META-ANALYSIS

The effects of exercise training in adult solid organ transplant recipients: A systematic review and meta-analysis

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ABSTRACT

Reduced exercise capacity can predispose solid organ transplant (SOT) recipients to higher risk of diabetes, cardiovascular complications, and mortality and impact their quality of life. This systematic review and meta-analysis investigated the effects of exercise training (versus no training) in adult SOT recipients. We conducted an electronic search of randomized controlled trials reporting on exercise interventions in SOT recipients. Primary outcomes were exercise capacity, quadriceps muscle strength, and health-related quality of life (HRQoL). Twenty-nine articles met the inclusion criteria. In 24 studies, there were either high risk of bias or some concerns about the potential risk of bias. There was an increase in exercise capacity (VO_2 peak) (SMD: 0.40; 95%CI 0.22–0.57; $P = 0.0$) and quadriceps muscle strength (SMD: 0.38; 95%CI 0.16–0.60; $P = 0.001$) in the exercise vs control groups. There were also improvements in several domains of the SF-36. Diastolic blood pressure improved in the exercise group compared to controls (SMD: −0.22; 95%CI −0.41–0.03; $P = 0.02$). Despite the considerable variation in exercise training characteristics and high risk of bias in the included studies, exercise training improved maximal exercise capacity, quadriceps muscle strength, HRQoL, and diastolic blood pressure and should be an essential part of the post-transplant care.

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Key words
exercise, exercise capacity, HRQoL, solid organ transplant, transplantation

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Introduction

Although transplantation provides individuals with end-stage diseases of the heart, lung, kidney, pancreas, or liver with a second chance of life and the opportunity to regain physical function and improve their health-related quality of life (HRQoL), these individuals continue to experience impaired exercise capacity [1] and low levels of physical activity (PA) [2,3] after transplantation. Impaired exercise capacity and low levels of PA can predispose transplant recipients to a higher risk of diabetes, cardiovascular complications, and mortality [4,5], and impact their HRQoL and ability to return to work [1,6,7].

Exercise training improves exercise capacity, muscle strength, glycemic control, and cardiovascular risk factors across many chronic diseases [8]. In recent years, there has been an increased number of publications on exercise interventions following solid organ transplantation (SOT) [9,10]. Most of these studies are limited by small sample size and were conducted on recipients of a single transplant type (i.e., organ specific) [9]. The literature across transplant types suggests that exercise intolerance is not completely related to the pretransplant condition and that many of the factors that affect exercise capacity following transplant are common across transplant types [1]. These factors include deconditioning, skeletal muscle dysfunction, episodes of organ rejection, and side effects of immunosuppressant medications [1].

Available systematic reviews on the effects of exercise training in SOT have generally focused on one type of transplant [11-16]. In contrast, a 2013 systematic review and meta-analysis by Did bury *et al.* [17] included 15 randomized controlled trials (RCTs) covering all SOT recipient types and most of the relevant outcomes. However, the authors were able to conduct meta-analysis on only one outcome (maximum oxygen consumption ($VO_{2\ max}$) and subgroup analysis only in heart transplant studies. Our preliminary search yielded at least 10 new RCTs since Didsbury *et al.*'s publication [17], suggesting it is timely to conduct an update of this work. Our primary objective is to investigate the effects of exercise training (versus no training) on maximal or functional exercise capacity, quadriceps muscle strength, and health-related quality of life (HRQoL) across the SOT types. A secondary objective is to investigate the effects of exercise training on cardiovascular risk factors, body composition, bone mineral density (BMD), systemic inflammation, anxiety and depression, physical activity, physical function, activities of daily living (ADL), return to work, healthcare utilization, adherence to the exercise program, and adverse events. The ultimate goal of our systematic review is to inform best practice in transplant rehabilitation and future research in the area of exercise in SOT.

Methods

The PRISMA guidelines for reporting systematic reviews [18] were followed and fulfilled. We registered our protocol on PROSPERO (International Prospective Register for Systematic Reviews) (registration number: CRD42016050648).

Search strategy

In collaboration with the research team, a health sciences librarian developed a search strategy to identify randomized controlled trials reporting on exercise interventions in heart, lung, kidney, liver, and pancreas transplant recipients (supporting document). The MEDLINE (Ovid) strategy was then adapted for Embase (Ovid), CINAHL, and Cochrane Central Register of Controlled Trials from inception to May 1, 2019. We did not limit the search by language or by year of publication [19]. ClinicalTrials.gov was used to identify clinical trials that were under way or recently completed. References of included studies and pertinent reviews [11,17,20] were hand-searched by one investigator, and forward searches for older studies (prior to 2014) were performed. The results were compiled, and duplicates removed using EndNote X9 (EndNote, Clarivate Analytics, Boston, MA) and Covidence systematic review software [21].

Inclusion criteria

To be eligible, published RCTs needed to meet the following "PICOT" criteria [22]:

1. *Population:* Adults recipients (> 18 years) of any solid organ transplant (SOT) (heart, lung, kidney, pancreas, or liver).
2. *Intervention:* any inpatient, outpatient, or home-based exercise program that lasted more than 3 weeks.
3. *Comparison:* Nonexercise program or a sham intervention (i.e., flexibility exercises or education).
4. *Outcomes:* Our primary outcomes were maximal or functional exercise capacity, quadriceps muscle strength, and HRQoL. Any HRQoL measure used in the articles was considered. We defined "maximal exercise capacity" as the peak exercise capacity measured using an incremental exercise test (treadmill or cycle ergometer).

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Functional exercise capacity was defined as the results of field walking tests (e.g., six-minute walk test). Any measure of quadriceps muscle strength was considered.

Our secondary outcomes included cardiovascular risk factors (blood pressure, fasting glucose, cholesterol, and triglycerides), body composition (fat mass, fat-free mass, body mass index (BMI), and bone mineral density (BMD)), systemic inflammation (IL-6 and TNF-alpha), anxiety and depression, measurements of physical activity measured either with a questionnaire or an activity monitor/pedometer, physical function, ADL, return to work, healthcare utilization (defined as family doctor visits, emergency visits, and hospital length of stay), adherence to the exercise program, and adverse events.
5*Time:* The intervention could have been offered any time post-transplant.

Exclusion criteria

Studies that compared two types of exercise training programs with no nonexercise control group were excluded. We also excluded nonrandomized trials, conference abstracts, articles published in nonpeer-reviewed journals, and in languages other than English, French, Spanish, or Portuguese.

Screening process and data extraction

Two researchers independently screened all titles and abstracts identified by the literature searches using Covidence software [21]. The same pair of reviewers applied the inclusion/exclusion criteria on the full text of the potentially eligible studies. Disagreements were resolved by consensus between the two reviewers. Reasons for exclusion of ineligible studies were recorded. Data extraction and verification were carried out by two reviewers and entered onto a standardized data extraction spreadsheet in Microsoft Excel. Details about study design, patient characteristics, details about the interventions, and primary and secondary outcomes were recorded. Discrepancies were resolved by consensus. When multiple articles reported different outcomes from the same study, this was noted on the tables. Authors of the primary studies were contacted when additional data were needed.

Assessing the risk of bias

Two reviewers independently assessed included RCTs for risk of bias using the criteria outlined in the RoB 2 tool, a revised Cochrane risk of bias tool for randomized trials [23], and includes the following domains: randomization process, deviation from intended interventions, missing outcome data, measurement of the outcomes, and incomplete outcome data. Disagreements on quality assessments were resolved by consensus in consultation with a third team member.

Data analysis and synthesis

Meta-analyses were performed when data of four or more studies were available [24]. Only data collected before and immediately after the training period were included in the meta-analysis. All analyses were done using Stata 15.1 (StataCorp, Texas). The effect size for each study was expressed as standardized mean differences (SMD) for continuous outcomes. The SMD allowed the comparison of study effect even when the tools used to measure the outcomes were in different units. Studies were weighted using sample size. The meta-analyses used the fixed effects model with inverse variance method. Heterogeneity was assessed using I^2 statistic.

For each study, all outcomes reported were treated as separate data points; several studies provided data on more than one outcome. Because measures from the same study are not independent from one another, the *P*-values were adjusted using Huber's formula as available in Stata [25]. Subgroup analyses (by level of supervision, timing post-transplant, frequency of the training, duration of the program, and type of training) were conducted when three or more studies contributed to a subgroup. Exercise training programs that lasted less than 3 months were considered as "short duration" and if they lasted more than 3 months as "long duration." Similarly, exercise training offered 3 times a week or less were considered as "less frequent" and those offered more than 3 times a week were considered as "more frequent." Exercise training programs that commenced within 12 months of transplantation were considered "early post-transplant" while those offered after 12 months post-transplant were considered "late post-transplant." None of the analysis showed significant heterogeneity as indicated by I^2 with P-values > 0.05.

Results

Search results

1490 unique manuscripts were identified by our search strategy of which 29 met our inclusion criteria. (Fig. 1). Twenty-one of the publications were unique studies.

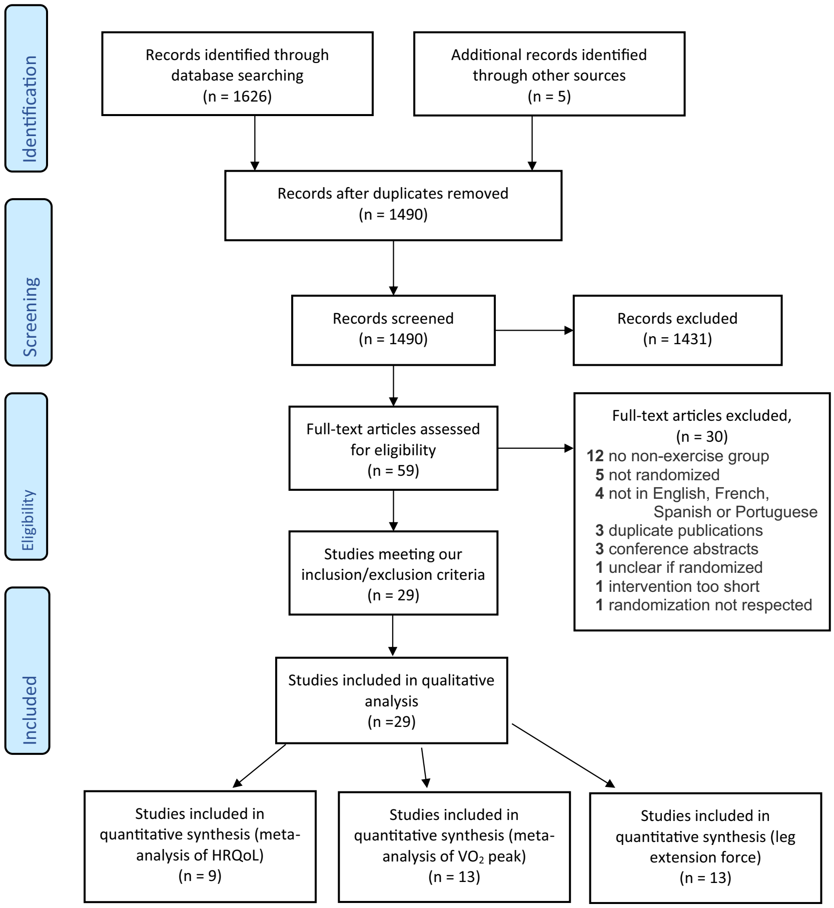

Figure 1 Study flow from identification to final inclusion of studies.

Eight of the publications [26-33] were reports of different outcomes from one of the 21 unique studies. Table 1 shows the characteristics of the studies. Seven hundred thirty-six patients were randomized to either an intervention exercise group or a control group where no exercise was expressly prescribed. Eleven of the 21 unique studies included recipients of a kidney transplant, six studied heart transplant recipients, two included lung transplant recipients, and two examined liver transplant recipients (Table 1). No study in pancreas transplant recipients was found.

Risk of bias assessment

Table 2 reports the risk of bias of the included RCTs. In the domain of measurement of outcomes, most studies were judged to be of high bias, since it was not known whether the outcome assessors were aware of the group to which the participants were randomized. Eight studies [26,34-40] were judged to have a high risk of bias, and in another sixteen there were some concerns about the potential for bias, usually because the necessary information was not included in the article. Five studies were judged to have a low risk of bias [29,33,41-43].

Exercise interventions

The exercise interventions varied in their delivery with two designed for patients to carry out the exercise at home, 17 were completely based at a central supervised location, and two used a combination of these strategies (Table 3). Seven programs included only aerobic training [41,43-48], six only resistance training [35,37,40,41,49,50], and nine used a combination of both types of training [34,36,38,39,42,51-54]. The frequency of training sessions varied between two and five times a week and programs lasted from 8 to 52 weeks in length. The timing of the intervention (number of years since transplantation) also varied across studies, ranging from one-week post-op [49] to approximately seven years post-transplant [47]. The majority of the studies measured outcomes immediately after the training period, and three studies also measured outcomes at

Table 1. Characteristics of 29 included studies (21 unique studies)

Study/Year	Population	Intervention	*n* analyzed	*n* dropouts	Time since transplant (weeks)	Key outcome measures included in study	Key findings
Kidney Transplant Recipients (11 unique studies)							
Leasure 1995	USA age range 18-45	aerobic resistance	5	3	8	Muscle strength (quadriceps, shoulder, hip flexion, and extension) body composition (muscle mass)	Differences in strength between the two groups at 20 weeks were inconsistent and did not demonstrate a meaningful pattern
Painter 2002	USA mean age = 41.5	aerobic	97	29 in exercise group; 41 in usual care	4-8	HQOL = SF-36 VO_2 peak muscle strength (quadriceps) body composition (BMI, lean body mass, fat mass, weight, BMD) creatinine, BUN, hematocrit, hemoglobin self-report of regular exercise participation	VO_2 peak and %-age-predicted VO_2 peak were significantly different between the two groups; physical function scale of the SF-36 approached a statistically significant difference between groups; quadriceps peak torque was significantly greater in the exercise group; exercise participation was significantly higher in exercise group
Painter 2003						Cardiovascular (resting SBP/ DBP, TC, HDL, TC-HDL ratio); METs	Significantly higher maximum METs achieved by the exercise group
Juskowa 2006	Poland mean age = 45.0	resistance	69	not reported	1	Cardiovascular (fasting glucose, TC, TG, LDL, TC-HDL ratio) inflammatory markers (IL-18); hemoglobin, fibrinogen, creatinine, total homocysteine folate, vitamin B_{12}, total protein, albumin	Inverse correlation was found between total homocysteine and interleukin-18 levels and muscle strength of the upper limbs. There was a positive correlation between muscle strength and improved graft function in the exercise group versus control groups
Kouidi 2013	Greece mean age = 52.4	aerobic resistance	23	1 in the exercise group	95	VO_2 peak cardiovascular (resting SBP/ DBP, maximum SBP/DBP, resting HR, maximum HR, HR variability measures (holter monitoring) exercise time, maximum pulmonary ventilation	VO_2 peak significantly increased in the exercise group increased cardiorespiratory fitness by exercise training was associated with an improved baroreflex sensitivity function and a modification of the sympatho-vagal control of heart rate variability toward a persistent increase in para-sympathetic tone.
Pooranfar 2014	Iran age range 20-50	aerobic resistance	44	not reported	100-150	Cardiovascular (TC, TG, HDL, LDL) Pittsburgh Sleep Quality Index (PSQI)	Quality and quantity of sleep significantly improved in exercise group LDL, TC and TG significantly improved in exercise group

Table 1. Continued.

Study/Year	Population	Intervention	*n* analyzed	*n* dropouts	Time since transplant (weeks)	Key outcome measures included in study	Key findings
Riess 2014	Canada Mean age = 54.7	aerobic resistance	31	2 in exercise group did not attend training; 1 control no follow-up testing	333	HQOL = SF-36 VO_2 peak muscle strength (quadriceps) cardiovascular (resting SBP/DBP, HR, cardiac output, stroke volume, mean arterial pressure, systemic vascular resistance, arteriovenous oxygen difference, TC, Framingham risk score) power output, respiratory exchange ratio, adherence to exercise, adverse events	Significant difference in VO_2 peak, power output, cardiac output and heart rate between groups leg press and leg extension 1RMs were significantly greater in the exercise group social function score and mental health composite score of the SF-36 were significantly better in the exercise group
Tzvetanov 2014	USA Mean age = 45.5	resistance	17	4 at 6 months; 6 at 12 months; all in control group	37	HRQOL = SF-36 body composition (BMI, fat-free mass) cardiovascular (fasting glucose, TC, HDL, LDL, TG) GFR, serum creatinine, hemoglobin A1c, employment rate, subjective pain score, adherence to program	Significant improvement in the vitality domain of the SF-36 in the exercise group; significant improvement in employment rate in the exercise group
Greenwood 2015	UK mean age = 52.2	(2 separate arms) aerobic arm; resistance arm	46	7 in each exercise group returned to work	25-30	HQOL = SF-36 VO_2 peak muscle strength (quadriceps) body composition (BMI, weight, waist girth) cardiovascular (resting SBP/DBP, resting HR, arterial stiffness (carotid-femoral pulse wave velocity (PWV)) inflammatory markers (IL-6, TNF-alpha, TNF receptors 1 and 2) STS-60, serum creatinine, fetuin A, high-sensitivity C-reactive protein, Duke Activity Status Index (DASI), adherence to program, adverse events	Significant mean difference in PWV between the aerobic exercise and control groups and significant mean difference in PWV between the resistance training and control groups; significant mean differences between the aerobic training and usual-care groups in relative VO_2 peak and absolute VO_2 peak; significant mean differences for relative VO_2 peak, absolute VO_2 peak, isometric quadriceps muscle force, and STS-60 between the resistance training and control groups

Table 1. Continued.

Study/Year	Population	Intervention	*n* analyzed	*n* dropouts	Time since transplant (weeks)	Key outcome measures included in study	Key findings
O'Connor 2016			42	3 in resistance group; 1 aerobic group lost for VO_2 peak; 0 in control group	25-33	VO_2 peak Body composition (weight) Cardiovascular (resting SBP/ DBP, hypertension, pulse wave velocity) respiratory exchange ratio, rejection episodes, new-onset diabetes, cardiovascular event deaths	Significant mean between-group difference in PWV between the exercise and control groups; Significant between-group difference in relative VO_2 peak when comparing exercise with control groups;
Karelis 2016	Canada mean age = 45.4	resistance	20	2 in exercise group; 2 in control group	6-8	HQOL = WHO-5 Well-being Index VO_2 peak body composition (BMI, lean body mass, waist/ hip circumference, % body fat, weight) muscle strength (leg press and chest press strength) cardiovascular (fasting glucose, resting SBP/DBP, TC, TG, HDL, LDL) hemoglobin A1c, Matsuda index and Stumvoll index for insulin sensitivity, adherence to program, adverse events	significant between-group difference for diastolic blood pressure and for triglycerides significant group effect in favor of the exercise group for WHO-5 well-being score
Shakoor 2016	Iran age range 20-50	aerobic resistance	32	1 in each group	100-150	cardiovascular (resting SBP/ DBP) DASS-21 questionnaire (depressive symptoms, anxiety, and stress scale	significant between-group differences in stress, anxiety, and depression as well as in systolic and diastolic blood pressure
Eatemadololama 2017	Iran mean age = 32	resistance	24	not reported	< 52	body composition (BMD)	BMD of the femur improved significantly following exercise (they did not do a between-group comparison, although in control group BMD decreased significantly)

Table 1. Continued.

Study/Year	Population	Intervention	*n* analyzed	*n* dropouts	Time since transplant (weeks)	Key outcome measures included in study	Key findings
Study/Year	**Population**	**Intervention**	***n* analyzed**		**Time since transplant (weeks)**	**Measures included in study**	**Significant findings between groups**
Heart Transplant Recipients (6 unique studies)							
Bernardi 2007	Italy mean age = 51.4	aerobic	24	not reported	25	VO_2 peak cardiovascular (resting SBP/ DBP, RR interval) exercise time maximal workload minute ventilation	VO_2 peak, exercise time, and maximal workload increased significantly in exercise group (no between group was conducted). Peak minute ventilation increased significantly in trained patients but not in controls. Systolic and diastolic blood pressure values decreased significantly in the exercise group. After physical training, the number of patients with signs of cardiac reinnervation increased significantly vs pretraining
Braith 2008	USA mean age = 54.4	aerobic	16	1 in exercise group; 3 in control group	10	VO_2 peak body composition (weight) cardiovascular (fasting glucose, TC, TG, HDL, LDL, mean arterial BP, endocardial rejection) 8-iso-PGF_2	Body mass was significantly greater in control vs trained after 12 weeks VO_2 peak and total exercise duration on the graded exercise test were significantly increased in the exercise group
Pierce 2008			14	6		cardiovascular (resting SBP/ DBP, right arterial pressure, right ventricular SBP/DBP, resting forearm blood flow, resting calf blood flow, resting HR) inflammatory markers (IL-6, TNF-alpha, sICAM-1) C-reactive protein, CMV IgG, white blood cells	Post hoc testing demonstrated a significant increase in plasma TNF-alpha and sICAM-1 concentrations in control group after 12 weeks, but no significant change in exercise group
Haykowsky 2009	Canada mean age = 58.0	aerobic resistance	43	1 in exercise group; 2 in control group	280	VO_2 peak muscle strength (upper extremity strength, lower extremity strength (leg press for quadriceps) cardiovascular (brachial artery vascular function, left ventricular systolic function)	VO_2 peak and peak power output were significantly higher in exercise group as compared to nonexercise group A significant increase in leg press and chest press maximal strength was found after 12 weeks of exercise

Table 1. Continued.

Study/Year	Population	Intervention	*n* analyzed	*n* dropouts	Time since transplant (weeks)	Key outcome measures included in study	Key findings
						respiratory exchange ratio compliance with program, adverse events	
Hermann 2011	Denmark mean age = 50.1	aerobic	27	1 in exercise group; 2 in control group	360	VO_2 peak body composition (BMI, hip/waist ratio) cardiovascular (fasting glucose, resting SBP/DBP, TC, TG) inflammatory markers (IL-6, TNF-alpha) hemoglobin A1c, creatinine C-reactive protein adiponectin, atrial natriuretic peptide, brain natriuretic peptide, copeptin, adverse events	In the exercise group systolic blood pressure fell significantly Peak oxygen uptake was significant increased in the exercise group compared to the control group Flow mediated vasodilation was significantly increased by exercise training compared to controls Plasma concentration of hsCRP was significantly decreased in the exercise group
Christensen 2012						HQOL = SF-36 Hospital anxiety and depression scale (HADS)	For self-perceived health (SF-36), a significant effect on mental health was found in the exercise group A significant reduction in patient-reported (HADS) anxiety and depression was seen in the exercise group as compared to control group
Monk-Hansen 2014			23	1 in exercise group; 3 in control group		echocardiographic parameters	diastolic function was not a limiting factor for exercise capacity in these stable heart transplant recipients.
Nytrøen 2012	Norway mean age = 50.5	aerobic	48	2 in exercise group; 2 in control group	208-260	HQOL = SF-36 VO_2 peak muscle strength (quadriceps, hamstrings) body composition (BMI, % body fat, weight) cardiovascular (resting SBP/DBP, resting HR, peak HR) inflammatory markers (IL-6, IL-8)	VO_2 peak and VE_{max} increased in the exercise group with no significant change in the control group, resulting in a significant difference between the groups at follow-up Peak heart rate and respiratory exchange ratio decreased during submaximal exercise in the exercise group with no significant change in the control group, resulting in a

Table 1. Continued.

Study/Year	Population	Intervention	*n* analyzed	*n* dropouts	Time since transplant (weeks)	Key outcome measures included in study	Key findings
						VE_{max}, respiratory exchange ratio, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), C-reactive protein, compliance with program, adverse events	significant difference between the groups at follow-up resting HR decreased slightly in the exercise group and increased slightly in the controls, resulting in a significant difference at follow-up quadriceps and hamstrings muscular exercise capacity increased significantly in the exercise, while remaining unchanged in the controls resulting in a significant difference in the change in total work in both quadriceps and hamstrings between the groups
Nytrøen 2013			43	4 in exercise group; 1 in control group		body composition (BMI, % body fat, visceral fat) intravascular ultrasound virtual histology	high-intensity interval training resulted in a significantly decreased rate of cardiac allograft vasculopathy progression in the exercise group compared to the control group
Rustad 2014			48	2 in exercise group; 2 in control group		echocardiography coronary angiography and endomyocardial biopsies	no significant differences between groups found
Yardley 2016			41	7 not eligible @5yrs: 2 medical cause; 2 physical inability; 3 deaths; not reported by group		HQOL = SF-36 VO_2 peak muscle strength (quadriceps, hamstrings) body composition (BMI, % body fat, weight) cardiovascular (resting SBP/DBP, TC) Hospital anxiety and depression scale (HADS) Beck depression inventory (BDI) frequency/intensity of daily physical activity (Sense Wear armband monitors) coronary angiography and Intravascular ultrasound	HADS anxiety parameters showed significant group differences from baseline to the 5-year follow-up, with positive, lower scores in the exercise group compared with those in the control group

Table 1. Continued.

Study/Year	Population	Intervention	*n* analyzed	*n* dropouts	Time since transplant (weeks)	Key outcome measures included in study	Key findings
Pascoalino 2015	Brazil mean age = 45	aerobic	40	2 in exercise group	328	(IVUS), electrocardiography VO_2 peak cardiovascular (resting SBP/DBP, 24-hour holter monitoring carotid-femoral pulse wave velocity (PWV)) norepinephrine, adverse events	VO_2 peak exercise time increased in the exercise group resulting in a significant difference between the groups Maximal norepinephrine was significantly different between groups Diastolic blood pressure was significantly better in the exercise group than the control group
Study/Year	**Population**	**Intervention**	***n* analyzed**		**Time since transplant (weeks)**	**Measures included in study**	**Significant findings between groups**
Lung Transplant Recipients (2 unique studies)							
Mitchell 2003	USA mean age = 52.0	resistance	16	not reported	8	muscle strength (lumbar extensor strength) body composition (BMD)	lumbar BMD in the exercise group increased significantly between groups and compared to a decrease in the control group The magnitude of lumbar strength gains in the exercise group at 48, 60, and 72 degrees of lumbar flexion were significantly greater than the control group
Langer 2012	Belgium mean age = 59.0	aerobic resistance	34	3 in exercise group; 3 in control group	1-2	HQOL = SF-36 VO_2 peak muscle strength (quadriceps, handgrip force) body composition (BMI, weight, BMD) cardiovascular (fasting glucose, resting SBP/DBP, TC, TG) 6MWD Hospital anxiety and depression scale (HADS) daily physical activity diary and monitor respiratory muscle force	immediately following the exercise training intervention statistically significant differences between groups in daily walking time, movement intensity during walking and daily steps and in physical fitness (6-minute walking distance and quadriceps force) were observed average 24-hour ambulatory blood pressures were significantly lower in the exercise group at 1-year post-transplant

Table 1. Continued.

Study/Year	Population	Intervention	*n* analyzed	*n* dropouts	Time since transplant (weeks)	Key outcome measures included in study	Key findings
Study/Year	**Population**	**Intervention**	***n* analyzed**		**Time since transplant (weeks)**	**Measures included in study**	**Significant findings between groups**
Liver Transplant Recipients (2 unique studies)							
Basha 2015	Egypt mean age = 50.8	aerobic resistance	30	not reported	25	body composition (fat mass, muscle mass) cardiovascular (TC, TG)	comparison between exercise and control groups post treatment revealed a significant decrease in fat mass, cholesterol, and triglyceride levels in the exercise group compared to control there was a significant increase in muscle mass in the exercise group compared to control
Moya-Nájera 2017	Spain mean age = 56.1	aerobic resistance	50	4 in exercise group	24	HQOL = SF-36 VO_2 peak muscle strength (hip extension, elbow flexion/ extension, shoulder flexion/ extension, shoulder abduction, and knee flexion/ extension (quadriceps) body composition (BMI, % body fat, weight) liver function–related blood tests adherence to program	the exercise group presented significant differences in maximal strength changes in hip extension and elbow flexion compared to the control group Significant between-group differences over time were detected in the physical functioning and vitality domains of the SF-36

HRQoL–health-related quality of life; VO_2–volume of oxygen; BMI–body mass index; BMD–bone mineral density; BUN–blood urea nitrogen; SF–36-short-form-36; SBP–systolic blood pressure; DBP–diastolic blood pressure; TC–total cholesterol; HDL–high-density lipoprotein; METs–metabolic equivalent task; IL–interleukin; TG–triglycerides; LDL–low-density lipoprotein; HR–heart rate; 1RM–one-repetition maximum; GFR–glomerular filtration rate; PWV–pulse wave velocity; TNF–tumor necrosis factor; STS-60–Sit-to-stand 60; A1C–glycated hemoglobin; WHO–World Health Organization; DASS-21–Depression, Anxiety and Stress Scale - 21 Items; 8-iso-PGF_2– 8-isoprostane-prostaglandin F_2; sICAM-1–soluble intercellular adhesion molecule-1; CMV IgG–cytomegalovirus Immunoglobulin G; hsCRP–high-sensitivity C-reactive protein; VE_{max} –maximum ventilation; HADS – hospital anxiety and depression scale; 6MWD – 6-minute walk distance.

Table 2. Risk of bias of the included studies

Study \ Domain	1	2	3	4	5	Overall bias
KIDNEY						
Leasure 1995	some concerns	some concerns	low risk	high risk	low risk	= high risk
Painter 2002	low risk	low risk	some concerns	high risk	low risk	= some concerns
Painter 2003	low risk	low risk	some concerns	some concerns	low risk	= some concerns
Juskowa 2006	low risk	some concerns	high risk	low risk	low risk	= some concerns
Kouidi 2013	low risk	low risk	low risk	high risk	low risk	= some concerns
Pooranfar 2014	some concerns	some concerns	high risk	high risk	low risk	= high risk
Riess 2014	low risk	low risk	low risk	high risk	low risk	= some concerns
Tzvetanov 2014	low risk	low risk	high risk	high risk	low risk	= high risk
Greenwood 2015	low risk	low risk	some concerns	low risk	low risk	= low risk
O'Connor 2017	low risk	low risk	some concerns	low risk	low risk	= low risk
Karelis 2016	some concerns	low risk	low risk	high risk	low risk	= some concerns
Shakoor 2013	some concerns	some concerns	low risk	high risk	low risk	= high risk
Eatemadololama 2017	some concerns	high risk	high risk	some concerns	some concerns	= high risk
HEART						
Bernardi 2007	some concerns	low risk	low risk	high risk	low risk	= some concerns
Braith 2008	some concerns	low risk	low risk	high risk	low risk	= some concerns
Pierce 2008	some concerns	some concerns	low risk	high risk	low risk	= high risk
Haykowsky 2009	low risk	low risk	low risk	high risk	low risk	= some concerns
Hermann 2011	low risk	low risk	low risk	high risk	low risk	= some concerns
Christensen 2012	low risk	low risk	low risk	high risk	some concerns	= some concerns
Monk-Hansen 2014	low risk	low risk	low risk	high risk	low risk	= some concerns
Nytrøen 2012	low risk	low risk	low risk	high risk	low risk	= some concerns
Nytrøen 2013	low risk	low risk	low risk	low risk	low risk	= low risk
Rustad 2014	low risk	low risk	low risk	high risk	low risk	= some concerns
Yardley 2017	low risk	low risk	low risk	high risk	low risk	= some concerns
Pascoalino 2015	low risk	low risk	low risk	low risk	low risk	= low risk
LUNG						
Mitchell 2003	some concerns	low risk	low risk	high risk	some concerns	= high risk
Langer 2012	low risk	low risk	low risk	low risk	low risk	= low risk
LIVER						
Basha 2015	some concerns	some concerns	some concerns	high risk	low risk	= high risk
Moya-Nájera 2017	some concerns	low risk	low risk	high risk	low risk	= some concerns

1: randomization process; 2: deviation from intended interventions; 3: missing outcome data; 4: measurement of the outcomes; 5: incomplete outcome data.

● = low risk; ● = some concerns; ● = high risk.

a later timepoint (one or five years) [30,33,42] to assess maintenance of the training outcomes.

Primary outcomes

Maximal exercise capacity (VO_2 peak)

Thirteen studies [41-48,50-54] assessed maximal exercise capacity (VO_2 peak) immediately after the training period. All of these studies had a component of aerobic training in their program except the study by Karelis *et al.* [50] which only included resistance training. Two studies [30,33] measured VO_2 peak at 9-month and 5-year follow-up. To reduce clinical heterogeneity, only studies that measured VO_2 peak immediately after the training period were included in the meta-analysis. There was an increase in VO_2 peak after the training period (SMD: 0.40; 95%CI 0.22–0.57; P = 0.0; n = 521; 13 trials) (Fig. 2).

Subgroup analysis with VO_2 peak data

Type of training

Only studies that offered aerobic exercise alone (SMD: 0.47; 95%CI 0.22–0.71; P < 0.001; n = 283; 7 trials) and

Table 3. Interventions used in 29 included manuscripts (21 unique studies)

Study/Year	Intervention	Setting	Intensity	Frequency x/week	Program duration (# of weeks)	Supervision
Kidney Transplant Recipients (13 unique studies)						
Leasure 1995	Walking or stationary bicycle; free weights for shoulder, hip, and knee exercises	Outpatient (some sessions potentially at home)	Individually tailored	3	12	1 session supervised (not specified by whom)
Painter 2002 Painter 2003	Walking and cycling	Home-based	85–95% of maximum heart rate	4	50	Not supervised
Juskowa 2006	Strengthening exercises (upper, lower limbs, and abs), breathing, coordination, isometric, and relaxation exercises	Outpatient	30-minute sessions	7	24	Supervised by a physiotherapist every second training session
Kouidi 2013	Interval fitness training (stationary cycling, jogging, step-aerobic exercises, calisthenics and dancing) Abdominal, upper, and lower limb strengthening exercises	Outpatient	Increasing difficulty	4	24	Supervised by two exercise trainers specialized in physical rehabilitation
Pooranfar 2014	Ergometer bicycle, treadmill, And free weights (9–17 stations)	Outpatient	40%–70% maximum heart rate intensity and resistive exercise with 45%–65% of maximum frequency	3	10	Not reported
Reiss 2014	Bicycle ergometer Lower extremity strengthening	Outpatient	60%–80% VO_2 peak; resistance gradually increasing	5	12	Supervised by exercise physiologists
Tzvetanov 2014	Low-impact, low-repetition, and resistance-based weight training	'A private environment'	Low-impact, low-repetition	2	25	Supervised by coach (not specified)
Greenwood 2015 O'Connor 2016	Recumbent stationary exercise cycles, a treadmill, and elliptical trainer (aerobic group); Upper and lower body muscle groups (bench press, latissimus pull down, bicep curl, triceps pull down, leg press, knee extension, hamstring curl, and calf raises (resist group)	Outpatient	Aerobic = REP=13-15; Resistance = high-intensity resistance training at 80% one-repetition maximum	2/week-hospital 1/week home	12	Supervised (not specified by whom)
Karelis 2016	Leg press; chest press; lateral pull downs; shoulder press; arm curls; triceps extensions; and sit-ups (warm-up on treadmill)	Combination outpatient and home-based	10 reps individualized weight; 7 exercises	3	16	Supervised by a kinesiology student

Table 3. Continued.

Study/Year	Intervention	Setting	Intensity	Frequency x/week	Program duration (# of weeks)	Supervision
Shakoor 2016	Stationary bicycle or treadmill; A circuit consisting of 9-17 Stations of free weights	Outpatient	Aerobic = mild- to moderate-intensity (40-60% maximum VO_2); resistance = 45- 65% intensity;	3	10	Not reported
Eatemadololama 2017	10 minutes stretching exercises, 10 minutes walking on treadmill, 10 minutes cycling, 20 minutes resistance training for the upper limb, 20 minutes resistance training for lower limb, and 10 minutes cool-down walk	Outpatient	Initial training resistance, 50% of one rep max; increased gradually	2	12	Supervised by an exercise specialist
Study/Year	**Intervention**	**Setting**	**Intensity**	**Frequency x/week**	**Program duration (# of weeks)**	**Supervision**
Heart Transplant Recipients (6 unique studies)						
Bernardi 2007	Cycling 50 rpm for 30 min 5 days/week at 60–70% of Their peak oxygen consumption (recalculated after 3 months)	Home-based	60-70% peak O_2 consumption	5	24	Unsupervised
Braith 2008 Pierce 2008	Treadmill walking increasing in duration	Outpatient	BORG 11-13	3	12	Supervised by an exercise physiologist or a nurse
Haykowsky 2009	Treadmill and cycling and upper extremity (chest press, latissimus dorsi pull down, and arm curls) and lower extremity (leg press) strength training (1–2 sets of 10 –15 repetitions	Outpatient	Aerobic = HR= 60–80% VO_2 peak; Resist = 50% of maximal strength	Aerobic = 5/week, Resist = 2/week	12	Supervised (not specified by whom)
Hermann 2011, Christensen 2012, Monk-Hansen 2014	High-intensity interval training (HIIT) on bicycle and staircase running	Outpatient cardiac rehab clinic	Approximately 80% of VO_2 peak or ~ 85% of maximal heart rate	3	8	Supervised (not specified by whom)
Nytrøen 2012 Nytrøen 2013 Rustad 2014 Yardley 2016	High-intensity interval training (HIIT) performed on a treadmill	Outpatient	85–95% of maximum heart rate	3	24	Supervised by a physiotherapist
Pascoalino 2015	Walking/jogging on a motorized treadmill	Outpatient	80% of the respiratory compensation point heart rate	3	12	2 sessions supervised; 1 session

Table 3. Continued.

Study/Year	Intervention	Setting	Intensity	Frequency x/week	Program duration (# of weeks)	Supervision
						unsupervised (not specified by whom)
Study/Year	**Intervention**	**Setting**	**Intensity**	**Frequency x/week**	**Program duration (# of weeks)**	**Supervision**
Lung Transplant Recipients (2 unique studies)						
Mitchell 2003	Lumbar extensor training	Outpatient	One set of variable resistance lumbar extensions through a 72-degree rom with a weight load that allowed 15-20 reps to muscle fatigue	1	24	Supervised by a technician certified in the proper use of the medx clinical lumbar extension machine
Langer 2012	Cycling, walking, stair climbing, and resistance exercises using leg press equipment	Outpatient	Borg score of 4–6	3	12	Supervised (not specified by whom)
Study/Year	**Intervention**	**Setting**	**Intensity**	**Frequency x/week**	**Program duration (# of weeks)**	**Supervision**
Liver Transplant Recipients (2 unique studies)						
Basha 2015	Warm-up on treadmill and stretching exercises for: quadriceps, hamstring and calf muscles, treadmill walking or running, progressive resistance training (bench press, leg press, shoulder press, leg extension, biceps curl, leg curl, triceps curl, and toe raises.)	Outpatient	First 2 weeks:60-70% hr max. 3rd-12th: 70-80% hr max	3	12	Supervised by a physiotherapist
Moya-Nájera 2017	Walking; elastic resistance bands used for squat, dead lift, rowing, shoulder flexion, shoulder abduction, and chest press Balance exercises	Outpatient	Intensity began at 5-6 rpe and increased 1 point every 2 months, finishing at 8-9	2	24	Supervised by a health personnel multi-disciplinary group that included a sport science professional trainer

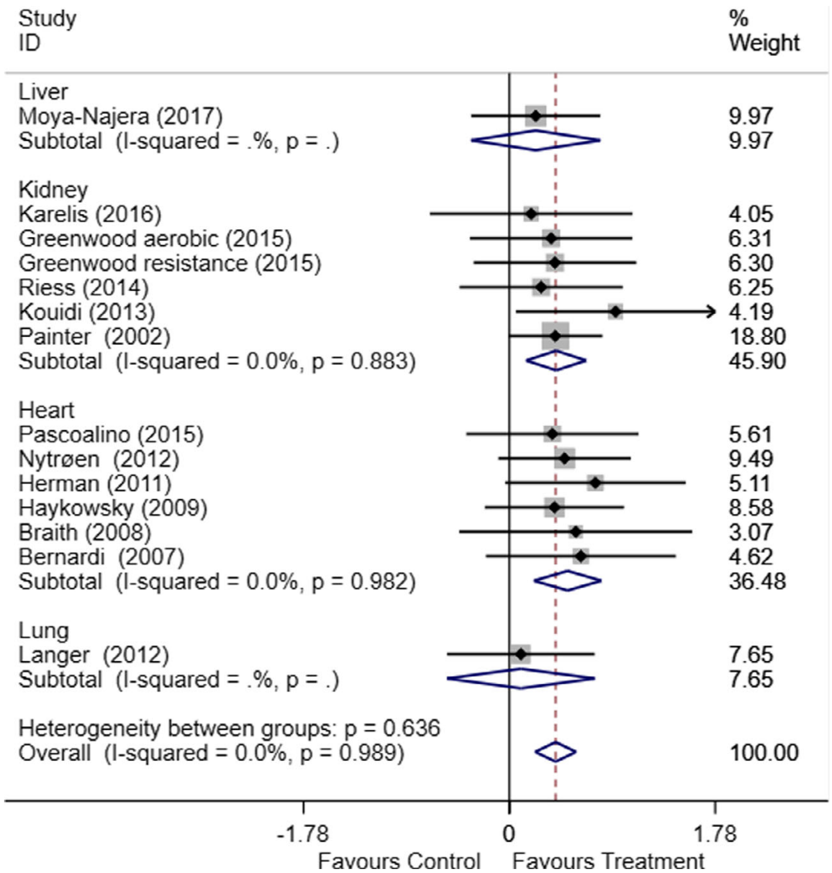

Figure 2 Effects of exercise training on peak exercise capacity (VO_2 peak).

a combination of aerobic with resistance training (SMD: 0.32; 95%CI 0.03–0.61; P = 0.03; n = 185; 5 trials) showed improvements in VO_2 peak (Fig. 3a).

Duration

Exercise training programs with both short (less than 3 months) (SMD: 0.37; 95%CI 0.12–0.62; P = 0.004; n = 261; 7 trials) and long durations (more than 3 months) (SMD: 0.43; 95%CI 0.18–0.67; P = 0.001; n = 260; 6 trials) were associated with improvements in VO_2 peak (Fig. 3b).

Frequency

Exercise training programs that were both less frequent (3 times a week or less) (SMD: 0.36; 95%CI 0.12–0.59; P = 0.002; n = 305; 8 trials) and more frequent (more than 3 times a week) (SMD: 0.45; 95%CI 0.18–0.72; P = 0.001; n = 216; 5 trials) were significantly associated with improvements in VO_2 peak (Fig. 3c).

Time post-transplant

Exercise training programs that commenced early (within 12 months) (SMD: 0.34; 95%CI 0.11–0.56; P = 0.003; n = 309; 7 trials) and late (more than 12 months) (SMD: 0.49; 95%CI 0.21–0.77; P = 0.001; n = 212; 6 trials) post-transplant were significantly associated with improvements in VO_2 peak (Fig. 3d).

Level of supervision

Only supervised exercise programs were effective in improving VO2 peak (SMD: 0.39; 95%CI 0.21–0.57; P = 0.000; n = 497; 12 trials). However, only one study [45] offered an unsupervised program (Fig. 3e).

Functional exercise capacity

Only one study included a measure of functional exercise capacity [42]. Langer *et al.* observed a statistically significant difference between groups in 6-minute-walk

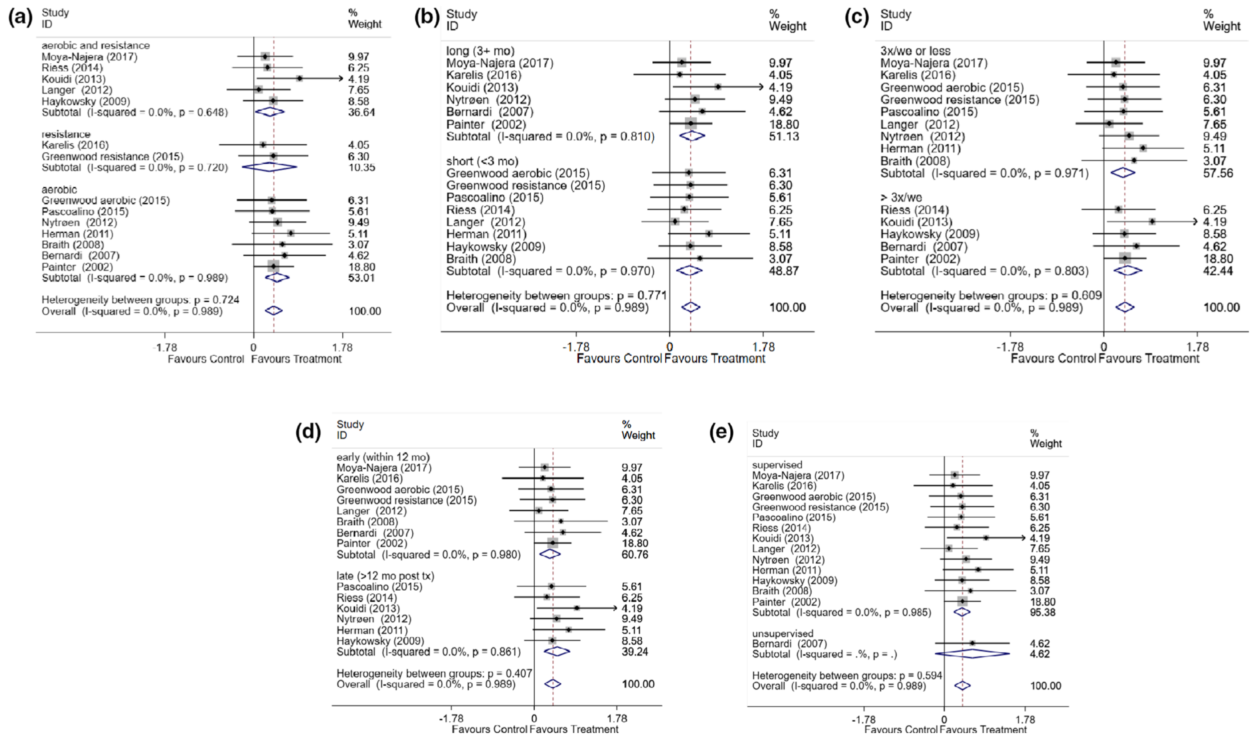

Figure 3 (a) Subgroup analyses of the VO_2 peak by type of training. (b) Subgroup analyses of the VO_2 peak by duration of the program. (c) Subgroup analyses of the VO_2 peak by frequency of the training. (d) Subgroup analyses of the VO_2 peak by timing post-transplant. (e) Subgroup analyses of the VO_2 peak by level of supervision.

distance (mean difference of 9 meters (% predicted)) immediately following the exercise training intervention (3 months after hospital discharge from lung transplantation), and this improvement was maintained at the 12-month follow-up (mean difference of 12 meters (% predicted)) despite no further formal exercise program [42].

Quadriceps muscle strength

Seven studies [36,41,42,44,48,53,54] assessed quadriceps muscle strength after the training period. Overall, there was an increase in quadriceps muscle strength after the training period (SMD: 0.38; 95%CI 0.16–0.60; $P = 0.001$; $n = 329$; 7 trials) (Fig. 4a). Subgroup analysis showed that quadriceps muscle strength improved significantly in the groups that received a combination of aerobic and resistance training (SMD: 0.54; 95%CI 0.17–0.91; $P = 0.04$; $n = 120$; 4 trials) but not in the groups that received aerobic and/or resistance training alone (Fig. 4b).

Health-related quality of life

Of the 10 studies reporting HRQoL, nine [27,30,40-42,44,48,53,54] used the SF-36™, and one used the WHO-5 Well-being Index [50]. Meta-analysis was performed with the SF-36 data that were collected immediately after the training program. Yardley *et al.* [30] reported data only from 5 years after the training program and was not included in the meta-analysis. There were improvements in the physical function (SMD: 0.27; 95%CI 0.05–0.48; $P = 0.015$; $n = 345$; 7 trials), physical role functioning (SMD: 0.26; 95%CI 0.005–0.51; $P = 0.046$; $n = 248$; 6 trials), general health (SMD: 0.43; 95%CI 0.17–0.69; $P = 0.001$; $n = 248$; 6 trials), social role functioning (SMD: 0.26; 95%CI 0.005–0.69; $P = 0.045$; $n = 248$; 6 trials), and mental health (SMD: 0.30; 95%CI 0.046–0.56; $P = 0.021$; $n = 248$; 6 trials) domains of the SF-36 after the training period (Fig. 5a–e). There were no improvements in the bodily pain, vitality, or emotional role functioning domains (Fig. 5f–g). Four studies [41,44,48,54] reported the composite scores for physical and mental functioning, but no significant improvement was seen in these composites scores after the training period.

Secondary outcomes

Cardiovascular risk factors

A meta-analysis including 11 articles (7 in kidney [33,39,41,44,50,52,54] and 4 in heart [26,43,47,48])

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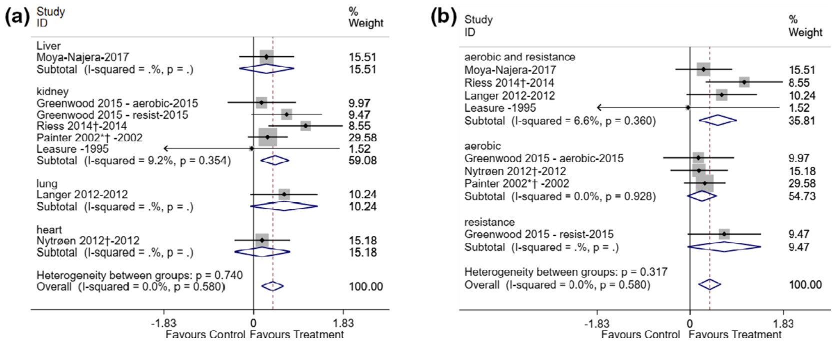

Figure 4 (a) Effects of exercise training on quadriceps muscle strength. (b) Subgroup analyses of quadriceps muscle strength by type of training.

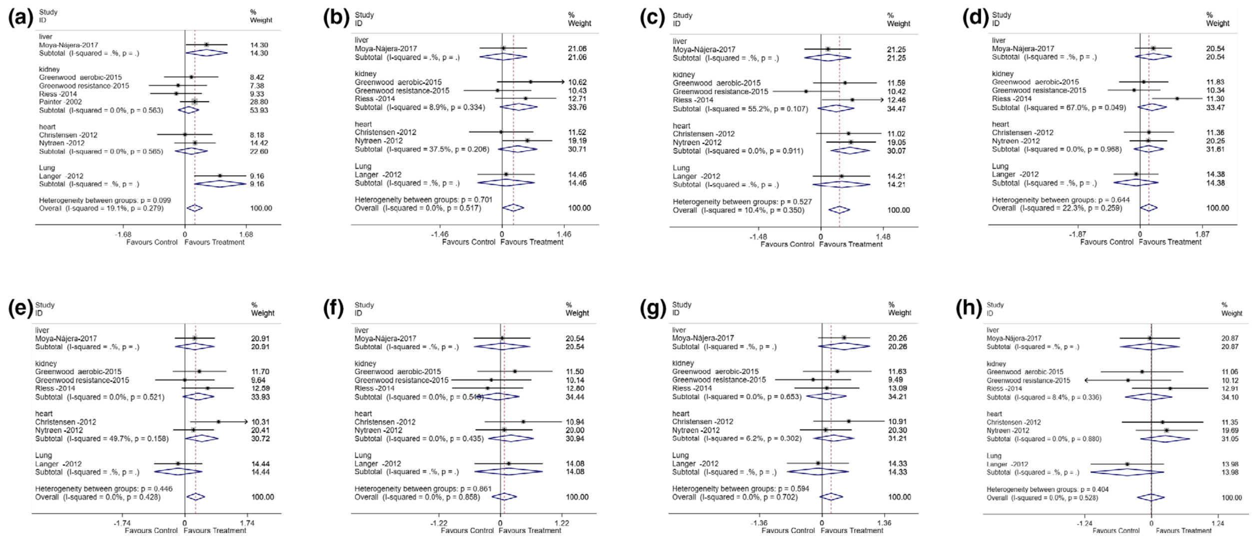

Figure 5 (a) Effects of exercise training on the physical function domain of the SF-36. (b) Effects of exercise training on the physical role functioning domain of the SF-36. (c) Effects of exercise training on the general health domain of the SF-36. (d) Effects of exercise training on the social role functioning domain of the SF-36. (e) Effects of exercise training on the mental health domain of the SF-36. (f) Effects of exercise training on the bodily pain domain of the SF-36. (g) Effects of exercise training on the vitality domain of the SF-36. (h) Effects of exercise training on the emotional role functioning of the SF-36.

showed no significant difference between groups in systolic blood pressure (SMD: −0.11; 95%CI −0.30–0.08; $P = 0.25$; $n = 483$; 11 trials) but showed an overall improvement in diastolic blood pressure (SMD: −0.22; 95%CI −0.41–0.03; $P = 0.02$; $n = 552$; 11 trials) in the exercise group compared to the control group. Five studies (two in kidney [49,50] and three in heart [46-48]) measured fasting glucose immediately after the training period but showed no significant difference between groups (SMD: 0.13; 95%CI −0.16–0.43; $P = 0.37$; $n = 175$; 5 trials). Pooled data from 8 trials (4 in kidney [32,38,49,50], 1 in liver [34] and 3 in heart [26,46,47]) showed no significant difference between groups in total cholesterol (SMD: −0.09; 95%CI −0.32–0.13; $P = 0.39$; $n = 316$; 8 trials) at the end of the exercise training period.

Adverse events

Adverse events were explicitly reported in only eight studies (4 in heart [31,47,48,51], 3 in kidney [41,50,54], and 1 in lung [37]). Six studies [31,41,47,50,51,54] reported no adverse events during the period of the study. Nytrøen *et al.* [48] reported that one of their patients in the control group had a myocardial infarction and Mitchell *et al.* [37] reported an increase in rejection episodes in the exercise group, although this was not statistically significant.

Table 4 presents a summary of the findings of the primary outcomes of this systematic review. Data on adherence to exercise, body composition, inflammatory markers, physical function, depression and anxiety, ADL, PA, return to work, and healthcare utilization are presented in the supporting document.

Discussion

Our systematic review showed that exercise training improves maximal exercise capacity, HRQoL, quadriceps muscle strength, and diastolic blood pressure in SOT recipients when compared to a control group who received no exercise. It also revealed that there is limited evidence that exercise training improves other cardiovascular risk factors, body composition, inflammatory markers, physical activity, physical function, return to work or depression, and anxiety in this population. However, these results must be interpreted with caution as there were fewer studies reporting these secondary outcomes. In addition, these outcomes were often not the primary endpoint in the articles reviewed and therefore the studies were likely not powered to show an effect. In 24 studies, there were either high risk of bias or some concerns about the potential risk of bias.

Our meta-analysis showed an overall improvement in exercise capacity (VO_2 peak) in SOT recipients as did Didsbury *et a*l. [17]. Other reviews have shown improvements in VO_2 peak in several single organ groups [11-16,20,55], but none of them conducted meta-analyses including liver and lung transplant recipients. Low VO_2 peak has been associated with higher risk for cardiovascular disease and is a predictor of mortality in chronic disease populations [8] and SOT recipients [1] so an improvement in VO_2 peak may improve prognosis and reduce risk for cardiovascular disease post-transplant. Indeed, our meta-analysis showed an improvement in diastolic blood pressure in the exercise group compared to the control group. The lack of significant difference in other cardiovascular risk factors may be related to the small number of studies that reported these outcomes, the short-term follow-up, and that the studies were not adequately powered to detect differences in these outcomes. In addition, we noted that the mean cholesterol and fasting glucose values at outset (pre-intervention) were normal in most of the studies which may explain the lack of change. Our findings related to cardiovascular risk factors are in contrast with the review by Li *et al.* [56] which showed significant reductions in fasting blood glucose, triglycerides, and body mass index in SOT recipients after exercise training. However, we noticed that Li et *al.* [56] included studies that did not meet our inclusion criteria (e.g., randomization was not respected [57] and Chinese language). Finally, it is important to note that most of the studies included in our meta-analysis of the VO_2 data included heart and kidney recipients; therefore, more studies including lung and liver groups are needed.

In contrast to the previous meta-analysis in SOT by Didsbury *et al.* [17], which showed that only exercise programs longer than 3 months in duration and

Table 4. Summary of the findings of the primary outcomes

Primary Outcomes	Results of the meta-analysis	Number of participants (studies)	Comments
Maximal Exercise Capacity (VO_2 peak)	SMD: 0.40; 95%CI 0.22–0.57; *P*=.0	521 (13 studies)	Significant increase in VO_2 peak after the training period
Quadriceps Muscle Strength	SMD: 0.38; 95%CI 0.16–0.60; *P* = 0.001	319 (7 studies)	Significant increase in leg extension force after the training period
HRQL			There were no improvements in the bodily pain, vitality or emotional role functioning domains
Physical Function	SMD: 0.27; 95%CI 0.05–0.48; *P* = 0.015	345 (7 studies)	
Physical Role Functioning	SMD: 0.26; 95%CI 0.005–0.51; *P* = 0.046	248 (6 studies)	
General Health	SMD: 0.43; 95%CI 0.17–0.69; *P* = 0.001	248 (6 studies)	
Social Role Functioning	SMD: 0.26; 95%CI 0.005–0.69; *P* = 0.045	248 (6 studies)	
Mental Health	SMD: 0.30; 95%CI 0.046–0.56; *P* = 0.021	248 (6 studies)	

HRQoL: Health-related quality of life; VO_2 peak: peak oxygen consumption; SMD: standardized mean difference; CI: confidence interval.

commenced within one year after the transplant were effective in improving VO_2 peak in heart transplant recipients, results of our subgroup analysis showed that exercise training improved VO_2 peak regardless of duration, frequency, and timing of commencement in SOT recipients. The results are likely different because Didsbury *et al.* [17] included only heart transplant recipients in their subgroup analysis. In addition, in this review, the majority of the studies classified as offering a shorter and less frequent exercise program provided sessions at least 3 times a week for 8 weeks which is considered the optimal minimum frequency and duration of an exercise program to confer benefits to SOT recipients [9]. The fact that there was improvement in VO_2 peak regardless of timing of commencement of the program shows that exercise limitation in SOT recipients can persist years post-transplant and is amenable to improvement with exercise [1,9]. We did observe, however, that the exercise program needs to offer aerobic training (either alone or in combination with resistance training) to increase VO_2 peak.

Our meta-analysis showed improvements in several domains of the SF-36. Although other reviews have shown similar improvements in HRQoL in kidney transplant recipients [14-16], our study is the first to include all SOT types in a meta-analysis. So far, other authors reporting on other organ groups have not been able to conduct meta-analysis with data from HRQoL tools due to the paucity of studies evaluating this outcome [11,17,55]. One of the primary goals of transplant is to improve HRQoL, so these findings support the importance of exercise in post-transplant management.

Of the eight [31,37,41,47,48,50,51,54] studies that included data on adverse events, two [37,48] reported some adverse events during the period of the study which do not appear to be related to the exercise. More information can perhaps be gleaned from the discussions of dropout rates (Table 1). For example, Langer *et al.* [42] had five patients lost to follow-up (3 in exercise group and 2 in the control group) due to "severe medical complications." It was not stated what these complications were or whether the authors thought that they were related to exercise. Braith *et al.* [46] reported that one patient withdrew from the exercise group because of a complication that was not related to the study. The study by Painter *et al.* [44] reported 70 dropouts, many for medical reasons (6 in the exercise group, 15 in the control group). These data suggest that SOT recipients' early post-transplant may be prone to many complications post-transplant. In fact, a study by Patcai *et al.* [58] showed that SOT recipients attending an inpatient rehabilitation program early post-transplant were ten times more likely to be readmitted to an acute hospital compared to other inpatient rehabilitation populations (e.g., cardiac, neurological, and amputee patients). Both in Langer *et al.*'s [42] and Painter *et al.*'s [32] studies, exercise training was offered quite early post-transplant (4-8 weeks in Painter *et al.* and 1-2 week in Langer *et al.*) which may explain the higher dropout rates. These findings have implications for the interaction between rehabilitation programs offering programs early post-transplant and the transplant programs.

Our review has some strengths and limitations. Strengths include a rigorous methodology (with an experienced librarian and statistician conducting the searches and statistical analysis) and expertise of the research team in knowledge synthesis and exercise in transplantation [9,10,59,60]. Another strength is the novel contributions of our study compared to previous reviews. Prior reviews were conducted on recipients of a single transplant type (i.e., organ specific) and included a smaller number of studies [11-16,20,55] preventing the pooling of results or were focused on a narrower list of outcome measures [56]. We have included 20 new studies [26,28-36,38-41,43,48,50,52-54] not included in Didsbury's review [17]. Interestingly, 11 of the newer studies involved kidney transplant recipients. In addition, Didsbury *et al.* were only able to conduct meta-analysis with data of VO_2 peak while we had enough data to conduct meta-analysis using data of VO_2 peak, SF-36, quadriceps muscle strength, and several additional secondary outcomes. Limitations of our review include the limited number of RCTs studying liver and lung transplant recipients (none in pancreas), as well as the small number of studies including our secondary outcomes of interest and long-term evaluation of the effects of exercise in this population. Eight studies were deemed to have high risk of bias, and the risk of bias of many other studies was unclear (Table 2).

Implications for clinical practice and research

Most of the exercise programs offered in the studies included in this review were supervised and hospital-based (only three studies offered a home-based exercise program). This mode of delivery is usually costly and recommended only for the early post-transplant phase [1-6months] and/or in case of medical instability [9]. Alternative ways of delivery such as home or community-based programs as well as tele-rehabilitation programs should be considered to increase access and keep the costs low, especially late post-transplant

(>6 months) [9]. Future research should investigate whether the effects of exercise on VO_2 peak, muscle strength, HRQoL, and diastolic blood pressure in SOT recipients can be maintained in the long term. Exercise training studies should also focus on outcomes such as cardiovascular risk factors, immune and graft function, healthcare utilization, and survival. These studies will need to include a long-term follow-up and likely be multi-centric to be statistically powered for these outcomes. Finally, more studies in liver, lung, and pancreas transplant recipients are needed.

In conclusion, despite the considerable variation in exercise training characteristics and high risk of bias in the included studies, this systematic review revealed that exercise training improves VO_2 peak, quadriceps muscle strength, HRQoL, and diastolic blood pressure in SOT recipients. Despite the underreporting of adverse events, exercise training should be considered as an essential part of the post-transplant care. SOT recipients early post-transplant may be more prone to complications post-transplant. To date, there is insufficient evidence that exercise training improves other cardiovascular risk factors, inflammatory markers, and healthcare utilization in SOT recipients. However, these findings must be interpreted with caution as there are few studies reporting these secondary outcomes which were likely not powered to show an effect.

Authorship

Tania Janaudis-Ferreira: designed the study, performed the study, assisted with data extraction, assisted with data analysis, interpreted the data, and wrote the manuscript. Catherine M. Tansey: extracted the data, and assisted with interpretation of the data and manuscript writing. Sunita Mathur, Tom Blydt-Hansen, Agnès Räkel André Bussières, and Sara Ahmed: designed the study, assisted with interpretation of the data, and provided critical feedback on the manuscript. Nathalia Parente de Sousa Maia: assisted with data extraction and provided critical feedback on the manuscript. Julie Lamoureaux: performed the meta-analysis and provided critical feedback on the manuscript. Jill Boruff: designed the search strategy and provided critical feedback on the manuscript.

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Conflict of interest

The authors of this manuscript have no conflicts of interest to disclose as described by *Transplant International*.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Ovid Medline (All) Search Strategy.

Appendix S2. Other Secondary Outcomes

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