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Exercise interventions for adults after liver transplantation (Review)

Pérez-Amate È, Roqué-Figuls M, Fernández-González M, Giné-Garriga M

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Exercise interventions for adults after liver transplantation.
Cochrane Database of Systematic Reviews 2023, Issue 5. Art. No.: CD013204.
DOI: 10.1002/14651858.CD013204.pub2.

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[Intervention Review]

Exercise interventions for adults after liver transplantation

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Editorial group: Cochrane Hepato-Biliary Group.
Publication status and date: New, published in Issue 5, 2023.

Citation: Pérez-Amate È, Roqué-Figuls M, Fernández-González M, Giné-Garriga M. Exercise interventions for adults after liver transplantation. *Cochrane Database of Systematic Reviews* 2023, Issue 5. Art. No.: CD013204. DOI: 10.1002/14651858.CD013204.pub2.

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ABSTRACT

Background

The finding that exercise is inversely related to metabolic syndrome after transplantation is novel and suggests that exercise interventions might provide a means for reducing metabolic syndrome complications in liver transplantation recipients. The use of exercise for increasing the physical activity daily levels by more frequent, higher intensity, and longer duration of training sessions, or the sum of these components may be necessary to counteract the effects of the pretransplant reduced activity, metabolic disturbances, and post-transplant immunosuppression, as well as improve physical function and aerobic capacity following liver transplantation. Regular physical activity has a long-term positive impact on recovery following various surgical procedures including transplantation, giving people the opportunity to return to an active life with their families, in society, and in their professional life. Likewise, specific muscle strength training may attenuate the loss of strength after liver transplantation.

Objectives

To evaluate the benefits and harms of exercise-based interventions in adults after liver transplantation compared to no exercise, sham interventions, or another type of exercise.

Search methods

We used standard, extensive Cochrane search methods. The latest search date was 2 September 2022.

Selection criteria

We included randomised clinical trials in liver transplantation recipients comparing any type of exercise with no exercise, sham interventions, or another type of exercise.

Data collection and analysis

We used standard Cochrane methods. Our primary outcomes were 1. all-cause mortality; 2. serious adverse events; and 3. health-related quality of life. Our secondary outcomes were 4. a composite of cardiovascular mortality and cardiac disease; 5. aerobic capacity; 6. muscle strength; 7. morbidity; 8. non-serious adverse events; and 9. cardiovascular disease post-transplantation. We assessed risk of bias of the individual trials using RoB 1, described the interventions using the TIDieR checklist, and used GRADE to assess certainty of evidence.

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Main results

We included three randomised clinical trials. The trials randomised 241 adults with liver transplantation, of which 199 participants completed the trials. The trials were conducted in the USA, Spain, and Turkey. They compared exercise versus usual care. The duration of the interventions ranged from two to 10 months. One trial reported that 69% of participants who received the exercise intervention were adherent to the exercise prescription. A second trial reported a 94% adherence to the exercise programme, with participants attending 45/48 sessions. The remaining trial reported a 96.8% adherence to the exercise intervention during the hospitalisation period.

Two trials received funding; one from the National Center for Research Resources (US) and the other from Instituto de Salud Carlos III (Spain). The remaining trial did not receive funding.

All trials were at an overall high risk of bias, derived from high risk of selective reporting bias and attrition bias in two trials. The results on all-cause mortality showed a higher risk of death in the exercise group versus the control group, but these results are very uncertain (risk ratio (RR) 3.14, 95% confidence interval (CI) 0.74 to 13.37; 2 trials, 165 participants; I^2 = 0%; very low-certainty evidence). The trials did not report data on serious adverse events excluding mortality or non-serious adverse events. However, all trials reported that there were no adverse effects associated with exercise. We are very uncertain on whether exercise compared with usual care has a beneficial or harmful effect on health-related quality of life assessed using the 36-item Short Form Physical Functioning subscale at the end of the intervention (mean difference (MD) 10.56, 95% CI −0.12 to 21.24; 2 trials, 169 participants; I^2 = 71%; very low-certainty evidence). None of the trials reported data on composite of cardiovascular mortality and cardiovascular disease, and cardiovascular disease post-transplantation. We are very uncertain if there are differences in aerobic capacity in terms of VO_{2peak} at the end of the intervention between groups (MD 0.80, 95% CI −0.80 to 2.39; 3 trials, 199 participants; I^2 = 0%; very low-certainty evidence). We are very uncertain if there are differences in muscle strength at end of the intervention between groups (MD 9.91, 95% CI −3.68 to 23.50; 3 trials, 199 participants; I^2 = 44%; very low-certainty evidence). One trial measured perceived fatigue using the Checklist Individual Strength (CIST). Participants in the exercise group showed a clinically important lower degree of fatigue perception than participants in the control group, with a mean reduction of 40 points in the CIST (95% CI 15.62 to 64.38; 1 trial, 30 participants).

We identified three ongoing studies.

Authors' conclusions

Based on very low-certainty evidence in our systematic review, we are very uncertain of the role of exercise training (aerobic, resistance-based exercises, or both) in affecting mortality, health-related quality of life, and physical function (i.e. aerobic capacity and muscle strength) in liver transplant recipients. There were few data on the composite of cardiovascular mortality and cardiovascular disease, cardiovascular disease post-transplantation, and adverse event outcomes. We lack larger trials with blinded outcome assessment, designed according to the SPIRIT statement and reported according to the CONSORT statement.

PLAIN LANGUAGE SUMMARY

Exercise interventions for adults after liver transplantation

Background

Levels of physical activity tend to decrease in people who receive a liver transplant. The benefits and harms of exercise interventions to protect against the development of heart and lung diseases, hypertension, type II diabetes, dementia, non-alcoholic fatty liver disease (conditions caused by a build-up of fat in the liver), cancer, or other life-threatening diseases which may develop rapidly have not yet been well studied.

What did we want to find out?

We wanted to determine the benefits and harms of exercise in adults after liver transplantation.

What did we do?

We searched medical databases for well-designed clinical trials in liver transplantation recipients comparing any type of exercise with no exercise, sham interventions, or another type of exercise.

What did we find?

We found three randomised clinical trials with 241 participants, of which 199 participants stayed until the end of the trial. A randomised trial is a study where participants are allocated at random (due to chance alone) to an experimental or a control group. The trials were conducted in the USA, Spain, and Turkey. The durations of the exercise were two, six, and 10 months in the different trials. All trials compared exercise-based interventions against usual care. All trials included adults who had received liver transplantation. The three trials assessed various exercise interventions (i.e. aerobic or resistance-based exercises, or both), and with different types of supervision and format (i.e. supervised or not, individual-based or group-based exercise). Aerobic exercise refers to the type of repetitive, structured physical activity that requires the body's metabolic system to use oxygen to produce energy. Aerobic exercise is a sustained exercise that

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increases blood flow to the muscles, strengthening the cardiovascular system and lungs. Resistance training or strength training is a form of physical activity that is designed to improve muscular fitness by exercising a muscle or a muscle group against external resistance. Different forms of resistance training include using free weights, weight machines, resistance bands, and the person's own bodyweight. Usual care consisted of traditional medical intervention with or without recommendations to remain active. The trial sites were at the hospital or at home.

Two trials received funding; one from the National Center for Research Resources and the other from Instituto de Salud Carlos III. The other trial did not receive funding.

We also identified three ongoing trials.

Main results

We are very uncertain whether exercise compared with usual care has a beneficial or harmful effect on death from any cause. Two studies reported eight deaths, which were more frequent in the exercise group. We are very uncertain whether exercise compared with usual care has a beneficial or harmful effect on health-related quality of life at the end of the intervention. We are very uncertain whether there is a difference in effect between exercise versus usual care on aerobic capacity (which indicates the level of cardiovascular (blood vessels and heart) fitness) at the end of the intervention. We are very uncertain whether exercise has an effect regarding muscle strength in people after liver transplantation. One trial reported a higher perception of fatigue in the exercise group.

The trials did not report data on serious or non-serious side effects. However, all trials reported that there were no side effects associated with participants who performed exercise. None of the trials reported data on other cardiovascular measures.

What are the limitations of the evidence?

Caution is needed in interpreting the review findings as the number of included trials is very limited and there were few data provided. We have little confidence in the evidence because it is highly possible that most trials chose to present a subset of results from their study by omitting complete outcomes, as well as in two studies hat presented only a selective dropout of some participants who differed from those who remained in the study. We also found that data on clinically important outcomes were lacking. We are not confident in the evidence of the effect of exercise training that included aerobic, resistance-based exercises, or a combination of both on physical function (that is, aerobic capacity and muscle strength) in liver transplant recipients due to its high uncertainty. We need larger trials with blinded outcome assessment (process of concealing treatment group identity from outcome assessors), designed according to guidance of clinical trial protocols and recommendations for reporting randomised trials.

How up to date is this evidence?

The review includes trials published by 2 September 2022.

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SUMMARY OF FINDINGS

Summary of findings 1. Exercise compared to control for adults after liver transplantation

Exercise compared to control for adults after liver transplantation

Patient or population: adults after liver transplantation
Setting: home or hospital, or both
Intervention: aerobic or strength exercise, or both
Comparison: usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with control	Risk with exercise				
All-cause mortality at end of intervention (range 2–10 months)	19 per 1000	60 per 1000 (14 to 254)	**RR 3.14** (0.74 to 13.37)	155 participants (2 RCTs)	⊕⊖⊖⊖ **Very low**[a,b]	Krasnoff 2006 reported 6 deaths (4 in the intervention group and 2 in the usual care group), but the authors did not report the causes of death. Yüksel Ergene 2022 reported 2 deaths (both in the intervention group). The causes of death were hepatic artery thrombosis and sepsis, which were diagnosed in the presence of multiorgan failure in the first post-transplant week as a surgical complication.
Serious adverse events, excluding mortality (range 2–10 months)	NA		—	(3 RCTs)	—	All trials described there were 0 adverse effects associated with the exercise intervention. There was no measurement of serious adverse effects specified.
Health-related quality of life (SF-36 Physical Functioning subscale) at end of administered interventions (range 6–10 months)	The mean health-related quality of life (SF-36) was 63.4	**MD 10.56 higher** (0.12 lower to 21.24 higher)	—	169 (2 RCTs)	⊕⊖⊖⊖ **Very low**[a,c,d]	Duration of the intervention was 10 months in Krasnoff 2006, and 6 months in Moya-Nájera 2017. Results combined corresponded to the composite SF-36 score in 1 trial, and the Physical subdomain in another.
Aerobic capacity (VO_{2peak}) at end of	The mean aerobic capacity	**MD 0.80 higher** (0.80 lower to 2.39 higher)	—	199 (3 RCTs)	⊕⊖⊖⊖ **Very low**[a,e]	Duration of the intervention was 10 months in Krasnoff 2006, 8 weeks in Yüksel Ergene 2022, and 6 months in Moya-Nájera 2017.

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administered interventions (range 2–10 months)	(VO_{2peak}) was 20.5					
Muscle strength at end of administered interventions (range 2–10 months)	The mean strength was 115.1 Newton	**MD 9.91 higher** (3.68 lower to 23.50 higher)	—	199 (3 RCTs)	⊕⊖⊖⊖ **Very low**[a,f]	Duration of the intervention was 10 months in Krasnoff 2006, 8 weeks in Yüksel Ergene 2022, and 6 months in Moya-Nájera 2017.
Non-serious adverse events (range 2–10 months)	NA	—	—	(3 RCTs)	—	All trials described there were no adverse effects associated with the exercise intervention. The trials specified no measurement of non-serious adverse effects.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **NA:** not applicable; **OIS:** optimal information size; **RCT:** randomised clinical trial; **RR:** risk ratio; **SD:** standard deviation; **VO_{2peak}:** peak oxygen uptake.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a] Risk of bias: trials were at overall high risk of bias (downgraded two levels due to methodological limitations).
[b] Imprecision: the number of participants did not reach the estimated OIS, and the CIs for both relative and absolute estimates of effect include the possibility of significant benefit and appreciable harm which would lead to different clinical conclusions (downgraded two levels). The OIS was estimated to be 766, based on a desired absolute difference of 5% in mortality.
[c] Inconsistency: substantial heterogeneity ($I^2 = 71\%$) which induced differences in the effect estimates obtained using fixed-effect models and random-effects models (downgraded one level).
[d] Imprecision: the number of participants reached the estimated OIS, but the CIs for estimates included the possibility of significant benefit and harm which would lead to different clinical conclusions (downgraded one level). The OIS was estimated to be 92, based on a desired difference of 10 points and an SD of 17.
[e] Imprecision: the number of participants reached the estimated OIS, but the CIs for estimates included the possibility of significant benefit and harm which would lead to different clinical conclusions, and the CIs were very wide due to small sample size (downgraded one level). The OIS was estimated to be 126, based on a desired difference of 9.5 and an SD of 19.
[f] Imprecision: the number of participants failed to reach the estimated OIS, the CIs for estimates included the possibility of significant benefit and harm which would lead to different clinical conclusions, and the CIs were very wide due to small sample size (downgraded two levels). The OIS was estimated to be 284, based on a desired difference of 12% and an SD of 36.

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BACKGROUND

Description of the condition

Levels of physical activity tend to decrease in recipients of liver transplantation (Durstine 2016). Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure (Caspersen 1985). The benefits of physical activity to protect against the development of multiple cardiorespiratory and metabolic illnesses and their complications, as well as malignant diseases, have been well documented (Bianchi 2008). The World Health Organization (WHO) guidelines from 2010 recommend 150 minutes of moderate-intensity or at least 75 minutes of vigorous-intensity aerobic physical activity in a week, or an equivalent combination of moderate- and vigorous-intensity activity accumulating at least 600 metabolic equivalent minutes per week, and muscle-strengthening activities involving major muscle groups on two or more days a week (WHO 2010). Insufficient physical activity in adults results when any of the previous criteria are not met (WHO 2008). Insufficient physical activity is one of the 10 leading risk factors for global mortality. People who are insufficiently physically active have a 20% to 30% increased risk of all-cause mortality compared to those who are sufficiently active (WHO 2020).

It is well established that organ transplantation is an effective therapy for end-stage organ failure, and it is widely practised around the world (Shimazono 2007). Nevertheless, there is a worldwide shortage of available organs, and many patients deteriorate or die while waiting (Dutkowski 2015). According to the Global Observatory on Donation and Transplantation, 32,348 liver transplantations were performed in 2017 (GODT 2017). Many new developments could increase the success of this procedure, which is already one of the major achievements in medicine during the second part of the 20th century (Dutkowski 2015).

Prevention of preliver transplantation disability including maintaining mobility, as well as timely postliver transplantation physical rehabilitation and medical treatments are key elements of successful employment-promoting strategies. Prolonging the working life of liver transplantation recipients would further strengthen the success of transplantation, and this is likely best achieved through multidisciplinary efforts ideally starting even before liver transplantation candidacy (Åberg 2016). Most consistent employment predictors include preliver transplantation employment status, male sex, functional/health status, and subjective work ability (Åberg 2016; Ilmarinen 2004).

The critical period for negative outcomes is during the first six months after liver transplantation: 46% of deaths and 65% of liver transplantations occurred within the first six months after surgery (Adam 2012). Diligent management of modifiable postliver transplantation factors including diabetes, hypertension, and renal insufficiency may impact long-term mortality (Watt 2010). The people who stayed alive beyond six months after liver transplantation have fewer technical complications, infections, and general complications (cerebrovascular, cardiovascular, pulmonary, and renal) (Adam 2012).

Cardiovascular disease is a leading cause of morbidity and mortality amongst people with end-stage failure of non-cardiac organ transplantation (Lentine 2012). A multidisciplinary approach is necessary for the evaluation and management of this cardiovascular situation in liver transplantation recipients (Lentine 2012).

Metabolic syndrome following liver transplantation is significantly higher than estimated for the general population (Kallwitz 2013). The prevalence of metabolic syndrome seemed to be inversely correlated with exercise intensity (Kallwitz 2013). Liver transplantation recipients who have metabolic syndrome after transplantation might be at increased risk of major vascular events after surgery (Laryea 2007). Disorders related to metabolic syndrome are frequent amongst liver transplantation recipients, who are at a higher risk of weight gain (Malik 2010). The greatest weight gain occurs within the first six months after liver transplantation (Richards 2005), which could be attenuated with increased physical activity levels. Weight control is mandatory in liver transplantation recipients to prevent atherosclerosis (Bianchi 2008). Resistance training offers a narrower scope of benefits for metabolic syndrome risk factors in comparison with aerobic exercise alone (Moreno-Cabañas 2021; Ostman 2017). Despite this, resistance training could maintain skeletal muscle mass and resting metabolic rate (Westcott 2012), preventing weight rebound effect of weight loss interventions to treat metabolic syndrome (Moreno-Cabañas 2021).

Although the intensity of fatigue is reduced after liver transplantation, fatigue remained the most distressing symptom one year after surgery (Gross 1999). Furthermore, severe complaints of fatigue in liver transplant recipients are associated with low levels of everyday physical activity (Gross 1999). A hypoactive lifestyle may lead to a negative spiral: hypoactivity leading to a reduction in physical fitness and deterioration of complaints of fatigue, leading to further hypoactivity. Results of another study implied that cardiorespiratory fitness and body composition were impaired in liver transplant recipients and that fitness was related with severity of fatigue (only cardiorespiratory fitness) and quality of life (particularly cardiorespiratory fitness) (van Ginneken 2007).

Description of the intervention

The term 'exercise' is defined as physical activity that is planned, structured, repetitive, and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective (Caspersen 1985). In the present systematic review, we aimed to analyse all types of exercise programmes such as aerobic-based, strength, balance, flexibility, co-ordination or endurance activities, or combinations thereof, undergone by adult recipients of liver transplantation.

Physical activity levels in the majority of solid-organ recipients are lower than the recommended for this population (Langer 2009; Masala 2012; Myers 2003; van den Ham 2005), which results in a highly sedentary and inactive lifestyle (van Adrichem 2016).

Low physical activity levels might have detrimental health effects. Some examples are increased peripheral muscle dysfunction present in all organ recipients in the preoperative period (Slapak 2005; Williams 2012), or a reduction in peak oxygen uptake (VO_{2peak}) ranging from 20% to 50% observed, despite near normal functioning of the transplanted organ (van Adrichem 2016; Williams 2012). Regular physical activity improved maximal workload, VO_{2peak} related to the predicted VO_{2peak} at the anaerobic threshold, and maximal oxygen pulse (Benda 2015).

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Peripheral muscle dysfunction could be aggravated during the postoperative period using immunosuppressive medication (Mitsui 2002; Williams 2012). However, exercise interventions in solid-organ recipients show peripheral adaptations (Mathur 2014), such as improved blood lactate (Kempeneers 1990), mitochondrial function (Guerrero 2005), muscle strength (Vivodtzev 2011), and an increase in oxidative type 1 muscle fibres (Vivodtzev 2011).

Reduced VO_2 levels at anaerobic threshold were correlated to increased mortality during the first 100 days after hepatic transplantation (Epstein 2004). Improvements in the overall VO_2 in exercise training groups showed significantly higher values compared with those treated with standard care (Didsbury 2013).

Exercise programmes initiated early after transplantation could decrease other comorbidities such as hypertension, diabetes, obesity, and hypercholesterolaemia in liver transplantation recipients (Burke 2004; Hüsing 2016; Jiménez-Pérez 2016; Ribeiro Hde 2014). Increased physical activity could also improve frequent physical symptoms in this population, such as weakness, fatigue, loss of range of motion, and joint discomfort (Hunt 1996; Nicholas 1994; Painter 2001; Tarter 1991).

Regular exercise training has been shown to improve 36-item Short Form (SF-36) Physical Function scores of health-related quality of life, especially in people with the lowest levels reported (Painter 2001).

How the intervention might work

It is plausible that more-frequent or higher-intensity or longer duration exercise training (or a combination of these) after liver transplantation might be necessary to counteract the effects of pretransplant inactivity, metabolic disturbances, and post-transplant immunosuppression (Laryea 2007). Exercise training might also improve physical function, and help normalise exercise capacity following liver transplantation. Likewise, specific muscle strength training may result in greater strength gains (Laryea 2007). The literature has defined several ways in which exercise interventions have improved quality of life and functional performance in postoperative liver transplanted adults. Thus, there are many types of exercise-based interventions that can improve quality of life. Physical activity is significantly correlated to a better quality of life after liver transplantation and is associated with less limitation in all physical scores and higher vitality scores (Beyer 1999; Painter 2001).

Regular exercise reduces the risk of chronic metabolic and cardiorespiratory diseases, in part because exercise exerts anti-inflammatory effects (Gleeson 2011). It also appears to improve health-related quality of life by enhancing functional performance in people compromised by poor health (Painter 2001). Physical activity after surgery is also associated with health benefits in addition to quality of life, such as decreased surgical complications and decreased onset of new comorbidities after surgery (Yang 2014). Physical activity levels following transplantation are also an indicator of patients' incidence of disease and capacity to undertake normal daily activities (Painter 2001).

Exercise interventions have beneficial effects on most of the cardiovascular risk factors in people with metabolic syndrome, such as waist circumference, high-density lipoprotein cholesterol, and systolic and diastolic blood pressure. Dynamic endurance training also favourably affects other important cardiovascular risk factors including low-density lipoprotein cholesterol, total cholesterol, body mass index (BMI), and VO_{2peak} values (Pattyn 2013).

People with the lowest anaerobic threshold values had significantly longer hospital stays than people with higher anaerobic threshold values. Also, people with low-quartile VO_{2peak} values had significantly longer intensive care unit stays (Bernal 2014).

People with chronic kidney or liver disease also demonstrate limitations in exercise capacity pretransplant, often due to secondary consequences of disuse such as muscle weakness (Williams 2012), rather than a consequence of their primary disease process (Mathur 2014). Thus, increasing their exercise time could improve their physical function, thereby improving self-reported quality of life.

Fatigue is a major problem in people after liver transplantation (van den Berg-Emons 2006a). A rehabilitation programme consisting of exercise training and physical activity counselling was well tolerated and seemed promising in reducing fatigue and improving fitness amongst liver transplantation recipients (van den Berg-Emons 2014).

The finding that exercise is inversely related to metabolic syndrome after transplantation is novel and suggests that physical activity might provide a means for reducing metabolic syndrome complications in liver transplantation recipients (Duffy 2010).

Aerobic and resistance exercise had a positive effect on the treatment of sarcopenic obesity and dyslipidaemia postliver transplantation. These types of exercises are involved in reducing fat mass and reducing cholesterol and triglyceride levels while increasing muscle mass (Basha 2015). Beyer and colleagues reported that, although the cardiovascular and neuromuscular fitness in liver transplant recipients improved after a supervised exercise programme during the postoperative year, maximal oxygen uptake and muscle strength remained 10% to 20% lower compared to healthy sex- and age-matched individuals (Beyer 1999).

Exercise is related to motivation. Biological, psychological, sensory, and situational factors all interact to influence exercise adherence. Biologically, body composition, aerobic fitness, and the presence of disease influence adherence. Attitudes and beliefs about the importance of exercise play a role in adherence, but so do individuals' expectations about the effects that exercise is having on them personally. Individuals with high levels of self-motivation are more likely to adhere to exercise programmes (Abernethy 2013).

Why it is important to do this review

The European Association of the Study of the Liver (EASL) guidelines recommend physical activity in liver transplantation recipients as part of their therapeutic regimens, with certainty of the evidence of grade III (EASL 2016). Liver transplanted people with osteopenia should perform regular weight-bearing exercise and receive calcium and vitamin D supplementation (grade II-3). EASL suggests that a cardiopulmonary exercise test should be conducted in people with multiple cardiovascular risk factors, and in people older than 50 years. If the target heart rate is not achieved during a standard exercise test, a pharmacological stress test is the test

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of choice (grade II-3). It also states that a healthy diet and regular exercise programmes represent additional effective management options for people with metabolic syndrome (grade III).

Only two non-Cochrane reviews analysed the effects of exercise in people with solid-organ transplantation (Didsbury 2013; Janaudis-Ferreira 2016). However, these reviews do not present any specific conclusions on people with liver transplantation. There have been no previous Cochrane Reviews on the topic either. Therefore, we consider it important to use Cochrane methods to assess the beneficial and harmful effects of exercise interventions in adults after liver transplantation.

OBJECTIVES

To evaluate the benefits and harms of exercise-based interventions in adults after liver transplantation compared to no exercise, sham interventions, or another type of exercise.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised clinical trials with a parallel group design, assessing the effects of exercise interventions in liver transplant recipients. We did not include trials if they did not report on the outcomes of interest to our review. We also considered for inclusion unpublished trials or trials published as abstracts provided that there were data for our review.

We did not expect to find cross-over or cluster randomised trials, and hence, these were not planned for inclusion.

Types of participants

Adults, at least 18 years old, of both sexes, who were recipients of liver transplantation.

Types of interventions

Experimental intervention

- Any type of exercise-based intervention (e.g. aerobic, strength, balance, flexibility, or endurance exercise programmes, or combinations thereof) of any frequency, intensity, and duration, undergone during the first year postliver transplantation.

Control intervention

- No exercise, sham interventions, or another type of exercise. The control intervention could also include usual care. Usual care consisted of traditional medical intervention with or without recommendations to remain active.

Types of outcome measures

We planned to analyse the outcomes at time points as specified below for each outcome. However, the primary time point for our main analyses was the 'end of the intervention'.

Primary outcomes

- All-cause mortality assessed at two time points — at the end of the exercise-based intervention, and at maximum follow-up, as reported by the trial authors — and expressed as the proportion of participants who died in each trial group.
- Serious adverse events (excluding mortality) as reported during and following the intervention and as described by the trial authors.
- Health-related quality of life assessed using validated questionnaires, such as the SF-36, assessed at any endpoint during and following the intervention, as reported by the trial authors.

Secondary outcomes

- Composite of cardiovascular mortality and cardiovascular disease assessed as new cardiovascular events in both groups at maximum follow-up.
- Aerobic capacity assessed with validated tests (e.g. on a treadmill or cycloergometer using a branching protocol), assessed at the end of the exercise-based intervention.
- Muscle strength assessed with handgrip, or other validated tests (e.g. isokinetic muscle function testing system), assessed at the end of the exercise-based intervention.
- Morbidity (e.g. fatigue, metabolic syndrome, body composition, sarcopenia), assessed at the end of the exercise-based intervention, and if applicable, at maximum follow-up, as reported by the trial authors — as the relative risk of developing complications postliver transplant in the intervention and control groups.
- Non-serious adverse events, defined as any adverse event not associated with the surgical intervention, during and following the intervention, and as reported by the trial authors.
- Cardiovascular disease post-transplantation, assessed with new cardiovascular events in both groups at maximum follow-up.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Hepato-Biliary Group (CHBG) Controlled Trials Register (searched internally by the CHBG Information Specialist via the Cochrane Register of Studies Web; 2 September 2022), the Cochrane Central Register of Controlled Trials (2022, Issue 8) in the Cochrane Library, MEDLINE Ovid (1946 to 2 September 2022), Embase Ovid (1974 to 2 September 2022), LILACS (Bireme; 1982 to 2 September 2022), Science Citation Index Expanded (1900 to 2 September 2022), and Conference Proceedings Citation Index – Science (1990 to 2 September 2022). The latter two were searched simultaneously through the Web of Science.

Appendix 1 shows the search strategies with the time spans of the searches.

Searching other resources

We searched the online trial registries ClinicalTrials.gov (ClinicalTrials.gov), European Medicines Agency (EMA; www.ema.europa.eu/ema), WHO International Clinical Trial Registry Platform (www.who.int/ictrp), and the US Food and Drug Administration (FDA; www.fda.gov) for ongoing or unpublished trials on 2 September 2022.

We also searched the reference lists of included trials and contacted experts in the International Society for Physical Activity and Health (www.ispah.org) to identify additional trials for inclusion.

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Data collection and analysis

We performed the review following the instructions in the *Cochrane Handbook for Systematic Reviews of Interventions* for data collection and analysis (Higgins 2021). We performed the analyses using Review Manager 5 (Review Manager 2020).

Selection of studies

Two review authors (EPA and MFG) independently assessed the studies through three stages: 1. title screening; 2. abstract screening; 3. full-text screening.

Two review authors (EPA and MFG) independently coded the studies at each stage of the review process as 'included', 'unclear', or 'excluded'. If they encountered any inclusion or exclusion discrepancies, the two review authors either resolved them by discussion or consulted a third review author (MGG) who acted as arbitrator. We removed duplicate publications. We listed multiple publications on an included trial within the main study ID. We recorded and presented the selection process in a PRISMA flow diagram (Page 2021a; Page 2021b; Panic 2013; Figure 1).

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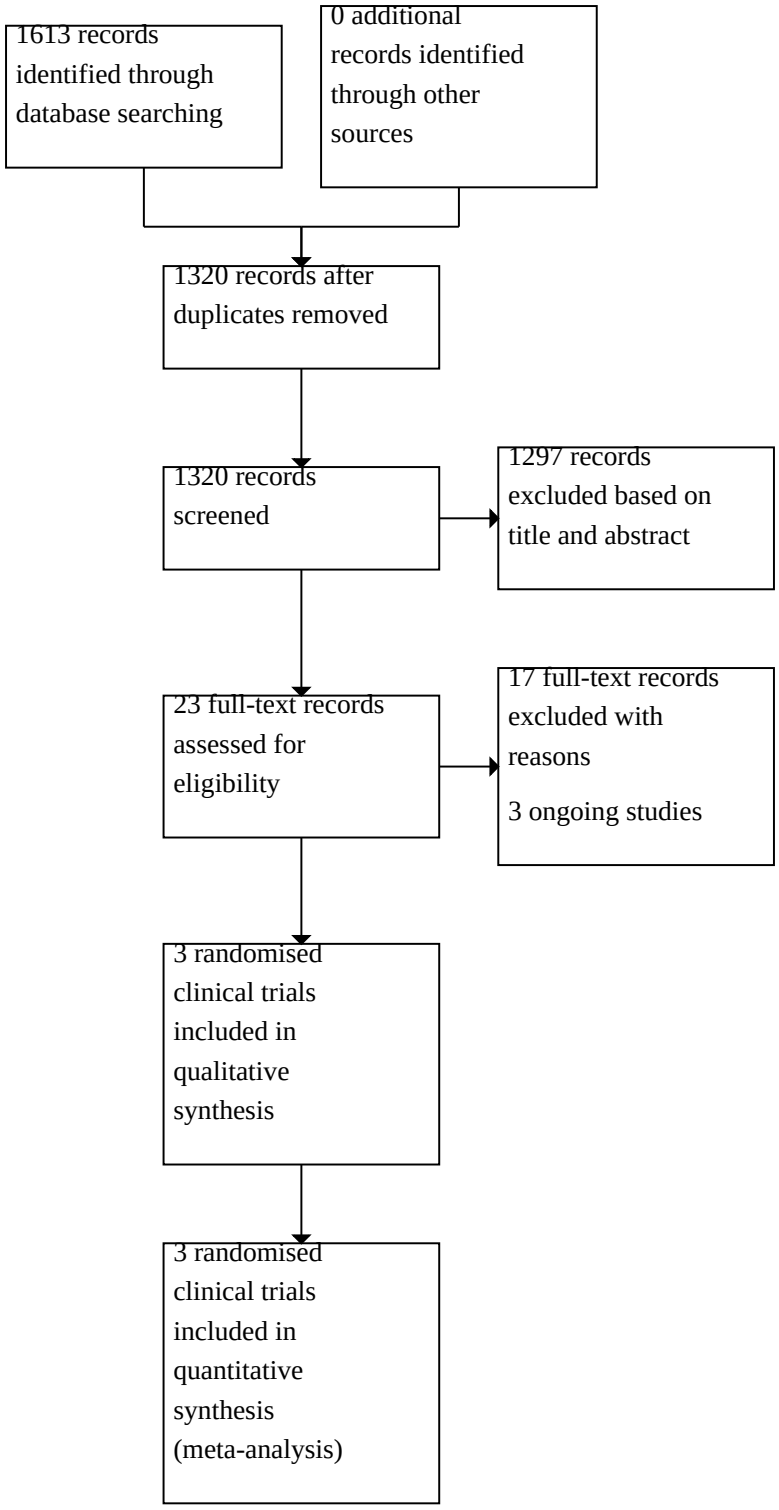
Figure 1. PRISMA flow diagram.



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Whenever we identified quasi-randomised studies or other observational studies of relevance to the participants or interventions of our review, we scanned the publications for data on harms, and we reported these data in a narrative format only, at the end of the Effects of interventions section. We chose to do this because adverse events are rarely reported in randomised clinical trials and because late occurring or rare adverse events can only be found in subsequent publications (Storebø 2018). We are aware that the decision not to search for all observational studies may have introduced bias to our review in terms of assessment of harms.

Data extraction and management

We extracted the following data from the included trials.

- Methodological information: study design, intervention duration, follow-up duration, study date, setting, randomisation characteristics, blinding description (if any), attrition of participants during the study and follow-up, whether the statistical analysis was intention-to-treat.
- Trial protocols: available or not, and where if available.
- Participant information: inclusion and exclusion criteria, sample size, mean age, time after liver transplantation, BMI.
- Intervention information: who delivered the intervention, objective of the intervention, type of exercise, number of sessions, frequency, duration, structure of intervention, setting. We used the template for intervention description and replication (TIDieR) checklist to better describe each intervention (Hoffmann 2014).
- Outcome information: data on both primary and secondary outcomes in the trials.
- Additional information: conflicts of interest; adherence to intervention; information on the nature and extent of any additional actions given as part of the intervention (co-interventions); intervention costs; source of study funding.

We recorded the descriptive data into the Characteristics of included studies table using Review Manager 5 (Review Manager 2020).

Assessment of risk of bias in included studies

We followed the recommendations of the *Cochrane Handbook for Systematic Reviews of interventions* (Higgins 2011), and methodological studies in order to assess the risk of bias in the trials that we identified for inclusion (Kjaergard 2001; Lundh 2017; Moher 1998; Savović 2012a; Savović 2012b; Savović 2018; Schulz 1995; Wood 2008). Specifically, we assessed bias risk as defined below.

We presented our bias risk assessments in Figure 2 and Figure 3 with a direct quote, specific study details, or both. As necessary, we attempted to contact authors of studies to request additional information that we used to assess bias. We documented this in 'Notes' in the risk of bias table.

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

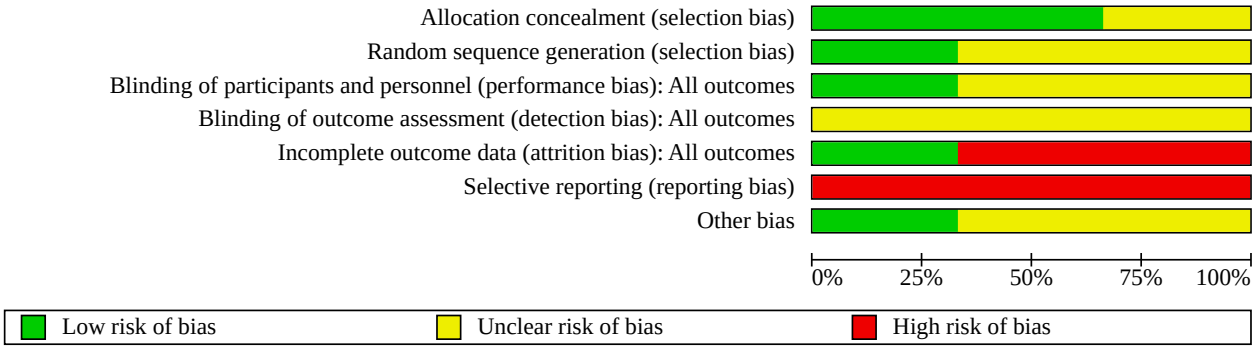

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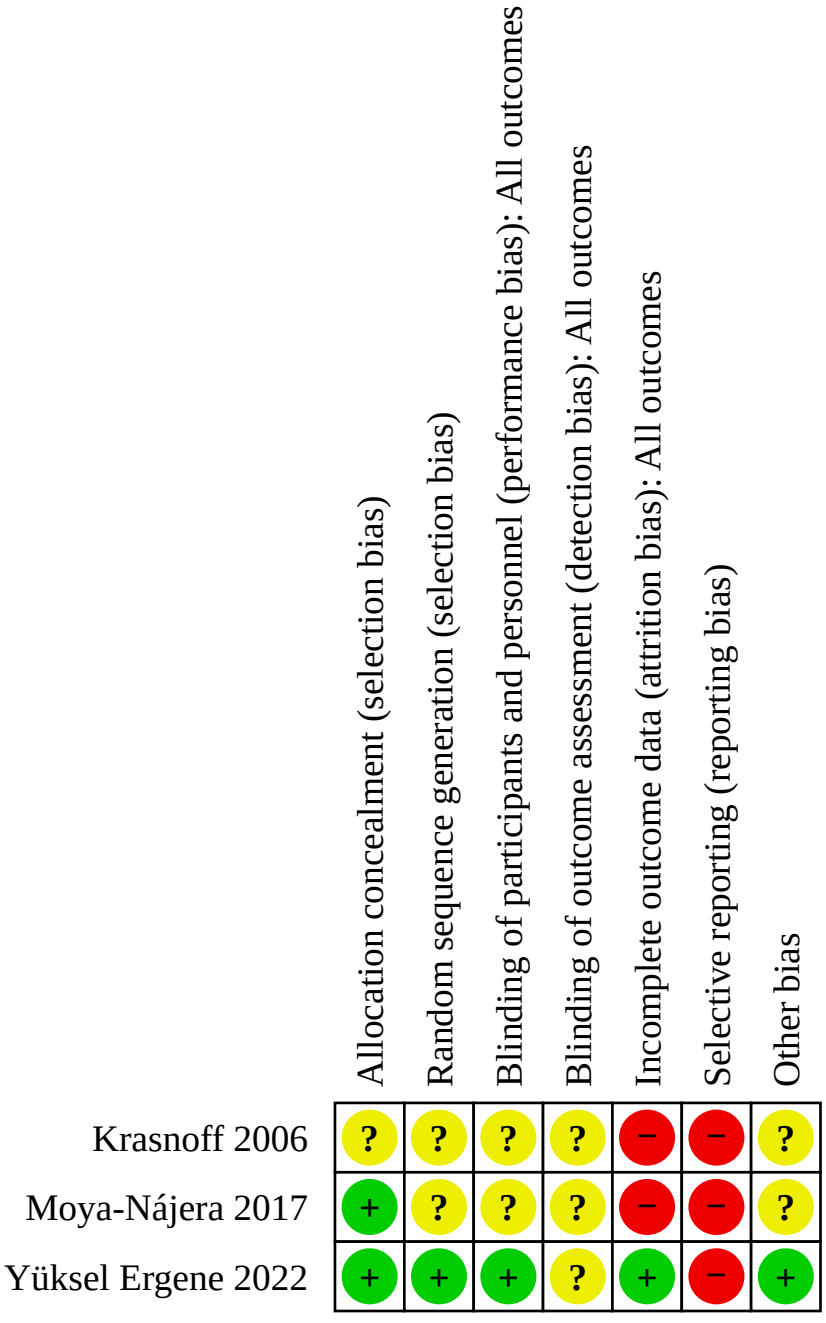
Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation sequence generation (selection bias)

- Low risk of bias: the study performed sequence generation using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, or throwing dice was considered adequate if an independent person not otherwise involved in the study performed them.
- Unclear risk of bias: the study authors did not specify the method of sequence generation.

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- High risk of bias: the sequence generation method was not random. However, no study could be labelled at high-risk since quasi-randomised studies were not included in the review.

Allocation concealment (selection bias)

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. A central and independent randomisation unit controlled allocation. The investigators were unaware of the allocation sequence (e.g. if the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Unclear risk of bias: the study authors did not describe the method used to conceal the allocation, so the intervention allocations may have been foreseen before, or during, enrolment.
- High risk of bias: it is likely that the investigators who assigned the participants knew the allocation sequence.

Blinding of participants and personnel (performance bias)

- Low risk of bias: either blinding of participants and key study personnel was ensured, and it was unlikely that the blinding could have been broken; or rarely that there was no blinding or incomplete blinding, but the review authors judged that the outcome was not likely to be influenced by lack of blinding.
- Unclear risk of bias: either there was insufficient information to permit a judgement of low or high risk, or the trial did not address this outcome.
- High risk of bias: either there was no blinding or incomplete blinding, and the outcome was likely to be influenced by lack of blinding; or blinding of key study participants and personnel was attempted, but it was likely that the blinding could have been broken, and the outcome was likely to be influenced by lack of blinding.

Blinded outcome assessment (detection bias)

- Low risk of bias: either blinding of outcome assessment was ensured, and it was unlikely that the blinding could have been broken; or rarely that there was no blinding of outcome assessment, but the review authors judged that the outcome measurement was not likely to be influenced by lack of blinding.
- Unclear risk of bias: either there was insufficient information to permit a judgement of low or high risk, or the trial did not address this outcome.
- High risk of bias: either there was no blinding of outcome assessment, and the outcome measurement was likely to be influenced by lack of blinding; or there was blinding of outcome assessment, but it was likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.

Incomplete outcome data (attrition bias)

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. The study used sufficient methods such as multiple imputation to handle missing data.
- Unclear risk of bias: there was insufficient information to assess whether missing data, in combination with the method used to handle missing data, were likely to induce bias in the results.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting (reporting bias)

- Low risk of bias: the study reported the following predefined outcomes: all-cause mortality, serious adverse events, and health-related quality of life. If the original trial protocol was available, the outcomes were to be those called for in that protocol. If we obtained the trial protocol from a trial registry (e.g. ClinicalTrials.gov), the outcomes sought were to be those enumerated in the original protocol if the trial protocol was registered before or at the time that the trial was begun. If the trial protocol was registered after the trial was begun, we did not consider those outcomes to be reliable.
- Unclear risk of bias: the study authors did not report all predefined outcomes fully, or it was unclear whether the study authors recorded data on these outcomes or not.
- High risk of bias: the study authors did not report one or more predefined outcomes.

Other bias

- Low risk of bias: the trial appeared free of other bias domains that could have put it at risk of bias (e.g. for-profit funding).
- Unclear risk of bias: the trial may or may not have been free of other domains that could have put it at risk of bias (e.g. for-profit funding).
- High risk of bias: there are other factors in the trial that could have put it at risk of bias (e.g. for-profit funding).

Overall bias assessment

- Low risk of bias: all domains were judged low risk of bias using the definitions described above.
- High risk of bias: one or more of the bias domains judged with unclear or high risk of bias.

Two review authors (EPA and MFG) independently assessed risk of bias. We resolved any disagreements by consensus or, where necessary, by inviting a third review author (MGG or MR) to arbitrate.

Measures of treatment effect

We used risk ratios (RR) as measures of treatment effect for dichotomous outcomes, with 95% confidence intervals (CI). We used mean differences (MDs) as measures of treatment effect for continuous outcomes, with 95% CI. If a continuous outcome was reported in the included trials using different measurement scales, and we could not convert them to a common measurement scale, then we planned to use standardised mean differences (SMD) as the measure of treatment effect (Higgins 2021).

Unit of analysis issues

The liver transplantation recipient as randomised was the unit of analysis in each trial. We did not expect to find and, therefore, did not plan to include cross-over trials or cluster-randomised trials (e.g. where groups are randomised rather than participants). Though highly unlikely, if cross-over trials are identified in future updates, we will use the results from the first period of the cross-over to avoid carry-over effects (Higgins 2022). Though highly unlikely, if cluster-randomised trials are identified in future updates, we will use intracluster correlation coefficients to compute effective sample sizes. We will follow appropriate methods to analyse the trials with such design (Higgins 2022).

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If a trial had reported data for specific outcomes at multiple time points, we planned to analyse the different time points separately. However, the primary time point for the main analysis was 'at the end of the intervention'.

If multiple-arm trials are included in future updates of the review, we will pool data from arms corresponding to different exercise regimens or modalities to be compared with data from the control arms, assess the risk of unit of analysis error and consider this in the assessment of the certainty of the evidence. Additionally, we will conduct stratified analyses by exercise regimen or modality to assess the efficacy of each regimen or modality.

If data on outcomes that may occur more than once (e.g. specific adverse events) are included in future updates of the review, we will extract data from the publications on the first occurrence of the outcome, and if not available, we will contact the trial authors to request these data.

Dealing with missing data

We conducted the review using available-case analysis, that is, an analysis of the data provided by the individual trials. As there were missing numerical outcome data in the trials, we contacted trial authors.

Assessment of heterogeneity

We assessed the trials as clinically homogeneous when the results were similar with regard to participants, interventions, and outcomes. We explored the degree of statistical heterogeneity using the I^2 statistic and Chi^2 test, and the corresponding P value, as well as Tau^2 for random-effects meta-analysis. We interpreted heterogeneity in the following way: no heterogeneity (I^2 = 25% or lower), low degree of heterogeneity (I^2 from 25% to 50%), substantial degree of heterogeneity (I^2 from 51% to 75%), and considerable (extreme) degree of heterogeneity (I^2 = 76% or higher). We draw these categories upon the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). We planned to explore sources of heterogeneity through subgroup analyses; for outcomes showing considerable heterogeneity, we had decided that pooled estimations of effect should be computed anyway, and take into account the degree of heterogeneity as a limitation of the certainty of evidence.

Assessment of reporting biases

In order to investigate the risk of reporting bias, we searched online trial registries and conference proceedings to identify unpublished studies. Given a sufficient number of included trials providing data for a primary outcome (i.e. at least 10), we planned to visually examine funnel plots for signs of asymmetry as recommended in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2021).

Also, to ascertain the risk of other reporting biases, in addition to careful reading of the included trial publications, we tried to find their original protocols or other publications of the same trials in order to identify deviations in the final publications.

Data synthesis

Meta-analysis

When data allowed it, we obtained pooled estimates of effect by combining effect measures with meta-analytic techniques. We meta-analysed the outcomes using the inverse variance method, applying a random-effects model for our main meta-analysis (DerSimonian 1986). We ran the meta-analyses using a fixed-effect model as sensitivity meta-analysis (DeMets 1987). When there were no discrepancies between the two models (e.g. one giving a significant intervention effect, the other no significant intervention effect), we reported only the results from the random-effects model. Otherwise, we planned to report both results.

We planned to perform our analyses at the end of the intervention (primary analysis) and at the end of follow-up.

We used Review Manager 5 provided by Cochrane to conduct the statistical analyses (Review Manager 2020).

Subgroup analysis and investigation of heterogeneity

We planned to perform the following subgroup analyses.

- Trials at overall high risk of bias compared to trials at overall low risk of bias. We aimed to analyse the differences in outcome measures between trials at high risk of selection, attrition, or reporting bias, and trials at low risk of bias (Viswanathan 2017).
- Participants aged less than 50 years old compared to participants aged 50 to 65 years old compared to participants aged more than 65 years old. Incidence of liver transplantation is higher between 50 and 65 years old (EASL 2016). We aimed to explore whether the effect of exercise differed by subgroups of age.
- Intervention during the first six months compared to six to 12 months after liver transplantation.

Sensitivity analysis

We planned to assess the robustness of our conclusions by performing a sensitivity analysis restricted to:

- trials with no missing data on the primary outcomes;
- assessment of imprecision with Trial Sequential Analysis (Castellini 2018).

We had planned to conduct a sensitivity analysis excluding trials with missing data which we were unable to gather; however, this was not possible as all trials had missing data.

Trial Sequential Analysis

We planned to conduct Trial Sequential Analysis for all outcomes.

Cumulative meta-analysis contains a risk of producing random errors due to sparse data and repetitive testing. To minimise random errors, we calculated the required information size (i.e. the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) (Thorlund 2017; TSA 2021; Wetterslev 2008). The diversity-adjusted required information size (DARIS) calculation should also account for the diversity, present in the meta-analysis (Wetterslev 2008; Wetterslev 2009; Wetterslev 2017). A more detailed description of Trial Sequential Analysis can be found at www.ctu.dk/tsa (Thorlund 2017; TSA 2021).

We controlled the risks of type I errors and type II errors for both dichotomous and continuous outcomes (Brok 2008; Brok 2009; Thorlund 2009; Thorlund 2010; Wetterslev 2008; Wetterslev 2009; Wetterslev 2017). For dichotomous outcomes, we estimated the DARIS based on the event proportion in the control group of

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the meta-analysis, an absolute risk increase of 5%, an alpha of 2% because of four primary outcome assessments (one outcome assessed at two time points, and two outcomes assessed at a single time point) and 1.4% because of six secondary outcomes, a beta of 10%, and the observed diversity in the trials in the meta-analysis (Jakobsen 2014; Wetterslev 2017). For continuous outcomes, we estimated the required information size based on the standard deviation observed in the control group of trials at low risk of bias, a minimal relevant difference of 50% of this observed standard deviation, an alpha of 2% because of four primary outcomes and 1.4% because of six secondary outcomes, a beta of 10%, and the observed diversity in the trials in the meta-analysis (Jakobsen 2014). Regarding quality of life, a continuous outcome, we conducted Trial Sequential Analysis as the included trials measured this using the same scale.

We added the trials according to the year of publication, and if more than one trial had been published in a year, we added trials alphabetically according to the last name of the first author. On the basis of the DARIS, trial sequential monitoring boundaries are constructed (Thorlund 2017). These boundaries determine the statistical inference one may draw regarding the cumulative meta-analysis that has not reached the required information size. If the cumulative Z-curve crosses the trial sequential monitoring boundary for benefit or harm before the DARIS is reached, firm evidence may be established, and further trials may be superfluous. In contrast, if the boundary is not surpassed, it is most probably necessary to continue performing trials to detect or reject a certain intervention effect. That can be determined by assessing if the cumulative Z-curve crosses the trial sequential monitoring boundaries for futility.

In Trial Sequential Analysis, we downgrade GRADE imprecision by two levels if the accrued number of participants is below 50% of the DARIS, and one level if it is between 50% and 100% of DARIS. Furthermore, we do not downgrade if the cumulative Z-curve crosses the monitoring boundaries for benefit, harm, or futility, or if DARIS is reached.

Summary of findings and assessment of the certainty of the evidence

We created a summary of findings table using GRADEpro GDT (GRADEpro GDT). We presented outcome results and assessed the certainty of evidence, when possible, on the primary outcomes (i.e. all-cause mortality, serious adverse events, and health-related quality of life), and two of our secondary outcomes (i.e. aerobic capacity and muscle strength). We presented the outcome results at the end of the intervention. Even though 'aerobic capacity' and 'muscle strength' are listed as secondary outcomes, they should be considered patient-important outcomes due to their direct association with performance in daily activities and maintenance of independence. Aerobic capacity was assessed with the treadmill or cycloergometer branching protocol (ACSM 2000).

The GRADE approach appraises the certainty of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed (GRADEpro GDT). The certainty of a body of evidence considers within-study risk of bias, indirectness of the evidence, heterogeneity of the data, imprecision of effect estimates, and risk of publication bias (Balshem 2011; Guyatt 2011a; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2011h; Guyatt 2013a; Guyatt 2013b; Guyatt 2013c; Guyatt 2013d; Guyatt 2017; Mustafa 2013). We estimated the optimal information size for each of the presented outcomes to assess imprecision, following GRADE guidelines (Schünemann 2013). We considered a high relevant clinical important difference of 5% increase for all-cause mortality. We considered moderate clinical important differences of 10 points for health-related quality of life (measured using the SF-36), 9.5 mL/kg/minute for aerobic capacity (measured with VO_2), and 12% for muscle strength. These values are higher than the minimum clinical important differences proposed in the literature (5 points for SF-36 (Ware 1993), +1.5 mL/kg/minute (Wilkinson 2019), and 9% to 10% change in leg-extensor power (Kirn 2016)), representing moderate benefits from the intervention. There were no differences between treadmill and cycle peak tests (Loftin 2004).

We reported any deviations from the published protocol in the Differences between protocol and review section.

RESULTS

Description of studies

See Characteristics of included studies, Characteristics of excluded studies, and Characteristics of ongoing studies tables.

Results of the search

Our searches on 2 September 2022 identified 1613 records (Figure 1). After removal of 293 duplicates, 1320 records remained. We excluded 1297 records based on title and abstract. We assessed 23 full-text records for eligibility. We included three randomised clinical trials (Krasnoff 2006; Moya-Nájera 2017; Yüksel Ergene 2022), excluded 17 full-text publications (Basha 2015; Berzigotti 2016; Cappelle 2021; Dickinson 2016; Garcia 2014; Gitto 2016; Hickman 2021; Katyayani 2019; Maffei 2017; Mandel 2010; Serper 2020; Tandon 2022; Tomás 2010; Tomás 2011; Tomás 2013; Totti 2019; van den Berg-Emons 2006b), and found three ongoing trials (ISRCTN13476586; NCT04246970; NCT04965142).

Amongst the retrieved electronic searches result, we identified one observational study of possible interest to our review which reported no adverse effects of exercise in liver transplantation recipients (Kallwitz 2013).

Figure 1 shows the PRISMA diagram.

Included studies

Trial characteristics

All three were randomised clinical trials, published in English (Krasnoff 2006; Moya-Nájera 2017; Yüksel Ergene 2022). The trials were conducted in the USA, Spain, and Turkey. One of the trials had published protocol (Yüksel Ergene 2022). We contacted the authors of the three trials to request further information on participant characteristics and treatment. We received a response from Moya-Nájera and colleagues and from Yüksel Ergene and colleagues (Moya-Nájera 2017; Yüksel Ergene 2022). See Characteristics of included studies table and Table 1 shows a summary of the interventions and providers in the three trials, following the TIDieR criteria.

All three trials used a parallel group design. The participants in the experimental group in the trial by Yüksel Ergene and colleagues were in hospital during the first two weeks after transplantation

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and were at home from the second until the eighth week of the intervention; the control group received usual care (Yüksel Ergene 2022). The participants in the experimental group in the trial by Moya-Nájera and colleagues were at the hospital and the participants in the control group received instructions to be more active at home (Moya-Nájera 2017). The participants in the experimental group in the trial by Krasnoff and colleagues were at home and the participants in the control group received usual care (Krasnoff 2006).

One trial received no funding (Yüksel Ergene 2022). One trial received funding from the National Center for Research Resources (US) and the other from Instituto de Salud Carlos III (Spain) (Krasnoff 2006; Moya-Nájera 2017).

Participant characteristics

The three trials randomised 241 adults with liver transplantation. However, the number of randomised participants who completed the interventions were as follows: 119/151 participants (Krasnoff 2006), 50/54 participants (Moya-Nájera 2017), and 30/36 participants (Yüksel Ergene 2022), with a total of 199 participants assessed at the end of the intervention. The mean age of participants was in the range of 49.5 (SD 11.3) to 57.1 (SD 7.4) years. The proportion of women was 33.3% (Yüksel Ergene 2022), 16.7% (Moya-Nájera 2017), and 60.5% (Krasnoff 2006). The reported transplantation time ranged between zero and six months. All trials reported a mean BMI indicating normal weight and overweight range of 24.5 kg/m² to 28.4 kg/m²at the beginning of the trials (Krasnoff 2006; Moya-Nájera 2017; Yüksel Ergene 2022). We did not have the BMI values at the end of the interventions.

One trial described the indications for liver transplantation (chronic hepatitis C, cholestatic/autoimmune, chronic hepatitis B, metabolic, fulminate liver failure, alcohol liver disease, and other), but not their frequencies (Krasnoff 2006). One trial described the causes of liver failure in the exercise group: cryptogenic cirrhosis (20%); alcoholic cirrhosis (13.3%); and viral hepatitis, hepatocellular carcinoma, or both (53.33%); and in the control group: cryptogenic cirrhosis (40%) and alcoholic cirrhosis (33.3%) (Yüksel Ergene 2022). The third trial did not report the indications for liver transplantation (Moya-Nájera 2017).

One trial included recipients from living donors (Yüksel Ergene 2022). The other two trials received the livers from dead donors and started the trial after surgery (Krasnoff 2006; Moya-Nájera 2017).

Intervention characteristics

Yüksel Ergene 2022 compared hospital (resistance exercise in the experimental group) with home-based exercise intervention (control group). This trial used standard supervised physiotherapy (i.e. usual care) in both groups.

Moya-Nájera 2017 compared hospital exercise intervention versus usual care with health advice. This trial used aerobic and resistance exercise in the experimental group. The control group received non-controlled (i.e. non-personalised) recommendations for mild physical activity such as walking every day at a low intensity level, but the participants in the control group were not provided with specific instructions about duration, heart rate, or intensity perception.

Krasnoff 2006 compared home-based exercise intervention (aerobic exercise and diet) with usual care (control group).

Overall, in two trials, 71 participants received an aerobic exercise intervention (Krasnoff 2006; Moya-Nájera 2017), and in two trials, 37 participants received resistance exercise intervention (Moya-Nájera 2017; Yüksel Ergene 2022).

The summarised dose of the aerobic exercise was as follows: for frequency: two to three sessions per week; for intensity: 60% to 85% of maximal heart rate (HR_{max}), for time: 30 to 75 minutes, and for type: walking, running, cycling, or combined circuit.

Krasnoff 2006 calculated the intensity of the exercise by incremental progressive cycle-ergometer test. Moya-Nájera 2017 calculated the intensity of the exercise using the Karvonen method (Karvonen 1957). The progression of the intensity was started at 60% HR_{max} in Krasnoff 2006, and at 70% HR_{max} in Moya-Nájera 2017. The progression of the intensity was finished at 80% HR_{max} in Krasnoff 2006, and at 85% HR_{max} in Moya-Nájera 2017. One trial included aerobic and resistance exercise and did not specify the duration of the aerobic part of the session (Moya-Nájera 2017).

The dose of resistance exercise in Moya-Nájera 2017 was: frequency: two to three sessions per week, intensity: moderate up to high, time: 75 minutes, and type: free weights or elastic bands. Yüksel Ergene 2022 prescribed the following resistance exercise dose: frequency: 2 sessions per day and 5 days per week, intensity: light up to moderate, time: 20 minutes, and type: elastic bands.

Moya-Nájera 2017 estimated the intensity of the exercise using the OMNI-RES Scale (Colado 2012) and Yüksel Ergene 2022 using the Borg Scale (Borg 1998). The progression of the intensity was started at three sets for 25 repetitions at a velocity of 2 seconds for each concentric and eccentric contraction and OMNI-RES Scale 5 to 6 (Moya-Nájera 2017). The progression of the intensity was finished at three sets for 15 repetitions at a velocity of 2 seconds for each concentric and eccentric contraction and OMNI-RES Scale 8 to 9 (Moya-Nájera 2017). The resistance exercises were squat, dead lift, rowing, shoulder flexion, shoulder abduction, and chest press (Moya-Nájera 2017). The progression of the intensity was started light to moderate on the Borg Scale (Yüksel Ergene 2022). One trial included aerobic and resistance exercise and did not specify the duration of resistance part of the session (Moya-Nájera 2017).

The duration of the intervention was 10 months in Krasnoff 2006, six months in Moya-Nájera 2017, and two months in Yüksel Ergene 2022.

Follow-up and withdrawals

The three trials assessed participants at end of intervention, with no additional follow-up (Krasnoff 2006; Moya-Nájera 2017; Yüksel Ergene 2022).

In Moya-Nájera 2017, the percentage of dropouts and withdrawals was 7.4% (four participants). In Krasnoff 2006, comparing home-based exercise intervention versus usual care, the percentage of dropouts and withdrawals was 14.6% (22 participants). In Yüksel Ergene 2022, the percentage of dropouts and withdrawals was 16.7% (six participants).

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The three trials used the following adherence strategies: in Krasnoff 2006, each participant in the experimental group received bimonthly follow-up counselling by telephone, postal mail, electronic mail, in person at the clinic, or a combination of these; Yüksel Ergene 2022 telephoned participants weekly to ensure adherence and that there were no adverse effects and a physiotherapist supervised the first two weeks, and in Moya-Nájera 2017, a professional supervised the training sessions. One trial reported that 69% of participants who received the intervention were adherent to the exercise prescription (Krasnoff 2006). Another trial reported a 94% adherence to the exercise programme attending 45 of a total 48 sessions (Moya-Nájera 2017). The remaining trial reported 96.8% adherence (14/450 sessions were not completed) during the hospitalisation period (Yüksel Ergene 2022).

Dealing with missing data

We received two replies to our requests for clarification of missing data (Moya-Nájera 2017; Yüksel Ergene 2022). The trial authors' replies allowed us to assess attrition bias in the trials by ascertaining the reasons for postrandomisation dropouts; the data reported and analysed did not include these participants. Krasnoff 2006 applied a modified intention-to-treat analysis, where participants were analysed according to their randomised group assignment, regardless of adherence to the assigned intervention; however, postrandomisation dropouts were not included in the primary analysis, which included only those participants who had complete data at all testing times.

Excluded studies

We excluded 17 studies. Nine studies were not randomised clinical trials (Cappelle 2021; Dickinson 2016; Garcia 2014; Gitto 2016; Katyayani 2019; Tomás 2011; Tomás 2013; Totti 2019; van den Berg-Emons 2006b), two studies reported insufficient data (Mandel 2010; Tomás 2010), three studies included participants irrelevant to our review (Berzigotti 2016; Hickman 2021; Tandon 2022), one study had an intervention irrelevant to our review (Maffei 2017), and two studies reported outcomes irrelevant to our review (Basha 2015; Serper 2020). See Characteristics of excluded studies table.

Studies awaiting classification

There are no studies awaiting classification.

Ongoing studies

We found three ongoing trials (ISRCTN13476586; NCT04246970; NCT04965142). See Characteristics of ongoing studies table.

Risk of bias in included studies

We present the risk of bias assessment of the three trials in Figure 2 and Figure 3.

Allocation

Allocation concealment

Two trials were at low risk of allocation concealment (Moya-Nájera 2017; Yüksel Ergene 2022). The remaining trial was at unclear risk of bias (Krasnoff 2006).

Random sequence generation

Two trials were at unclear risk of bias regarding random sequence generation (Krasnoff 2006; Moya-Nájera 2017). The remaining trial was at low risk of bias (Yüksel Ergene 2022).

Blinding

We assessed two trials at unclear risk of bias regarding blinding of participants and personnel because neither provided information (Krasnoff 2006; Moya-Nájera 2017). The remaining trial was at low risk of bias because participants, family members, and ward staff were not informed of group allocation (exercise or standard physiotherapy) and analysis was performed by a blinded statistician (Yüksel Ergene 2022). All trials were at unclear risk of bias regarding blinding of outcome assessors (Krasnoff 2006; Moya-Nájera 2017; Yüksel Ergene 2022). This was due to the insufficient information to permit judgement of risk of bias regarding blinding of outcome assessors.

Incomplete outcome data

All included trials had missing data. We judged one trial at low risk of attrition bias (Yüksel Ergene 2022). The remaining two trials were at high risk of attrition bias (Krasnoff 2006; Moya-Nájera 2017).

Selective reporting

Two trials were at high risk of bias regarding selective reporting as we could not find the published protocols. Information on what outcomes were planned to be assessed in these two trials was not reported (Krasnoff 2006; Moya-Nájera 2017). The remaining trial was also at high risk of reporting bias because we found the published protocol but one preplanned outcome (health-related quality of life) was not reported in the published paper (Yüksel Ergene 2022).

Other potential sources of bias

One trial seemed free from for-profit support, and we considered it at low risk of bias (Yüksel Ergene 2022). The other two trials received funding but there was insufficient information to assess whether an important risk of bias existed (Krasnoff 2006; Moya-Nájera 2017).

Effects of interventions

See: **Summary of findings 1** Exercise compared to control for adults after liver transplantation

See Summary of findings 1.

Primary outcomes

All-cause mortality

Two trials provided data on all-cause mortality (Krasnoff 2006; Yüksel Ergene 2022). Krasnoff 2006 did not assess mortality as an outcome, but it was recorded as a reason from dropping out from the study; consequently, the denominators correspond to the number of participants who completed the study (primary analysis population) plus the deceased participants (dropouts). The result on all-cause mortality showed a higher risk of death in the exercise group compared with the control group, but these results were very uncertain (RR 3.14, 95% CI 0.74 to 13.37; 2 trials, 155 participants; I^2 = 0%; very low-certainty evidence; Analysis 1.1).

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Krasnoff 2006 reported four deaths in the experimental (home-based aerobic exercise and diet) group and two in the control group (usual care) at the end of intervention. However, the trial did not report the causes of the deaths, neither during nor after the end of the intervention, so we do not know what these deaths were associated with (i.e. with the exercise intervention, postoperative complications, or other reasons) (Krasnoff 2006). Yüksel Ergene 2022 reported two deaths in the experimental group and none in the control group at end of intervention. The causes of death were hepatic artery thrombosis and sepsis, which were diagnosed in the presence of multiorgan failure in the first post-transplant week as a surgical complication.

Subgroup analysis and investigation of heterogeneity

We could not perform the prespecified subgroup analyses on all-cause mortality by grouping the trials by risk of bias, participants' age, and time since transplantation because the two trials were at an overall high or unclear risk of bias, none presented disaggregated data by age, and both trials administered the interventions in the first six months after liver transplantation (see Subgroup analysis and investigation of heterogeneity; Krasnoff 2006; Yüksel Ergene 2022).

Sensitivity analysis

We could not conduct the sensitivity analysis on all-cause mortality restricted to trials with no missing data because both trials had missing data (Krasnoff 2006; Yüksel Ergene 2022).

We attempted Trial Sequential Analysis for the comparison of exercise versus control and the outcome all-cause mortality at the end of intervention. The accrued information of 165 participants constituted only 0.02% of the DARIS of 791,801 participants. DARIS was calculated based on the mortality rate in the control groups of the meta-analysis, an expected absolute risk difference of 5%, observed diversity of 0%; an alpha of 2%; and a beta of 10% (power = 90%). Given the small amount of information available, it was not appropriate to estimate O'Brian-Fleming boundaries. We downgraded the certainty of evidence two levels as the accrued number of participants was below 50% of the DARIS.

Serious adverse events

None of the trials reported occurrence of serious adverse events. All three trials described there were no adverse effects associated with the exercise intervention (Krasnoff 2006; Moya-Nájera 2017; Yüksel Ergene 2022).

Health-related quality of life

Two trials provided data on health-related quality of life assessed using the SF-36 Physical Functioning subscale (Krasnoff 2006; Moya-Nájera 2017). Self-reported health-related quality of life at end of intervention was higher in the exercise group compared with the control group, but these results were very uncertain (MD 10.56, 95% CI −0.12 to 21.24; 2 trials, 169 participants; I^2 = 71%; very low-certainty evidence; Analysis 1.2).

Subgroup analysis and investigation of heterogeneity

We could not perform the prespecified subgroup analyses grouping the trials by risk of bias, participants' age, and time since transplantation on health-related quality of life because both trials were at an overall high risk of bias, none presented disaggregated data by age, and all trials conducted the interventions in the first six months after liver transplantation (see Subgroup analysis and investigation of heterogeneity; Krasnoff 2006; Moya-Nájera 2017).

Sensitivity analysis

We could not conduct the sensitivity analysis on health-related quality of life restricted to trials with no missing data because both trials had missing data (Krasnoff 2006; Moya-Nájera 2017). Sensitivity analysis of health-related quality of life applying the fixed-effect model led to a similar point estimate, but unreliable significant results (MD 8.77, 95% CI 3.58 to 13.95).

Trial Sequential Analysis was conducted for the comparison of exercise versus control on the outcome health-related quality of life at the end of the intervention. The accrued information of 169 participants constituted only 25.8% of the DARIS of 654 participants. DARIS was calculated based on a desired effect of 10, the observed empirical variance, observed diversity of 76%; an alpha of 2%; and a beta of 10% (power = 90%). The Z-value neither crossed the conventional statistical boundaries of 5% nor the O'Brian-Fleming boundaries. The Trial Sequential Analysis-adjusted 95% CI overlapped with the zone of no effect (MD 0) and was compatible with both a potential benefit and a potential harm; thus, the Trial Sequential Analysis yielded an inconclusive result (figure not shown). These results are in agreement with the GRADE assessment of limitations in evidence due to imprecision.

Secondary outcomes

Composite of cardiovascular mortality and cardiovascular disease

None of the trials reported composite of cardiovascular mortality and cardiovascular disease (Krasnoff 2006; Moya-Nájera 2017; Yüksel Ergene 2022).

Aerobic capacity

Two trials provided data on aerobic capacity in terms of VO_{2peak} (Krasnoff 2006; Moya-Nájera 2017). The remaining trial provided data on aerobic capacity in terms of the 6-Minute Walking Test (Yüksel Ergene 2022); we transformed these results into VO_{2peak}. We are very uncertain about the result of aerobic capacity in terms of VO_{2peak} at the end of the intervention between the treatment and control groups (MD 0.80, 95% CI −0.80 to 2.39; 3 trials, 199 participants; I^2 = 0%; very low-certainty evidence; Analysis 1.3).

Subgroup analysis and investigation of heterogeneity

We could not perform prespecified subgroup analyses for aerobic capacity because all three trials were at an overall high risk of bias, were in the same category of transplantation time (all at six months), and none presented disaggregated data, and data by age (see Subgroup analysis and investigation of heterogeneity; Krasnoff 2006; Moya-Nájera 2017; Yüksel Ergene 2022).

Sensitivity analysis

We could not conduct the sensitivity analysis on aerobic capacity, restricted to trials with no missing data because all three trials had missing data (Krasnoff 2006; Moya-Nájera 2017; Yüksel Ergene 2022).

Trial Sequential Analysis was conducted for the comparison of exercise versus control and outcome VO_{2peak} at the end of intervention. The accrued information of 199 participants

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constituted only 5.9% of the DARIS of 3346 participants. DARIS was calculated based on a desired effect of 9.5, the observed variance for the study with lower risk of bias, the observed diversity of 0%; an alpha of 1.4%; and a beta of 10% (power = 90%). The Z-value neither crossed the conventional statistical boundaries of 5% nor the O'Brian-Fleming boundaries. The Trial Sequential Analysis-adjusted 95% CI overlapped with the zone of no effect (MD 0) and was compatible with both a potential benefit and a potential harm; thus, the Trial Sequential Analysis yielded an inconclusive result (figure not shown). We downgraded the certainty of the evidence two levels due to imprecision as the accrued number of participants was below 50% of the DARIS.

Muscle strength

Three trials provided data on muscle strength. Two trials measured strength using an isokinetic muscle function testing system (Biodex III and Biodex IV, Shirley, New York, USA), using the peak torque (the highest torque produced during the set of repetitions) (Krasnoff 2006; Moya-Nájera 2017). However, Krasnoff 2006 used pound-feet (ft·lb) units and Moya-Nájera 2017 used newtons (N). One trial measured strength using a hand-held dynamometer (Power Track Commander II) (Yüksel Ergene 2022). Yüksel Ergene 2022 used kilograms (kg) units. One newton-metre (Nm) is the torque resulting from a force of 1 N applied perpendicularly to the end of a moment arm that is 1 m long. One newton-metre is equal to approximately 0.738 ft·lb. We converted foot-pound (ft·lb) to newton metre (N·m), and newton metre to newton. Note that the latter conversion assumes the force is applied perpendicularly to the radius of 1 m. We are very uncertain if there are differences in muscle strength at end of intervention between intervention and control (MD 9.91 N, 95% CI −3.68 to 23.50; 3 trials, 199 participants; I^2 = 44%; very low-certainty evidence; Analysis 1.4).

Subgroup analysis and investigation of heterogeneity

We could not perform prespecified subgroup analyses on muscle strength because all three trials were at an overall high risk of bias, were in the same category of transplantation time (all at six months), and none presented disaggregated data, and data by age (see Subgroup analysis and investigation of heterogeneity; Krasnoff 2006; Moya-Nájera 2017).

Sensitivity analysis

We could not conduct the sensitivity analysis on muscle strength, restricted to trials with no missing data because all three trials had missing data (Krasnoff 2006; Moya-Nájera 2017; Yüksel Ergene 2022).

Trial Sequential Analysis was conducted for the comparison of exercise versus control and the outcome muscle strength at the end of intervention. The accrued information of 199 participants constituted only 28.9% of the DARIS of 689 participants. DARIS was calculated based on a desired effect of 12, the observed variance for the study with lower risk of bias, the observed diversity of 48%; an alpha of 1.4%; and a beta of 10% (power = 90%). The Z-value neither crossed the conventional statistical boundaries of 5% nor the O'Brian-Fleming boundaries. The Trial Sequential Analysis-adjusted 95% CI overlapped with the zone of no effect (MD 0) and was compatible with both a potential benefit and a potential harm; thus, the Trial Sequential Analysis yielded an inconclusive result (figure not shown). We downgraded the certainty of the evidence two levels due to imprecision as the accrued number of participants is below 50% of the DARIS.

Morbidity

One trial measured perception of fatigue using the Checklist Individual Strength (CIST) that ranges from 0 to 100 and higher scores indicating a higher level of fatigue. Participants in the experimental group showed a lower degree of fatigue perception than participants in the control group, with a mean reduction of 40.0 points in the CIST (95% CI 15.6 to 64.4; 1 trial, 30 participants) (Yüksel Ergene 2022).

Non-serious adverse events

None of the trials reported serious adverse events. All trials described there were no adverse effects associated with exercise (Krasnoff 2006; Moya-Nájera 2017; Yüksel Ergene 2022).

Cardiovascular disease post-transplantation

None of the trials reported composite of cardiovascular disease post-transplantation (Krasnoff 2006; Moya-Nájera 2017; Yüksel Ergene 2022).

Adverse effects of exercise in recipients of liver transplantation reported in observational studies

Through our searches for randomised clinical trials, we found one observational study which reported no serious and non-serious adverse effects of exercise in recipients of liver transplantation (Kallwitz 2013).

DISCUSSION

Summary of main results

We included three randomised clinical trials with 241 randomised participants (Krasnoff 2006; Moya-Nájera 2017; Yüksel Ergene 2022). The trials were conducted in different countries (the USA, Spain, and Turkey). All trials were at overall high risk of bias. For our meta-analyses, we included quantitative data information from all trials with 199 participants who completed the exercise intervention. As there were only three trials, we could not assess potential publication bias in our meta-analyses via funnel plot asymmetry.

Two trials reported data on all-cause mortality (primary outcome), showing an increase in the risk of all-cause mortality for participants in the experimental group (exercise). We are very uncertain on whether exercise compared with usual care has a beneficial or harmful effect on all-cause mortality. Given that one trial did not report the causes of deaths during and after the intervention (Krasnoff 2006), we are unable to assess if these deaths are associated with the exercise intervention, postoperative complications, or other reasons. One trial reported deaths associated with surgical complications (Yüksel Ergene 2022).

Two trials reported data on health-related quality of life (primary outcome) (Krasnoff 2006; Moya-Nájera 2017). We are very uncertain whether exercise compared with usual care has a beneficial or harmful effect on health-related quality of life assessed using the SF-36 Physical Functioning subscale at the end of the intervention.

None of the trials reported data on serious adverse events, excluding mortality (primary outcome), the composite of

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cardiovascular mortality and cardiovascular disease, proportion of participants with one or more non-serious adverse events, and cardiovascular disease post-transplantation (secondary outcomes). One trial reported differences in the fatigue perception in the experimental group. All trials reported that there were no adverse effects associated with exercise.

All three trials reported data on the secondary outcomes related to aerobic capacity and muscle strength.

One trial compared the effects of aerobic-based exercise combined with a nutritional intervention versus usual care (Krasnoff 2006). One trial compared the effects of aerobic and strength exercise training in the hospital versus general recommendations for mild physical activity (Moya-Nájera 2017). One trial compared the effects of hospital-based resistance exercise training versus usual care (home-based exercise) (Yüksel Ergene 2022).

The Trial Sequential Analysis was compatible with both a potential benefit and potential harm, and yielded an inconclusive result for all-cause mortality, aerobic capacity, health-related quality of life, and muscle strength. The evidence suggests high uncertainty in the results for the three outcomes at end of the exercise intervention between the experimental and control groups (GRADEpro GDT; Santesso 2020). We found no follow-up studies with long-term data after the end of the intervention.

Subgroup analyses were not performed because data were insufficient.

Overall completeness and applicability of evidence

The included trials covered only aerobic exercise, or a combination of aerobic and strength exercise. One trial conducted the exercise programme in hospital, one trial between hospital and home, and one trial conducted the exercise programme at home. The treatment duration was between 2 and 10 months. We performed meta-analysis on two of our predefined primary outcomes, namely, all-cause mortality and health-related quality of life. We could also perform meta-analysis on two of our predefined secondary outcomes, namely, aerobic capacity and muscle strength. We could describe one of our predefined secondary outcomes, namely, morbidity, associated with fatigue perception. We found no trials that reported patient-centred outcomes such as composite of cardiovascular mortality and cardiovascular disease, and cardiovascular disease post-transplantation.

Krasnoff 2006 reported 49 participants receiving home-based exercise whereas Moya-Nájera 2017 included 22 participants in hospital exercise group. Yüksel Ergene 2022 administered the hospital intervention in the first two weeks post-transplantation and home-based exercise from the second to the eighth week. A higher percentage of liver recipients participated in home-based exercise interventions, but there were insufficient data to analyse (and verify) the adherence to the exercise intervention in any of these settings.

Quality of the evidence

Lack of clinically relevant data and risk of bias are serious limitations of our review and findings. The trials did not provide sufficient details to enable us to judge the quality of randomisation (generation of randomisation and allocation sequence); blinding of participants, personnel, and outcomes; or selective outcome reporting bias. Thus, the certainty of the evidence related to our primary outcome health-related quality of life was very low due to imprecision and inconsistency of the evidence.

We could not construct funnel plots because data were derived from a maximum of three trials. The included trials had small sample sizes thus publication bias was considered. Two trials received funding from National Center for Research Resources (US) or from Instituto de Salud Carlos III (Spain), and the other trial did not receive funding.

Potential biases in the review process

To avoid bias during the review process, we performed our systematic review based on Cochrane methodology (Higgins 2011; Higgins 2021). We followed our peer-reviewed and published protocol with predefined participants, interventions, comparisons, outcomes, and time to follow-up (Pérez-Amate 2018). We applied comprehensive search strategies which covered published studies and registered study protocols.

We extracted all available data to perform our predefined analyses, including subgroup and sensitivity analyses.

One observational study, retrieved with the searches for randomised clinical trials, reported no rare late-occurring adverse events (Kallwitz 2013).

One of the limitations of our review was that we could not perform all prespecified subgroup analyses because information data were insufficient.

We conducted Trial Sequential Analyses for the outcomes (all-cause mortality and health-related quality of life (primary outcomes), and aerobic capacity and muscle strength (secondary outcomes)) as sensitivity analysis to compare assessment of imprecision with Trial Sequential Analysis and GRADE (Thorlund 2017; TSA 2021; Wetterslev 2008; Wetterslev 2017). The Trial Sequential Analysis results were in agreement with the GRADE assessment of limitations in evidence due to imprecision.

Our search was conducted in September 2022. It is possible that further studies of relevance to our review could have been published since then (i.e. in addition to the ongoing studies that we found in our search). This must be dealt with in future updates.

Agreements and disagreements with other studies or reviews

We found two non-Cochrane meta-analyses on exercise for people with solid organ transplantation (De Smet 2023; Didsbury 2013). Didsbury 2013 included 15 randomised clinical trials in their meta-analysis, but only one of the trials was in participants after liver transplantation (Krasnoff 2006). This trial is also included in our review. Didsbury 2013 reported benefits in preventing weight gain and reducing the incidence of type 2 diabetes in the population including exercise programmes longer than eight weeks. This meta-analysis did not assess the effects of exercise on patient-centred outcomes such as mortality, adverse events, or health-related quality of life.

De Smet 2023 aimed to assess the effectiveness and safety of exercise training in liver transplant recipients, and concluded that "exercise training in liver transplant recipients is safe, benefits the

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physical function aspect of health-related quality of life, and may lead to improved cardiorespiratory and muscular fitness." Despite having the same objective as our review, they presented substantial differences in the methodology applied and the review conduct that may explain the differing conclusions.

De Smet 2023 included eight alleged randomised clinical trials. Of these, three trials are the ones included in this review, and the other five did not meet our inclusion criteria: three were non-randomised trials (design corroborated by contacting the study authors) (Garcia 2014; Tomás 2011; Tomás 2013); one did not initiate the study intervention within the first year post-transplantation (interquartile range: two to six years) (Hickman 2021); one did not assess any of the outcomes in this review (Basha 2015), and one reported data that were insufficient for our planned analysis (Mandel 2010). The methods to conduct and report our review were more rigorous, as we used the TIDieR guideline (Hoffmann 2014) to describe interventions in sufficient detail to allow their replication, and we assessed the certainty of evidence using the GRADE system.

Several authors have explored the role of exercise in improving outcomes after liver transplantation (Cicognani 2015; Neale 2017; Neuberger 2019; Painter 2001), which also considered that physical activity could reduce the negative impact of post-transplantation in health-related quality of life maintaining a healthy lifestyle, sense of well-being in transplant recipients, as well as a faster return to work and to their family and societal roles (Janaudis-Ferreira 2019). It has been noted that it could be important to involve policy-makers in the design of a preventive strategy model based on the co-operation amongst transplantation centres (i.e. hospital settings), sport medicine centres, and sport facilities to conducting supervised exercise programmes within a multidisciplinary team including physiotherapists and physical activity experts (Beekman 2018; Roi 2014). The literature points to additional outcomes that could benefit from exercise, and that may be considered in future updates to this review. Kömürkara 2022 affirmed that severity of fatigue was lower in the exercise group than in the control group after the progressive relaxation exercises were performed for four weeks. Also, people with end-stage liver disease, hepatocellular carcinoma, or both presented loss of skeletal muscle mass (sarcopenia) and physical deconditioning, both of which worsen patients' quality of life, and negatively impact on the pre- and post-transplant prognosis (Beekman 2018; Carey 2019; Ooi 2019). This latter outcome should be considered in future research. Finally, we did not consider frailty amongst liver transplantation recipients and this could be another important and compelling outcome for future intervention studies in order to improve the design of the exercise programmes. Lai and colleagues analysed a pretransplant Liver Frailty Index as a predictor of post-transplant robustness (Lai 2018). Frailty has recently emerged as a critical determinant in the field of cirrhosis and liver transplantation. An intervention with interactive behavioural interviewing process to engage patients in their care and promoting home exercise (NCT04836923).

Exercise interventions could benefit from being delivered in combination with behaviour change techniques. Beekman and colleagues reported that patients need to be supported and empowered (i.e. identifying barriers and motivations for regular physical activity practise, setting goals, receiving positive feedback) in order for them to be able to care for their healthy lifestyle choices (i.e. physical activity practise) in the long term (Beekman 2018). Serper and colleagues suggested that a home-based exercise programme combined with health engagement questions has the potential to change patient behaviour in transplantation (Serper 2020). Also, a cardioprotective lifestyle intervention delivered via telehealth is feasible for liver transplant recipients and may improve access to specialist care to support metabolic health and wellness after transplant (Hickman 2021). Including these behaviour change techniques may improve the patients' adherence to the intervention, reduce patient dropouts, and enhance regular physical activity practise in the longer term.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence from our systematic review is highly uncertain. There is currently insufficient evidence to suggest prescribing exercise-based interventions for liver transplantation recipients for improving the following outcomes: composite of cardiovascular mortality and cardiovascular disease, and cardiovascular disease post-transplantation. However, all three trials reported that there were no adverse effects associated with exercise in the experimental intervention. Based on two trials, exercise slightly increased health-related quality of life in the experimental groups (GRADEpro GDT; Santesso 2020). One trial reported a reduction in fatigue perception in the participants in the exercise group. Based on the very low-certainty evidence, we do not know the effect of exercise on all-cause mortality, aerobic capacity, and muscle strength in the proportion of participants less than one year after liver transplantation, comparing exercise with no intervention.

Implications for research

This systematic review emphasises the need for larger randomised clinical trials aimed at assessing the benefits and harms of exercise training following liver transplantation. Since blinding of study participants, personnel, and outcomes in randomised trials on exercise training are very difficult to perform, a better methodological approach should be a priority in future trials. More specific and detailed reporting of losses to follow-up should be considered in upcoming studies. In order to minimise methodological heterogeneity and advance knowledge in this field, future trials should consider: 1. collecting outcome measures immediately before and after exercise training intervention and a follow-up of at least six months after the end of the intervention; 2. designing an evidence-based exercise programme including aerobic and resistance training with a minimum duration of six months combined with behaviour change techniques to be able to modify the physical activity behaviour; 3. using validated measurements for physical function outcomes (i.e. aerobic capacity, strength); 4. choosing disease-specific health-related quality of life questionnaires; and 5. reporting the values for each domain that contributes to health-related quality of life as well as the total score obtained from health-related quality of life questionnaires. Exploring other variables such as mortality, adverse effects, or cardiovascular disease derived from the exercise programmes will also be essential. Frailty and sarcopenia outcomes could also improve the quality of interventions. We need larger trials with blinded outcome assessment, designed according to the SPIRIT statement (Chan 2013a; Chan 2013b), and reported according to the CONSORT statement (www.consort-statement.org).

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The three identified ongoing studies, with no data reported to date, on muscle strength exercise with or without aerobic and balance training may add information on peripheral muscle strength, respiratory strength, aerobic capacity, health-related quality of life, morbidity, mortality, or fatigue (ISRCTN13476586; NCT04246970; NCT04965142).

Future research could also consider mixed interventions with relaxation techniques, and nutritional and psychological interventions to improve, for example, health-related quality of life, fatigue, and metabolic syndrome incidence.

ACKNOWLEDGEMENTS

The authors wish to acknowledge the assistance of the editorial team of the Cochrane Hepato-Biliary Group. We specially thank Ms Sarah Louise Klingenberg for conducting the search strategies, and Dr Christian Gluud and Ms Dimitrinka Nikolova for their valuable input. We also would like to thank Jordi Vilaró and Mercè Sitjà for their input in the review process.

The following people from the Cochrane Hepato-Biliary Group Editorial Team or approached by the Cochrane Hepato-Biliary Group Editorial Team were involved in the editorial process of this review.

- Sign-off Editor (final editorial decision): Christian Gluud, Co-ordinating Editor, the Cochrane Hepato-Biliary Group, Denmark
- Contact Editor (provided comments and editorial decision): Brian Davidson, UK
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- Copy Editor (copy editing and production): Anne Lawson, Central Production Service, Cochrane, UK

Cochrane Review Group funding acknowledgement: the Danish State is the largest single funder of the Cochrane Hepato-Biliary Group through its investment in the Copenhagen Trial Unit, Centre for Clinical Intervention Research, the Capital Region, Rigshospitalet, Copenhagen, Denmark.

Disclaimer: the views and opinions expressed in this review are those of the review authors and do not necessarily reflect those of the Danish State or the Copenhagen Trial Unit.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Krasnoff 2006

Study characteristics	
Methods	Study design: randomised clinical trial
Participants	Country: USA Number randomised: 151

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Krasnoff 2006 *(Continued)*

	Postrandomisation dropouts: 32 Revised sample size: 119 Transplantation time: 2 months Mean age: 50 years (EG) and 51 years (CG) Women: 72 (60.5%) Mean BMI: 24.5 kg/m^2 (EG) and 25.3 kg/m^2 (CG) Indications of liver transplantation: chronic hepatitis C, cholestatic/autoimmune, chronic hepatitis B, metabolic, fulminate liver failure, alcohol liver disease, and other All recipients were from living donors: no Adverse effects of exercise: there was no attempt to direct healthier participants into the EG Follow-up: assessment of outcomes at end of intervention (10 months) Setting: home Years of recruitment: from January 1998 and September 2001 Recruitment rate: 51.7% Participants were recruited 2 months after liver transplantation. Participants were tested at 2 (baseline), 6, and 12 months after liver transplantation Inclusion criteria: 2 months after orthotopic liver transplantation from the outpatient transplant clinics at the University of California at San Francisco and California Pacific Medical Center Exclusion criteria: living too far from the medical centre for follow-up; medical complications; death within the first 2 months following orthotopic liver transplantation; language barrier; lost to clinical follow-up; orthopaedic limitations; psychiatric or neurological disorders; absolute contraindications to exercise testing as established by the American College of Cardiology/American Heart Association or the ACSM Dropouts: trial authors grouped the reasons for dropouts as: • illness (2 in the EG vs 3 in the CG) • moved (2 in the EG vs 1 in the CG) • lost to follow-up (1 in the EG vs 2 in the CG) • death (1 in the EG vs 1 in the CG) • missed 6-month assessment (5 in the EG vs 5 in the CG) After 6-month assessment and to 12 months assessment: • death (3 in the EG vs 1 in the CG) • illness (2 in the EG vs 0 in the CG) • lost to follow-up (0 in the EG vs 3 in the CG) Dropouts after randomisation and until the end of treatment: 32 participants Analysis, excluding the dropouts, was performed with 119 participants (49 in the EG and 70 in the CG).
Interventions	Participants were randomly assigned to 2 groups **EG: exercise and diet intervention (49 participants)** Home-based exercise prescription based on recommendations by the US Surgeon General's Report on Physical Activity and Health, CDC, and ACSM. Home-based exercise consisted of cardiovascular exercise

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Krasnoff 2006 *(Continued)*

	(i.e. walking, cycling) ≥ 3 times/week for ≥ 30 minutes starting at 60–65% HR_{max} and progressed to 75–80% HR_{max} or 13–15/20 on the Borg Scale rating of perceived exertion. Dietary intervention based on the National Cholesterol Education Program. Diet modification goals included a caloric balance to attain and maintain ideal bodyweight ± 10% and a total fat intake ≤ 30% of total calories. Fruit and vegetable intake ≥ 5 servings per day and fibre (soluble and insoluble) intake ≥ 25 g/day were also recommended. The aim of the intervention was to improve exercise capacity, muscle strength, body composition, nutritional intake, and quality of life. A clinical exercise physiologist and a registered dietitian delivered the intervention. Duration of intervention: 10 months Intervention costs: no information **CG: usual care (70 participants)**
Outcomes	• All-cause mortality • Exercise capacity • Muscle strength • Body composition • Health-related quality of life • Nutritional assessment
Notes	To maximise adherence, each intervention participant received bimonthly follow-up counselling by telephone, postal mail, electronic mail, in person at clinic, or a combination of these. 69% of participants were adherent to the exercise prescription (cardiovascular exercise, ≥ 3 times per week, ≥ 30 minutes/session, 60–80% HR_{max}) with a minimum of 50% follow-up. Study author contacted: June 2020, but to date, study authors did not provide further details on the intervention. Conflict of interest: not stated Study funding: National Center for Research Resources, MO1RR-0079, US Public Health Service (NIH-NINR R01 NR04120-01A2).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Participants were randomly divided into 2 groups, but the exact randomisation method was not reported.
Random sequence generation (selection bias)	Unclear risk	Method of concealment was not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided on blinding of participants and personnel.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not described whether investigators were blinded to outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	High risk	Of the 151 randomised, 22 dropped out and 10 missed their 6-month testing session. Dropout rates between the groups were similar. There were no differ-

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Krasnoff 2006 *(Continued)*

		ences between the dropouts and those who completed the study in any of the assessed variables at baseline. However, there was a difference in liver function test between those who completed all testing sessions and those who missed a testing session. The authors analysed the participants with complete data at all testing times. There was no imputation of data for those who did not complete all testing sessions.
Selective reporting (reporting bias)	High risk	The study authors did not report all-cause mortality. We found no reference to the protocol of the trial, neither did we find a published protocol on ClinicalTrials.gov.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias existed.

Moya-Nájera 2017

Study characteristics	
Methods	Study design: randomised clinical trial
Participants	Country: Spain Number randomised: 54 Postrandomisation dropouts: 4 Revised sample size: 50 Transplantation time: 6 months Mean age: 57 years (EG) and 55 years (CG) Women: 9 (16.7%) Mean BMI: 28.4 kg/m^2 (EG) and 27.3 kg/m^2 (CG) Indications of liver transplantation: not stated All recipients were from living donors: no Adverse effects of exercise: no significant changes in liver function tests Follow-up: assessed at end of intervention (6 months) Setting: hospital and home Years of recruitment: July 2011 to February 2013 Recruitment rate: 33.3% Inclusion criteria: aged 18–67 years; primary liver transplant within 6 months; ECOG Performance Status ≥ 1 Exclusion criteria: refused to participate; had undergone a combined transplant; history of prior non-liver organ transplant; had undergone retransplantation or split liver non-cirrhotic or cancer indication (exception to hepatocellular carcinoma); had a limiting comorbid disease precluding physical exercise (cardiac disease, orthopaedic limb, motor problems)
Interventions	Participants were randomly assigned to 2 groups **EG: exercise (22 participants)**

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Moya-Nájera 2017 *(Continued)*

	2 sessions/week during 24 weeks in a group and hospital setting. Each session 75 minutes Balance exercise: 3 sets × 30 seconds balance exercise with open eyes using props for instability. Resistance-based exercises performed: squat, dead lift, rowing, shoulder flexion, shoulder abduction, and chest press. Intensity started at 5–6 RPE to 8–9 RPE. • 1–3 months: 3 sets × 25 reps at a velocity of 2 seconds for each concentric and eccentric contraction • 4–6 months: 3 sets × 15 reps at a velocity of 2 seconds for each concentric and eccentric contraction Aerobic exercise: 90-second walk following the Karvonen method (Karvonen 1957), starting at 70–85%. The aim of the intervention was to improve both static and dynamic postural balance, hip extensor strength, agility, and flexibility. The intervention was delivered by a qualified health personnel multidisciplinary group, formed by the clinical team and Exercise Science Professionals. Duration of intervention: 6 months Intervention costs: no information **CG: usual medical care (28 participants)** Guidelines for this usual medical care included non-controlled recommendations for mild physical activity such as walking every day at a low intensity level. Participants were not provided with specific instructions about duration, heart rate, or intensity perception. Cointervention: none
Outcomes	• Aerobic capacity • Muscle strength • Body composition • Health-related quality of life • Blood test results
Notes	94% adherence to exercise programme. Study author contacted: yes, study author provided details on the intervention in June 2020. Conflict of interest: none Study funding: partially funded by the Instituto de Salud Carlos III, Spain

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Random number table.
Random sequence generation (selection bias)	Unclear risk	Method of concealment not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided on blinding of participants and personnel.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described whether investigators were blinded to outcome assessment.

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Moya-Nájera 2017 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	4 dropouts in the exercise group (2 participants with hepatitis C virus recurrent disease and 2 unjustified reasons).
Selective reporting (reporting bias)	High risk	Study authors did not report on serious adverse events and all-cause mortality. We found no reference to the protocol of the trial, neither did we find a published protocol on ClinicalTrials.gov.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias existed.

Yüksel Ergene 2022

Study characteristics	
Methods	Study design: randomised clinical trial
Participants	Identifier: NCT04546048 Country: Turkey Number randomised: 36 Postrandomisation dropouts: 6 Revised sample size: 30 Transplantation time: 6 months Mean age: 52 years (EG) and 55 years (CG) Women: 10 (33.3%) Mean BMI: 26.0 kg/m^2 (EG) and 27.6 kg/m^2 (CG) Indications of liver transplantation: cryptogenic cirrhosis; alcoholic cirrhosis; and viral hepatitis, hepatocellular carcinoma, or both All recipients were from living donors: yes Adverse effects of exercise: 0 adverse events associated with the resistance training programme Follow-up: assessment of outcomes at end of intervention (2 months) Setting: hospital and home Years of recruitment: from September 2018 to June 2019 Recruitment rate: 41.9% Inclusion criteria: aged ≥ 18 years; completed all preoperative physiotherapeutic evaluation procedures; haemodynamically stable and spontaneously breathing postoperatively; could read, write, and understand Turkish Exclusion criteria: comorbid conditions that would affect their exercise performance (e.g. a lung pathology requiring regular use of a bronchodilator or neuromusculoskeletal complications/limitations requiring an assistive device); difficulty following verbal instructions; history of multiorgan transplantation; undergoing retransplantation
Interventions	Participants were randomly assigned to 2 groups. **EG: exercise (15 participants)**

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Yüksel Ergene 2022 *(Continued)*

	Resistance training that targeted deltoid and quadriceps as major limb muscles by using a series of 150-cm long elastic bands that provided increasing intensity and usual medical care. • Training protocol consists of 2–3 sets of 6–10 reps, with 1- to 2-minute rest between sets, and 2 × 20-minute sessions/day conducted 5 days/week • Intensity gradually increased based on individual ability • Exercise load established at a light-to-moderate intensity using Borg Scale • Also comprised functional exercises that started with a half squat (5 reps daily) and progressed to sit-to-stand chair exercises (5 reps twice daily) according to physical fitness level • Setting: 0–2 weeks: hospital; 2–8 weeks: home • Participants were telephoned weekly to ensure adherence and that there were no adverse effects. Duration of intervention: 2 months Intervention costs: no information **CG: usual medical care (15 participants)** Usual medical care consisted of standard supervised physiotherapy follow-up, which was part of the post-transplant care at the study centre: preoperative education and postoperative respiratory physiotherapy, active/active assistive exercises, and early mobilisation. Respiratory physiotherapy included positioning, lung expansion manoeuvres, bronchial hygiene techniques, and incentive spirometer use. Graded early mobilisation was initiated when participants were clinically stable. Participants were advised on coping with daily tasks and educated on a home-based discharge programme, considering individual rehabilitation needs and graded activity principles. Follow-up calls were provided weekly to maintain the 8-week walking and to schedule appointments.
Outcomes	• Muscle strength • Aerobic capacity • Inspiratory and expiratory muscle strength • Physical performance • Fatigue
Notes	96.8% adherence during hospitalisation Study author contacted: yes, study author provided details on the intervention in October 2022. Conflict of interest: none Study funding: no funding received

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Web-based random integer generator (random.org).
Random sequence generation (selection bias)	Low risk	Randomisation performed by an independent researcher, who was not otherwise involved in the study.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, family members, and ward staff were not informed of group allocation; a blinded statistician performed the analysis.
Blinding of outcome assessment (detection bias)	Unclear risk	It was not described whether investigators were blinded to outcome assessment.

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Yüksel Ergene 2022 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Of the 36 participants randomised, 6 dropped out. Dropout rates between the groups were the same. The reasons for dropping out were: 2 participants died, 1 presented mental incompatibility, and 3 were unwilling to continue in the study.
Selective reporting (reporting bias)	High risk	The trial protocol and statistical analysis plan were registered before conducting the research and accepted for publication before unblinding by the Health Sciences Institutional Registry System. The registered protocol (NCT04546048) stated health-related quality of life as a secondary outcome, to be measured by 36-item Short-Form and The Liver Disease Symptom Index 2.0. However, the final publication did not report on this outcome.
Other bias	Low risk	No other bias identified.

ACSM: American College of Sports Medicine; BMI: body mass index; CDC: Centers for Disease Control and Prevention; CG: control group; ECOG: Eastern Cooperative Oncology Group; EG: experimental group; HR_{max}: maximal heart rate; rep: repetition; RPE: rated perceived exertion.

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

Study	Reason for exclusion
Basha 2015	Outcomes irrelevant to our review. Excluded as we did not include trials that did not report on the prespecified outcomes of our review.
Berzigotti 2016	Participant population irrelevant to our review.
Cappelle 2021	Not a randomised clinical trial.
Dickinson 2016	Not a randomised clinical trial.
Garcia 2014	Not a randomised clinical trial. Following personal correspondence with authors on 1 July 2021, we were informed that the study was not randomised: (quote) "Did you publish your protocol before the RCT?" Reply: it was not a randomised trial.
Gitto 2016	Not a randomised clinical trial.
Hickman 2021	Participant population irrelevant to our review. Some of the included participants presented > 1-year post-transplantation.
Katyayani 2019	Not a randomised clinical trial.
Maffei 2017	Intervention irrelevant to our review.
Mandel 2010	Reported data were insufficient. Study described as randomised. However, excluded as the reported data were insufficient for our planned analysis.
Serper 2020	Outcomes irrelevant to our review.
Tandon 2022	Participant population irrelevant to our review.

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Study	Reason for exclusion
Tomás 2010	Reported data were insufficient. Study described as randomised. However, excluded as reported data were insufficient for our planned analysis.
Tomás 2011	Not a randomised clinical trial.
Tomás 2013	Not a randomised clinical trial.
Totti 2019	Not a randomised clinical trial.
van den Berg-Emons 2006b	Not a randomised clinical trial.

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

ISRCTN13476586

Study name	Home-based exercise and motivational programme before and after liver transplantation: ExaLT Trial
Methods	Randomised clinical trial
Participants	Country: UK Estimated enrolment: 266 participants Transplantation time: 0 months Follow-up in months: 2 months Setting: hospital and home Years of recruitment: June 2021 to December 2025 Exclusion criteria: listed for liver transplant due to super-urgent liver transplant (according to the King's College criteria), multiorgan transplantation (e.g. combined liver and kidney transplant), or live-related donor liver transplant; regraft liver transplant; inability to safely comply with the exercise intervention due to severe hepatic encephalopathy (defined as grade 3 or 4; as judged by the principal or nominated co-investigators) or oxygen-dependent hepatopulmonary syndrome; no liver failure, including: liver cancer in the absence of cirrhosis polycystic liver disease or rare metabolic/genetic conditions (e.g. glycogen storage disorders); refusal or lacks capacity to give informed consent to participate in the trial, at the point of study visit 1
Interventions	Eligible participants will be randomised 1:1 to receive either exercise or control. **Exercise group** (133 participants): remotely monitored home-based exercise and theory-based motivation support programme whilst on the liver transplantation waiting list (maximum 12 months) to 24 weeks after liver transplantation. **Control group** (133 participants): patient exercise advice leaflet before and after liver transplantation. The study intervention will be variable due to the unpredictable nature of the timing of liver transplantation (median waiting time 72 days (95% CI 64 to 80) registered between 2018 and 2021). All patients that are transplanted within 52 weeks of randomisation will receive a fixed 24-week intervention after liver transplantation. 2 phases Phase 1: participants will attend the hospital in line with their routine waiting list clinic appointment (where possible), at baseline line (visit 1), weeks 6 (visit 2), 12 (visit 3), 24 (visit 4), 36 (visit 5),

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ISRCTN13476586 *(Continued)*

	and 48 (visit 6). At these visits, a repeat of the baseline assessment, including LFI and DASI, will be undertaken. The results of these assessments, review of the participant exercise diary and discussions with the participant themselves will be used to progress exercises and revise goals of their home-based exercise programme if they are in the intervention arm. The end of the study intervention will be at 52 weeks if the participant has not undergone liver transplantation. At this stage, they will be asked if they wish to continue in the study (data collection). Phase 2: after liver transplantation the trial physiotherapists will review the participant on the postliver transplantation ward, within 48 hours of discharge from ICU.
Outcomes	Primary outcome • Physical Component Score from the SF-36v2 health-related quality of life questionnaire 24 weeks after liver transplantation (scale 0–100) Key secondary outcome • Comprehensive Complication Index 24 weeks after liver transplantation (scale 0–100) Other secondary outcome measures to be assessed at 24 weeks after liver transplantation (unless stated) • Mental Component Score of SF-36v2 health-related quality of questionnaire • LFI, DASI • Preliver transplantation morbidity (United Kingdom Model for End-Stage Liver Disease, Model for End-Stage Liver Disease – Sodium, hospital admissions) and mortality (assessed up to day of liver transplantation) • Postliver transplantation length of ICU/hospital stay and hospital readmissions (frequency, duration (days)) • Postliver transplantation 30-, 90-, 180-, and 365-day mortality • Habitual physical activity levels (daily time spent in light, moderate, and vigorous intensity physical activity) using Actigraph accelerometers • 'Dose' of exercise completed (measure of the frequency, intensity, and duration of exercise) • Adherence to home-based exercise programme (intervention arm only) • Perceptions of the healthcare climate (how need supportive/empowering the physiotherapist is), measured using the Health Care Climate Questionnaire • Basic psychological need satisfaction (i.e. feelings of autonomy, relatedness, competence), measured using the Basic Psychological Need Satisfaction in Exercise Scale • Self-determined motivation to exercise, using Behavioural Regulation in Exercise Questionnaire-2
Starting date	
Contact information	
Notes	Estimated study completion date: December 2025 Study author contacted: exalt@trials.bham.ac.uk

NCT04246970

Study name	Prehabilitation and posttransplant training program in liver transplantation (PreLiveR-T)
Methods	Randomised clinical trial

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NCT04246970 *(Continued)*

Participants	Country: Spain Estimated enrolment: 60 participants Transplantation time: 3 months Follow-up in months: 24 months Setting: hospital and home Years of recruitment: not yet recruiting Exclusion criteria: any orthopaedic, motor, functional, neurological, cognitive, or linguistic limitation that prevents the realisations of the prehabilitation programme; inability to perform psychometric tests; oesophageal varices not treated with ligature or beta-blockers; varicose veins with a high risk of digestive haemorrhage; haemoglobin < 80 g/L; contraindication to weight loading; impossibility to comply with the prehabilitation programme (hospital admission, work, geographical location); multiorgan transplantation and liver retransplantation; refusal or lacks capacity to give informed consent
Interventions	Participants were randomly assigned to 2 groups. **Prehabilitation exercise group** (20 participants): aerobic and strength training for 2 months before liver transplantation. Supervised training programme of 8 weeks and a frequency of 2 days/week. Includes interval aerobic exercise: 5 cycles of 2 minutes at 70% of watts or heart rate of cardiopulmonary exercise testing and 3 minutes of active rest at 40%; peripheral muscle training and balance exercises in a circuit of 10 phases, 10–15 reps, for 1–3 sets (the participants will work at moderate intensity, ≤ 5–6/10 on the modified Borg Scale); inspiratory muscle training through a threshold loading device (2 sessions/day, 3 sets of 15 reps, at 60–70% of the maximum inspiratory pressure (cmH_2O)); ventilatory re-education by an incentive inspirator based on the vital capacity evaluated in the initial spirometry. Both the aerobic modality and the resistance training will increase the intensity of work (heart rate, watts, kilograms or cmH_2O) at 2–5% every 2 weeks complying with the principle of training overload. **Prehabilitation post-transplant exercise group** (20 participants): aerobic and strength training divided into: • prehabilitation (2 months before lung transplantation) • training, divided in 2 successive periods: supervised training (months 3–6 after lung transplantation) and unsupervised training (6–12 months after lung transplantation) • long-term follow-up (2 years after lung transplantation). Prehabilitation will be followed by a post-transplant training programme. In this, the participant will perform supervised exercise (interval aerobic exercise and resistance training) 2 days/week, and a physical exercise programme at home until completing 5 sessions/week in the aerobic modality. In the unsupervised phase, the participant will continue with the learned physical exercise programme, but without supervision, 5 sessions/week (including a minimum of 2 non-consecutive sessions to perform resistance training). **Control group** (20 participants): conventional medical care
Outcomes	• Morbidity • Mortality • Number of hospitalisation days • Number of days with supplementary oxygen therapy or mechanical ventilation, or both • Progression in the activities of daily life • Change in functional capacity: measurement of oxygen uptake • Change in functional capacity: 6-minute walking test • Change in peripheral muscle strength: handgrip strength, quadriceps femoris strength, and biceps brachii strength

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NCT04246970 *(Continued)*

	• Change in respiratory strength • Change in performance on the Short Physical Performance Battery • Change in muscle mass • Change in quality of life
Starting date	
Contact information	
Notes	Estimated study completion date: January 2025 Study author contacted: yes, with no response

NCT04965142

Study name	Feasibility of a home exercise program to manage post-transplant metabolic syndrome
Methods	Randomised clinical trial
Participants	Country: Canada Actual enrolment: 40 participants Transplantation time: 12–18 months (lung and liver recipients) Follow-up in months: 3 months Setting: home Years of recruitment: from August 2021 to January 2023 Exclusion criteria: active cardiovascular disease (recent myocardial infarction, significant coronary artery disease on cardiac catheterisation, heart failure, uncontrolled arrhythmias, chest pain, dizziness, or fainting in the last 3 months); neuromuscular disease or orthopaedic limitations; physically active with ≥ 150 minutes/week of moderate-intensity aerobic activity
Interventions	**Exercise group** (20 participants): home-based exercise group will be asked to exercise 3–5 times/week (≥ 150 minutes of aerobic exercises (i.e. walking, cycling, or treadmill) of at least moderate intensity) and to complete resistance training (resistance bands or free weights) at least twice/week over a 12-week period supervised by an exercise professional. The resistance training will be personalised, aiming for 6–10 exercises targeting the major muscle groups, progressing to 3 sets of 8–12 reps. Participants will receive 1 counselling session on healthy eating and physical activity at start of study and an exercise manual. **Control group** (20 participants): participants will receive 1 counselling session on healthy eating and physical activity at start of study.
Outcomes	Primary outcomes • Recruitment: recruitment-success percentage and reasons for non-participation • Adherence to exercise training: measured using an exercise diary completed by participants and reviewed through weekly communication • Study retention: measuring attrition throughout the intervention • Adverse events during exercise training: throughout study period • Participant satisfaction with exercise training and study participation (exercise group): multiple choice and free form questionnaire assessing the participants' satisfaction • Participant satisfaction with study participation (control group): multiple choice and free form questionnaire assessing participants' satisfaction

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NCT04965142 *(Continued)*

Secondary outcomes

- Total cholesterol: using fasting blood sample
- Triglycerides: using fasting blood sample
- High-density lipoprotein: using fasting blood sample
- Low-density lipoprotein: using fasting blood sample
- Fasting blood glucose: using fasting blood sample
- Haemoglobin A1c: using blood sample, which allows assessment of mean level of blood sugar over the previous 3 months
- Insulin resistance: using the Homeostatic Model Assessment of Insulin Resistance protocol (fasting insulin × fasting blood glucose)
- C-peptide: using blood testing in a subset of participants on exogenous insulin therapy
- C-reactive protein: using blood samples
- Health-related quality of life: using SF-36 Health Survey
- Physical function: using Short-Physical Performance Battery to assess participants' balance, gait speed, and ability to rise from a chair 5 times.
- Physical Activity Questionnaire: using Physical Activity Scale for the Elderly – a short survey created to assess physical activity levels in older adults. Measures frequency, duration, and intensity level of physical activities over 1 week to assign a score ranging from 0 to 793, with higher scores indicating greater levels of physical activity.
- Self-efficacy with exercise training (exercise group): using Exercise Self-Efficacy Scale – a 4-point rating Likert scale in which participants rate their confidence with carrying out their regular physical activities and exercise. Uses a 100-point percentage scale, ranging from 0% (not at all confident) to 100% (highly confident). Higher scores represent higher self-efficacy to exercise.
- Self-efficacy with exercise training (control group): using Exercise Self-Efficacy Scale – a 4-point rating Likert scale in which participants rate their confidence with carrying out their regular physical activities and exercise. Uses a 100-point percentage scale, ranging from 0% (not at all confident) to 100% (highly confident). Higher scores represent higher self-efficacy to exercise.
- Nutritional Questionnaire: using Rapid Eating and Activity Assessment for Patients survey to assess nutrient intake and help with lifestyle counselling. Survey contains 27 questions with higher scores indicating higher diet quality (score range 27–81).
- Lifestyle and Environmental Questionnaire: a questionnaire developed by the study authors' research team to assess familiarity and comfort levels surrounding technology, barriers to exercise, and assess previous experience with exercise. Composed of 10 multiple-choice questions with each question assessed independently.

Other outcomes

- Liver fibrosis: using liver Fibroscan (transient elastography) assessment performed in a subset of liver transplant recipients to assess the degree of liver fibrosis (thickening/scarring of tissues). Fibrosis result measured in kilopascal. Test is optional.
- Fat free mass index: using bioelectrical impedance. Test is optional.
- Body fat mass index: using bioelectrical impedance. Test is optional.
- 12-lead electrocardiogram: measuring p wave, QRS complex, QT interval, T waves, and ST segments to ensure they are within normal limits before starting exercise program. Performed in all study participants.

Starting date	
Contact information	
Notes	Actual study completion date: January 2023 Study author contacted: Dmitry.Rozenberg@uhn.ca

CI: confidence interval; DASI: Duke Activity Score Index; ICU: intensive care unit; LFI: Liver Frailty Index; rep: repetition; SF-36v2: 36-item Short Form version 2.0.

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DATA AND ANALYSES

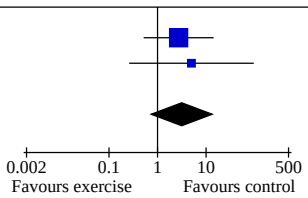
Comparison 1. Exercise versus control interventions for adults after liver transplantation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 All-cause mortality	2	155	Risk Ratio (IV, Random, 95% CI)	3.14 [0.74, 13.37]
1.2 Health-related quality of life (SF-36)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.2.1 End of intervention	2	169	Mean Difference (IV, Random, 95% CI)	10.56 [-0.12, 21.24]
1.3 Aerobic capacity (VO_{2peak})	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.3.1 End of intervention	3	199	Mean Difference (IV, Random, 95% CI)	0.80 [-0.80, 2.39]
1.4 Muscle strength	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.4.1 End of intervention	3	199	Mean Difference (IV, Random, 95% CI)	9.91 [-3.68, 23.50]

Analysis 1.1. Comparison 1: Exercise versus control interventions for adults after liver transplantation, Outcome 1: All-cause mortality

Study or Subgroup	Exercise Events	Exercise Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Krasnoff 2006	4	53	2	72	76.0%	2.72 [0.52 , 14.29]
Yüksel Ergene 2022	2	15	0	15	24.0%	5.00 [0.26 , 96.13]
Total (95% CI)		**68**		**87**	**100.0%**	**3.14 [0.74 , 13.37]**
Total events:	6		2			

Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 1 (P = 0.72); I² = 0%
Test for overall effect: Z = 1.55 (P = 0.12)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Allocation concealment (selection bias)
(B) Random sequence generation (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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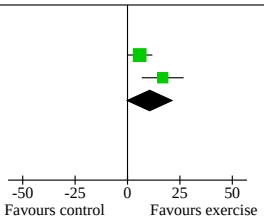
Analysis 1.2. Comparison 1: Exercise versus control interventions for adults after liver transplantation, Outcome 2: Health-related quality of life (SF-36)

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
1.2.1 End of intervention									
Krasnoff 2006 (1)	82.5	8.9	49	76.7	23.6	70	56.8%	5.80 [-0.26 , 11.86]	? ? ? ? − − ?
Moya-Nájera 2017	88.2	10.5	22	71.4	24.2	28	43.2%	16.80 [6.82 , 26.78]	+ ? ? ? − − ?
Subtotal (95% CI)			**71**			**98**	**100.0%**	**10.56 [-0.12 , 21.24]**	
Heterogeneity: Tau² = 42.75; Chi² = 3.41, df = 1 (P = 0.06); I² = 71%									
Test for overall effect: Z = 1.94 (P = 0.05)									
Test for subgroup differences: Not applicable									



Footnotes

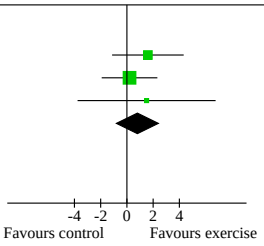
(1) Intervention could be aerobic with or without resistance exercises. Control consisted in traditional medical intervention with or without recommendations to be more active.

Risk of bias legend

(A) Allocation concealment (selection bias)
(B) Random sequence generation (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.3. Comparison 1: Exercise versus control interventions for adults after liver transplantation, Outcome 3: Aerobic capacity (VO_{2peak})

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
1.3.1 End of intervention									
Krasnoff 2006 (1)	24.2	7	49	22.6	8.1	70	34.2%	1.60 [-1.13 , 4.33]	? ? ? ? − − ?
Moya-Nájera 2017	18.8	3.8	22	18.6	3.8	28	56.6%	0.20 [-1.92 , 2.32]	+ ? ? ? − − ?
Yüksel Ergene 2022	15.8	7.2	15	14.3	7.5	15	9.2%	1.50 [-3.76 , 6.76]	+ + + ? + − +
Subtotal (95% CI)			**86**			**113**	**100.0%**	**0.80 [-0.80 , 2.39]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.71, df = 2 (P = 0.70); I² = 0%									
Test for overall effect: Z = 0.98 (P = 0.33)									



Footnotes

(1) Intervention could be aerobic with or without resistance exercises. Control consisted in traditional medical intervention with or without recommendations to be more active.

Risk of bias legend

(A) Allocation concealment (selection bias)
(B) Random sequence generation (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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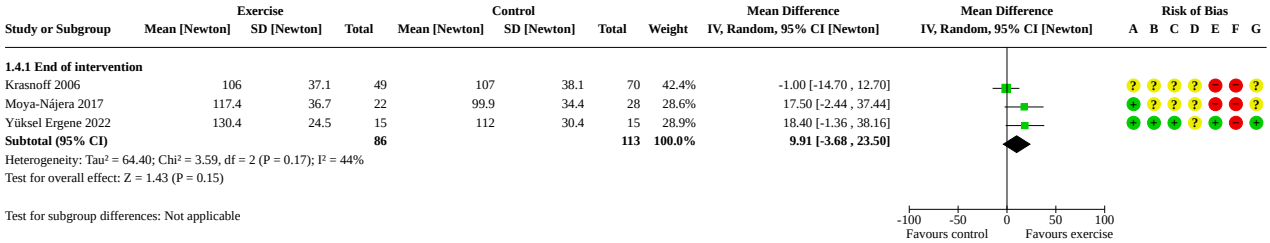
Analysis 1.4. Comparison 1: Exercise versus control interventions for adults after liver transplantation, Outcome 4: Muscle strength



Risk of bias legend
(A) Allocation concealment (selection bias)
(B) Random sequence generation (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

ADDITIONAL TABLES

Table 1. Characteristics of each intervention – summarised using TIDieR criteria

Item	Yüksel Ergene 2022	Moya-Nájera 2017	Krasnoff 2006
Brief name	Resistance exercise	Aerobic and resistance exercise	Aerobic exercise and diet
What (materials and procedures) **and progression**	Intensity: 150-cm long elastic bands that provided increasing intensity. Intensity was gradually increased based on individual ability. Exercise load was established at a light-to-moderate intensity using the Borg Scale. Type: exercises were applied in the chair-sitting position (recommended) or sitting on the edge of the bed. The training programme also comprised functional exercises that started with a half squat (5 reps daily) and progressed to sit-to-stand chair exercises (5 reps twice daily) according to the physical fitness level.	**Aerobic** Intensity: 90-second walk following the Karvonen method, starting at a calculated intensity of 70% at baseline, increasing by 2.5% every month until they reached 85% at end of study. Type: walking, combined circuit **Resistance** Intensity: started at 5–6 on the RPE scale and increased 1 point every 2 months, finishing at 8–9. 6–9 months: 3 sets × 25 reps at velocity 2 seconds for each concentric and eccentric contraction. 9–12 months: 3 sets × 15 reps at velocity 2 seconds for each concentric and eccentric contraction squat, dead lift, rowing, shoulder flexion, shoulder abduction, and chest press.	Intensity: began at 60–65% HR_{max} to 75–80% or a 13–15/20 RPE Type: walking, cycling

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Table 1. Characteristics of each intervention – summarised using TIDieR criteria *(Continued)*

		Type: elastic bands	
Who provided	Researcher – physiotherapist	A qualified health personnel multidisciplinary group that included a sport science professional as trainer.	Clinical exercise physiologist. The exercise prescription was based on recommendations by the US Surgeon General's Report on Physical Activity and Health, CDC and ACSM
Where	Intervention from 0 to 2 weeks and exercise tests at Organ Transplantation Centre of Memorial Ataşehir Hospital, Turkey.	Intervention and exercise tests at La Fe Hospital, Spain.	Intervention at home and exercise test at University of California at San Francisco and California Pacific Medical Center, USA.
When and how much	Frequency: 2 sessions/day and 5 days/week Time: 20 minutes/session	Frequency: 2 sessions/week Time: 75 minutes/session	Frequency: ≥ 3 sessions/week Time: ≥ 30 minutes/session
Tailoring	Progression of interventions depended on participant exercise tolerance. The study did not specify the planning of this progression.	Progression of interventions depended on participant exercise tolerance.	Progression of interventions depended on participant exercise tolerance. The study did not specify the planning of this progression.
Modification of intervention throughout trial	Not reported	Not reported	Not reported
Fidelity (strategies to improve)	Participants were telephoned weekly to ensure adherence and that there were no adverse effects.	Supervised exercise sessions enhanced adherence	Each intervention participant received bimonthly follow-up counselling by telephone, postal mail, electronic mail, in-person at clinic, or a combination of these. The contact strategy for participants differed, depending on what was most convenient and effects with each participant. Each follow-up counselling session included a review of current behaviours (based on logs and diaries), recommendations for programme progression, new goal setting, discussion of problems (i.e. muscle soreness) and barriers (i.e. illness or holiday), with suggestions for changes and encouragement for continued participation. In addition, a biannual newsletter including exercise and nutrition-related information and tips for adherence was mailed to the exercise participants. All participants received parking reimbursement for the 3 testing sessions.
Fidelity (extent)	96.8% adherence (14/450 were not completed) during hospitalisation.	94% adherence to the exercise programme (45/48 sessions attended). Dropouts 4/26 in exercise group and 0/28 in control group.	Adherence was determined across the entire 10-month study period from exercise logs, 3-day food diaries and telephone follow-ups. They created an arbitrary classification of adherence that required ≥ 50% adherence to both the exercise prescription and the diet recommendations. Participants with < 50% adherence to the exercise and dietary prescriptions were classified as non-adherers.

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Table 1. Characteristics of each intervention – summarised using TIDieR criteria *(Continued)*

	The result was 37% of adherence in intervention group. Dropouts: 16/65 in exercise group and 16/86 in control group. Authors did not report reasons for deaths during and after the interventions.

ACSM: American College of Sports Medicine; CDC: Centers for Disease Control and Prevention; HR_{max}: maximal heart rate; rep: repetition; RPE: rated perceived exertion.

APPENDICES

Appendix 1. Search strategies

Database	Time span	Search strategy
Cochrane Hepato-Biliary Group Controlled Trials Register (searched via the Cochrane Register of Studies Web)	2 September 2022	(exercise* or physical activit* or training or (oxygen and (uptake or consumption))) AND ((liver or hepat*) and (transplant*or graft*))
Cochrane Central Register of Controlled Trials in the Cochrane Library	2022, Issue 8	#1 MeSH descriptor: [Exercise] explode all trees #2 (exercise or physical activit* or training or (oxygen and (uptake or consumption))) #3 #1 or #2 #4 MeSH descriptor: [Liver Transplantation] explode all trees #5 (liver or hepat*) and (transplant* or graft*) #6 #4 or #5 #7 #3 and #6
MEDLINE Ovid	1946 to 2 September 2022	1. exp Exercise/ 2. (exercise or physical activit* or training or (oxygen and (uptake or consumption))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 3. 1 or 2 4. exp Liver Transplantation/ 5. ((liver or hepat*) and (transplant* or graft*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 6. 4 or 5 7. 3 and 6 8. (randomized controlled trial or controlled clinical trial).pt. or clinical trials as topic.sh. or trial.ti. 9. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, original title, name of substance word, subject

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(Continued)

		heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 10. 7 and (8 or 9)
Embase Ovid	1974 to 2 September 2022	1. exp exercise/ 2. (exercise or physical activit* or training or (oxygen and (uptake or consumption))).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 3. 1 or 2 4. exp liver transplantation/ 5. ((liver or hepat*) and (transplant* or graft*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 6. 4 or 5 7. 3 and 6 8. Randomized controlled trial/ or Controlled clinical study/ or trial.ti. 9. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 10. 7 and (8 or 9)
LILACS (Bireme)	1982 to 2 September 2022	(exercise$ or physical activit$ or training or (oxygen and (uptake or consumption))) [Words] and ((liver or hepat$) and (transplant$ or graft$)) [Words]
Science Citation Index Expanded (Web of Science)	1900 to September 2022	#5 #4 AND #3 #4 TI=(random* or blind* or placebo* or meta-analys* or trial*) OR TS=(random* or blind* or placebo* or meta-analys*) #3 #2 AND #1 #2 TS=((liver or hepat*) and (transplant* or graft*)) #1 TS=(exercise or physical activit* or training or (oxygen and (uptake or consumption)))
Conference Proceedings Citation Index – Science (Web of Science)	1990 to 2 September 2022	#5 #4 AND #3 #4 TI=(random* or blind* or placebo* or meta-analys* or trial*) OR TS=(random* or blind* or placebo* or meta-analys*) #3 #2 AND #1 #2 TS=((liver or hepat*) and (transplant* or graft*)) #1 TS=(exercise or physical activit* or training or (oxygen and (uptake or consumption)))

HISTORY

Protocol first published: Issue 11, 2018

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CONTRIBUTIONS OF AUTHORS

EPA drafted the protocol, extracted the data, participated in the analysis, and drafted the review.

MRF drafted the protocol, performed the analysis, and drafted the review.

MFG extracted the data, and revised the review.

MGG drafted the protocol, extracted the data, drafted the review, and revised the review.

All review authors approved the current review version to be published.

DECLARATIONS OF INTEREST

EPA: none.

MRF: none.

MFG: none.

MGG: none.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Capital Region, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

  Help with review preparation

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We updated and modified text for a better clarity.

We changed the formulation of the outcomes "loss of aerobic capacity" and "loss of muscle strength" to "aerobic capacity" and "muscle strength".

We rewrote the text in Why it is important to do this review.

We removed 'for-profit bias' as a separate risk of bias domain, and we considered 'for-profit support', as part of Other bias.

We moved Trial Sequential Analysis text into Sensitivity analysis.

We added text on GRADE and the summary of findings table.

We defined the intervention in the control group as 'usual care,' which consisted of traditional medical intervention with or without recommendations to walk, at low intensity, at home.

We dismissed Clavien-Dindo classification for description of serious adverse effects because it reported surgical complications, and we introduced the reported serious adverse effects described in the studies.

At the review stage, we removed the two exploratory outcomes 'Separately reported serious adverse events', and 'Separately reported non-serious adverse events' because of latest Cochrane recommendations on exploratory outcomes.

We deleted the *Assessment of significance* that were defined in the protocol.

We did not perform the subgroup analysis as planned (intervention during the first six months compared to six to 12 months after liver transplantation) because the three included trials did not specify the exact months of participants post-transplantation.

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INDEX TERMS

Medical Subject Headings (MeSH)

*Cardiovascular Diseases [prevention & control]; Exercise Therapy [adverse effects]; Fatigue [etiology]; *Liver Transplantation [adverse effects]; *Metabolic Syndrome [complications]; Quality of Life

MeSH check words

Adult; Humans

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