 [-1.10 , 1.20]
Selvadurai 2002 (8)	5.24	1.671821	44	22	7.8%	5.24 [1.96 , 8.52]
Total (95% CI)			**250**	**216**	**100.0%**	**1.38 [0.22 , 2.55]**

Heterogeneity: Tau² = 1.71; Chi² = 21.65, df = 9 (P = 0.01); I² = 58%
Test for overall effect: Z = 2.33 (P = 0.02)
Test for subgroup differences: Not applicable

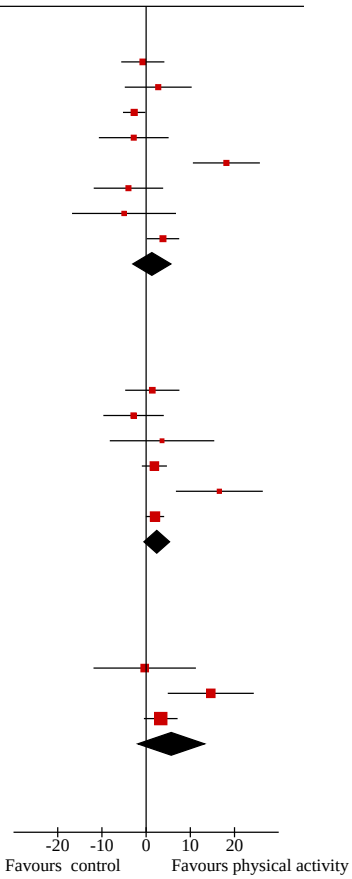


Footnotes

(1) After 3 months (partially supervised activity)
(2) After 24 months (supervised activity)
(3) After 12 months (partially supervised activity)
(4) After 12 months (6 months' partially supervised activity followed by 6 months' unsupervised activity with access to study resources)
(5) After 3 months (supervised activity)
(6) After 2 months (supervised activity)
(7) Annual rate of change over 36 months (supervised activity)
(8) At hospital discharge (supervised activity)

Analysis 1.6. Comparison 1: Physical activity versus control, Outcome 6: Change in FEV_1 (% predicted)

Study or Subgroup	MD	SE	Physical activity Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.6.1 End of active intervention ≤ 6 months						
Beaudoin 2017 (1)	-0.75	2.489	8	6	14.5%	-0.75 [-5.63 , 4.13]
Hebestreit 2010 (2)	2.74	3.86	20	15	11.5%	2.74 [-4.83 , 10.31]
Hebestreit 2022 (3)	-2.697	1.29442	60	57	16.8%	-2.70 [-5.23 , -0.16]
Hommerding 2015 (1)	-2.8	4.026384	17	17	11.1%	-2.80 [-10.69 , 5.09]
Kriemler 2013 (3)	18.16	3.866315	25	10	11.5%	18.16 [10.58 , 25.74]
Rovedder 2014 (1)	-4	4.008105	19	22	11.2%	-4.00 [-11.86 , 3.86]
Sawyer 2020 (4)	-5	6	7	7	7.7%	-5.00 [-16.76 , 6.76]
Selvadurai 2002 (5)	3.81	1.875793	44	22	15.8%	3.81 [0.13 , 7.49]
Subtotal (95% CI)			**200**	**156**	**100.0%**	**1.30 [-3.01 , 5.61]**
Heterogeneity: Tau² = 27.18; Chi² = 33.27, df = 7 (P < 0.0001); I² = 79%						
Test for overall effect: Z = 0.59 (P = 0.56)						
1.6.2 End of active intervention > 6 months						
Douglas 2015 (6)	1.4	3.129478	34	33	14.2%	1.40 [-4.73 , 7.53]
Gupta 2019 (7)	-2.84	3.487575	25	27	12.3%	-2.84 [-9.68 , 4.00]
Hebestreit 2010 (8)	3.6	6.03	19	13	5.2%	3.60 [-8.22 , 15.42]
Hebestreit 2022 (8)	1.871	1.447894	60	57	28.5%	1.87 [-0.97 , 4.71]
Kriemler 2013 (8)	16.57	5.013367	26	8	7.1%	16.57 [6.74 , 26.40]
Schneiderman-Walker 2000 (9)	2.01	1.055703	30	35	32.6%	2.01 [-0.06 , 4.08]
Subtotal (95% CI)			**194**	**173**	**100.0%**	**2.41 [-0.49 , 5.31]**
Heterogeneity: Tau² = 5.60; Chi² = 10.48, df = 5 (P = 0.06); I² = 52%						
Test for overall effect: Z = 1.63 (P = 0.10)						
1.6.3 Follow-up (no active intervention)						
Hebestreit 2010 (10)	-0.32	5.91	18	13	23.8%	-0.32 [-11.90 , 11.26]
Kriemler 2013 (11)	14.63	4.964087	23	8	28.5%	14.63 [4.90 , 24.36]
Selvadurai 2002 (12)	3.31	1.942849	44	22	47.6%	3.31 [-0.50 , 7.12]
Subtotal (95% CI)			**85**	**43**	**100.0%**	**5.68 [-1.88 , 13.23]**
Heterogeneity: Tau² = 27.41; Chi² = 5.20, df = 2 (P = 0.07); I² = 62%						
Test for overall effect: Z = 1.47 (P = 0.14)						

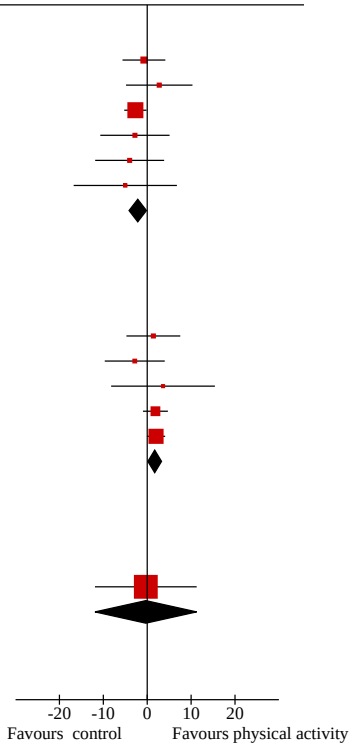


Footnotes

(1) After 3 months (partially supervised activity)
(2) After 3–6 months (partially supervised activity)
(3) After 6 months (partially supervised activity)
(4) After 2 months (supervised activity)
(5) At hospital discharge (supervised activity)
(6) After 24 months (supervised activity)
(7) After 12 months (partially supervised activity)
(8) After 12 months (6 months' partially supervised activity followed by 6 months' unsupervised activity with access to study resources)
(9) Annual rate of change over 36 months (partially supervised activity)
(10) 8–12 months (usual care for all participants following end of active intervention periods)
(11) 12 months (usual care for all participants following end of active intervention periods)
(12) 1 month (usual care for all participants following end of active intervention periods)

Analysis 1.7. Comparison 1: Physical activity versus control, Outcome 7: Change in FEV_1 (% predicted): sensitivity analysis

Study or Subgroup	MD	SE	Physical activity Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.7.1 End of active intervention ≤ 6 months						
Beaudoin 2017 (1)	-0.75	2.489	8	6	16.5%	-0.75 [-5.63 , 4.13]
Hebestreit 2010 (2)	2.74	3.86	20	15	6.9%	2.74 [-4.83 , 10.31]
Hebestreit 2022 (3)	-2.697	1.29442	60	57	61.1%	-2.70 [-5.23 , -0.16]
Hommerding 2015 (1)	-2.8	4.026384	17	17	6.3%	-2.80 [-10.69 , 5.09]
Rovedder 2014 (1)	-4	4.008105	19	22	6.4%	-4.00 [-11.86 , 3.86]
Sawyer 2020 (4)	-5	6	7	7	2.8%	-5.00 [-16.76 , 6.76]
Subtotal (95% CI)			**131**	**124**	**100.0%**	**-2.16 [-4.14 , -0.17]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.56$, df = 5 (P = 0.77); $I^2 = 0\%$						
Test for overall effect: Z = 2.13 (P = 0.03)						
1.7.2 End of active intervention > 6 months						
Douglas 2015 (5)	1.4	3.129478	34	33	6.4%	1.40 [-4.73 , 7.53]
Gupta 2019 (6)	-2.84	3.487575	25	27	5.2%	-2.84 [-9.68 , 4.00]
Hebestreit 2010 (7)	3.6	6.03	19	13	1.7%	3.60 [-8.22 , 15.42]
Hebestreit 2022 (7)	1.871	1.447894	60	57	30.1%	1.87 [-0.97 , 4.71]
Schneiderman-Walker 2000 (8)	2.01	1.055703	30	35	56.6%	2.01 [-0.06 , 4.08]
Subtotal (95% CI)			**168**	**165**	**100.0%**	**1.71 [0.15 , 3.26]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.90$, df = 4 (P = 0.75); $I^2 = 0\%$						
Test for overall effect: Z = 2.15 (P = 0.03)						
1.7.3 Follow-up (no active intervention)						
Hebestreit 2010 (9)	-0.32	5.91	18	13	100.0%	-0.32 [-11.90 , 11.26]
Subtotal (95% CI)			**18**	**13**	**100.0%**	**-0.32 [-11.90 , 11.26]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						

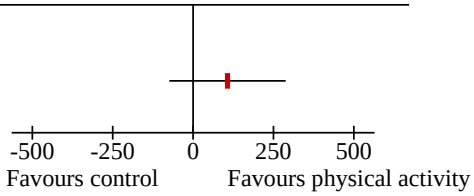


Footnotes

(1) After 3 months (partially supervised activity)
(2) After 3–6 months (partially supervised activity)
(3) After 6 months (partially supervised activity)
(4) After 2 months (supervised activity)
(5) After 24 months (supervised activity)
(6) After 12 months (partially supervised activity)
(7) After 12 months (6 months' partially supervised activity followed by 6 months' unsupervised activity with access to study resources)
(8) Annual rate of change over 36 months (partially supervised activity)
(9) 8–12 months (usual care for all participants following end of active intervention periods)

Analysis 1.8. Comparison 1: Physical activity versus control, Outcome 8: Change in FEV_1 (mL)

Study or Subgroup	MD	SE	Mean Difference IV, Fixed, 95% CI
1.8.1 End of active intervention > 6 months			
Moorcroft 2004 (1)	107	92.34	107.00 [-73.98 , 287.98]

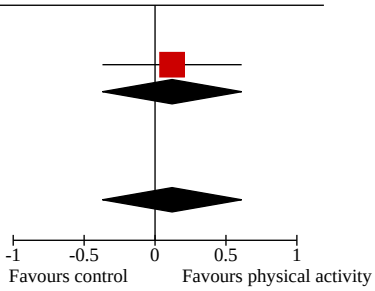


Footnotes

(1) After 12 months (unsupervised activity)

Analysis 1.9. Comparison 1: Physical activity versus control, Outcome 9: Change in FEV_1 (z-score)

Study or Subgroup	MD	SE	Physical activity Total	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
1.9.1 End of active intervention > 6 months						
Douglas 2015 (1)	0.12	0.250358	34	33	100.0%	0.12 [-0.37 , 0.61]
Subtotal (95% CI)			**34**	**33**	**100.0%**	**0.12 [-0.37 , 0.61]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.48 (P = 0.63)						
Total (95% CI)			**34**	**33**	**100.0%**	**0.12 [-0.37 , 0.61]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.48 (P = 0.63)						
Test for subgroup differences: Not applicable						

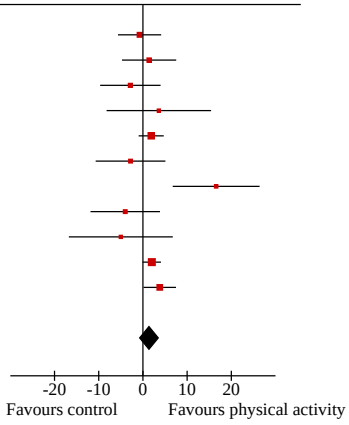


Footnotes

(1) After 24 months (supervised activity)

Analysis 1.10. Comparison 1: Physical activity versus control, Outcome 10: Change in FEV_1 (% predicted): combined subgroups

Study or Subgroup	MD	SE	Physical activity Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
Beaudoin 2017 (1)	-0.75	2.489	8	6	10.9%	-0.75 [-5.63 , 4.13]
Douglas 2015 (2)	1.4	3.129478	34	33	8.1%	1.40 [-4.73 , 7.53]
Gupta 2019 (3)	-2.84	3.487575	25	27	7.0%	-2.84 [-9.68 , 4.00]
Hebestreit 2010 (4)	3.6	6.03	19	13	2.8%	3.60 [-8.22 , 15.42]
Hebestreit 2022 (5)	1.871	1.447894	60	57	17.8%	1.87 [-0.97 , 4.71]
Hommerding 2015 (1)	-2.8	4.026384	17	17	5.6%	-2.80 [-10.69 , 5.09]
Kriemler 2013 (5)	16.57	5.013367	26	8	3.9%	16.57 [6.74 , 26.40]
Rovedder 2014 (1)	-4	4.008105	19	22	5.6%	-4.00 [-11.86 , 3.86]
Sawyer 2020 (6)	-5	6	7	7	2.9%	-5.00 [-16.76 , 6.76]
Schneiderman-Walker 2000 (7)	2.01	1.055703	30	35	20.9%	2.01 [-0.06 , 4.08]
Selvadurai 2002 (8)	3.81	1.875793	44	22	14.6%	3.81 [0.13 , 7.49]
Total (95% CI)			**289**	**247**	**100.0%**	**1.37 [-0.74 , 3.47]**
Heterogeneity: $Tau^2 = 4.39$; $Chi^2 = 17.45$, df = 10 (P = 0.06); $I^2 = 43\%$						
Test for overall effect: Z = 1.27 (P = 0.20)						
Test for subgroup differences: Not applicable						



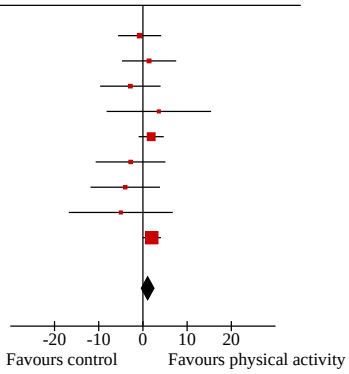
Footnotes

(1) After 3 months (partially supervised activity)
(2) After 24 months (supervised activity)
(3) After 12 months (partially supervised activity)
(4) After 12 months (6 months partially supervised activity followed by 6 months unsupervised activity with access to study resources)
(5) After 12 months (6 months' partially supervised activity followed by 6 months' unsupervised activity with access to study resources)
(6) After 2 months (supervised activity)
(7) Annual rate of change over 36 months (partially supervised activity)
(8) At hospital discharge (supervised activity)

Analysis 1.11. Comparison 1: Physical activity versus control, Outcome 11: Change in FEV_1 (% predicted): sensitivity analysis

Study or Subgroup	MD	SE	Physical activity Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
Beaudoin 2017 (1)	-0.75	2.489	8	6	8.5%	-0.75 [-5.63 , 4.13]
Douglas 2015 (2)	1.4	3.129478	34	33	5.4%	1.40 [-4.73 , 7.53]
Gupta 2019 (3)	-2.84	3.487575	25	27	4.3%	-2.84 [-9.68 , 4.00]
Hebestreit 2010 (4)	3.6	6.03	19	13	1.4%	3.60 [-8.22 , 15.42]
Hebestreit 2022 (5)	1.871	1.447894	60	57	25.1%	1.87 [-0.97 , 4.71]
Hommerding 2015 (1)	-2.8	4.026384	17	17	3.2%	-2.80 [-10.69 , 5.09]
Rovedder 2014 (1)	-4	4.008105	19	22	3.3%	-4.00 [-11.86 , 3.86]
Sawyer 2020 (6)	-5	6	7	7	1.5%	-5.00 [-16.76 , 6.76]
Schneiderman-Walker 2000 (7)	2.01	1.055703	30	35	47.2%	2.01 [-0.06 , 4.08]
Total (95% CI)			**219**	**217**	**100.0%**	**1.07 [-0.36 , 2.49]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.62$, df = 8 (P = 0.58); $I^2 = 0\%$
Test for overall effect: Z = 1.47 (P = 0.14)
Test for subgroup differences: Not applicable

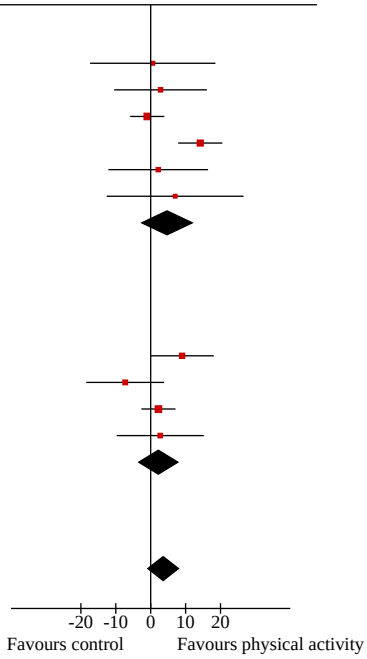


Footnotes

(1) After 3 months (partially supervised activity)
(2) After 24 months (supervised activity)
(3) After 12 months (partially supervised activity)
(4) After 12 months (6 months' partially supervised activity followed by 6 months' unsupervised activity with access to study resources)
(5) After 12 months (6 months partially supervised activity followed by 6 months unsupervised activity with access to study resources)
(6) After 2 months (supervised activity)
(7) Annual rate of change over 36 months (supervised activity)

Analysis 1.12. Comparison 1: Physical activity versus control, Outcome 12: Change in HRQoL: CFQ-R physical functioning domain

Study or Subgroup	MD	SE	Physical activity Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.12.1 End of active intervention ≤ 6 months						
Beaudoin 2017 (1)	0.59	9.16	8	6	4.7%	0.59 [-17.36 , 18.54]
Hebestreit 2010 (2)	2.82	6.78	20	14	7.3%	2.82 [-10.47 , 16.11]
Hebestreit 2022 (2)	-0.98	2.498748	60	56	17.1%	-0.98 [-5.88 , 3.92]
Klijn 2004 (3)	14.2	3.228668	11	9	15.0%	14.20 [7.87 , 20.53]
Kriemler 2013 (2)	2.16	7.282994	11	8	6.6%	2.16 [-12.11 , 16.43]
Sawyer 2020 (4)	7	10	7	7	4.1%	7.00 [-12.60 , 26.60]
Subtotal (95% CI)			**117**	**100**	**54.7%**	**4.67 [-2.55 , 11.90]**
Heterogeneity: Tau² = 44.87; Chi² = 14.24, df = 5 (P = 0.01); I² = 65%						
Test for overall effect: Z = 1.27 (P = 0.21)						
1.12.2 End of active intervention > 6 months						
Douglas 2015 (5)	9	4.631628	34	33	11.3%	9.00 [-0.08 , 18.08]
Hebestreit 2010 (6)	-7.3	5.690595	19	11	9.0%	-7.30 [-18.45 , 3.85]
Hebestreit 2022 (6)	2.21	2.4937	60	56	17.1%	2.21 [-2.68 , 7.10]
Kriemler 2013 (6)	2.74	6.364314	26	8	7.9%	2.74 [-9.73 , 15.21]
Subtotal (95% CI)			**139**	**108**	**45.3%**	**2.19 [-3.42 , 7.80]**
Heterogeneity: Tau² = 12.92; Chi² = 4.94, df = 3 (P = 0.18); I² = 39%						
Test for overall effect: Z = 0.77 (P = 0.44)						
Total (95% CI)			**256**	**208**	**100.0%**	**3.57 [-0.81 , 7.95]**
Heterogeneity: Tau² = 22.94; Chi² = 19.76, df = 9 (P = 0.02); I² = 54%						
Test for overall effect: Z = 1.60 (P = 0.11)						
Test for subgroup differences: Chi² = 0.28, df = 1 (P = 0.59), I² = 0%						

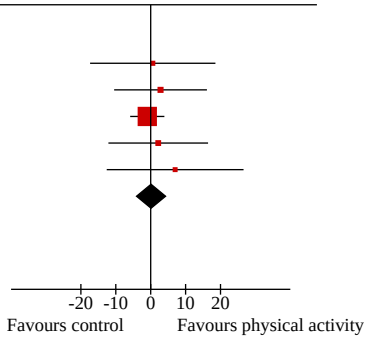


Footnotes

(1) After 3 months (partially supervised activity)
(2) After 6 months (partially supervised activity)
(3) After 3 months (supervised activity)
(4) After 2 months (supervised activity)
(5) After 24 months (supervised activity)
(6) After 12 months (6 months' partially supervised activity followed by 6 months' unsupervised activity with access to study resources)

Analysis 1.13. Comparison 1: Physical activity versus control, Outcome 13: Change in HRQoL: CFQ-R physical functioning domain: sensitivity analysis

Study or Subgroup	MD	SE	Physical activity Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.13.1 End of active intervention ≤ 6 months						
Beaudoin 2017 (1)	0.59	9.16	8	6	5.4%	0.59 [-17.36 , 18.54]
Hebestreit 2010 (2)	2.82	6.78	20	14	9.8%	2.82 [-10.47 , 16.11]
Hebestreit 2022 (2)	-0.98	2.498748	60	56	71.9%	-0.98 [-5.88 , 3.92]
Kriemler 2013 (2)	2.16	7.282994	11	8	8.5%	2.16 [-12.11 , 16.43]
Sawyer 2020 (3)	7	10	7	7	4.5%	7.00 [-12.60 , 26.60]
Subtotal (95% CI)			**106**	**91**	**100.0%**	**0.10 [-4.05 , 4.25]**
Heterogeneity: Tau² = 0.00; Chi² = 0.91, df = 4 (P = 0.92); I² = 0%						
Test for overall effect: Z = 0.05 (P = 0.96)						



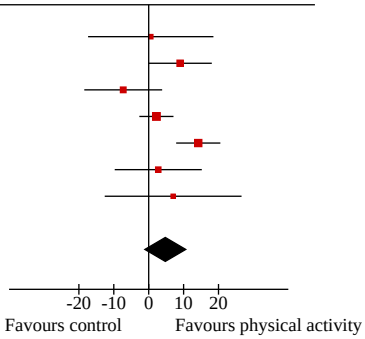
Footnotes

(1) After 3 months (partially supervised activity)
(2) After 6 months (partially supervised activity)
(3) After 2 months (supervised activity)

Analysis 1.14. Comparison 1: Physical activity versus control, Outcome 14: Change in HRQoL: CFQ-R physical functioning domain: combined subgroups

Study or Subgroup	MD	SE	Physical activity Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
Beaudoin 2017 (1)	0.59	9.16	8	6	7.6%	0.59 [-17.36 , 18.54]
Douglas 2015 (2)	9	4.631628	34	33	16.4%	9.00 [-0.08 , 18.08]
Hebestreit 2010 (3)	-7.3	5.690595	19	11	13.7%	-7.30 [-18.45 , 3.85]
Hebestreit 2022 (4)	2.21	2.4937	60	56	22.8%	2.21 [-2.68 , 7.10]
Klijn 2004 (5)	14.2	3.228668	11	9	20.6%	14.20 [7.87 , 20.53]
Kriemler 2013 (4)	2.74	6.364314	26	8	12.1%	2.74 [-9.73 , 15.21]
Sawyer 2020 (6)	7	10	7	7	6.7%	7.00 [-12.60 , 26.60]
Total (95% CI)			**165**	**130**	**100.0%**	**4.76 [-1.09 , 10.61]**

Heterogeneity: Tau² = 32.79; Chi² = 15.13, df = 6 (P = 0.02); I² = 60%
Test for overall effect: Z = 1.59 (P = 0.11)
Test for subgroup differences: Not applicable

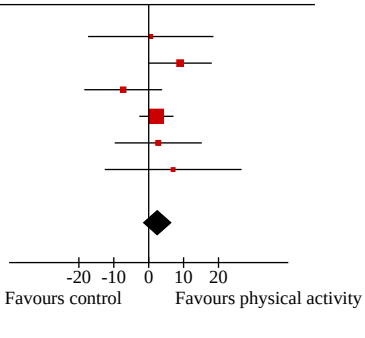


Footnotes
(1) After 3 months (partially supervised activity)
(2) After 24 months (supervised activity)
(3) After 12 months (6 months partially supervised activity followed by 6 months unsupervised activity with access to study resources)
(4) After 12 months (6 months' partially supervised activity followed by 6 months' unsupervised activity with access to study resources)
(5) After 3 months (supervised activity)
(6) After 2 months (supervised activity)

Analysis 1.15. Comparison 1: Physical activity versus control, Outcome 15: Change in HRQoL: CFQ-R physical functioning domain: combined subgroups – sensitivity analysis

Study or Subgroup	MD	SE	Physical activity Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
Beaudoin 2017 (1)	0.59	9.16	8	6	4.6%	0.59 [-17.36 , 18.54]
Douglas 2015 (2)	9	4.631628	34	33	17.3%	9.00 [-0.08 , 18.08]
Hebestreit 2010 (3)	-7.3	5.690595	19	11	11.6%	-7.30 [-18.45 , 3.85]
Hebestreit 2022 (3)	2.21	2.4937	60	56	53.3%	2.21 [-2.68 , 7.10]
Kriemler 2013 (3)	2.74	6.364314	26	8	9.4%	2.74 [-9.73 , 15.21]
Sawyer 2020 (4)	7	10	7	7	3.9%	7.00 [-12.60 , 26.60]
Total (95% CI)			**154**	**121**	**100.0%**	**2.44 [-1.43 , 6.30]**

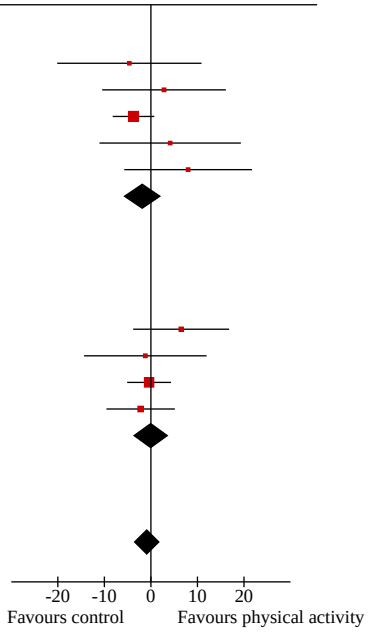
Heterogeneity: Tau² = 1.08; Chi² = 5.20, df = 5 (P = 0.39); I² = 4%
Test for overall effect: Z = 1.24 (P = 0.22)
Test for subgroup differences: Not applicable



Footnotes
(1) After 3 months (partially supervised activity)
(2) After 24 months (supervised activity)
(3) After 12 months (6 months' partially supervised activity followed by 6 months' unsupervised activity with access to study resources)
(4) After 2 months (supervised activity)

Analysis 1.16. Comparison 1: Physical activity versus control, Outcome 16: Change in HRQoL: CFQ-R respiratory symptoms

Study or Subgroup	MD	SE	Physical activity Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.16.1 End of active intervention ≤ 6 months						
Beaudoin 2017 (1)	-4.63	7.91	8	6	2.8%	-4.63 [-20.13 , 10.87]
Hebestreit 2010 (2)	2.82	6.78	20	14	3.8%	2.82 [-10.47 , 16.11]
Hebestreit 2022 (3)	-3.74	2.281685	60	56	33.7%	-3.74 [-8.21 , 0.73]
Kriemler 2013 (3)	4.14	7.750524	26	8	2.9%	4.14 [-11.05 , 19.33]
Sawyer 2020 (4)	8	7	7	7	3.6%	8.00 [-5.72 , 21.72]
Subtotal (95% CI)			**121**	**91**	**46.9%**	**-1.87 [-5.66 , 1.92]**
Heterogeneity: Tau² = 0.00; Chi² = 3.86, df = 4 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.97 (P = 0.33)						
1.16.2 End of active intervention > 6 months						
Douglas 2015 (5)	6.5	5.257524	34	33	6.4%	6.50 [-3.80 , 16.80]
Hebestreit 2010 (6)	-1.2	6.71708	20	14	3.9%	-1.20 [-14.37 , 11.97]
Hebestreit 2022 (6)	-0.39	2.402836	60	56	30.4%	-0.39 [-5.10 , 4.32]
Kriemler 2013 (6)	-2.2	3.750949	26	8	12.5%	-2.20 [-9.55 , 5.15]
Subtotal (95% CI)			**140**	**111**	**53.1%**	**-0.05 [-3.61 , 3.51]**
Heterogeneity: Tau² = 0.00; Chi² = 1.93, df = 3 (P = 0.59); I² = 0%						
Test for overall effect: Z = 0.03 (P = 0.98)						
Total (95% CI)			**261**	**202**	**100.0%**	**-0.90 [-3.50 , 1.69]**
Heterogeneity: Tau² = 0.00; Chi² = 6.26, df = 8 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.68 (P = 0.50)						
Test for subgroup differences: Chi² = 0.47, df = 1 (P = 0.49), I² = 0%						

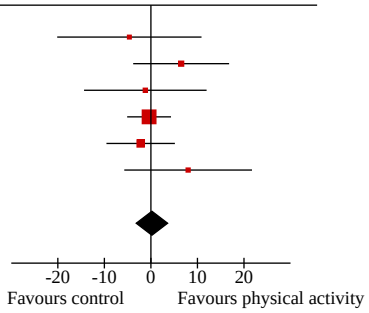


Footnotes

(1) After 3 months (partially supervised activity)
(2) After 3–6 months (partially supervised activity)
(3) After 6 months (partially supervised activity)
(4) After 2 months (supervised activity)
(5) After 24 months (supervised activity)
(6) After 12 months (6 months' partially supervised activity followed by 6 months' unsupervised activity with access to study resources)

Analysis 1.17. Comparison 1: Physical activity versus control, Outcome 17: Change in HRQoL: CFQ-R respiratory symptoms: combined subgroups

Study or Subgroup	MD	SE	Physical activity Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
Beaudoin 2017 (1)	-4.63	7.91	8	6	4.7%	-4.63 [-20.13 , 10.87]
Douglas 2015 (2)	6.5	5.257524	34	33	10.7%	6.50 [-3.80 , 16.80]
Hebestreit 2010 (3)	-1.2	6.71708	20	14	6.5%	-1.20 [-14.37 , 11.97]
Hebestreit 2022 (3)	-0.39	2.402836	60	56	51.1%	-0.39 [-5.10 , 4.32]
Kriemler 2013 (3)	-2.2	3.750949	26	8	21.0%	-2.20 [-9.55 , 5.15]
Sawyer 2020 (4)	8	7	7	7	6.0%	8.00 [-5.72 , 21.72]
Total (95% CI)			**155**	**124**	**100.0%**	**0.22 [-3.15 , 3.58]**
Heterogeneity: Tau² = 0.00; Chi² = 3.56, df = 5 (P = 0.61); I² = 0%						
Test for overall effect: Z = 0.13 (P = 0.90)						
Test for subgroup differences: Not applicable						

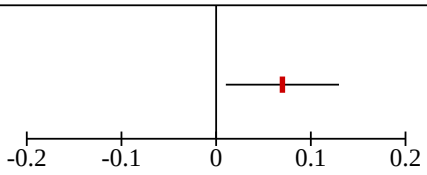


Footnotes

(1) After 3 months (partially supervised activity)
(2) After 24 months (supervised activity)
(3) After 12 months (6 months' partially supervised activity followed by 6 months' unsupervised activity with access to study resources)
(4) After 2 months (supervised activity)

Analysis 1.18. Comparison 1: Physical activity versus control, Outcome 18: Change in HRQoL: Quality of Well-Being scale

Study or Subgroup	MD	SE	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
1.18.1 Follow-up (no active intervention)				
Selvadurai 2002 (1)	0.07	0.030488	0.07 [0.01 , 0.13]	

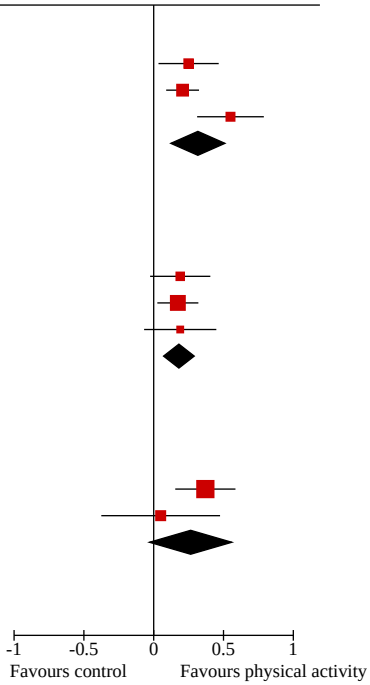


Footnotes

(1) 1 month after hospital discharge (usual care for all participants following end of active intervention periods)

Analysis 1.19. Comparison 1: Physical activity versus control, Outcome 19: Change in peak work capacity (W/kg bodyweight) during maximal exercise

Study or Subgroup	MD	SE	Physical activity Total	Control Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
1.19.1 End of active intervention ≤ 6 months							
Hebestreit 2010 (1)	0.25	0.11	22	14	30.5%	0.25 [0.03 , 0.47]	
Hebestreit 2022 (2)	0.207	0.059988	53	50	41.5%	0.21 [0.09 , 0.32]	
Kriemler 2013 (2)	0.55	0.121861	15	10	28.1%	0.55 [0.31 , 0.79]	
Subtotal (95% CI)			**90**	**74**	**100.0%**	**0.32 [0.12 , 0.51]**	
Heterogeneity: Tau² = 0.02; Chi² = 6.42, df = 2 (P = 0.04); I² = 69%							
Test for overall effect: Z = 3.20 (P = 0.001)							
1.19.2 End of active intervention > 6 months							
Hebestreit 2010 (3)	0.19	0.11	17	12	26.0%	0.19 [-0.03 , 0.41]	
Hebestreit 2022 (3)	0.173	0.074967	53	50	55.9%	0.17 [0.03 , 0.32]	
Kriemler 2013 (3)	0.19	0.131924	15	8	18.1%	0.19 [-0.07 , 0.45]	
Subtotal (95% CI)			**85**	**70**	**100.0%**	**0.18 [0.07 , 0.29]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 2 (P = 0.99); I² = 0%							
Test for overall effect: Z = 3.22 (P = 0.001)							
1.19.3 Follow-up (no active intervention)							
Hebestreit 2010 (4)	0.37	0.11	20	13	67.1%	0.37 [0.15 , 0.59]	
Kriemler 2013 (5)	0.05	0.216974	11	7	32.9%	0.05 [-0.38 , 0.48]	
Subtotal (95% CI)			**31**	**20**	**100.0%**	**0.26 [-0.03 , 0.56]**	
Heterogeneity: Tau² = 0.02; Chi² = 1.73, df = 1 (P = 0.19); I² = 42%							
Test for overall effect: Z = 1.76 (P = 0.08)							

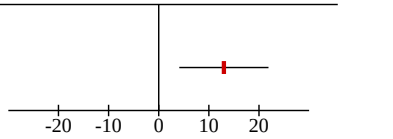


Footnotes

(1) After 3–6 months (partially supervised activity)
(2) After 6 months (partially supervised activity)
(3) After 12 months
(4) 8–12 months (usual care for all participants following end of active intervention periods)
(5) 12 months (usual care for all participants following end of active intervention periods)

Analysis 1.20. Comparison 1: Physical activity versus control, Outcome 20: Change in peak work capacity (W) during maximal exercise

Study or Subgroup	MD	SE	Physical activity Total	Control Total	Mean Difference IV, Fixed, 95% CI
1.20.1 End of active intervention ≤ 6 months					
Klijn 2004 (1)	13	4.538277	11	9	13.00 [4.11 , 21.89]

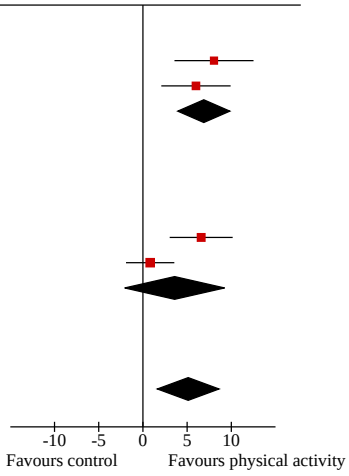


Footnotes

(1) After 3 months (supervised activity)

Analysis 1.21. Comparison 1: Physical activity versus control, Outcome 21: Change in peak work capacity (% predicted) during maximal exercise

Study or Subgroup	MD	SE	Physical activity Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.21.1 End of active intervention ≤ 6 months						
Hebestreit 2022 (1)	8.04	2.281055	53	50	22.0%	8.04 [3.57 , 12.51]
Sawyer 2020 (2)	6	2	7	7	24.1%	6.00 [2.08 , 9.92]
Subtotal (95% CI)			**60**	**57**	**46.1%**	**6.89 [3.94 , 9.83]**
Heterogeneity: Tau² = 0.00; Chi² = 0.45, df = 1 (P = 0.50); I² = 0%						
Test for overall effect: Z = 4.58 (P < 0.00001)						
1.21.2 End of active intervention > 6 months						
Hebestreit 2022 (3)	6.59	1.817283	53	50	25.4%	6.59 [3.03 , 10.15]
Schneiderman-Walker 2000 (4)	0.82	1.394167	30	35	28.5%	0.82 [-1.91 , 3.55]
Subtotal (95% CI)			**83**	**85**	**53.9%**	**3.59 [-2.06 , 9.24]**
Heterogeneity: Tau² = 14.02; Chi² = 6.35, df = 1 (P = 0.01); I² = 84%						
Test for overall effect: Z = 1.24 (P = 0.21)						
Total (95% CI)			**143**	**142**	**100.0%**	**5.12 [1.63 , 8.61]**
Heterogeneity: Tau² = 9.17; Chi² = 11.23, df = 3 (P = 0.01); I² = 73%						
Test for overall effect: Z = 2.88 (P = 0.004)						
Test for subgroup differences: Chi² = 1.03, df = 1 (P = 0.31), I² = 2.9%						

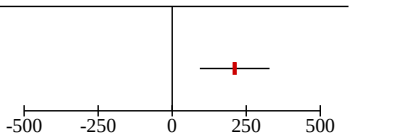


Footnotes

(1) After 6 months (partially supervised activity)
(2) After 2 months (supervised activity)
(3) After 12 months (6 months' partially supervised activity followed by 6 months' unsupervised activity with access to study resources)
(4) Annual rate of change over 3 years (partially supervised activity)

Analysis 1.22. Comparison 1: Physical activity versus control, Outcome 22: Change in time to symptom limitation (T_{lim} in sec) during constant work submaximal exercise

Study or Subgroup	MD	SE	Physical activity Total	Control Total	Mean Difference IV, Fixed, 95% CI
1.22.1 End of active intervention ≤ 6 months					
Sawyer 2020 (1)	211	60	7	7	211.00 [93.40 , 328.60]

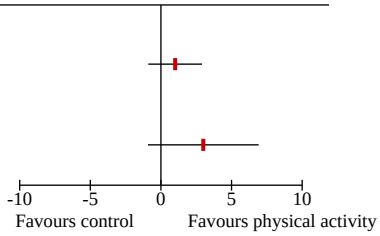


Footnotes

(1) After 2 months (supervised activity)

Analysis 1.23. Comparison 1: Physical activity versus control, Outcome 23: Change in VO_2 (mL/min per kg bodyweight and % predicted) during constant work submaximal exercise

Study or Subgroup	MD	SE	Physical activity Total	Control Total	Mean Difference IV, Fixed, 95% CI
1.23.1 End of active intervention ≤ 6 months - VO_2 peak expressed as mL/min per kg bodyweight					
Sawyer 2020 (1)	1.01	0.97	7	7	1.01 [-0.89 , 2.91]
1.23.2 Active intervention ≤ 6 months - VO_2 peak expressed as % predicted					
Sawyer 2020 (1)	3	2	7	7	3.00 [-0.92 , 6.92]

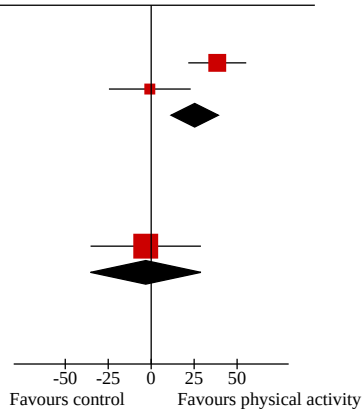


Footnotes

(1) After 2 months (supervised activity)

Analysis 1.24. Comparison 1: Physical activity versus control, Outcome 24: Change in 6MWT distance (m)

Study or Subgroup	MD	SE	Physical activity Total	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
1.24.1 End of active intervention ≤ 6 months						
Del Corral 2018 (1)	38.45	8.605044	20	20	66.5%	38.45 [21.58 , 55.32]
Rovedder 2014 (2)	-0.8	12.13635	19	22	33.5%	-0.80 [-24.59 , 22.99]
Subtotal (95% CI)			**39**	**42**	**100.0%**	**25.32 [11.56 , 39.08]**
Heterogeneity: Chi^2 = 6.96, df = 1 (P = 0.008); I^2 = 86%						
Test for overall effect: Z = 3.61 (P = 0.0003)						
1.24.2 End of active intervention > 6 months						
Del Corral 2018 (3)	-3.17	16.380209	20	20	100.0%	-3.17 [-35.27 , 28.93]
Subtotal (95% CI)			**20**	**20**	**100.0%**	**-3.17 [-35.27 , 28.93]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.19 (P = 0.85)						



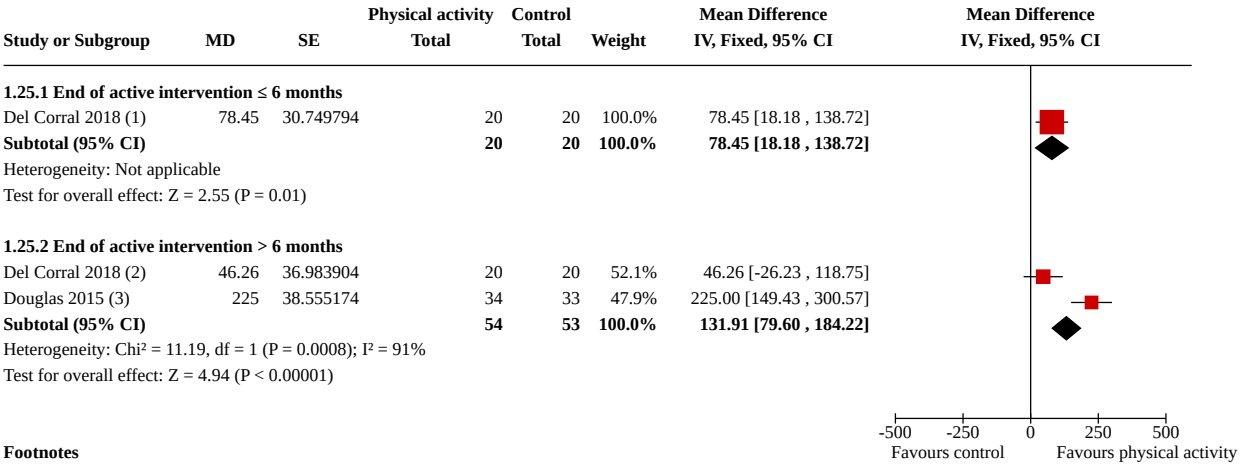
Footnotes

(1) After 6 weeks (partially supervised activity)

(2) After 3 months (partially supervised activity)

(3) 12 months (6 weeks' partially supervised activity followed by 12 months' supervised activity by parents/caregivers with access to study resources)

Analysis 1.25. Comparison 1: Physical activity versus control, Outcome 25: Change in modified shuttle walk distance (m)



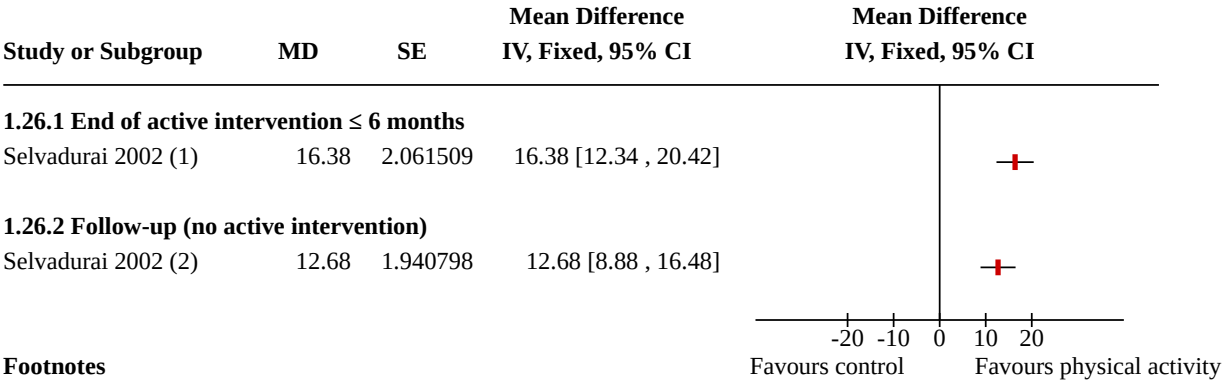
Footnotes

(1) After 6 weeks (partially supervised activity)

(2) After 12 months (6 weeks' partially supervised activity followed by 12 months' supervised activity by parents/caregivers with access to study resources)

(3) After 24 months (supervised activity)

Analysis 1.26. Comparison 1: Physical activity versus control, Outcome 26: Change in quadriceps muscle strength (Nm)



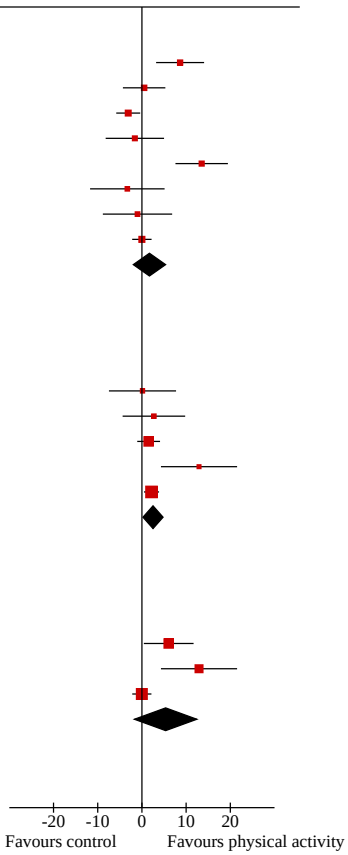
Footnotes

(1) At hospital discharge (supervised activity)

(2) 1 month after hospital discharge (usual care for all participants following end of active intervention periods)

Analysis 1.27. Comparison 1: Physical activity versus control, Outcome 27: Change in FVC (% predicted)

Study or Subgroup	MD	SE	Physical activity Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.27.1 End of active intervention ≤ 6 months						
Beaudoin 2017 (1)	8.64	2.768869	8	6	12.6%	8.64 [3.21 , 14.07]
Hebestreit 2010 (2)	0.5	2.45	20	15	13.4%	0.50 [-4.30 , 5.30]
Hebestreit 2022 (3)	-3.1	1.381242	60	57	15.9%	-3.10 [-5.81 , -0.39]
Hommerding 2015 (1)	-1.6	3.37	17	17	11.1%	-1.60 [-8.21 , 5.01]
Kriemler 2013 (3)	13.52	3.026136	26	10	11.9%	13.52 [7.59 , 19.45]
Rovedder 2014 (1)	-3.3	4.3	19	22	9.0%	-3.30 [-11.73 , 5.13]
Sawyer 2020 (4)	-1	4	7	7	9.7%	-1.00 [-8.84 , 6.84]
Selvadurai 2002 (5)	-0.01	1.117798	44	22	16.4%	-0.01 [-2.20 , 2.18]
Subtotal (95% CI)			**201**	**156**	**100.0%**	**1.70 [-1.95 , 5.35]**
Heterogeneity: Tau² = 19.94; Chi² = 35.42, df = 7 (P < 0.00001); I² = 80%						
Test for overall effect: Z = 0.91 (P = 0.36)						
1.27.2 End of active intervention > 6 months						
Gupta 2019 (6)	0.13	3.873423	25	27	7.8%	0.13 [-7.46 , 7.72]
Hebestreit 2010 (7)	2.71	3.61	19	12	8.8%	2.71 [-4.37 , 9.79]
Hebestreit 2022 (7)	1.52	1.31512	60	57	33.3%	1.52 [-1.06 , 4.10]
Kriemler 2013 (7)	12.92	4.394221	23	11	6.2%	12.92 [4.31 , 21.53]
Schneiderman-Walker 2000 (8)	2.17	0.869065	30	35	43.9%	2.17 [0.47 , 3.87]
Subtotal (95% CI)			**157**	**142**	**100.0%**	**2.51 [0.24 , 4.78]**
Heterogeneity: Tau² = 2.30; Chi² = 6.53, df = 4 (P = 0.16); I² = 39%						
Test for overall effect: Z = 2.17 (P = 0.03)						
1.27.3 Follow-up (no active intervention)						
Hebestreit 2010 (9)	6.06	2.87	17	11	33.4%	6.06 [0.43 , 11.69]
Kriemler 2013 (10)	12.92	4.394221	23	8	26.0%	12.92 [4.31 , 21.53]
Selvadurai 2002 (11)	-0.02	1.106439	44	22	40.7%	-0.02 [-2.19 , 2.15]
Subtotal (95% CI)			**84**	**41**	**100.0%**	**5.37 [-1.69 , 12.43]**
Heterogeneity: Tau² = 30.68; Chi² = 11.16, df = 2 (P = 0.004); I² = 82%						
Test for overall effect: Z = 1.49 (P = 0.14)						
Test for subgroup differences: Chi² = 0.82, df = 2 (P = 0.66), I² = 0%						

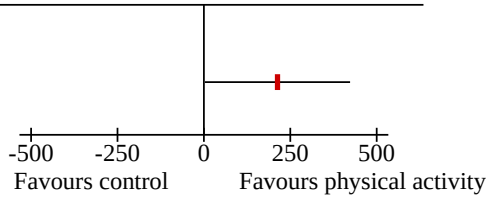


Footnotes

(1) After 3 months (partially supervised activity)
(2) After 3–6 months (partially supervised activity)
(3) After 6 months (partially supervised activity)
(4) After 3 months (supervised activity)
(5) At hospital discharge (supervised activity)
(6) After 24 months (partially supervised activity)
(7) After 12 months (6 months' partially supervised activity followed by 6 months' unsupervised activity with access to study resources)
(8) Annual rate of change over 3 years (partially supervised activity)
(9) 6–12 months (usual care for all participants following end of active intervention periods)
(10) 12 months (usual care for all participants following end of active intervention periods)
(11) 1 month after hospital discharge (usual care for all participants following end of active intervention periods)

Analysis 1.28. Comparison 1: Physical activity versus control, Outcome 28: Change in FVC (mL)

Study or Subgroup	MD	SE	Mean Difference IV, Fixed, 95% CI
1.28.1 End of active intervention > 6 months			
Moorcroft 2004 (1)	213	107.14	213.00 [3.01 , 422.99]

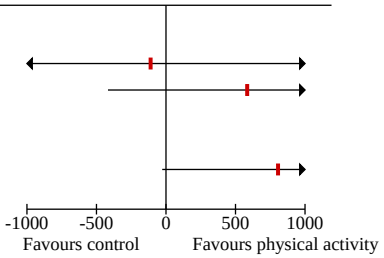


Footnotes

(1) After 12 months (supervised activity)

Analysis 1.29. Comparison 1: Physical activity versus control, Outcome 29: Change in objectively measured physical activity (steps per day)

Study or Subgroup	MD	SE	Physical activity Total	Control Total	Mean Difference IV, Fixed, 95% CI
1.29.1 End of active intervention ≤ 6 months					
Beaudoin 2017 (1)	-110.58	1097.03	8	6	-110.58 [-2260.72 , 2039.56]
Hebestreit 2022 (2)	584	510.774121	55	50	584.00 [-417.10 , 1585.10]
1.29.2 End of active intervention > 6 months					
Hebestreit 2022 (3)	806	425.056845	55	50	806.00 [-27.10 , 1639.10]



Footnotes

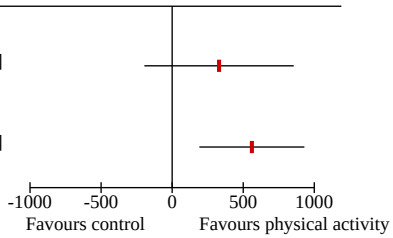
(1) After 3 months (partially supervised activity)

(2) After 6 months (partially supervised activity)

(3) After 12 months (6 months' partially supervised activity followed by 6 months' unsupervised activity with access to study resources)

Analysis 1.30. Comparison 1: Physical activity versus control, Outcome 30: Change in objectively measured physical activity (aerobic steps per day)

Study or Subgroup	MD	SE	Physical activity Total	Control Total	Mean Difference IV, Fixed, 95% CI
1.30.1 End of active intervention ≤ 6 months					
Hebestreit 2022 (1)	330	268.115843	51	50	330.00 [-195.50 , 855.50]
1.30.2 End of active intervention > 6 months					
Hebestreit 2022 (2)	561	188.487453	51	50	561.00 [191.57 , 930.43]



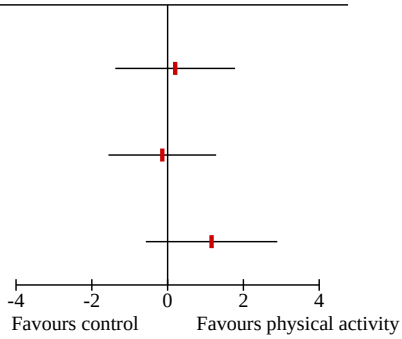
Footnotes

(1) After 6 months (partially supervised activity)

(2) After 12 months (6 months' partially supervised activity followed by 6 months' unsupervised activity with access to study resources)

Analysis 1.31. Comparison 1: Physical activity versus control, Outcome 31: Change in objectively measured moderate-to-vigorous physical activity (hours per week)

Study or Subgroup	MD	SE	Physical activity Total	Control Total	Mean Difference IV, Fixed, 95% CI
1.31.1 End of active intervention ≤ 6 months					
Kriemler 2013 (1)	0.2	0.806226	25	9	0.20 [-1.38 , 1.78]
1.31.2 End of active intervention > 6 months					
Kriemler 2013 (2)	-0.14	0.72481	24	8	-0.14 [-1.56 , 1.28]
1.31.3 Follow-up (no active intervention)					
Kriemler 2013 (3)	1.16	0.884666	20	7	1.16 [-0.57 , 2.89]



Footnotes

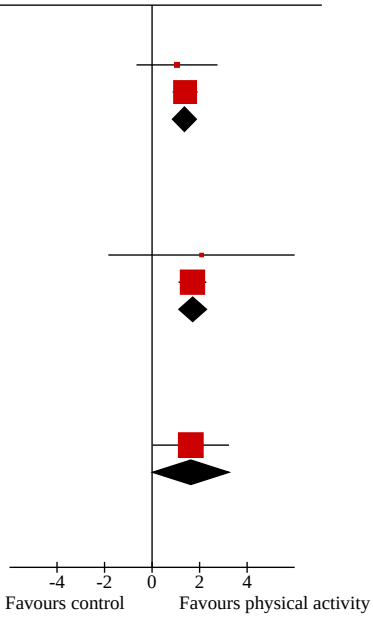
(1) After 6 months (partially supervised activity)

(2) After 12 months (6 months' partially supervised activity followed by 6 months' unsupervised activity with access to study resources)

(3) 12 months (usual care for all participants following end of active intervention periods)

Analysis 1.32. Comparison 1: Physical activity versus control, Outcome 32: Change in self-reported vigorous physical activity (hours per week)

Study or Subgroup	MD	SE	Physical activity Total	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
1.32.1 End of active intervention ≤ 6 months						
Hebestreit 2010 (1)	1.05	0.87	20	15	8.6%	1.05 [-0.66 , 2.76]
Hebestreit 2022 (2)	1.39	0.267568	60	57	91.4%	1.39 [0.87 , 1.91]
Subtotal (95% CI)			**80**	**72**	**100.0%**	**1.36 [0.86 , 1.86]**
Heterogeneity: Chi² = 0.14, df = 1 (P = 0.71); I² = 0%						
Test for overall effect: Z = 5.32 (P < 0.00001)						
1.32.2 End of active intervention > 6 months						
Hebestreit 2010 (3)	2.08	2	19	12	2.2%	2.08 [-1.84 , 6.00]
Hebestreit 2022 (3)	1.7	0.299286	60	57	97.8%	1.70 [1.11 , 2.29]
Subtotal (95% CI)			**79**	**69**	**100.0%**	**1.71 [1.13 , 2.29]**
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.85); I² = 0%						
Test for overall effect: Z = 5.77 (P < 0.00001)						
1.32.3 Follow-up (no active intervention)						
Hebestreit 2010 (4)	1.63	0.82	7	11	100.0%	1.63 [0.02 , 3.24]
Subtotal (95% CI)			**7**	**11**	**100.0%**	**1.63 [0.02 , 3.24]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.99 (P = 0.05)						

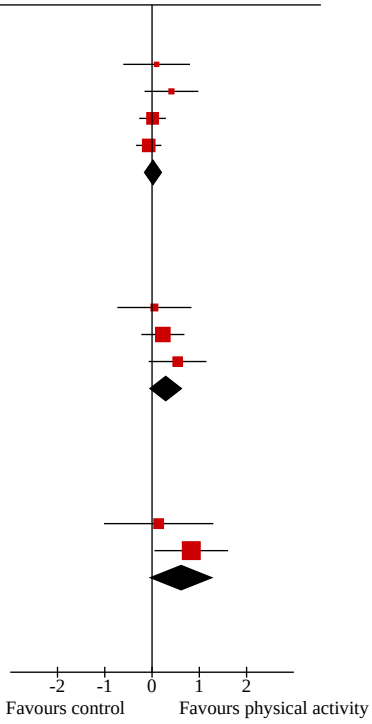


Footnotes

(1) After 3–6 months (partially supervised activity)
(2) After 6 months (partially supervised activity)
(3) After 12 months (6 months' partially supervised activity followed by 6 months' unsupervised activity with access to study resources)
(4) 8–12 months (usual care for all participants following end of active intervention periods)

Analysis 1.33. Comparison 1: Physical activity versus control, Outcome 33: Change in BMI (kg/m²)

Study or Subgroup	MD	SE	Physical activity Total	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
1.33.1 End of active intervention ≤ 6 months						
Beaudoin 2017 (1)	0.097	0.36	8	6	6.3%	0.10 [-0.61 , 0.80]
Hebestreit 2010 (2)	0.41	0.29	21	15	9.8%	0.41 [-0.16 , 0.98]
Hebestreit 2022 (3)	0.01	0.143881	60	57	39.7%	0.01 [-0.27 , 0.29]
Kriemler 2013 (3)	-0.07	0.136438	26	10	44.2%	-0.07 [-0.34 , 0.20]
Subtotal (95% CI)			**115**	**88**	**100.0%**	**0.02 [-0.16 , 0.20]**
Heterogeneity: Chi² = 2.29, df = 3 (P = 0.51); I² = 0%						
Test for overall effect: Z = 0.21 (P = 0.83)						
1.33.2 End of active intervention > 6 months						
Hebestreit 2010 (4)	0.05	0.4	20	12	17.8%	0.05 [-0.73 , 0.83]
Hebestreit 2022 (4)	0.23	0.232229	60	57	52.9%	0.23 [-0.23 , 0.69]
Moorcroft 2004 (5)	0.54	0.311715	25	17	29.3%	0.54 [-0.07 , 1.15]
Subtotal (95% CI)			**105**	**86**	**100.0%**	**0.29 [-0.04 , 0.62]**
Heterogeneity: Chi² = 1.07, df = 2 (P = 0.59); I² = 0%						
Test for overall effect: Z = 1.71 (P = 0.09)						
1.33.3 Follow-up (no active intervention)						
Hebestreit 2010 (6)	0.14	0.59	18	11	31.2%	0.14 [-1.02 , 1.30]
Kriemler 2013 (7)	0.83	0.397183	23	8	68.8%	0.83 [0.05 , 1.61]
Subtotal (95% CI)			**41**	**19**	**100.0%**	**0.61 [-0.03 , 1.26]**
Heterogeneity: Chi² = 0.94, df = 1 (P = 0.33); I² = 0%						
Test for overall effect: Z = 1.87 (P = 0.06)						

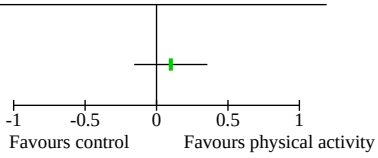


Footnotes

(1) After 3 months (partially supervised activity)
(2) After 3–6 months (partially supervised activity)
(3) After 6 months (partially supervised activity)
(4) After 12 months (6 months' partially supervised activity followed by 6 months' unsupervised activity with access to study resources)
(5) After 12 months (unsupervised activity)
(6) 8–12 months (usual care for all participants following end of active intervention periods)
(7) 12 months (usual care for all participants following end of active intervention periods)

Analysis 1.34. Comparison 1: Physical activity versus control, Outcome 34: Change in BMI (z-score)

Study or Subgroup	Physical activity Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.34.1 End of active intervention ≤ 6 months							
Hommerding 2015 (1)	0.2	0.5	17	0.1	0.2	17	0.10 [-0.16 , 0.36]



Footnotes

(1) After 3 months (partially supervised activity)

Analysis 1.35. Comparison 1: Physical activity versus control, Outcome 35: Number of pulmonary exacerbations

Number of pulmonary exacerbations

Study	Physical activity (n)	Control (n)	Incidence rate ratio	95% CI	P value
Number of exacerbations at end of 6 months' partially supervised active intervention (mixed Poisson regression model)					
Hebestreit 2022	27	23	1.07	0.60 to 1.90	0.83
Number of exacerbations after 12 months: 6 months' partially supervised activity followed by 6 months unsupervised activity with access to study resources (mixed Poisson regression model)					
Hebestreit 2022	61	53	1.28	0.85 to 1.94	0.24

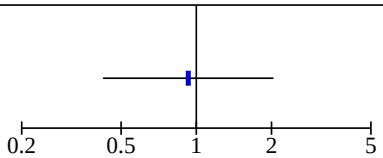
Analysis 1.36. Comparison 1: Physical activity versus control, Outcome 36: Time to first pulmonary exacerbation

Time to first pulmonary exacerbation

Study	Hazard ratio	95% CI	P value
Hebestreit 2022	1.34	0.65 to 2.80	0.43

Analysis 1.37. Comparison 1: Physical activity versus control, Outcome 37: Number of hospitalisations

Study or Subgroup	Physical activity Events	Total	Control Events	Total	Odds Ratio IV, Fixed, 95% CI
1.37.1 Hospitalisations during 12 months of active intervention					
Hebestreit 2022 (1)	18	60	18	57	0.93 [0.42 , 2.04]

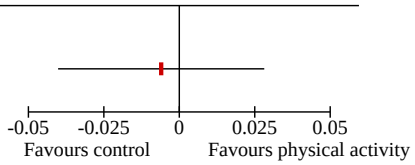


Footnotes

(1) No. participants hospitalised during study (6 months' partially supervised activity + 6 months' unsupervised with access to study resc

Analysis 1.38. Comparison 1: Physical activity versus control, Outcome 38: Change in whole body bone mineral density (g/cm²)

Study or Subgroup	MD	SE	Physical activity Total	Control Total	Mean Difference IV, Fixed, 95% CI
1.38.1 End of active intervention > 6 months					
Gupta 2019 (1)	-0.006	0.017425	25	27	-0.01 [-0.04 , 0.03]

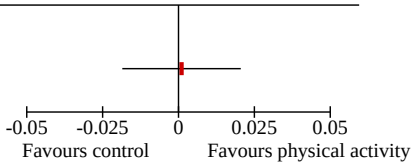


Footnotes

(1) After 12 months (partially supervised activity)

Analysis 1.39. Comparison 1: Physical activity versus control, Outcome 39: Change in lumbar spine bone mineral density (g/cm²)

Study or Subgroup	MD	SE	Physical activity Total	Control Total	Mean Difference IV, Fixed, 95% CI
1.39.1 End of active intervention > 6 months					
Gupta 2019 (1)	0.001	0.009957	25	27	0.00 [-0.02 , 0.02]

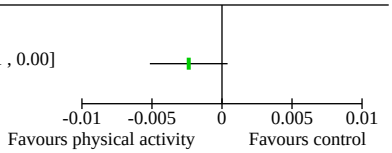


Footnotes

(1) After 12 months (partially supervised activity)

Analysis 1.40. Comparison 1: Physical activity versus control, Outcome 40: Change in metabolic parameters (HbA1c (%))

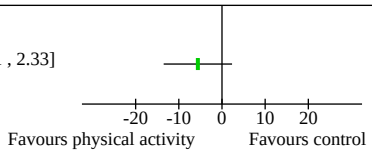
Study or Subgroup	Physical activity Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
1.40.1 End of active intervention ≤ 6 months								
Beaudoin 2017 (1)	-0.000875	0.00216712	8	0.0015	0.00238048	4	-0.00 [-0.01 , 0.00]	



Footnotes
(1) After 3 months (partially supervised activity)

Analysis 1.41. Comparison 1: Physical activity versus control, Outcome 41: Change in metabolic parameters (glucose AUC)

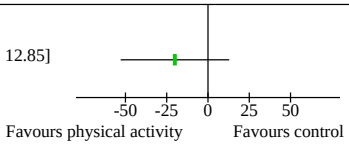
Study or Subgroup	Physical activity Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
1.41.1 End of active intervention ≤ 6 months								
Beaudoin 2017 (1)	-5.46375	5.12236256	8	0.125	8.84794835	6	-5.59 [-13.51 , 2.33]	



Footnotes
(1) After 3 months (partially supervised activity)

Analysis 1.42. Comparison 1: Physical activity versus control, Outcome 42: Change in metabolic parameters (total insulin AUC)

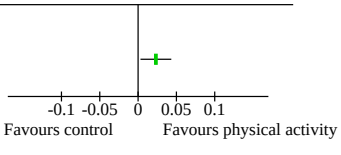
Study or Subgroup	Physical activity Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
1.42.1 End of active intervention ≤ 6 months								
Beaudoin 2017 (1)	-8.2157143	33.5157803	8	11.8083333	29.0755983	6	-20.02 [-52.90 , 12.85]	



Footnotes
(1) After 3 months (partially supervised activity)

Analysis 1.43. Comparison 1: Physical activity versus control, Outcome 43: Change in metabolic parameters (insulin sensitivity index)

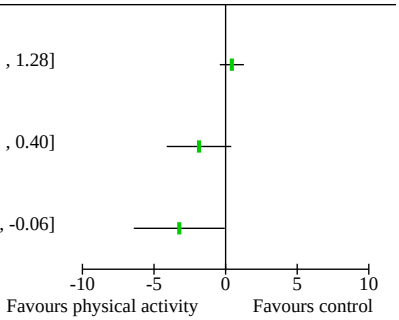
Study or Subgroup	Physical activity Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
1.43.1 End of active intervention ≤ 6 months								
Beaudoin 2017 (1)	0.01586571	0.01688779	8	-0.007365	0.02041611	6	0.02 [0.00 , 0.04]	



Footnotes
(1) After 3 months (partially supervised activity)

Analysis 1.44. Comparison 1: Physical activity versus control, Outcome 44: Change in plasma glucose (mmol/L) during an oral glucose tolerance test: end of active intervention ≤ 6 months

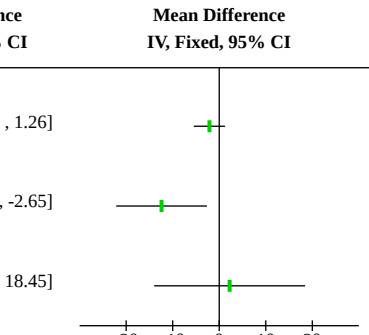
Study or Subgroup	Physical activity Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.44.1 Change in fasting plasma glucose (mmol/L)							
Beaudoin 2017 (1)	0.00688	0.494866	8	-0.428333	0.959988	6	0.44 [-0.41 , 1.28]
1.44.2 Change in 1-hour plasma glucose (mmol/L)							
Beaudoin 2017 (1)	-1.79	1.662117	7	0.06833	2.360004	6	-1.86 [-4.11 , 0.40]
1.44.3 Change in 2-hour plasma glucose (mmol/L)							
Beaudoin 2017 (1)	-2.34125	1.258371	8	0.89667	3.816525	6	-3.24 [-6.41 , -0.06]



Footnotes
(1) After 3 months (partially supervised activity)

Analysis 1.45. Comparison 1: Physical activity versus control, Outcome 45: Change in plasma insulin (µIU/mL) during an oral glucose tolerance test: end of active intervention ≤ 6 months

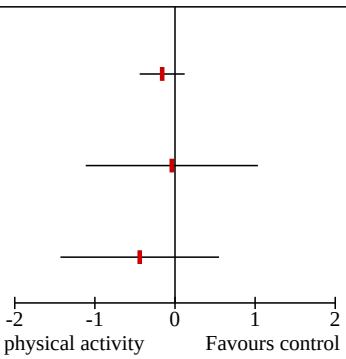
Study or Subgroup	Physical activity Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.45.1 Pretest measurement							
Beaudoin 2017 (1)	-0.377143	1.371631	7	1.72317	4.001887	6	-2.10 [-5.46 , 1.26]
1.45.2 After 60 minutes							
Beaudoin 2017 (1)	-4.277714	6.741404	7	8.115	10.45679	6	-12.39 [-22.14 , -2.65]
1.45.3 After 120 minutes							
Beaudoin 2017 (1)	-1.291143	13.68341	7	-3.522833	15.81846	6	2.23 [-13.98 , 18.45]



Footnotes
(1) After 3 months (partially supervised activity)

Analysis 1.46. Comparison 1: Physical activity versus control, Outcome 46: Change in blood glucose (mmol/L) during an oral glucose tolerance test: end of active intervention > 6 months

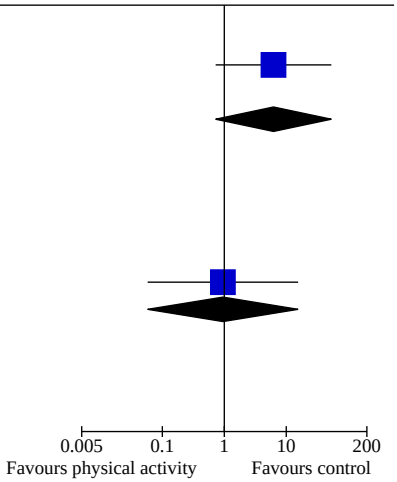
Study or Subgroup	MD	SE	Physical activity Total	Control Total	Mean Difference IV, Fixed, 95% CI
1.46.1 Change in fasting blood glucose (mmol/L)					
Hebestreit 2022 (1)	-0.16	0.143184	41	40	-0.16 [-0.44 , 0.12]
1.46.2 Change in blood glucose level (mmol/L) at 60 minutes					
Hebestreit 2022 (1)	-0.04	0.548285	31	36	-0.04 [-1.11 , 1.03]
1.46.3 Change in blood glucose level (mmol/L) at 120 minutes					
Hebestreit 2022 (1)	-0.44	0.504911	41	40	-0.44 [-1.43 , 0.55]



Footnotes
(1) After 9 months (6 months' partially supervised activity followed by 6 months' unsupervised activity with access to study resources)

Analysis 1.47. Comparison 1: Physical activity versus control, Outcome 47: Adverse events and serious adverse events

Study or Subgroup	Physical activity Events	Total	Control Events	Total	Weight	Odds Ratio IV, Fixed, 95% CI
1.47.1 Adverse events related to physical activity: end of active intervention > 6 months						
Hebestreit 2022 (1)	6	60	1	57	100.0%	6.22 [0.72 , 53.40]
Kriemler 2013 (2)	0	29	0	10		Not estimable
Subtotal (95% CI)		**89**		**67**	**100.0%**	**6.22 [0.72 , 53.40]**
Total events:	6		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.67 (P = 0.10)						
1.47.2 Serious adverse events related to physical activity: end of active intervention > 6 months						
Hebestreit 2022 (1)	1	60	1	57	100.0%	0.95 [0.06 , 15.54]
Subtotal (95% CI)		**60**		**57**	**100.0%**	**0.95 [0.06 , 15.54]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.04 (P = 0.97)						



Footnotes

(1) No. participants with adverse event during 12-month active intervention (6 months' partially supervised activity + 6 months' unsupervised

(2) Number of participants who experienced an adverse event during the 12 months active intervention (6 months partially supervised activity followed by 6 months u

ADDITIONAL TABLES

Table 1. Study results for Santana-Sosa 2012

Variable	Group	Pretraining	Post-training	Detraining[a]	P value	Comments
Age (mean (SEM)) years	Intervention	11 (3)	—	—	—	—
	Control	10 (2)	—	—	—	
Sex (% boys)	Intervention	55	—	—	—	
	Control	64	—	—	—	
VO_2 peak (mean (95% CI)) mL/min per kg bodyweight	Intervention	N/A	3.9 (1.8 to 6.1)	−3.4 (−5.7 to 1.7)	0.036	Higher in controls at baseline (P = 0.023).
	Control	N/A	−2.2 (−5.3 to 0.1)	−0.7 (−4.4 to 5.9)		Data were presented in a figure in the original publication.
Leg press (mean (95% CI)) kg	Intervention	N/A	24.9 (14.3 to 34.4)	−1.0 (−4.1 to 3.3)	< 0.001	Data are reported in a figure in the original publication.
	Control	N/A	N/A	N/A		Significantly higher in controls at baseline (P = 0.014).
Bench press (mean (95% CI)) kg	Intervention	N/A	10.5 (7.0 to 14.0)	−1.2 (−3.6 to 3.0)	< 0.001	Significantly higher in controls at baseline (P = 0.007).
	Control	N/A	N/A	N/A		Data presented in a figure in the original publication.

Table 1. Study results for Santana-Sosa 2012 *(Continued)*

Seated row (mean (95% CI)) kg	Intervention	N/A	12.7 (9.2 to 16.0)	−0.2 (−3.6 to 3.2)	< 0.001	Significantly higher in controls at baseline (P = 0.009).
	Control	N/A	N/A	N/A		Data presented in a figure in the original publication.
Oxygen saturation at peak exercise (mean (SEM)) %	Intervention	94.9 (0.9)	95.6 (0.8)	94.5 (1.2)	N/A	—
	Control	95.7 (0.5)	96.4% (0.4)	96.1 (0.5)		
FEV_1 (mean (SEM)) L	Intervention	1.87 (0.24)	1.94 (0.23)	1.90 (0.25)	0.769	—
	Control	1.77 (0.17)	1.87 (0.15)	1.79 (0.19)		
FVC (mean (SEM)) L	Intervention	2.41 (0.24)	2.49 (0.25)	2.56 (0.29)	0.920	—
	Control	2.29 (0.19)	2.36 (0.20)	2.40 (0.24)		
PI_{max} (mean (SEM)) cmH_2O	Intervention	64.0 (5.5)	69.8 (6.8)	75.2 (6.2)	0.797	—
	Control	61.5 (6.9)	72.2 (7.2)	76.4 (7.5)		
HRQoL score – children's report (median (range))	Intervention	696 (495–741)	719 (550–734)	—	0.257	HRQoL was assessed before and after the intervention.
	Control	649 (578–768)	638 (461–791)	—		P value for comparison pre versus post-training.
HRQoL score – parents' report (median (range))	Intervention	896 (688–1011)	889 (811–973)	—	0.143	HRQoL was assessed before and after the intervention.
	Control	911 (842–1028)	978 (684–1059)	—		
Weight (mean (SEM)) kg	Intervention	39.9 (3.5)	40.5 (3.4)	41.4 (3.4)	0.723	—
	Control	34.0 (2.6)	35.1 (2.8)	36.2 (3.0)		
BMI (mean (SEM)) kg/m^2	Intervention	18.4 (1.0)	18.3 (0.7)	18.5 (0.7)	0.959	—
	Control	17.2 (0.8)	17.1 (0.8)	17.4 (0.9)		
Fat-free mass (mean (SEM)) %	Intervention	78.1 (2.7)	79.4 (2.8)	78.8 (2.9)	0.115	—
	Control	81.1 (2.5)	80.9 (2.1)	81.1 (2.2)		
Body fat (mean (SEM)) %	Intervention	21.9 (2.7)	20.6 (2.8)	21.2 (2.9)	0.115	—
	Control	18.9 (2.5)	19.1 (2.1)	18.9 (2.2)		
Compliance with physical training (mean (SEM)) %	Intervention	—	95.1 (7.4)	—	—	73% of children completed all training sessions.
	Control	—	—	—		
Adverse effects	Intervention	—	—	—	—	No adverse effects occurred during training or maximal exercise testing.
	Control	—	—	—		

[a]Described in the original papers as "detraining" but corresponding to our definition of 'off training'.
BMI: body mass index; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; HRQoL: health-related quality of life; N/A: not applicable; PI_{max}: maximum inspiratory mouth pressure; SEM: standard error of the mean; VO_2 peak: peak oxygen consumption.

Table 2. Study results for Santana-Sosa 2014

Variable	Group	Pretraining	Post-training	Detraining[a]	P value	Comments
Age (mean (SEM)) years	Intervention	11 (1)	—	—	—	—
	Control	10 (1)	—	—	—	
Sex (% boys)	Intervention	60	—	—	—	—
	Control	60	—	—	—	
VO_2 peak (mean (95% CI) mL/min per kg body-weight	Intervention	N/A	6.9 (3.4 to 10.5)	−1.5 (−2.7 to −0.4)	< 0.001	Significantly higher in controls at baseline (P = 0.034).
	Control	N/A	N/A	N/A		
Leg press (mean (SEM)) kg	Intervention	62.5 (6.5)	89.5 (9.3)	88.6 (9.2)	< 0.001	Higher in controls at baseline (P = 0.046).
	Control	45.2 (4.7)	43.9 (5.1)	43.9 (5.4)		
Bench press (mean (SEM)) kg	Intervention	26.4 (2.7)	38.4 (3.2)	35.9 (2.9)	< 0.001	—
	Control	23.2 (2.9)	21.6 (3.2)	21.7 (3.6)		
Lateral row (mean (SEM)) kg	Intervention	30.5 (3.6)	43.0 (4.2)	35.9 (2.9)	< 0.001	—
	Control	23.2 (3.0)	22.0 (3.1)	21.7 (3.6)		
Oxygen saturation at peak exercise (mean (SEM)) %	Intervention	94.7 (0.7)	94.5 (0.7)	93.1 (0.8)	N/A	—
	Control	96.4 (0.4)	96.2 (0.5)	96.1 (0.6)		
FEV_1 (mean (SEM)) L	Intervention	1.65 (0.19)	1.74 (0.23)	1.69 (0.24)	0.486	—
	Control	1.57 (0.26)	1.55 (0.26)	1.59 (0.26)		
FVC (mean (SEM)) L	Intervention	2.23 (0.27)	2.34 (0.29)	2.28 (0.28)	0.156	—
	Control	1.90 (0.33)	1.85 (0.32)	1.92 (0.32)		
PI_{max} (mean (SEM)) cmH_2O	Intervention	68.3 (6.3)	107.6 (8.4)	103.2 (8.1)	< 0.001	—
	Control	69.5 (9.7)	71.8 (10.0)	66.7 (9.4)		
HRQoL score (median (range))	Intervention	629 (505–701)	688 (609–791)	—	0.071	HRQoL was assessed before and after the intervention.
	Control	636 (626–745)	638 (626–737)	—		

Table 2. Study results for Santana-Sosa 2014 *(Continued)*

Weight (mean (SEM)) kg	Intervention	36.4 (3.1)	37.8 (3.2)	38.3 (3.1)	0.342	—
	Control	31.5 (4.6)	32.4 (4.7)	32.7 (4.5)		
Fat-free mass (mean (SEM)) % of total	Intervention	81.6 (1.3)	82.6 (1.0)	82.5 (1.0)	0.001	—
	Control	82.9 (1.8)	82.8 (1.8)	82.5 (1.9)		
Body fat (mean (SEM)) % of total	Intervention	18.4 (1.3)	17.4 (1.2)	17.5 (1.1)	0.023	—
	Control	17.1 (1.8)	17.2 (1.8)	17.5 (1.9)		
Compliance with physical training (mean (SEM)) %	Intervention	—	97.5 (1.7)	—	—	70% of children completed all training sessions.
	Control	—	—	—		
Adverse effects	Intervention	—	—	—	—	No adverse effects occurred during training or exercise testing.
	Control	—	—	—		

[a]Described in the original papers as "detraining" but corresponding to our definition of 'off training'.
CI: confidence interval; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; HRQoL: health-related quality of life; N/A: not applicable; PI_{max}: maximum inspiratory mouth pressure; SEM: standard error of the mean; VO_2 peak: peak oxygen consumption.

Table 3. Health-related quality of life (HRQoL) results for Rovedder 2014

Health-related quality of life	Exercise group (n = 19) (median (IQR))	Control group (n = 22) (median (IQR))	P value
HRQoL scale – physical	6.1 (–4 to 8)	2.4 (–10 to 13)	0.742
HRQoL scale – respiratory	3.8 (0 to 11)	–4.7 (–1 to 7)	0.925
SF-36 – functional capacity	2.8 (–10 to 15)	2.0 (–11 to 10)	0.916
SF-36 – physical aspects	11.8 (–25 to 50)	6.8 (–6 to 31)	0.705
SF-36 – pain	–7.2 (–28 to 11)	8.0 (7 to 17)	0.100
SF-36 – general health	3.7 (–5 to 10)	–3.5 (–11 to 5)	0.197
SF-36 – vitality	1.2 (–15 to 20)	7.5 (–1 to 21)	0.416
SF-36 – social aspects	15.2 (0 to 33)	21.2 (0 to 66)	0.989
SF-36 – emotional aspects	4.7 (–12 to 37)	4.5 (–12 to 25)	0.914
SF-36 – mental health	–0.8 (–12 to 12)	0.9 (–9 to 13)	0.752

Pre–post changes in HRQoL measured using the CFQ and SF-36.

CFQ: Cystic Fibrosis Questionnaire; HRQoL: health-related quality of life; IQR: interquartile range; n: number of participants; SF-36: Medical Outcomes Study 36-Item Short-Form Health Survey.

APPENDICES

Appendix 1. Search methods – electronic searches

Database or resource	Strategy
ClinicalTrials.gov	[BASIC SEARCH FORM] SEARCH 1 STATUS: All studies CONDITION OF DISEASE: cystic fibrosis OTHER TERMS: exercise training SEARCH 2 STATUS: All studies CONDITION OF DISEASE: cystic fibrosis OTHER TERMS: physical activity
WHO International Clinical Trials Registry Platform (ICTRP)	[BASIC SEARCH] SEARCH 1 exercise training AND cystic fibrosis SEARCH 2 physical activity AND cystic fibrosis

WHAT'S NEW

Date	Event	Description
21 April 2022	New citation required and conclusions have changed	Despite a larger number of studies included in the current version of the review, the conclusions have not substantially changed compared to previous versions (Bradley 2002; Bradley 2008; Radtke 2015; Radtke 2017). Nevertheless, the current review extends our knowledge of clinically relevant and patient-centred outcomes, including adverse events and glycaemic control. Moreover, our certainty in the beneficial effects of regular physical activity and exercise training on aerobic exercise ca-

Date	Event	Description
		pacity has strengthened, while there were no beneficial effects on lung function and health-related quality of life (Bradley 2002; Bradley 2008; Radtke 2015; Radtke 2017).
21 April 2022	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register identified 113 references which were potentially eligible for inclusion in this updated review. Two references (abstracts) were identified through other sources. Additional searches of online databases identified a further 505 references (clinicaltrials.gov: 369 references; the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP): 136 references). After initial screening and the removal of duplicates, we assessed 100 new references. **Included studies** Four new references to three unique studies have been included (Alexander 2019; Donadio 2020; Hatziagorou 2019), and there were 10 new references for five already included studies (Carr 2018; Douglas 2015; Hebestreit 2010; Hommerding 2015; Santana-Sosa 2014). There were six references for two studies previously listed as ongoing but now included (Gupta 2019; Sawyer 2020), and one reference for a further study previously listed as ongoing under the study ID Hebestreit 2016. This study has now been included and renamed Hebestreit 2022. We found two new references for studies listed as "awaiting classification" as clinical trials registry entries, which have now been included (Del Corral 2018; Güngör 2021). There were also three new references for a further study previously listed as "awaiting classification" under the study ID Lorenc 2015. This study has now been included and renamed Carr 2018. One study, previously listed as ongoing under the study ID Donadio 2017, has been confirmed to be related to the included study Hommerding 2015 and the 2017 reference has been added to the Hommerding 2015 study ID. **Excluded studies** 59 references to 35 new studies have been excluded with reasons (ACTRN12620001237976; Bass 2019; Bellini 2018; Cantin 2005; Combret 2018; Combret 2021; Cox 2013; de Marchis 2017; Dwyer 2019; Gruber 1998; Hütler 2002; IRCT20161024030474N4; Kaak 2011; Kaltsakas 2021; Lang 2019; Macleod 2008; Martinez Rodriguez 2017; Montero-Ruiz 2020; Moola 2017; NCT00129350; NCT01759342; NCT02199340; NCT03420209; NCT04888767; NTR2092; Pryor 1979; Radtke 2018b; RBR-34677v; RBR-5g9f6w; Reuveny 2020; Ruddy 2015; Spoletini 2020; Ward 2018; White 1997; Young 2019; Zeren 2019). There were five new additional references to already excluded studies (Dwyer 2011; Falk 1988; Lima 2014; Reix 2012; Zeren 2019). Seven studies, previously listed as awaiting classification were excluded: investigators of three studies (with one new reference to one study) informed us that no paper will be published (Happ 2013; Mandrusiak 2011; NCT00792194); the investigators of one study did not reply to our email (Oliveira 2010); and for four studies, no contact details could be found online to contact study investigators (Almajan-Guta 2011; Housinger 2015; Johnston 2004; Phillips 2008). **Ongoing studies** Two new studies (Curran 2020; Monteiro 2019), and 10 trial registry records have been added to "ongoing studies" (ISRCT-

Date	Event	Description
		N92573472; NCT03273959; NCT03970369; NCT04249999; NCT04543929; NCT04683809; NCT04742049; NCT05147285; NCT05173194; NCT05239611). **Studies awaiting classification** There were three new references for two studies already (and still) listed as "awaiting classification" (Cox 2019; Powers 2016), and two records were added from the trials registry searches (IRCT20190407043190N1; NCT04293926). We identified three new references to a further study that was previously listed as ongoing under the ID NCT02700243; this study has been completed and was added to "awaiting classification" (Bishay 2017). **Online trials registry searches** A search of Clinicaltrials.gov on 4 March 2022 identified 236 study records (after removal of 129 duplicates). Of these, 191 were physical activity interventions and were disregarded without further assessment (not listed in the review); 19 records had already been identified and listed in this review; 18 records were not randomised controlled trials (i.e. observational studies with single-group assignment); in five studies the control group was not eligible for this review ('no physical activity intervention'); and three registered studies were prematurely terminated by the investigators. A search of the WHO International Clinical Trials Registry Platform (ICTRP) on 16 March 2022 identified 136 records to 134 unique studies, none of which were new studies. In summary, in this 2022 update we have included five new studies (Alexander 2019; Del Corral 2018; Donadio 2020; Güngör 2021; Hatziagorou 2019), one additional study previously listed as "awaiting classification" (Carr 2018), and three studies previously listed as ongoing (Gupta 2019; Hebestreit 2022; Sawyer 2020). We have also excluded 35 new studies (ACTRN12620001237976; Bass 2019; Bellini 2018; Cantin 2005; Combret 2018; Combret 2021; Cox 2013; de Marchis 2017; Dwyer 2019; Gruber 1998; Happ 2013; Hütler 2002; IRCT20161024030474N4; Kaak 2011; Kaltsakas 2021; Lang 2019; Macleod 2008; Martinez Rodriguez 2017; Montero-Ruiz 2020; Moola 2017; NCT01759342; NCT02199340; NCT03420209; NCT04888767; NTR2092; Pryor 1979; Radtke 2018b; RBR-34677v; RBR-5g9f6w; Reuveny 2020; Ruddy 2015; Spoletini 2020; Ward 2018; White 1997; Young 2019; Zeren 2019), added 12 new studies to "ongoing studies" (Curran 2020; ISRCTN92573472; Monteiro 2019; NCT03273959; NCT03970369; NCT04249999; NCT04543929; NCT04742049; NCT04683809; NCT05147285; NCT05173194; NCT05239611), and added three studies to "awaiting classification" (Cox 2019; IRCT20190407043190N1; NCT04293926).

HISTORY

Protocol first published: Issue 4, 2000
Review first published: Issue 2, 2002

Date	Event	Description
1 November 2017	Amended	Formatting issues resolved
19 October 2017	New citation required but conclusions have not changed	Despite the inclusion of two new studies our conclusions remain the same.
19 October 2017	New search has been performed	A search of the Cystic Fibrosis and Genetic Disorders Review Group's Cystic Fibrosis Trials Register identified 38 new references which were potentially eligible for inclusion in the review. There was one additional reference to an already included study (Schneiderman-Walker 2000) and six additional references to five already excluded studies (Amelina 2006; del Corral Nunez-Flores 2014; Kuys 2011; Lima 2014; Salonini 2015). Six references to two new studies has been included (Beaudoin 2017; Douglas 2015) and seven references to five new studies are listed as 'Awaiting classification' (Housinger 2015; Johnston 2004; Carr 2018a; Mandrusiak 2011; Oliveira 2010). One study with two references is ongoing (Hebestreit 2022) and a total of 16 references to 13 new studies have been excluded (Bieli 2017; Bongers 2015; Calik-Kutukcu 2016; Chang 2015; Dwyer 2017; Giacomodonato 2015; Haynes 2016; Kriemler 2016; Ozaydin 2010; Patterson 2004; Shaw 2016; Vallier 2016; Wheatley 2015). A search of clinicaltrials.gov identified 11 additional studies. Five studies were added to 'Awaiting classification' (NCT00609050; NCT00792194; NCT02552043; NCT03100214; Powers 2016), one study was added under ongoing studies (Bishay 2017a) and five studies were excluded (NCT02277860; NCT02715921; NCT02821130; NCT03117764; NCT02875366). A search of the WHO ICTRN identified three additional studies; one is listed as awaiting classification (ACTRN12617001009303) and two have been added under ongoing studies (Donadio 2017; Gupta 2017a). From this update we have stated a minimum duration of the intervention as being at least two weeks.
15 June 2015	New citation required but conclusions have not changed	Two authors from the original review have stepped down at this update and a new team of authors have taken on the review. The title of the review has been changed from 'Physical training for cystic fibrosis' to 'Physical exercise training for cystic fibrosis' as the new team felt this better reflected the content of the review. Despite the inclusion of new studies and data in this update of the review, the conclusions remain the same.
15 June 2015	New search has been performed	A search of the Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Register identified 32 new references which were potentially eligible for inclusion in this review. Three new studies (one reference each) were included (Roveddder 2014; Santana-Sosa 2012; Santana-Sosa 2014). Two studies previously listed as excluded have been reassessed and moved to included studies with two new references each (although one paper referred to both studies) (Hebestreit 2010; Kriemler 2013). One study has been moved from 'Awaiting classification' to included studies with an additional two references (Hommerding 2015).

Date	Event	Description
		One was an additional reference to an already excluded study (Kuys 2011). A total of 14 new studies (20 references) were excluded (Alarie 2012; Amelina 2006; Asher 1982; Balfour Lynn 1998; del Corral Nunez-Flores 2014; Dwyer 2011; Gruet 2012; Lima 2014; Lowman 2012; Petrovic 2013; Rand 2012; Reix 2012; Salonini 2015; Vivodtzev 2013). One study (one reference) has been listed as 'Awaiting classification' until we are able to obtain further information (Almajan-Guta 2011).
22 May 2012	Amended	Contact details updated.
7 March 2011	New search has been performed	A total of two new references were identified in a search of the Group's CF Trials Register. One study was excluded as it compared Nintendo Wii exercise training to an existing exercise programme and hence did not meet the inclusion criteria (Kuys 2011). The other study did meet the inclusion criteria but outlined in its abstract that recruitment was ongoing and for this reason it has been listed as an ongoing study; results will be included in the review once the study has been completed (Phillips 2008a). In addition some amendments were made to the Background in order to incorporate updated guidelines and a relevant survey.
19 January 2009	Amended	The fourth primary outcome 'mortality' was moved to Secondary outcomes in line with Cochrane Collaboration guidance to limit the number of primary outcomes to three.
5 January 2009	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register did not identify any references to trials which are potentially eligible for inclusion in this review.
12 November 2008	Amended	Converted to new review format.
14 November 2007	Amended	The generic inverse variance method has been used to analyse data which were previously not able to be presented in the 'Statistical Analysis'. The 'Synopsis' has been replaced by a new 'Plain Language Summary'.
14 November 2007	New search has been performed	The search identified 11 new references. Of these, two were additional references to already excluded studies (Albinni 2004; Edlund 1986). The remaining nine studies did not fulfil the inclusion criteria; four of these studies which seemed eligible from the title, have been excluded on the basis of trial design and are listed under 'Excluded studies' (Acquino 2006; Balestri 2004; Orenstein 2004; Stanghelle 1998). The study which was previously listed as 'Awaiting assessment' has been moved to the list of excluded studies after correspondence with the study authors (Hebestreit 2003).
13 November 2007	New citation required and conclusions have changed	Substantive amendment
25 May 2005	New search has been performed	A further article has been included (Klijn 2004).

Date	Event	Description
		The full paper of the trial by Moorcroft (Moorcroft 2004) has also been included. Following publication of this paper, the details about the published abstracts of this trial, previously listed in the 'Characteristics of included studies' table, under Dodd 1998 and Moorcroft 2000 have been listed under Moorcroft 2004. We contacted authors of trials already included in the review regarding confirmation of data and requests for additional data. Their responses have been included in section detailing the search strategy. One trial has been moved from the 'Studies awaiting assessment' section to the 'Excluded studies' section of the review (Tuzin 1998). One trial has been added to the section 'Studies awaiting assessment' section (Hebestreit 2003). The authors have been contacted and have indicated that this study is in preparation for publication.
31 July 2003	Amended	The presentation of the data in MetaView has been re-formatted.
31 July 2003	New search has been performed	The full paper of the Selvadurai trial has now been included, previously only the abstract of this trial was included in the review (Selvadurai 2002). A further two trials added to the 'Excluded studies' section of the review (Barry 2001; Kriemler 2001).

CONTRIBUTIONS OF AUTHORS

The title for the protocol was conceived by the Cochrane Cystic Fibrosis and Genetic Disorders Group.

Both Judy Bradley and Fidelma Moran designed and assisted in writing the protocol and produced the earlier versions of the full review.

For 2015 and 2017 updates, TR and SK were responsible for acquisition of data, analysis and interpretation of data, drafting and critical revision of the manuscript.

For the 2022 update, TR, SS and SJN were responsible for acquisition of data, analysis and interpretation of data, drafting and critical revision of the manuscript. SK and HH provided important methodological input during the preparation of this review.

SJNprovided statistical support for the 2015, 2017 and 2022 updates. All authors provided intellectual input, critically reviewed the manuscript and approved the final version of this updated review.

TR acts as guarantor for this review.

DECLARATIONS OF INTEREST

HH has received financial compensation for travel and accommodation or free meeting participation (or both) at the European Cystic Fibrosis Society conference and the North American Cystic Fibrosis Conference for chairing or presenting at sessions focusing on exercise in cystic fibrosis. For writing an educational booklet on exercise in cystic fibrosis, HH has received money from Novartis. HH is also the lead investigator on one of the studies included in this review (Hebestreit 2010). As he is the lead investigator of the international multicentre trial ACTIVATE-CF (Hebestreit 2022), his institution has received grants from the Mukoviszidose e.V. and a Vertex Innovation Award.

TR was a core study team member of the ACTIVATE-CF trial (Hebestreit 2022). TR has received financial compensation for chairing and presenting at exercise sessions at the European Cystic Fibrosis Society conference. He has also received financial support (travel, accommodation) from Vifor Pharma Switzerland to participate at the European Cystic Fibrosis Society and European Respiratory Society conference.

SK is the lead investigator on one of the studies included in the review (Kriemler 2013), and was a core team member of the ACTIVATE-CF trial (Hebestreit 2022)

SJN declares no known potential conflicts of interest.

SS declares no known potential conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- National Institute for Health Research, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Post hoc changes for the 2022 update

Title of the review

We replaced the previous title of 'Physical exercise training for cystic fibrosis' with 'Physical activity and exercise training in cystic fibrosis'. This change was motivated by the fact that the review includes studies focusing on exercise training – a subcomponent of physical activity – as well as studies focusing more generally on physical activity interventions versus usual care. This is important considering the technological advances in measuring and monitoring daily physical activity with step counters and fitness trackers. So-called 'wearables' are becoming popular tools in physical activity interventions and are used as motivational elements, for individual monitoring and as part of individual goal setting (see examples in Ongoing studies).

Structure of the review

We restructured the review with regard to type of physical activity (including exercise) and duration of the active physical activity programme. Studies in this review are now presented in three categories according to the duration of their active physical activity programme:

1. studies with an active intervention duration of up to and including six months;
2. studies with an active intervention duration longer than six months; and
3. studies implementing a follow-up period (i.e. when participants revert to usual care).

Systematic reviews investigating the effects of behavioural change interventions on changes in physical activity revealed beneficial effects for various populations, and with some indication for differential effects of studies lasting six months and longer (Barrett 2021; Howlett 2019). However, the 'ideal' intervention duration for increasing physical activity and changing behaviour is not available in the literature, and may differ between different populations. We implemented the categories described above, and focused on long-term studies (where the physical activity programme lasted longer than six months) to be able to capture the long-term effects of physical activity and exercise on health outcomes, and to get an overview of the spectrum of potential adverse events and risks associated with physical activity. Moreover, effects on bone health are unlikely to be observed in studies with durations of up to six months. We prioritised the time period of longer than six months' duration to evaluate intervention effects in the meta-analysis and the Summary of findings 1. Additionally, we were interested in the long-term effects of physical activity interventions once the active intervention has ceased. Although we do not focus on behavioural change as an outcome, in a chronic disease such as CF maintaining a level of exercise capacity and physical activity may indicate a change in behaviour in the long term.

We removed the original comparisons of aerobic, anaerobic or a mix of combined aerobic and anaerobic exercise training compared to no exercise training from the review. In fact, no exercise can be considered solely aerobic or anaerobic in regard to energy supply. To date, the vast majority of research in the field of exercise in CF lung disease focuses on combinations of endurance-type and strengthening exercises. Categorisation of physical activity and exercise training studies into aerobic, anaerobic or a combination of aerobic and anaerobic is often not possible and may lead to potential misclassification. Moreover, there is evidence to suggest that both endurance-type and strengthening exercises elicit improvements in exercise capacity in people with CF (Kriemler 2013; Orenstein 2004). Consequently, the main comparison in this updated review is any type of exercise training compared to no exercise training (usual care). Finally, the measurement of physical activity has substantially improved over recent decades, and 'wearables' are more frequently used in exercise research to monitor physical activity and improve adherence. These developments also affect the design of studies, with increasingly more studies applying a partially supervised approach (coaching), including the use of online tools to motivate people with CF to increase their physical activity levels (i.e. irrespective of whether the training regimen is aerobic, anaerobic or a combination of both).

Changes to primary and secondary outcomes

We shortened the list of outcomes to focus on clinically relevant and patient-centred outcomes.

Primary outcomes

With regard to HRQoL, the CFQ and CFQ-R include different quality of life domains (e.g. physical functioning, role/school, vitality, emotion, treatment burden) and three symptoms scales (i.e. weight, respiratory and digestion). The CFQ-R is the most widely used disease-specific instrument to assess HRQoL in CF lung disease and is applied in many pharmacological and non-pharmacological studies, including exercise interventions. We decided to restrict outcomes from this instrument to the respiratory symptom scale, for which a minimal important difference is available (Quittner 2009), and the physical functioning domain as an important patient-reported outcome in physical activity and exercise training studies. The physical functioning domain and the respiratory symptoms scale from the CFQ-R correlate with FEV_1 and maximal exercise capacity measured by cardiopulmonary exercise testing (Hebestreit 2014), both of which are important health-related markers in CF lung disease.

Secondary outcomes

We decided to remove the outcome mortality as it is very unlikely that 'classical' physical activity interventions and exercise training studies with durations of three to 12 months, for example, will report on mortality. People with end-stage CF lung disease (i.e. at a higher risk for lung transplantation, mortality or both) are usually excluded from exercise trials, and FEV_1 is frequently reported as an exclusion criterion (Radtke 2017). We also removed the outcomes anaerobic exercise capacity, antibiotic use, and compliance with physical activity and exercise training from the review.

We reduced outcome measures for body composition (now only reporting BMI) and additional indices of exercise capacity and lung function to the most important and frequently used outcomes in recently published and ongoing physical activity intervention studies. Additional indices of exercise capacity, such as peak heart rate, minute ventilation and lactate during exercise tests, are of limited value and not patient-centred outcomes in exercise trials. Moreover, functional capacity tests such as the 12-minute walk test or 3-minute step test are rarely used in exercise research and we removed them from the list of outcomes. We reduced the outcome 'anaerobic exercise capacity and muscle strength' to quadriceps muscle strength (i.e. isometric strain gauge or dynamometry (or both) measurements and isokinetic dynamometry measurements) as it is feasible, reliable and applied in people with chronic respiratory disease (Maltais 2014). Further, we now only report FVC and have removed other additional indices of lung function because $FEF_{25–75}$ of vital capacity, total lung capacity, functional residual capacity, residual volume, pulmonary diffusing capacity for carbon monoxide and pulmonary diffusing capacity for nitric oxide are less important outcomes for people with CF. Finally, we added hospitalisations (i.e. number of hospitalisations and number of days in hospital) to secondary outcomes as there is evidence that a higher level of physical activity is associated with reduced hospital admission (Cox 2016).

Risk of bias

For the domain 'blinding of participants and personnel (performance bias)', we changed the risk of bias from 'unclear' to 'high risk of bias' as blinding of participants to exercise is not possible.

Post hoc changes for the 2017 update

We added summary of findings tables, in line with Cochrane guidance.

We stipulated that the duration of each included study should be at least two weeks, which is the typical length of (drug) treatment for pulmonary exacerbations where people with CF may also take part in in-hospital exercise training. Moreover, from an exercise physiology perspective, less than two weeks of structured exercise are unlikely to elicit meaningful changes in the chosen outcomes measures.

We added the Lung Clearance Index (LCI) derived from multiple-breath washout to secondary outcome "4. Additional indices of pulmonary function and respiratory muscle strength". The LCI is a relatively new and much examined pulmonary function outcome measure and included in many clinical studies including exercise training interventions.

We also added the diffusing capacity for carbon monoxide (DLCO) and the diffusing capacity for nitric oxide (DLNO) to secondary outcome "4. Additional indices of pulmonary function and respiratory muscle strength". Non-invasive measurement of the pulmonary diffusing capacity can provide novel physiological insights into the exercise training effects on pulmonary function beyond the much examined FEV_1, derived from spirometry.

Post hoc changes for the 2015 update

The title of the review was changed from 'Physical training for cystic fibrosis' to 'Physical exercise training for cystic fibrosis' as the new team felt this better reflected the content of the review.

The fourth primary outcome 'mortality' was moved to secondary outcomes in line with Cochrane guidance to limit the number of primary outcomes to three. For this update, primary and secondary outcome measures were changed as follows:

Primary outcomes

We limited the primary outcome measures to:

1. Exercise capacity by peak oxygen uptake (VO_2 peak);
2. Pulmonary function by forced expiratory volume in one second (FEV_1);
3. Health-related quality of life (HRQoL).

In CF, VO_2 peak and FEV_1 are strong predictors of mortality, objectively measurable and are often used as primary outcomes in studies of exercise training. The outcome measure HRQoL is an important participant-reported outcome measure and is related to physical fitness in people with CF. None of the other primary outcomes from previous reviews has been shown to be of predictive value in CF and they should be considered explorative endpoints. All previous primary outcomes for pulmonary function are now integrated under the secondary outcome number 4 "Additional indices of pulmonary function and respiratory muscle strength", and exercise capacity variables, including effort, oxygenation and fatigue, are integrated into the secondary outcome number 3 " Additional indices of exercise capacity".

Secondary outcomes

We removed the secondary outcomes "Symptom scores", "Compliance with other treatment, such as chest physiotherapy, nutritional regimens" and "Cost evaluation". These outcomes are of unclear relevance, difficult to measure reliably and are rarely reported in physical training studies. We added the secondary outcome "Physical activity" because it is an important outcome in exercise training studies. The outcome "Measures of bone mineral density and diabetic control" was separated into "Bone health" and "Diabetic control" because these outcomes are unrelated and should be studied and reported separately. The outcome "Weight" was removed as a separate outcome and is now integrated within the outcome "Body composition" which comprises all measures of nutrition including bodyweight, body fat and fat-free mass. The secondary outcome "Number of acute exacerbations, intravenous antibiotic courses and time off work or school" was separated as "Acute exacerbations (a) number of exacerbations; (b) time to first exacerbation" and "Antibiotic use (including oral, intravenous or inhaled antibiotics)".

INDEX TERMS

Medical Subject Headings (MeSH)

*Cystic Fibrosis [drug therapy]; Exercise; Forced Expiratory Volume; Quality of Life

MeSH check words

Adolescent; Adult; Humans