Let's get physical: Aerobic capacity, muscle strength, and muscle endurance in pediatric transplant recipients

by

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Abstract

Pediatric heart and kidney transplant recipients appear to have lower physical fitness than healthy children. This study sought to quantify the fitness level of transplant recipients and investigate clinical and lifestyle factors that may affect physical fitness.

First, a systematic review and meta-analysis of existing literature about fitness after pediatric transplantation was conducted. Several databases were searched for peer-reviewed publications since 1990. Articles were selected for their relevance to age (0-18 years), condition (heart, lung, kidney, liver, or bone marrow transplant), methodology (at least one fitness assessment), and comparator (healthy control or normative values). Transplant recipients were compared to healthy children, and were analyzed in sub-groups of type of organ transplant and type of fitness test. Thirty-two studies were included in the final qualitative synthesis, and 24 of those were included in the meta-analysis. There were 13 studies in heart transplant (HTx) recipients, 11 in kidney transplant (KTx) recipients, 5 in liver transplant (LiTx) recipients, 4 in bone marrow transplant (BMT) recipients, and 0 in lung transplant recipients. VO_2max was not significantly different between types of organ transplant. The mean difference in VO_2max between studies in BMT was 12.18 (10.23, 14.12) ml/kg/min, in HTx was 11.89 (10.85, 12.94) ml/kg/min, in KTx was 11.74 (10.22, 13.25) ml/kg/min, and in LiTx was 9.87 (7.14, 12.60) ml/kg/min. There were no consistent methods for measuring muscle function in transplant recipients, except curl-ups were measured in LiTx, and there was no difference between LiTx and controls for this test.

Next, a prospective trial was developed to address gaps in the literature, and gain a deeper understanding of the underlying causes of fitness impairment in children living with transplants. Aerobic capacity (6MWT), muscle strength (hand-held dynamometry), muscle endurance (push-ups, curl-ups, wall-sit), physical activity level (PAQ), and quality of life (PedsQL 4.0) of HTx and KTx recipients were measured at a one-time, 1.5-hour fitness assessment. Clinical variables were collected from patient charts. Twenty controls, 22 HTx, and 6 KTx recipients were included in the study. All groups were similar in age, but the KTx group was shorter (125.8 (110.5-150.9) cm) than the control (150.6 (116.5-187.9) cm) and HTx groups (137.9 (110.0-180.7) cm). The age at transplant and time post-transplant were similar in HTx and KTx groups. 6MWT percent predicted distance was shorter in HTx (87.2 (69.9-118.6) %) than controls (99.9 (80.4-120) %). Muscle strength was lower in the upper body of HTx (6.15 (4.35-11.3) kg/m²) versus controls (8.48 (4.80-10.8) kg/m²), and in the lower body of KTx (9.27

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(8.65-19.1) kg/m^2) versus controls (15.4 (11.7-21.3) kg/m^2). Muscle endurance was lower in the upper body of both HTx (28.6 (0.00-250) %) and KTx (8.35 (0.00-150) %) versus controls (112 (48.9-400) %), in the core of HTx (115 (0.00-450) %) versus controls (167 (46.7-500) %), and in the lower body of KTx (18.5 (10.0-54.0) s) versus controls (62.0 (11.0-203) s). 6MWT percent predicted distance was moderately correlated with stroke (R=-0.562, P<0.01), but not persisting neuromotor deficits from stroke (R=-0.351, P=0.11), when analyzed by rank bivariate analysis. No other clinical variables were correlated with 6MWT percent predicted distance or wall-sit time.

Recipients of different types of transplant have similar changes in aerobic capacity, but different changes in muscle function as compared to healthy children. This finding would suggest that transplantation has a similar effect on overall fitness level, but different effects on muscle function depending on the type of transplant and duration of corticosteroid use. Further studies are needed to provide more information about the differences in muscle strength and endurance in different types of pediatric transplant. In the interim, physical therapy or physical activity interventions may help to improve the fitness level of pediatric transplant recipients.

Preface

  This thesis is an original work by Chantal Allan. No part of this thesis has been previously published.

  The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board. The study titled "Let's Get Physical: Aerobic capacity, muscle strength and endurance after pediatric transplantation" (Pro00067592) received approval on September 23rd, 2016.

  Some of the research conducted for this thesis forms part of a Canada-wide research collaboration, led by Dr. Lori West and Dr. Simon Urschel at the University of Alberta. The muscle testing equipment was provided by Dr. Sunita Mathur from the University of Toronto. The chart data collection for participants in Vancouver was conducted by Yan Jiang. The chart data collection for participants in Calgary and Edmonton was conducted collaboratively by myself and Ingrid Larsen at the University of Alberta, and Dr. Steven Greenway at the University of Calgary. The literature search for the systematic review was conducted by Robin Featherstone, MLIS. The second reviewer for the literature screening and quality assessment was Dr. Karen Hunter. Methodological guidance and quality assessment were conducted by Dr. Meghan Sebastianski. The methods for the data extraction for the meta-analysis were a combined effort on the part of Dr. Ben Vandermeer and myself. The research team at the University of Calgary was led by Dr. Steven Greenway. The research team at the University of British Columbia was led by Dr. Tom Blydt-Hansen. I was responsible for coordinating the efforts at all three of our testing sites, including applying for ethics and conducting testing. All data analysis, presentation, and writing were done by me, with input from my committee.

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List of Abbreviations

1RM	One repetition maximum
6RM	Six repetition maximum
ACEi	Angiotensin converting enzyme inhibitor
BMT	Bone marrow transplant
BP	Blood pressure
C	Control data
CCB	Calcium-channel blocker
CI	Confidence interval
CNI	Calcineurin inhibitor
ECG	Electrocardiography
ECMO	Extracorporeal membrane oxygenation
Echo	Echocardiography
Hg	Hemoglobin
HHD	Hand-held dynamometry
HR	Heart rate
HTx	Heart transplant
KTx	Kidney transplant
LiTx	Liver transplant
LuTx	Lung transplant
MET	Metabolic equivalent
MVPA	Moderate to vigorous physical activity
N	Normative data
PA	Physical activity
PAQ	Physical Activity Questionnaire
PedsQL	Pediatric Quality of Life Questionnaire version 4.0
PTLD	Post-transplant lymphoproliferative disease
QOL	Quality of life
RER	Respiratory exchange ratio
SD	Standard deviation
SE	Standard error
Tx	Transplant
UK	United Kingdom
USA	United States of America
VAD	Ventricular assist device
VO_2max	Volume of oxygen consumption at maximal exercise

Chapter 1: Introduction

1.1 Introduction to long-term outcomes in pediatric transplantation

Once considered a high-risk procedure, pediatric solid organ transplantation is now highly successful, with survival rates over 80% at 5 years after the transplant procedure of most organs(1, 2). These recent advances have led to questions about the quality of life – rather than survival – of patients living with a new organ, lifelong medications, and chronic condition. Lack of energy and physical ability are common complaints among pediatric transplant recipients. These complaints have been captured in the literature, that qualitatively reports low quality of life associated with physical functioning(3). However, information about the underlying cause(s) of fitness impairment and direct assessment of impact on quality of life are needed to design better activity recommendations and rehabilitation programs for these patients.

1.2 Aerobic capacity

1.2.1 Aerobic capacity

Aerobic capacity is an overall measure of fitness level, that is typically measured by volume of oxygen consumption at maximal exercise (VO_2max)(4). Some physiological systems that affect aerobic capacity include: the respiratory system for bringing oxygen into the blood stream from the atmosphere; the blood itself that carries oxygen to working skeletal muscle; the heart that pumps blood to skeletal muscle; the capillaries where oxygen is offloaded to skeletal muscle; and, skeletal muscle itself(5).

To measure VO_2max, participants breathe through a non-restrictive tube that measures carbon dioxide production, from which oxygen consumption is calculated(6). When the test is performed properly, oxygen consumption increases with exercise intensity, and eventually reaches a plateau, even as exercise intensity increases. The volume of oxygen consumption at which this plateau is reached provides the value of VO_2max.

Many different tests are used to assess aerobic capacity, either by direct measurement of VO_2max, or by proxy measure on a field test. For a field test, typically a measure such as exercise time, distance walked, or laps ran are measured. Some of the most common tests for aerobic capacity are summarized in the following sections.

1.2.2 Bruce protocol

The Bruce protocol is a standardized method of conducting an incremental exercise test in order to obtain VO_2max. During the test, the participant runs on a treadmill at increasing intensity until volitional exhaustion(7). The result of the Bruce protocol is exercise time, which reflects aerobic capacity. It is also possible to measure VO_2max while someone performs the Bruce protocol, which provides a more accurate measure of aerobic capacity.

One advantage of the Bruce protocol is that it is highly standardized and used widely in the field of fitness testing. This standardization facilitates comparison with other studies, and produces more valid results. There are also normative and predicted values for the Bruce protocol. In addition, it is possible to measure VO_2max directly using this test, which is the gold standard for measuring aerobic capacity.

One limitation of the Bruce protocol is that not all participants will achieve their true VO_2max during the test. Some participants will not have the motivation to continue exercising to their limit, ending their session before their true maximal effort. In these cases, the highest value of oxygen consumption is used as the VO_2max, and underestimates the true value. Other participants may not reach their true VO_2max due to health conditions, such as cardiorespiratory disease, because symptoms interfere with exercise capacity before maximal exertion may be achieved.

To determine whether participants achieved maximal exertion, respiratory exchange ratio or blood lactate concentration is measured. A value of respiratory exchange ratio (ratio of CO_2 exhaled to O_2 inhaled) ≥ 1.15, blood lactate concentration ≥ 8.0 mmol•L^{-1}, or heart rate $\geq 95\%$ age-predicted maximum heart rate (where max HR = 220 − age) suggests that a participant has reached their maximal effort, and their VO_2max test value is representative of their aerobic capacity(8). If a participant does not achieve these criteria despite maximal effort, we call their volume of oxygen consumption VO_2peak. In children, VO_2peak is considered an acceptable approximation of VO_2max(9).

1.2.3 Progressive aerobic cardiovascular endurance run (PACER)

When equipment to measure oxygen consumption is not available or its use is not feasible, field tests can be used to measure aerobic capacity, and sometimes estimate VO_2max. In children, the progressive aerobic cardiovascular endurance run (PACER) is commonly used.

This test is part of a fitness battery used in many American schools, called the FITNESSGRAM(10). For this test, participants run between markers set 20 meters apart in a given amount of time – that becomes increasingly shorter throughout the test – until they are no longer able to reach the next marker in the designated time(10). The test is scored by the number of laps completed, and VO_2max can be estimated from the test result(10).

The advantages of the PACER are that it requires very little equipment, and there are published healthy standards based on a cohort of thousands of American children(10). Plus, it is a maximal test, so it captures the same intensity of exercise as the Bruce protocol. Though the PACER does not directly measure oxygen consumption, it correlates well with VO_2max, and it provides more accurate estimates of VO_2max than submaximal tests, like the six-minute walk test(11).

1.2.4 Six-minute walk test (6MWT)

The six-minute walk test (6MWT) is a sub-maximal aerobic capacity test that was developed to test individuals with exercise limitations, such as the cardiorespiratory patient population. The 6MWT is a highly standardized test that requires participants to walk the longest distance they can between two markers, 30 meters apart, in six minutes(12). In most populations, like healthy adults and adolescents, there are age- and gender-corrected prediction formulas to estimate VO_2max values from the 6MWT distance(13, 14). However, since the correlations between 6MWT distance and VO_2max in children are weak, it is not recommended to estimate these values in the pediatric population(15).

The advantages of the 6MWT include its use in the clinic, feasibility, and its safety in cardiorespiratory populations. The 6MWT is commonly used in the clinic to evaluate physical ability pre-transplant, and to assess functional capacity in the perioperative time frame post-transplant. For this reason, 6MWT values may be acquired from patient charts, or compared to chart values longitudinally. Also, it is an accessible test that requires little equipment and resources to perform. Last, since it is a submaximal test, it is less likely to elicit symptoms in chronically ill patients, allowing better comparison between patient and control groups.

However, since this test does not require participants exert maximal effort, no conclusions can be drawn about participant's physiology at maximal exercise. Also, in healthy participants, there is a ceiling-effect where 6MWT distance become limited by height – due to its association with stride length – rather than fitness level(16).

1.2.5 Assessing fitness level using aerobic capacity measures

Though measures of aerobic capacity reflect the overall fitness level of an individual, they do not capture other elements of fitness that may limit a person's functioning or desire to participate in physical activity, such as muscle strength, endurance, or flexibility.

1.3 Muscle strength

1.3.1 Muscle strength

Muscle strength is defined as the maximum force that a muscle group can exert(17). In daily life, muscle strength is important for things like lifting or moving heavy items, climbing stairs, and getting up from a seated or laying position. Muscle strength measurements are more specific for a certain muscle group than aerobic capacity measurements, because they primarily reflect the functioning of the musculoskeletal system(18).

The major determinants of muscle strength include muscle mass, fiber type composition, muscle cell metabolism, and neural recruitment of muscle fibers. The greater the muscle mass, the greater the muscle strength, since there are more units available to contract to produce force(19). However, since generating force is an event that happens quickly, it is important that this muscle mass is composed of muscle fibers that can contract quickly. Therefore, the fiber type distribution (slow- vs. fast-twitch fibers) also has an effect on strength. There is a correlation between a higher number of fast-twitch (type 2b) muscle fibers and greater diameter of these fibers, and increased strength(18, 20). This correlation can be explained, in part, by the type of metabolism of fast-twitch muscle fibers. These fibers rely primarily on glycolysis, or anaerobic metabolism to generate energy(20). This type of metabolism generates energy more quickly than oxidative phosphorylation, or aerobic metabolism, but it makes the fibers tire more quickly as well. Neural recruitment of muscle fibers can also affect muscle strength. First, the magnitude of signals coming from the central nervous system and going to skeletal muscle increases with training(21). Also, with training, motor units (a motor neuron and its corresponding muscle fibers) fire more rapidly, and may fire more in synchronization with one another(21). Increased magnitude of signals, and motor unit firing rate and synchronization can increase muscle strength in trained individuals.

Muscle strength is usually measured by a device that produces a value of torque in newton meters or foot pounds. Muscle strength can be measured in large or small muscle

groups, both providing different types of information. Some of the more common tests for muscle strength are summarized in the following sections.

1.3.2 Dynamometry

A dynamometer is a device that measures the force generated against its sensor while a participant is pushing as hard and fast as they can against the device in a particular motion(22). This measure of torque reflects the muscle strength of the muscle group(s) being tested.

Dynamometers may be computerized dynamometers or hand-held devices. Computerized dynamometers, like the BioDex for example, are the gold standard for strength testing(23). A hand-held dynamometer (HHD) is a small device that can be used to test the force generated by a muscle group, using the appropriate manual muscle testing technique(24). Though this testing method does not provide the same level of muscle group isolation as a computerized dynamometer, a recent systematic review concluded that the amount of data provided by a HHD and its practicality make it an acceptable method of measuring muscle strength(25). Also, it is more affordable and can be easily transported to enable multi-center studies using the same equipment at each site. However, it is important to consider that HHD uses manual muscle testing, which requires more coordination and strength from many muscle groups to properly execute the movements.

1.3.3 Manual muscle testing

Muscle strength can be assessed by manual muscle testing (MMT), with or without dynamometry(26). In fact, MMT is one of the most common techniques for measuring muscle strength in the setting of physiotherapy. MMT is a method of assessing strength in isolated muscle groups, which provides information about specific muscles in the body. It can be used to identify weak muscles for future training, or as a proxy measure for larger functional groups. When performed without a dynamometer, the examiner decides on a score from a 5-point scale to determine muscle strength(24). These scores range from 0 which describes no visible or palpable muscle contraction, to 5 which describes full range of motion against gravity with maximal resistance(24). When combined with HHD, the device is held where the examiner would normally place their hands, and peak force, torque, and time can be measured(26).

Though MMT is less standardized than the BioDex, it provides an affordable alternative that uses either no equipment, or equipment that is easily transportable. However, these

techniques require a great deal of coordination from the participant, since they must use their own strength, rather than being strapped to equipment, to isolate the muscle group being studied. Further, testing reliability is dependent on the person rating the strength (MMT) or holding the dynamometer (HHD) having consistent technique, and remaining consistent for all participants and time points being compared(26).

1.4 Muscle endurance

1.4.1 Muscle endurance

Muscle endurance is defined as the number of times a movement can be repeated (dynamic endurance), or the amount of time a position can be held (static endurance), before exhaustion(27). Muscle endurance is important in everyday activities such as maintaining posture, standing for long periods of time, and sitting upright. Muscle endurance relies primarily on the muscular component of the musculoskeletal system(28).

The main determinants of muscle endurance are fiber type composition and muscle cell metabolism. Because endurance activities include holding a position for a period of time, or repeating slow movements, slow-twitch (type 1) fibers are primarily utilized in muscle endurance. These fibers mainly rely on oxidative phosphorylation, or aerobic metabolism, to generate energy(20, 28). Though type 1 fibers do not contract as quickly as type 2b fibers that are primarily used in strength, type 1 fibers are able to generate energy for longer periods, so they fatigue less quickly. Therefore, the more type 1 fibers a person has, the better their muscle endurance will be(20).

There are many different types of tests for muscle endurance, and because tests are used so widely in the literature, there is no gold standard. However, some of the more common muscle endurance tests that are used in children are summarized below.

1.4.2 FITNESSGRAM (90˚ push-ups and curl-ups)

The FITNESSGRAM is a fitness battery that was designed for standardized testing in American schools(10). It comprises many different types of fitness tests, including the PACER (*section 1.2.3*). Included in the fitness battery are two types of dynamic muscle endurance tests, the 90˚ push-up test, and the curl-up test.

The 90° push-up test is a modified push-up test, where participants perform a push-up to a cadence. In this type of push-up, the bottom position is indicated by a 90° angle at the elbow, and that position is held for slightly less than a second before the participant is asked to push back up to a plank position. The test is scored by number of repetitions until exhaustion, or until the examiner has detected two breaches in proper form by the participant. This test is considered an endurance test because it measures the number of repetitions, however it requires quite a bit of strength to be able to perform even one single push-up. For this reason, this test is criticised as an endurance test.

The curl-up test is similar to the push-up test, whereby there is a cadence to move up and down. However, in this test, the participant uses their core muscles to lift their upper body off the ground, until their fingers, which are elongated by the participant's sides, reach a set distance from their starting position. Though the curl-up test is considered a dynamic endurance test, it receives similar criticism to the 90° push-up test because of the strength versus endurance debate that was previously mentioned(29).

Despite their criticisms, both the 90° push-up and curl-up tests have been performed widely in America, and a large reference data set is available for these tests. Therefore, they are often used in fitness assessment in children.

1.4.3 Timed wall-sit

The timed wall-sit test is a new muscle endurance test that assess muscle endurance of the lower body. The timed wall-sit test was first described in 2012 in the setting of injury risk assessment in football players(30). The timed wall-sit test involves taking a seated position against a wall, without a chair for support, and holding the position as long as possible. The time from the beginning of the test until exhaustion, or until the participant breaks proper form twice, is the measure of endurance for this test.

One advantage of the wall-sit test is that it requires very little equipment (a timer and a wall). Also, in contrast to the push-up and curl-up tests, participants use gravity to settle into the position, rather than strength to lift themselves. However, limited data about the validity and reliability of this test currently exists in the literature.

1.5 Factors that affect fitness

1.5.1 Fitness limitations in transplantation

In healthy individuals, it is thought that oxygen delivery, mainly determined by cardiac output, is the main determinant of VO_2max(31). In children, with age, absolute VO_2max increases over time, but VO_2max relative to body weight in kilograms has a different pattern. In healthy male children, relative VO_2max increases or remains constant until a peak around age 17-21 years, after which relative VO_2max declines. In healthy female children, relative VO_2max increases or remains constant until a peak around age 12, after which relative VO_2max declines. It is unknown whether these patterns occur in the pediatric transplant population.

In individuals with chronic illness, symptoms or other factors may limit aerobic capacity before oxygen delivery. In some settings of illness, systems that affect oxygen and nutrient delivery can limit muscle strength and endurance before the musculoskeletal reserves are exhausted(32, 33). The determinants of fitness in the pediatric transplant population are not well understood. Some potential limiting factors in the pediatric transplant population are described in the following sections.

1.5.2 Calcineurin inhibitor (CNI) treatment

Calcineurin inhibitor (CNI) medications, such as tacrolimus and cyclosporine, are standard anti-rejection therapies in pediatric transplantation. Though these drugs have desirable effects on T cell function, they may have undesirable side effects on muscle function (34). Figure 1-1 shows the effects of calcineurin in a muscle cell(34). As shown in the figure by *Michel et al. 2004*, under stimulation of muscle contraction above native levels, calcineurin stimulates transcription of factors that increase synthesis of oxidative muscle fibers (type 1 and 2a) and muscle hypertrophy. If calcineurin is inhibited, oxidative muscle fibers, and overall muscle mass may be reduced. Studies in rat skeletal muscle have shown that cyclosporine A treatment results in a decrease mitochondrial respiration(35), oxidative activity(36), and capillarity(36). Though it has been shown that tacrolimus, the CNI of choice in pediatric heart transplant recipients at Canadian centres, exhibits NFAT-interfering activity in T-cells(37), it is unknown whether it has similar effects within skeletal muscle cells or on overall muscle physiology. Further studies are needed to determine the specific effects of tacrolimus in skeletal muscle, and whether the effects of CNIs affect functional capacity in humans.

1.5.3 Corticosteroid treatment

Corticosteroids are known to interfere with muscle function. It has been shown that corticosteroids can affect glycogen metabolism in human skeletal muscle(38), and glutamine synthase induction in rat skeletal muscle(39). In adult renal transplant recipients taking prednisone, cross-sectional area of muscle fibers, especially type 2b fibers, is reduced(40), and these alterations are minimized when steroids are withdrawn(41). The effects of prednisone on muscle physiology have not been investigated in recipients of other types of transplant. In patients with glucocorticoid excess, myopathy is usually observed in the proximal, rather than distal, skeletal muscles(42).

1.5.4 Heart graft function

The oxygen demand of peripheral systems increases greatly during exercise, which means the heart must pump more blood to match this demand(4). The heart can pump more blood by increasing the number of times it contracts in a given time, known as heart rate, or by increasing the amount of blood it pumps with each contraction, known as stroke volume. If either heart rate, stroke volume, or their product, called cardiac output, are reduced, oxygen and nutrient delivery to the muscles may limit exercise capacity(43). Progressive graft failure, chronic rejection, and baseline damage may all play a role in limiting the heart's response to exercise (44, 45). In fact, exercise testing is often used to test heart function, and evaluate level of graft function in heart transplant recipients(46).

Both heart rate and stroke volume may be affected by graft function, which varies by graft among individuals, and by time within individuals(47). During transplantation, the heart is denervated from the host. To compensate for reduced sympathetic neural tone, catecholamines are released from the adrenal gland to act on β_1-receptors in the heart, which increase heart rate and contractility(48). Catecholamines are higher at baseline in individuals with heart transplants, and they increase with exercise to increase cardiac output to match the demands of the working tissues(48, 49). This hormonal response is slower than the neural response of healthy individuals, so transplant recipients must warm-up gradually before starting physical activity to avoid syncope. At maximal exercise, heart rate is usually lower than non-transplanted individuals; however, to maintain cardiac output, there is usually a compensation in stroke volume via Frank-Starling mechanisms(49). The Frank-Starling theory states that by increasing preload, or volume of blood in the heart, the stretch in the heart increases, which then increases the ejection fraction, or amount of blood pumped out of the heart(50).

There is conflicting evidence about transplanted heart reinnervation in the pediatric recipient. There is some evidence to suggest that the graft in pediatric heart transplant recipients reinnervates(51-54). However, it is not clear whether this happens in only a subset of individuals or all individuals, the timing of this reinnervation, or to what extent the heart regains neural function.

1.5.5 Kidney graft function

During exercise, it is important to stay hydrated, maintain blood pressure, maintain electrolyte balance, and be able to excrete muscle breakdown products. The kidney plays a role in all of these mechanisms, so any problems with kidney graft function could affect a renal transplant recipient's ability to exercise.

After exercise, it has been shown that kidney transplant recipients have lower proteinuria than healthy controls(55). It was hypothesized by the authors that this reduction in proteinuria may occur because the denervated kidney receives less catecholamine signals, which would normally increase glomerular membrane permeability. However, further studies are needed to continue to explore how the function of the renal graft may affect a transplant recipient's exercise capacity.

1.5.6 Hemoglobin level

Hemoglobin level affects a person's ability to deliver oxygen to the working muscle during exercise(31). Even if a person is not anemic or hemoglobin-deficient by clinical standards, they may have a sub-optimal hemoglobin level for maximal exercise. Hemoglobin level has a greater effect on types of exercise that use aerobic metabolism, such as aerobic capacity and muscle endurance.

In kidney transplantation, erythropoietin production may be affected, either by the graft(56) or by taking enalapril(57), which results in lower hemoglobin levels. For this reason, most kidney transplant recipients take iron, and their hemoglobin is monitored closely. Despite these interventions, hemoglobin level may not return to normal in renal transplant recipients(58).

1.5.7 Physical activity level

Physical activity type and level can affect a person's fitness and physical ability(59). Physical activity type determines which physiological systems are developed (for example, aerobic capacity versus muscle strength). Physical activity level determines to what extent those systems are developed.

In the pediatric heart and kidney transplant population, physical activity level is typically lower than healthy peers(60, 61). This finding is likely explained by a variety of factors, including physician recommendations, protective parenting, and patient fatigue. However, more research is needed to determine specific barriers to physical activity level in the pediatric transplant population.

1.5.8 Natural ability and genetics

Some children are naturally better than others at certain physical activities, making them more likely to perform better at certain fitness tests. This natural ability is likely a combination of both genetic and environmental factors. This range in natural ability affects any study that assesses fitness, and is part of the inherent variability among individual participants.

1.5.9 Motor coordination and cognitive ability

Performing fitness tests requires the participant to both understand what is being asked of them, and have the coordination to execute the task that they have been asked to perform. These cognitive and motor abilities vary by age and stage of development, and may be affected by other clinical conditions that are present in pediatric transplant recipients, like developmental delay or persisting deficits from a stroke.

The pediatric transplant recipient population has a greater incidence of cognitive disabilities and neuromotoric limitations, due to developmental problems, disorders associated with congenital disease, or treatment complications, such as stroke caused by ventricular assist device(62). Cognitive disabilities may affect a child's ability to follow commands, which is a key component to performing movements necessary for fitness testing. Motor disabilities may affect a child's ability to perform movements, despite their ability to cognitively execute a command. Therefore, when evaluating fitness in the pediatric transplant population, one must consider whether to include patients with neuromotoric deficits to reflect the full scope of the population,

or to exclude these patients to gain a better understanding of the factors that relate more directly to transplantation.

1.5.10 Pre- and post-transplant course

Pre-transplant course varies on an individual basis, and is affected by pre-transplant diagnosis and organ availability. In pediatric heart transplantation, there are two main categories of pre-transplant course: congenital heart disease or cardiomyopathy(63).

Generally, patients with congenital heart disease are sick from the beginning of their development, and often have one or more surgeries to attempt to repair their defects before referring to transplant. Therefore, they spend the majority of their pre-transplant life living with significant illness. In many cases, patients are bedridden or unable to participate in physical activity for a significant amount of time before and immediately after receiving an organ. Though it has not been well studied in the pediatric transplant population, it is reasonable to expect that there is some muscle wasting while patients are ill or recovering from surgery, which may affect their muscle development.

On the other hand, patients with myocarditis may be quite well until they acquire a virus, or patients with cardiomyopathy may feel well until they start feeling symptoms of an underlying genetic disorder. These patients may have years of healthy life and development before being listed for transplant. Other patients with cardiomyopathy are sick from birth, like congenital heart disease patients. Therefore, it is important to remember that each patient has their own journey before transplantation, and there is a great deal of variability in pre-transplant course.

Post-transplant course can be equally variable. Some patients are out of the hospital and back to living at home after 2 weeks, and others remain in hospital for years after their transplant. The longer the time spent in hospital, the greater the risk of muscle wasting(64).

1.5.11 Summary

There are many variables that may affect fitness after pediatric transplantation, but further studies are needed to gain a better understanding of how these factors may affect fitness level and physical function.

1.6 Considerations for fitness testing in pediatric transplant recipients

1.6.1 Small sample sizes

Though transplantation is the treatment of choice for end-stage organ failure in children, there are few candidates, and even fewer donors available. This results in a small group of children living with transplants, with a wide geographic distribution in Canada. Therefore, prospective studies are limited to either small sample sizes, or designing methodology that can be transported, or completed using different equipment at different centers. In a population with such large variability in terms of clinical course and status, it can be difficult to achieve sufficient power to draw meaningful conclusions. The alternative, to design strict inclusion and exclusion criteria, may introduce bias to studies by selecting a subset of the population that is perhaps healthier than the entire population. When designing a study for the pediatric transplant population, it is important to be very precise with study aims and selection criteria, in order to ensure data analysis will provide meaningful data.

1.6.2 Stage of development

A unique consideration for fitness testing in the pediatric population is the occurrence of puberty. This stage of development usually occurs by age 11 in girls and age 13 in boys(65). When males reach pubescence, there are more circulating androgens in their body, which allows them to have greater gains in muscle mass with exercise(66, 67). In females, it is postulated that growth hormone and insulin-like growth factor contribute to increased muscle development(68).

In pediatric kidney transplantation, though many patients are affected by short stature, it appears that pubertal growth is not affected(69). Similarly, even though some pediatric heart transplant recipients are shorter as children, their pubertal development is not affected(70). However, the supporting studies were only conducted in small cohorts, so further evidence would be encouraged to support this finding.

Even in cohorts with normal puberty development, it is encouraged to include a similar proportion of participants before and after the onset of puberty among groups, in order to control for this factor.

1.6.3 Timing of testing

Like any surgery, after transplantation, there is a physical recovery period post-operatively. Next, there is a period of adaptation to life with a functioning organ, where exercise capacity gradually improves(52). In pediatric heart transplant recipients, this time period is thought to be around the two-year mark(71). Then, exercise capacity levels off, and eventually starts to decrease with time post-transplant(71). When exercise capacity begins to decline, there is an association with coronary artery vasculopathy. These findings, however, are limited to data from one study. Further longitudinal studies would be needed to confirm these findings. For kidney transplant recipients, there is little evidence regarding how fitness level changes with time after transplant, though it is conceivable that a pattern similar to pediatric heart transplantation exists.

1.6.4 Appropriate outcome measures

Though many studies have measured aerobic capacity using VO_2max testing(47, 72-75), there is a wide variety of muscle strength and endurance tests in the pediatric transplant literature. It is possible that the reason for this variability is that no existing tests address the needs of the pediatric transplant population. Push-ups and curl-ups, which are muscle endurance tests, require strength to perform the movement, as mentioned in *section 1.4.2*. However, many transplant patients lack the strength to perform even a single push- or curl-up, limiting the use of these tests to assess muscle endurance. Other, more accessible measures, would be encouraged for use in this population. Once such an ideal parameter or set of parameters is established, perhaps there could be more consistency in the literature.

1.7 Rationale

1.7.1 Systematic review and meta-analysis

Though it is known that pediatric transplant recipients have lower fitness levels than their healthy peers, the level to which that fitness is impaired, and the causes of this impairment are not understood. In part, this is due to the small sample size of existing studies. By synthesizing existing data, a more complete and comprehensive profile of fitness level in

pediatric transplant recipient may be generated. By comparing studies of all types of transplant, both the unique and common challenges associated with each type of transplant may be captured. A systematic review and meta-analysis would provide information to researchers and physiotherapists, who can design transplant-specific rehabilitation programs and activity recommendations that focus on the fitness parameters and muscle groups that are most affected by pediatric transplantation.

1.7.2 Fitness assessment

Though a systematic review and meta-analysis would synthesize existing knowledge, gaps in the literature still need to be filled to gain a better understanding of the level and causes of impaired fitness in the pediatric transplant population. First, there is little data regarding muscle strength and endurance in pediatric transplantation, which may be a key component to understanding fitness due to the effects from immunosuppressive regimens and clinical course. Next, since current studies show that cardiac output is normal during exercise in pediatric heart transplant recipients, further investigations are needed to evaluate the effect of non-graft, transplant-related clinical factors on fitness level. Last, a new tool for the study of muscle endurance which uses gravity, rather than strength to attain proper form for the test, may provide a more specific assessment of the muscle endurance component of fitness in pediatric transplant recipients, which could be used in research and in the clinic going forward. The more the cause of fitness impairment is understood, the more effective therapy, activity recommendations, and rehabilitation programs can be developed to improve physical functioning and long-term outcomes in pediatric transplant recipients.

1.8 Hypotheses

Since prior studies have shown that fitness parameters are impaired in the pediatric transplant population, it is hypothesized that aerobic capacity, muscle strength, and muscle endurance measured in both the meta-analysis and fitness assessment will be significantly lower than healthy comparators. Because each organ has a unique contribution to exercise adaptation and treatment regimens differ by type of transplant, it is hypothesized that there will be different values for fitness parameters among types of organ transplant. It is hypothesized that some clinical factors, such as duration of corticosteroid use and hemoglobin level, will correlate

with fitness parameters. Last, it is hypothesized that wall-sit time will be a valid measure of muscle endurance in the pediatric transplant population.

1.9 Research aims

1) To quantify the degree of muscle strength, muscle endurance, and aerobic capacity for transplant recipients as compared to healthy controls, and compare these variables among different types of organ transplants.
2) To investigate the relationship between clinical factors and fitness parameters to gain a better understanding of the clinical course of pediatric transplant recipients may affect their fitness level.
3) To investigate the relationship among the timed wall-sit test, other muscle endurance tests, muscle mass, and muscle strength to assess how the wall-sit test may relate to other functional and anatomical muscle function parameters that are commonly measured in the pediatric transplant population.

1.10 Tables and figures

Figure 1-1 The role of calcineurin in muscle development
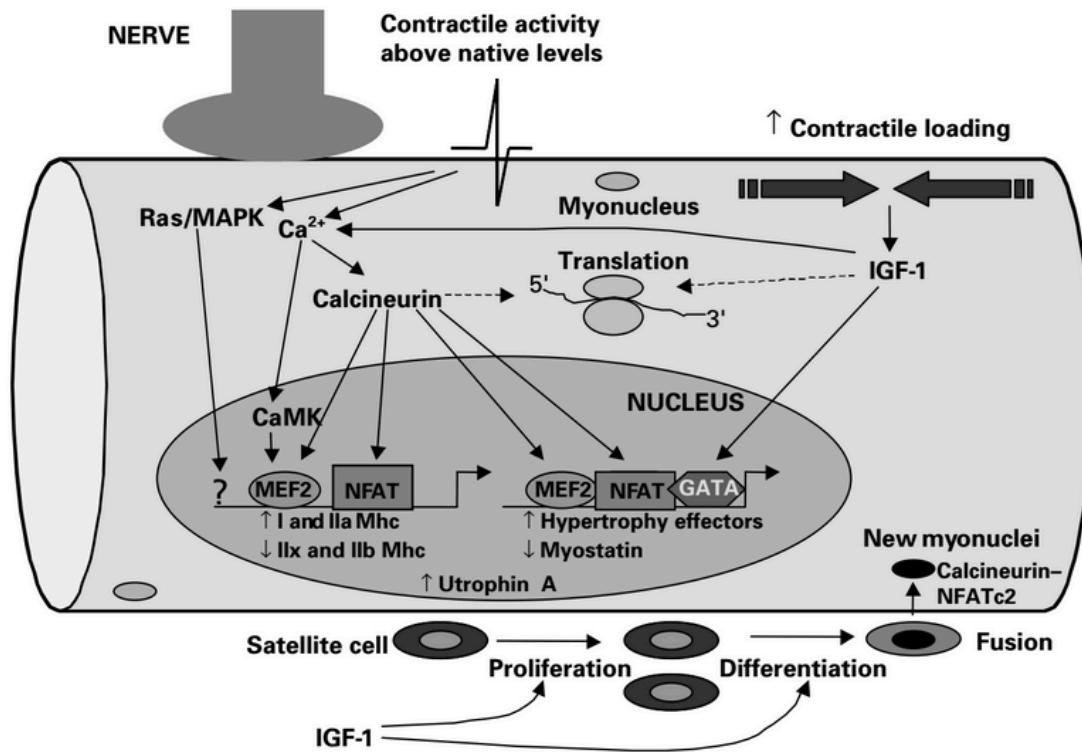
The role of calcineurin in muscle development, taken from *Michel et al. 2004*(34).

Chapter 2: Methods – Systematic Review and Meta-Analysis

2.1 Cochrane method

The Cochrane method for systematic review was followed for this study(76). The protocol for this systematic review was registered with PROSPERO (CRD42016050205), an international prospective register of systematic reviews. The study was registered with PROSPERO so that other researchers conducting systematic reviews were aware that our review was ongoing, and that work was not duplicated.

2.2 Questions

The research questions for the literature search included: What is the effect of each type of pediatric transplant on fitness, as defined by level of aerobic capacity, muscle strength, muscle endurance, and flexibility, after transplantation? How is quality of life affected by fitness after pediatric transplantation? Which clinical factors affect fitness after pediatric transplantation?

2.3 PICOTSD

2.3.1 PICOTSD

As per the Cochrane method, this study used the following search parameters: population (P), intervention (I), comparison (C), outcome (O), time (T), setting (S), design (D). The values for each parameter are defined in the following sections.

2.3.2 Population

The population for this study was pediatric transplant recipients. Pediatric age was defined as 0-17 years (inclusive) at the time of transplant, and any time post-transplant. Therefore, adult participants were included in the analysis if they were transplanted as children. Studies where even one participant may have been transplanted over 17 years old were excluded. If individual patient data was presented where some patients did and some patients did not

meet the inclusion criteria, the study was included, and only the data for those patients who met the study criteria were included in the meta-analysis.

2.3.3 Intervention

The intervention for this study was pediatric transplantation (age 0-17 years). The types of transplant included were heart (HTx), lung (LuTx), liver (LiTx), kidney (KTx), and bone marrow (BMT). Studies with participants who received multi-organ transplant (i.e. heart-lung, kidney-pancreas, etc.) were excluded. Studies with participants who received multiple transplants of the same organ type were included.

2.3.4 Comparison

To be included, studies must have had a comparison to either a healthy control group, or normative data. A healthy participant was defined as a person living without a transplant or other chronic illness that would significantly affect their ability to exercise. When studies referenced another study as their normal comparison, they were included in the review. However, if no comparison was made to the referenced data, the study was excluded. If the referenced data was not from a healthy population, the study was excluded.

2.3.5 Outcome

Primary measures included aerobic capacity, muscle strength, and muscle endurance. Studies were included if they had any one of the primary measures, regardless of the methodology they used to assess those fitness variables. This very inclusive criteria were chosen in order to gain the most comprehensive view of fitness level in the pediatric transplant population, and discuss methodology in the field going forward.

Secondary measures included physical activity level and quality of life. Studies with a secondary measure were only included if they also had a primary measure.

2.3.6 Time

Studies from 1990 to present were included. The data collection period was 2 years to search, screen, and analyze all the relevant articles in the literature. The data collection period started in August 2016 and continued until August 2018.

2.3.7 Setting

Fitness assessments may have been performed in hospitals, university-sanctioned facilities, or any outpatient clinic.

2.3.8 Design

In an effort to be inclusive, all types of primary literature were included, such as cross-sectional studies, cohort studies, case-control studies, and randomized controlled trials, except case studies. For cohort studies, the fitness assessment from the earliest time point post-transplant was used for the meta-analysis to avoid any potential bias towards increased physical activity from being enrolled in a fitness study. Secondary sources were excluded, such as reviews and book chapters.

2.4 Inclusion and exclusion criteria

Inclusion criteria were the PICOTSD criteria outlined above. Exclusion criteria were studies prior to 1990, other transplant types (small bowel, pancreas, skin), animal studies, studies in languages other than English and French, opinion pieces, review papers, case-studies, and duplicate data.

2.5 Search strategy

The following databases were searched: Ovid Medline (1946 to Present), Ovid Embase (1988 to Present), and CINAHL Plus with Full Text via EBSCOhost (1937 to Present). The search strategies combined subject headings and text words for three concepts: organ transplantation, pediatric patients and exercise testing. Database search strategies were limited to publications from 1990 to current, and used search filters to exclude animal studies, opinion pieces (comments, editorials, etc.) and case studies. See Appendix A for Medline strategy.

ProQuest Dissertations and Theses Global (1861 to Present) were searched for relevant doctoral and master's theses from 1990 to current. Proceedings from the past two years of the Canadian Society of Transplantation-Canadian National Transplant Research Program (CST-CNTRP) Annual Joint Scientific Meeting, International Society of Heart and Lung Transplantation, and the International Congress of The Transplant Society were hand-searched.

All search results were managed using EndNote X5 citation manager software and converted to Microsoft Excel for analysis.

2.6 Study selection

Results from the initial search were sorted based on inclusion and exclusion criteria in study abstracts, using Microsoft Excel. The process was repeated by a second researcher, and in the case of discrepancies, the two reviewers discussed whether the articles in question should proceed to secondary screening. The inclusion/exclusion process was repeated based on the full journal article for the secondary screening. The secondary screening form that was created for this study can be found in Appendix B. The selection process was tracked and summarized in a PRISMA flow diagram(77).

2.7 Qualitative review

A qualitative review of the included studies was written to answer the study questions in section 2.2. The contributions of each study to the assessment of fitness level were evaluated, and other clinical factors that may have correlated with fitness in each study were noted. Study methodology was also reviewed, and recommendations were made for the field going forward.

2.8 Quality assessment

The Newcastle-Ottawa Scale for assessing quality of nonrandomised studies in meta-analyses was used to assess internal validity of included studies(78). Separate scales were used for each cohort, cross-sectional, and case-control studies. The Newcastle-Ottawa Scale produces a score out of 10, with 10 being the highest, that described the quality of the article. The quality assessment was conducted by two reviewers, and studies were discrepancies were assessed by a

third reviewer. If the scores were still different, the first and third reviewer met to decide on the final quality score.

2.9 Data extraction and extrapolation

2.9.1 Data extraction

Measurements of aerobic capacity, muscle strength, and muscle endurance were extracted from all studies. Four measures of aerobic capacity were extracted: measured or predicted VO_2max, exercise time during the Bruce protocol, number of laps from the PACER, and distance walked on the 6MWT. Two muscle endurance measures were extracted: number of push-ups, and number of curl-ups. The parameters extracted for muscle strength were dynamometry, HHD, and hand-grip strength. When it was available, torque was extracted for muscle strength. If torque was not presented in the study, force was extracted as the measure of muscle strength. For each test, the mean difference and pooled standard deviation for both the transplant and healthy comparators were extracted.

For all studies, the countries involved in the study, type of organ transplant, number of recruiting centers, number of transplant recipients and controls, sex distribution, enrollment age, enrollment time post-transplant, type of fitness test, fitness testing equipment, fitness test score, percent of healthy values, type of control data (controls vs. normative data), mean age, mean time post-transplant, and mean age at transplant were also extracted for each study. These values were summarized into two tables, describing the included studies, and the study characteristics.

Data was collected in both Microsoft Excel and Review Manager version 5.3(79).

2.9.2 Data extrapolation

To handle missing data or data with incorrect statistics, published guidelines were followed(80). These guidelines were used to convert median and range to mean and standard deviation values, as well as standard error to standard deviation. When there were no clear guidelines, data was extrapolated in the following manners.

When data were presented as $x \pm y$ for a given fitness variable, but there was no indication of the type of values that were presented, it was assumed that x was the mean. To determine if y was standard error (SE) or standard deviation (SD), the values were compared to

other studies in the same comparison group (e.g. heart transplant aerobic capacity), and the type of error was chosen accordingly. If it was determined that the error type was SE, it was converted to SD, like the other studies where data were presented as mean ± SE.

When control data was presented as percent predicted ± SD or SE, and the control data from another study was referenced, the control data was calculated using the following equations, that were created by the research team:

$$control\ mean\ (absolute\ value) = \frac{experimental\ mean\ (absolute\ value)}{\frac{control\ mean\ (\%\ predicted)}{100\%}}$$

$$control\ error\ (absolute\ value) = control\ mean\ (absolute\ value) \cdot \frac{control\ error\ (\%\ predicted)}{100\%}$$

In these cases, the N-value for the control group was set to match the N-value for the experimental group, making the assumption that authors calculated the percent predicted values for the experimental group by comparing individual patient data points to the referenced values, rather than comparing the experimental group mean to referenced values. However, the study characteristics for the referenced study are still reported in the tables of included studies (Table 3-1) and study characteristics (Table 3-2) to provide the reader with an idea of the data set from which the reference values were computed.

When the reference value mean, but not SD, was presented in the patient study, the SD was calculated for all participants in the reference study. Though this SD may not be from the exact same data set as the mean calculation, it provides a reasonable estimate.

When the experimental group was subdivided, a weighted average of the subgroups was taken to determine the mean and error for the group as a whole. The whole group data were used in the meta-analysis.

When control data were presented as separate age, height, and/or sex groups, but not as a comparison group as a whole, there were two methods. When the individual patient data were presented for the transplant group, then a control mean and error value were taken for the corresponding age, height, and/or gender group for each patient, and the mean of the mean and mean of the error were used for the comparison group. When the individual patient data were not present, the age or height for the group as a whole was used, and a weighted average of these values based on the gender ratio was used, if applicable. In both of these cases, the N-value was

calculated as a sum of the N-value of all the subgroups used to calculate the control data. When the N-value for each subgroup was not presented, the following calculation was used:

$$control\ N\ value = \frac{total\ N\ value}{total\ \#\ subgroups} \cdot \#\ subgroups\ used\ for\ control\ N\ value\ calculation$$

When data were presented as mean with 95% confidence interval, a normal distribution was assumed so that the following equation was used to calculate the standard deviation:

$$95\%\ CI\ =\ mean\ \pm\ ((z\ score)(SD/\sqrt{n}))$$

When data were presented as individual patient data points on a graph, and summary values were not given, the values were taken from the graph, and the mean and SD were calculated. If a line was present for one data set, and individual patient data presented for the other on the same graph, then values from the data set presented as a line were extracted at the same *x*-values as the other, individual data point set.

If a study presented individual patient data, but some of the patients were not part of the study population (in most cases, they were too old), the mean and standard deviation were calculated for the points of the individuals that met the study criteria. In one study, patients were compared to two control groups, one of the same chronological age, and one of the same body surface area. The ages were presented for the patients but not the controls. Nine out of 10 patients met the study criteria, and the body surface area group was slightly younger than the chronological age group, so all 10 values for the body-surface area matched group were used to calculate the comparator values.

When a study presented two or more transplanted groups, separated into different clinical categories, a weighted average based on N-value was calculated for each parameter.

When a study presented multiple healthy control groups or reference values, and comparisons were made between the transplant group and each of these control groups, the control group that had the greatest degree of matching and controlled variables was used.

2.10 Meta-analysis

A quantitative meta-analysis of common measures of aerobic capacity, muscle strength, and muscle endurance were performed. The data were divided into subgroups by type of transplant, type of fitness test, and type of healthy comparator.

Eight studies were excluded from the meta-analysis. Three studies (N=2 HTx, N=1 KTx) were excluded because they were the only studies that measured aerobic capacity with ml/min or L/min, and thus could not be compared with other studies with ml/kg/min units. Two studies were excluded because they were the only studies with the same test within their organ group (N=2 KTx). One study was excluded because there was insufficient data for the referenced normative values (no standard error or deviation; N=1 KTx). Two studies were excluded because they presented the same data as a previously published study (N=1 HTx, N=1 KTx).

Forest plots were used to report results for each sub-group comparison. Continuous variable analysis was used for all groups and subgroups, because all extracted data was continuous. A fixed effects analysis was used, assuming that the effect of each subgroup related to the condition of that group (i.e. fitness impairment in heart transplantation was related to the heart transplant). A I^2 test was used to measure and report heterogeneity. Data for each study, group, and subgroup are reported as mean difference (95% confidence intervals). Subgroups differences were tested by subgroup analysis (P<0.01).

Summary data for the N-value of the transplant group, N-value of the control group, gender ratio, age, time post-transplant, were age at time of transplant were calculated for all included studies, and reported by type of organ transplant as mean ± SD.

RevMan 5.3 software was used to create forest plots and analyze meta-data(79). Microsoft excel was used to generate summary data.

Chapter 3: Results – Systematic Review and Meta-Analysis

3.1 Literature search and screening

The literature search produced 6,484 results in total, of which 4,394 remained after duplicates were removed (Figure 3-1). After primary screening, 4,261 records were excluded because they did not meet the study criteria (any PICOTSD parameter), and 133 full-text articles were assessed for eligibility.

Of the 133 full-text articles that were screened, 101 were excluded. Fifty-six articles were excluded for population, 11 for comparator, 10 for intervention, 9 for language, 5 for publication type, 5 for study design, and 5 for outcome.

Thirty-two studies were included in the final qualitative synthesis, and 24 of those were included in the meta-analysis. Reasons for excluding studies from the meta-analysis included duplicate data sets in different studies (N=2), missing data (N=1), and being the only study in a subgroup to use a given test or unit (N=5). Five studies presented data for more than one fitness test, and both results were included in the meta-analysis. One study presented data for more than one type of transplant (LiTx and KTx). For that study, the data was split into each type of transplant and then analyzed in the respective subgroup.

3.2 Included studies

3.2.1 Details of included studies

Of the 32 included studies, 13 related to HTx, 10 to KTx, 4 to LiTx, 4 to BMT, 1 to both KTx and LiTx, and 0 to LuTx (Table 3-1). Studies ranged in date from 1992-2016. Studies were performed in 25 countries, including 9 in the Unites States of America, 7 in Italy, 3 in Canada, 3 in Norway, 2 in Brazil, 1 in Belgium, 1 in Colombia, 1 in Denmark, 1 in France, 1 in France and Czech Republic, 1 in Spain, 1 in the United Kingdom, and 1 in 14 South American countries, including Brazil, Argentina, Chile, Venezuela, Mexico, Cuba, Colombia, Costa Rica, Nicaragua, Guatemala, Ecuador, Honduras, Paraguay, and Peru. Sixteen studies used healthy controls within the study for comparison, and 16 studies used normative data from other studies as the healthy comparison. The average number of Tx recipients per study was 29 ± 23 patients, 29 ±

37 healthy participants in controlled studies, and 193 ± 116 healthy participants in studies with normative data.

3.2.2 Characteristics of included patients

Table 3-2 shows the characteristics of the populations in each study, and Table 3-3 shows the summary of these values, organized by type of organ transplant.

Overall, there were more males than females studied. The HTx group included 61 ± 10 % males, the KTx group included 62 ± 14 % males, the LiTx group included 50 ± 16 % males, and the BMT group included 58 ± 5 % males. The trends were similar in the gender composition of the control groups for these studies. The HTx controls were 61 ± 16 % male, in the KTx controls, 57 ± 11 % male, in the LiTx controls, 55 ± 6 % male, and the BMT controls, 52 ± 1 % male.

All studies reported the age of the transplant group. The mean age was similar between types of organ transplant, but the kidney group was slightly older (15.2 ± 3.4 y) than the bone marrow (13.6 ± 5.3 y), heart (12.9 ± 3.5 y), and liver (12.3 ± 3.1 y) transplant groups. The age of the control group was reported in 26 of 32 studies. Similar to the transplant groups, the mean age of the control group was highest in the KTx study controls (16.2 ± 2.7 y), and lower in the other types of transplant controls (heart = 12.4 ± 2.5 y; liver = 11.3 ± 2.2 y; bone marrow = 11.3 ± 2.0 y).

The mean age at transplant was reported in 18 out of 32 studies. The mean age at transplant was younger in the liver group (5.7 ± 3.8 y) than the other three groups (heart = 8.5 ± 3.4 y; kidney = 8.7 ± 3.7 y; bone marrow 8.5 ± 5.1 y).

The time post-transplant was reported in 29 out of 32 studies. The mean time post-transplant was different in each group. From shortest to longest, the mean time post-transplant was 3.2 ± 2.0 y in the BMT group, 4.1 ± 2.1 y in the HTx group, 6.0 ± 3.1 y in the KTx group, and 7.2 ± 3.8 y in the LiTx group.

3.3 Aerobic capacity

3.3.1 Overview

All (N=32) studies measured aerobic capacity. Twenty-four studies measured VO_2max (N=10 on treadmill, N=13 on cycle ergometer, N=1 on both treadmill and cycle ergometer), 6

measured exercise time, 3 used the 6MWT, and 2 used the PACER. Sixteen studies used control groups in their study, whereas 16 studies compared their patient population results to normative data. When looking at the combined percent predicted aerobic capacity of each test in each type of transplant, HTx had the lowest score at 71 ± 12 %, followed by LiTx at 72 ± 10 %, then BMT at 73 ± 15 %, and then KTx at 75 ± 14 % (Table 3-3).

3.3.2 VO$_2$max

VO$_2$max was the only variable measured in all 4 types of transplant in the study. VO$_2$max was lower in the transplant population than the healthy comparison group in all studies. The mean difference in VO$_2$max between transplant recipients and healthy participants was greatest in the BMT group -12.18 (-14.12, -10.23) ml/kg/min, followed by the HTx group at -11.89 (-12.94, -10.85) ml/kg/min, then the KTx group at -11.74 (-13.25, -10.22) ml/kg/min, and last, the LiTx group at -9.87 (-12.60, -7.14) ml/kg/min (Figure 3-2). The mean difference was significantly lower in each transplant group, and in the whole transplant group, as compared to controls (P<0.01). The overall heterogeneity (I^2) was 85%, being highest in the HTx group (89%), then the BMT group (88%), then the KTx group (84%), and last the LiTx group (54%).

When HTx VO$_2$max was divided into sub-groups by type of healthy comparison, the mean difference between transplant recipient VO$_2$max and healthy values was greater when normative values were used -14.94 (-16.83, -13.04) than when in-study healthy controls were used -10.55 (-11.81, -9.30) (P<0.01; Figure 3-3). This difference was also observed in the KTx group. The mean difference between transplant recipient VO$_2$max and healthy values was greater when normative values were used -14.45 (-17.20, -11.71) than when in-study healthy controls were used -10.54 (-12.36, -8.72) (P<0.01; Figure 3-4).

3.3.3 Exercise time

Exercise time was measured in 1 study in the BMT group, 1 study in the KTx group, and 4 studies in the HTx group. Exercise time was lower in the transplant population than the healthy comparison group in all studies.

The mean difference in exercise time between BMT recipients and healthy controls in the study by Eames et al. 1997 was -1.50 (-2.29, -0.71) minutes. The mean difference between KTx recipients and healthy controls in the study by Matteucci et al. 1996 was -1.60 (-3.63, 0.43) minutes.

The mean difference in exercise time between HTx recipients and controls in the 4 analyzed studies was -3.27 (-3.83, -2.71) minutes (Figure 3-5). HTx recipient exercise time was significantly lower than that of the control groups (P<0.01). Heterogeneity was high (I^2=93%) among HTx studies in this analysis.

3.3.4 6MWT

6MWT distance was measured by 1 LiTx and 2 KTx studies. 6MWT distance was lower in the transplant population than the healthy comparison group in all studies.

The mean difference in 6MWT distance between LiTx recipients and controls in the study by da Silva et al. 2014 was -176.00 (-211.67, -140.33) meters.

The mean difference in 6MWT distance between KTx recipients and controls in the two analyzed studies was -152.66 (-177.94, -127.38) meters (Figure 3-6). KTx recipient 6MWT distance was significantly lower than that of the control group (P<0.01). Heterogeneity was high in the analyzed studies (I^2=98%).

3.3.5 PACER

PACER laps were measured by 1 KTx study, and 2 LiTx studies. PACER laps were lower in the transplant population than the healthy comparison group in all studies.

In a study by Krasnoff et al. 2006, the mean difference between the KTx recipient and control PACER scores in the KTx was -21.3 (-27.32, -15.28) laps.

In the group of studies assessing PACER in LiTx (N=2), the mean difference between the LiTx recipient and control scores was -8.44 (-12.06, -4.80) laps (Figure 3-7). PACER lap number was significantly lower in LiTx than controls (P<0.01). Heterogeneity among studies was high (I^2=81%).

3.4 Muscle strength

Three studies measured muscle strength in the pediatric transplant population. One study had a control group and 2 studies used normative values for healthy comparison. The type of muscle strength tests varied, so meta-analysis was not possible.

Feber et al. 1997 was the first to report muscle strength in the pediatric KTx population. In this study, maximum grip force, as measured by dynamometry, was 30.96 ± 18.89 kPa in the left hand, and 35.22 ± 17.66 kPa in the right hand. There were no comparisons made to healthy control or normative values.

Krasnoff et al. 2006 reported that knee extension peak torque in KTx recipients was 54.4 ± 19.8 ft·lb, which was only 67% of the mean value of the normative population(81). LiTx recipient muscle strength was also reported in that study. In LiTx recipients, knee extension peak torque was 49.8 ± 14.8 ft·lb, which was 67% percent of the mean value of the normative population. There was no error reported for the healthy population, so the mean difference and confidence interval could not be computed.

San Juan et al. 2007 studied muscle strength in BMT recipients. They used the 6-repetition maximum (6RM) test, which is a dynamic strength test, before and after an 8-week strength training program. Pre-training values, estimated from a graph, for each 6RM test were as follows: bench press strength was 29 ± 8 kg, seated row strength was 22 ± 5 kg, and leg press strength was 65 ± 16 kg. There were no comparisons to a healthy control group, or normative values for this test. Strength in each muscle group increased after the training period.

3.5 Muscle endurance

Three studies measured muscle endurance. All three used the curl-up test, but only two had healthy comparisons that could be used for meta-analysis. One study used controls within the study as healthy comparators, and 2 studies used normative values as the healthy comparison.

The mean difference in number of curl-ups between LiTx recipients and FITNESSGRAM standards was -4.60 (-12.62, 3.42) repetitions (Figure 3-8). Krasnoff et al. 2006 also measured muscle endurance with curl-ups in the KTx population. In this study, KTx recipients completed a mean and SD of 18.5 ± 15.2 repetitions, which corresponded to 68.0 ± 43.7 % of the minimum healthy fitness zone. KTx and LiTx curl-up repetitions were compared, and there was no significant difference between these two groups.

Patterson et al. 2016 reported curl-ups in their LiTx population (N=23) as well, though no healthy comparison was made. The mean number of curl-ups was 11 ± 12 repetitions, which is lower than the values reported by Unnithan et al. 2001 (12 ± 16.5 repetitions) and Krasnoff et al. 2006 (18.5 ± 23.5 repetitions). Number of push-ups according to the FITNESSGRAM protocol was also assessed in LiTx in the study by Patterson et al. 2016. Again, there was no

comparison to healthy values, but the number of push-ups was 3 ± 4 repetitions in the LiTx population.

3.6 Flexibility

Two studies measured flexibility. One study used healthy controls, and the other did not present healthy comparison data. Krasnoff et al. 2006 measured flexibility using the back-saver sit and reach test from the FITNESSGRAM. The results for the KTs patients were 12.4 ± 3.6 inches, and the results for the LiTx patients were 12.5 ± 3.3 inches. Most KTx (72%) and LiTx (91%) recipients were able to achieve the minimum of the healthy fitness zone. No quantifiable healthy comparison was presented. In another study of LiTx recipients by Unnithan et al, 2001, LiTx achieved 10.4 ± 2.0 inches on the back-saver sit and reach test. The mean difference in back-saver sit and reach between LiTx recipients and controls was 0.10 (-0.87, 1.07), which was not significant.

3.7 Physical activity level

3.7.1 Overview

Nine studies reported physical activity level. Six studies used controls within the study for healthy comparison, whereas three studies used normative data for healthy comparison. Two studies assessed PA level in HTx recipients, three in KTx recipients, two in LiTx, one in both KTx and LiTx, and one in BMT recipients. The type of physical activity level test varied, so meta-analysis was not possible.

3.7.2 Heart transplant recipients

Calzolari et al. 1998 and Pastore et al. 2001 presented the same PA data about the same cohort, measuring physical activity level using a questionnaire that asked about activity in and out of school. Most transplant recipients participated in physical activity in school (N=13/14), but not outside of school (N=2/14). This finding was in contrast to the control group, where all participants (N=14) participated in physical activity both in and out of school. The level of physical activity was not measured in these studies.

3.7.3 Kidney transplant recipients

Krasnoff et al. 2006 found that KTx recipients were extremely inactive, based on the Previous Day Physical Activity Recall instrument(82), spending only 8% of their after school time doing physical activity.

A study by Lubrano et al. 2012 quantified physical activity level using a questionnaire that provides a total number of hours per week that a participant is physically active(83). Out of 16 participants, 10 were inadequately active (<3 hrs/wk), and 6 were adequately active (>3 hrs/wk). VO_2max in physically active KTx recipients was similar to sedentary controls and sedentary KTx, and significantly lower than physically active controls.

Tangeraas et al. 2011 studied pediatric KTx recipients that were tested in adulthood using the International Physical Activity Questionnaire(84), which provides a metabolic equivalent (MET) score. The physical activity level of the KTx population was 904 ± 1627 MET-mins per week. Physical activity level was not measured in the control group. In this population, there was a relationship between total physical activity level and VO_2max. As total PA increased, VO_2max in all participants increased. Tangeraas et al. 2010 used the same MET scale to calculate moderate to vigorous physical activity (MVPA) per day. Eighty-six percent (N=19) of KTx did MVPA less than the recommended 60 minutes per day. The daily MVPA for all KTx in the study was 26 ± 20 minutes.

3.7.4 Liver transplant recipients

In LiTx recipients, a study by Patterson et al. found that MVPA levels, as measured by accelerometry, were reduced at 31.60 ± 15.06 minutes per day, falling below the recommended 60 minutes daily. In that study, there was no correlation between physical activity level (MVPA time) and physical fitness (VO_2max).

As with the KTx recipients in their study, Krasnoff et al. 2006 found that LiTx were extremely inactive, based on the Previous Day Physical Activity Recall instrument(82), spending only 8% of their after school time doing physical activity.

Unnithan et al. used a questionnaire that asks children to compare their physical activity level to that of their peers(85). Half of LiTx recipients (N=11/22) rated their PA level "as active as friends". This value was similar to the control group (N=10/21). Less LiTx (N=2/22) than controls (N=8/21) rated themselves as "more active then friends". More LiTx (N=8/22) than

controls (N=2/22) rated themselves as "less active than friends". The same number of participants in each group (N=1/22 LiTx, and N=1/21 controls) found the comparison too difficult to answer.

3.7.5 Bone marrow transplant recipients

A study by Mathiesen et al. 2014 measured self-reported physical activity level in pediatric BMT recipients, aged 7-24 years at the time of the study. They asked participants to choose the number of hours they participated in organized sport in a week, from 0, 1-3 hours, or 3 or more hours. Out of 63 patients, 11 participated in 0 hours, 26 participated in 1-3 hours, and 26 participated in 3 or more hours of physical activity in organized sport per week. Further, VO_2max was lower in BMT recipients with zero hours of sports activity versus 3 hours of sports activity per week. Physical activity level was not measured in the control population.

3.8 Quality of life

Quality of life was assessed in 3 studies. Two studies used controls as the healthy comparators, and 1 study used normative data as the healthy comparison.

In a study of LiTx by Vandekerckhove et al. 2016, QOL was assessed with the PedsQL questionnaire(86). In that study, total score out of 100 was significantly lower in LiTx (77.6±11) than controls (83.6±13.9; P<0.05). The mean difference in PedsQL score between LiTx and controls was -6.00 (-12.57, 0.57). However, the physical functioning sub-score was not significantly different between groups. In that study, physical functioning did not correlate with VO_2max, but it did correlate with test duration.

Fatigue and self-efficacy were measured in LiTx recipients in a study by Patterson et al. 2016. The fatigue score, as measured by the PedsQL Multidimensional Fatigue Scale (87), was 68.60 ± 13.73 out of 100. Self-efficacy was measured by the Children's Self-Perceptions of Adequacy in and Predilection of Physical Activity Scale (88), and the score in the LiTx group was 56 ± 8. Though the healthy values for these tools were not reported, the authors did state that both fatigue and self-efficacy values were lower than reported values in healthy children.

Quality of life was also measured in BMT recipients in a study by San Juan et al. 2007, where the Child Report Form of the Child's Health and Illness Profile-Child Edition and Adolescent Edition were used(89). The average score over all sections (satisfaction, comfort, resilience, risk avoidance, and achievement), pre-intervention, was 3.4 ± 0.6 out of 5.0 for the

BMT group, and 4.0 ± 0.4 out of 5.0 for the control group. The mean difference between BMT recipients and controls was -0.60 (-1.10, -0.10) out of 5.

3.9 Summary of findings

VO$_2$max was lowest in BMT recipients, followed by HTx recipients, KTx recipients, then LiTx recipients. VO$_2$max was lower in transplant recipients in studies that used in-study controls as their healthy comparators, as opposed to normative values from the literature. Differences in aerobic capacity were also seen between transplant recipients and healthy comparators when assessing exercise time in HTx recipients, six-minute walk test distance in KTx recipients, and PACER laps in LiTx recipients. Physical activity is lower in transplant recipients than healthy comparators, and in some studies there is a relationship between physical acitivity level and VO$_2$max. Quality of life was assessed in LiTx and BMT, and were lower in transplant recipients versus healthy comparators in all studies. In one study, physical functioning was associates with exercise time, but not VO$_2$max.

3.10 Tables and figures

Figure 3-1 PRISMA diagram


```
Identification

┌─────────────────────────┐      ┌─────────────────────────┐
│ Records identified through│     │ Additional records       │
│ database searching        │     │ identified through other │
│ (n = 6,476)               │     │ sources (n = 8)          │
└─────────────────────────┘      └─────────────────────────┘
              │                              │
              └──────────────┬───────────────┘
                             ▼
Screening
              ┌─────────────────────────┐
              │ Records after duplicates │
              │ removed (n = 4,394)      │
              └─────────────────────────┘
                             │
                             ▼
              ┌─────────────────┐      ┌─────────────────┐
              │ Records screened │─────▶│ Records excluded │
              │ (n = 4,394)      │      │ (n = 4,261)      │
              └─────────────────┘      └─────────────────┘
                             │
Eligibility                  ▼
              ┌─────────────────┐      ┌──────────────────────────┐
              │ Full-text        │─────▶│ Full-text articles        │
              │ articles         │      │ excluded, with reasons    │
              │ assessed for     │      │ (n = 101)                 │
              │ eligibility      │      │ Population (n = 56)       │
              │ (n = 133)        │      │ Comparator (n = 11)       │
              └─────────────────┘      │ Intervention (n = 10)     │
                             │          │ Language (n = 9)          │
                             ▼          │ Publication type (n = 5)  │
              ┌─────────────────┐      │ Study design (n = 5)      │
              │ Studies included │      │ Outcome (n = 5)           │
              │ in qualitative   │      └──────────────────────────┘
              │ synthesis        │
              │ (n = 32)         │
              └─────────────────┘
Included                     │
                             ▼
              ┌─────────────────┐
              │ Studies included │
              │ in quantitative  │
              │ synthesis        │
              │ (meta-analysis)  │
              │ (n = 24)         │
              └─────────────────┘
```

PRISMA diagram of the results of the literature search and screening process.

Table 3-1 Details of included studies

			Study descriptors		Transplant group							Control group			Other measures									
Author	Year	Country	N-centres	N-patients	Enrollment age (years)	Enrollment time post-tx (years)	Fitness test	Equipment	Measured variable	Score unit	C or N?	Normative data study author and year	N-controls	HR	BP	ECG	Echo	RER	Hg	Body comp	PA	Muscle	QOL
Heart																							
Christos et al.	1992	USA	1	7	13.3-16	1+	Upright, discontinuous exercise to volitional exhaustion	Cycle ergometer	VO2max	ml/kg/min	C	n/a	7	Y	Y				Y	Y			
Hsu et al.	1993	USA	1	31	6+	not reported	Progressive, upright, symptom-limited, maximal exercise testing	Cycle ergometer	VO2max	ml/kg/min	N	Cooper et al. 1984	109	Y		Y		Y					
Felici et al.	1996	Italy	1	11	8 to 16	1.5 to 3	Bruce protocol	Treadmill	VO2max Time	ml/kg/min minutes	C	n/a	9	Y	Y	Y	Y						
Garofano	1997	Columbia	1	22	not reported	1 to 7	Incremental	Cycle ergometer	VO2max	ml/min	C	n/a	18	Y	Y	Y							
Calzolari et al.	1998	Italy	1	14	5 to 15	1 to 7	Bruce protocol	Treadmill	VO2max Time	ml/kg/min minutes	C	n/a	14	Y	Y	Y						Y	
Pastore et al.	2001	Italy	1	same cohort as heart patients in Calzolari et al. 1998																			
Marconi et al.	2002	Italy	1	14	<14	1 mo. +	Graded, incremental, symptom-limited exercise test	Cycle ergometer	VO2max	ml/kg/min	C	n/a	9	Y				Y					
Abarbanell et al.	2004	USA	1	24	6+	5.7+	Pediatric ramp protocol	Treadmill	VO2max Time	ml/kg/min minutes	C	n/a	25	Y	Y			Y		Y			
Davis et al.	2006	USA	1	28	not reported	not reported	Graded ramp protocol to maximal volition	Cycle ergometer and treadmill	VO2max	ml/kg/min	N	Cooper et al. 1984	109	Y	Y	Y	Y	Y		Y			
Singh et al.	2007	USA	1	35	7 to 18	0.5 to 1.4	Bruce protocol	Treadmill	Time	minutes	C	n/a	35	Y			Y						
Dipchand et al.	2009	Canada	1	58	6+	0.5 to 11.5	Graded exercise testing until volitional fatigue	Cycle ergometer	VO2max	ml/kg/min	N	Washington et al. 1988	151	Y	Y			Y		Y			
Altamirano-Diaz et al.	2013	Canada	1	8			Stress test, progressive, graded, to exhaustin	Cycle ergometer	VO2max	ml/kg/min	C	n/a	8	Y	Y		Y	Y		Y			
Giardini et al.	2013	UK	1	128	not reported	not reported	Continuous, incremental, maximal exercise test to volitional exhaustion	Cycle ergometer	VO2max	ml/kg/min	C	n/a	160	Y		Y				Y			
Kidney																							
Matteucci et al.	1996	Italy	1	10	6+	6 mo. +	Symptom-limited, maximal exercise test to volitional exhaustion	Treadmill	Time	minutes	C	n/a	10	Y	Y	Y	Y		Y				
Feber et al.	1997	France, Czech Republic	1	26	8 to 18.9	1+	Continuous, increase power, to exhaustion	Cycle ergometer	VO2max	ml/kg/min	N	Washington et al. 1988	151			Y			Y		Y		
Daudet et al.	2005	France	1	32	children	1+	Continuous, increase power, to exhaustion	Cycle ergometer	VO2max	L/min	N	Alpert et al. 1982	not reported	Y	Y	Y	Y		Y				
Krasnoff et al.	2006	USA	1	36	10 to 18	3 mo. +	Symptom-limited, graded exercise testing with branching protocol	Treadmill	VO2max	ml/kg/min	N	Nagle et al. 1977	240	Y	Y	Y		Y		Y	Y	Y	
							PACER	Track	Laps	laps	N	Meredith et al. 1999											
Painter et al.	2007	Italy	1	same cohort as kidney patients in Krasnoff et al. 2006																			
Tangeraas et al.	2010	Norway	1	22	8 to 18	1+	Incremental exercise test to volitional exhaustion	Treadmill	VO2max	ml/kg/min	N	Fredriksen et al. 1999	196		Y				Y		Y		
Tangeraas et al.	2011	Norway	1	31	19 to 41	1+	Oslo protocol (tx), Bruce protocol (controls)	Treadmill	VO2max	ml/kg/min	C	n/a	36	Y		Y		Y		Y	Y		
Hirth et al.	2012	Norway	1	34	2 to 17	1+	Graded exercise testing until volitional fatigue	Treadmill	VO2max	ml/kg/min	N	Fredriksen et al. 1999	196	Y	Y					Y			
Lubrano et al.	2012	Italy	1	16	not reported	2+	Bruce protocol	Treadmill	VO2max	ml/kg/min	C	n/a	36	Y	Y	Y	Y			Y	Y		
Ferrari et al.	2013	South America (14 countries)	14	25	6 to 18	not reported	Six-minute walk test	Track	Distance	meters	N	Geiger et al. 2007	496		Y					Y			
Watanabe et al.	2015	Brazil	1	21	6 to 16	3 mo. +	Six-minute walk test	Track	Distance	meters	N	Geiger et al. 2007	119	Y	Y				Y	Y			
Liver																							
Unnithan et al.	2001	USA	1	27	not reported	not reported	PACER	Track	Laps	laps	C	n/a	33					Y	Y	Y	Y		
Krasnoff et al.	2006	USA	1	36	10 to 18	3 mo. +	Symptom-limited, graded exercise testing with branching protocol	Treadmill	VO2max	ml/kg/min	N	Nagle et al. 1977	240	Y	Y	Y		Y		Y	Y	Y	
							PACER	Track	Laps	laps	N	Meredith et al. 1999											
da Silva et al.	2014	Brazil	1	22	6 to 17	not reported	Six-minute walk test	Track	Distance	meters	N	Aquino et al. 2010	67	Y									
Patterson et al.	2016	Canada	1	23	8 to 18	1+	Maximal incremental exercise testing	Cycle ergometer	VO2max	ml/kg/min	N	Washington et al. 1988	151	Y	Y	Y		Y		Y	Y	Y	Y
Vandekerckhove et al.	2016	Belgium	1	28	6 to 16	6 mo. +	Continuous ramp protocol to volitional exhaustion	Cycle ergometer	VO2max	ml/kg/min	C	n/a	28	Y	Y	Y	Y	Y		Y			Y
Bone marrow																							
Eames et al.	1997	USA	1	63	1.9 to 32	1+	Bruce protocol	Treadmill	Time	min	N	Cumming et al. 1978	327	Y	Y	Y	Y						
Hogarty et al.	2000	USA	1	33	7+	0.3 to 11.8	Maximal ramp protocol to volitional exhaustion	Cycle ergometer	VO2max	ml/kg/min	N	Cooper et al. 1984	109	Y		Y	Y	Y	Y				
San Juan et al.	2007	Spain	1	8	8 to 16	<1	Volitional exhaustion	Treadmill	VO2max	ml/kg/min	C	n/a	8	Y								Y	Y
Mathiesen et al.	2014	Denmark	1	63	6+	3 to 10	Incremental exerise test	Cycle ergometer	VO2max	ml/kg/min	C	n/a	33	Y								Y	

Details of included studies by type of transplant (N=32). *USA: United States of America; tx: transplant; mo.: months; VO$_2$max: volume of oxygen consumption at maximal exercise; C: control group; N: normative values; HR: heart rate; BP: blood pressure; ECG: electrocardiography; Echo: echocardiography; RER: respiratory exchange ratio; Hg: hemoglobin; PA: physical activity; QOL: quality of life*

Table 3-2 Characteristics of included patients

Study descriptors		Transplant group							Control group				Comparison
Author	Year	N-value	No. males (%)	Age (years)	Age at Tx (yrs)	Time post-Tx (yrs)	Measured variable	Fitness test score	N-value	No. males (%)	Age (years)	Fitness test score	C or N? %healthy
Heart													
Christos et al.	1992	7	6 (86)	15.1 (SD) 1.9	not reported	2.1 (SD) 0.75	VO2max	22.0 (SD) 8.0 ml/kg/min	7	6 (86)	14.7 (SD) 1.9	33 (SD) 8 ml/kg/min	69% C
Hsu et al.	1993	31	21 (68)	13.0 (SD) 4.0	11.7 (SD) 4.1	1.3 (SD) 0.8	VO2max	20.0 (SD) 6.0 ml/kg/min	109	58 (53)	12.0 (SD) 3	32.8 (SD) 10.8 ml/kg/min	61% N
Felici et al.	1996	11	6 (55)	12.0 (SD) 4.6	not reported	not reported	VO2max	28.5 (SD) 4.0 ml/kg/min	9	4 (44)	10.9 (SD) 2.3	52.8 (SD) 5.8 ml/kg/min	54% C
							Time	11.3 (SD) 1.5 minutes				15.0 (SD) 2.0 minutes	75% C
Garofano	1997	22	15 (68)	15.5 (SD) 3.3	not reported	not reported	VO2max	1094 (SD) 357 ml/min	18	11 (61)	14.0 (SD) 3.0	1846 (SD) 597 ml/min	59% C
Calzolari et al.	1998	14	8 (57)	9.4 (SD) 3.0	not reported	3.6 (SD) 1.9	VO2max	33.0 (SD) 7.9 ml/kg/min	14	8 (57)	not reported	36.0 (SD) 2.2 ml/kg/min	92% C
							Time	9.3 (SD) 1.5 minutes				13.0 (SD) 1.5 minutes	72% C
Pastore et al.	2001	*same cohort as heart patients in Calzolari et al. 1998*											
Marconi et al.	2002	14	10 (71)	13.9 (SD) 4.0	10.6 (SD) 0.2	3.3 (SD) 2.4	VO2max	27 (SD) 7.1 ml/kg/min	9	9 (100)	12.9 (SD) 0.9	42.8 (SD) 5.3 ml/kg/min	63% C
Abarbanell et al.	2004	24	13 (54)	9.7 (SD) 2.3	0.095 (SD) 0.068	9.7 (SD) 2.3	VO2max	32.3 (SD) 5.6 ml/kg/min	25	16 (64)	10.5 (SD) 1.4	36.8 (SD) 5.5 ml/kg/min	86% C
							Time	10.3 (SD) 2.0 minutes				11.1 (SD) 1.5 minutes	93% C
Davis et al.	2006	28	17 (61)	13.8 (SD) 5.0	10.9 (SD) 5.6	3.1 (SD) 2.3	VO2max	25.0 (SD) 6.7 ml/kg/min	109	58 (53)	12.0 (SD) 3	42.2 (SD) 6.5 ml/kg/min	59% N
Singh et al.	2007	35	21 (60)	13.3 (SD) 2.8	12.4 (SD) 2.8	1.0 (SD) 0.23	Time	9.1 (SD) 2.0 minutes	35	21 (60)	13.5 (SD) 3.0	14.4 (SD) 2.3 minutes	63% C
Dipchand et al.	2009	58	17 (59)	10.0 (SD) 3.8	6.0 (SD) 4.0	1.75 (SD) 2.8	VO2max	30.0 (SD) 8.0 ml/kg/min	151	81 (54)	10.0 (SD) 1.3	44.4 (SD) 6.5 ml/kg/min	67% N
Altamirano-Diaz et al.	2013	8	4 (50)	15.0 (SD) 5.0	7.5 (SD) 4.6	9.3 (SD) 5.1	VO2max	32.0 (SD) 8.8 ml/kg/min	8	4 (50)	15.0 (SD) 5.0	43.4 (SD) 7.6 ml/kg/min	74% C
Giardini et al.	2013	128	66 (52)	13.9 (SD) 2.6	8.5 (SD) 5.1	6.0 (SD) 4.1	VO2max	29.6 (SD) 7.2 ml/kg/min	160	87 (54)	12.8 (SD) 2.0	40.5 (SD) 7.2 ml/kg/min	73% C
Mean	2002	32	61%	12.9 (SD) 3.5	8.5 (SD) 3.4	4.1 (SD) 2.1			55	61%	12.4 (SD) 2.5		71%
SD	7	34	10%						60	16%			12%
Kidney													
Matteucci et al.	1996	9	6 (67)	15.2 (SD) 4.5	not reported	4.4 (SD) 4.1	Time	11 (SD) 2.6 minutes	10	7 (70)	not reported	12.6 (SD) 1.8 minutes	90% C
Feber et al.	1997	26	12 (46)	13.6 (SD) 3.5	not reported	3.6 (SD) 1.9	VO2max	40.9 (SD) 14.0 ml/kg/min	151	81 (54)	10.0 (SD) 1.3	44.4 (SD) 6.5 ml/kg/min	92% N
Daudet et al.	2005	32	13 (41)	13.9 (SD) 3.4	not reported	3.6 (SD) 1.9	VO2max	1.57 (SD) 0.6 L/min		not reported		2.20 (SD) 0.51 L/min	71% N
Krasnoff et al.	2006	25	16 (64)	15.7 (SD) 2.3	not reported	3.4 (SD) 4.1	VO2max	30.1 (SD) 8.8 ml/kg/min	240	120 (50)	15.5 (SD) 1.2	47.8 (SD) 4.8 ml/kg/min	75% N
							Laps	20.6 (SD) 11.4 laps		not applicable (criterion)		41.9 (SD) 10.3 laps	49% N
Painter et al.	2007	*same cohort as kidney patients in Krasnoff et al. 2006*											
Tangeraas et al.	2010	22	16 (73)	14.0 (SD) 2.5	7.6 (SD) 3.3	7.2 (SD) 3.4	VO2max	36.0 (SD) 10.3 ml/kg/min	196	106 (54)	12.0 (SD) 1.5	53.0 (SD) 6.2 ml/kg/min	63% N
Tangeraas et al.	2011	31	19 (61)	26.9 (SD) 5.5	12.4 (SD) 3.8	18.1 (SD) 5.5	VO2max	37.9 (SD) 11.0 ml/kg/min	36	18 (50)	33.5 (SD) 5.5	44.4 (SD) 9.0 ml/kg/min	85% C
Hirth et al.	2012	34	21 (62)	11.9 (SD) 3.7	6 (SD) 4.0	5.9 (SD) 3.3	VO2max	36.2 (SD) 10.9 ml/kg/min	196	21 (62)	11.7 (SD) 3.8	52.8 not reporte ml/kg/min	66% N
Lubrano et al.	2012	16	14 (88)	16.0 (SD) 2.5	not reported	not reported	VO2max	26.6 (SD) 2.3 ml/kg/min	36	28 (78)	14.7 (SD) 2.9	37.8 (SD) 4.3 ml/kg/min	70% C
Ferrari et al.	2013	25	14 (56)	13.5 (SD) 3.3	not reported	not reported	Distance	430 (SD) 80 meters	496	248 (50) not repol (SD) 2.5		659 (SD) 35 meters	65% N
Watanabe et al.	2015	21	not reported	11.3 (SD) 2.4	not reported	2.1 (SD) 0.9	Distance	575 (SD) 61 meters	119	57 (48)	not reported	636 (SD) 63 meters	92% N
Mean	2008	24	62%	15.2 (SD) 3.4	8.7 (SD) 3.7	6.0 (SD) 3.1			164	57%	16.2 (SD) 2.7		75%
SD	6	8	14%						149	11%			14%
Liver													
Unnithan et al.	2001	29	20 (69)	8.9 (SD) 4.8	4.3 (SD) 4.0	4.7 (SD) 3.0	Laps	11.5 (SD) 8.4 laps	34	22 (65)	8.4 (SD) 3.8	16.8 (SD) 9.8 laps	68% C
Krasnoff et al.	2006	11	5 (45)	14.5 (SD) 2.6	not reported	10.9 (SD) 4.4	VO2max	33.4 (SD) 8.2 ml/kg/min	240	120 (50)	15.5 (SD) 1.2	47.8 (SD) 4.8 ml/kg/min	75% N
							Laps	17.6 (SD) 7.6 laps		not applicable (criterion)		31.9 (SD) 7.1 laps	55% N
da Silva et al.	2014	22	not reported	12.4 (SD) 2.9	10.5 (SD) 3.9	2.8 (SD) 3.0	Distance	511 (SD) 72 meters	67	36 (54)	10.8 (SD) 1.9	687 (SD) 80 meters	74% N
Patterson et al.	2016	23	7 (30)	14.0 (SD) 2.5	4.5 (SD) 4.1	9.5 (SD) 4.7	VO2max	33.2 (SD) 7.6 ml/kg/min	151	81 (54)	10.0 (SD) 1.3	43.1 (SD) 6.7 ml/kg/min	77% N
Vandekerckhove et al.	2016	28	15 (54)	11.6 (SD) 2.9	3.3 (SD) 3.1	8.2 (SD) 3.7	VO2max	37.5 (SD) 9.3 ml/kg/min	28	15 (54)	11.6 (SD) 2.9	44.1 (SD) 8.8 ml/kg/min	85% C
Mean	2011	23	50%	12.3 (SD) 3.1	5.7 (SD) 3.8	7.2 (SD) 3.8			104	55%	11.3 (SD) 2.2		72%
SD	7	7	16%						90	6%			10%
Bone marrow													
Eames et al.	1997	63	39 (62)	11.7 (SD) 7.5	6.4 (SD) 4.4	3.3 (SD) 3.8	VO2max	11 (SD) 2.7 min	327	167 (51)	11.0 (SD) 0.33	12.5 (SD) 1.7 min	88% N
Hogarty et al.	2000	33	20 (61)	17.4 (SD) 6.5	11.3 (SD) 7.1	1.6 (SD) 2.2	VO2max	24.7 (SD) 5.1 ml/kg/min	109	58 (53)	12.0 (SD) 3	40.1 (SD) 5.9 ml/kg/min	62% N
San Juan et al.	2007	8	4 (50)	10.9 (SD) 2.8	not reported	0.7 (SD) 0.4	VO2max	25.9 (SD) 8.2 ml/kg/min	8	4 (50)	10.9 (SD) 2.6	43.0 (SD) 8.0 ml/kg/min	60% C
Mathiesen et al.	2014	63	37 (59)	14.4 (SD) 4.3	7.8 (SD) 3.8	7.0 (SD) 1.7	VO2max	37.4 (SD) 8.5 ml/kg/min	33	17 (52)	not reported	44.6 (SD) 6.5 ml/kg/min	84% C
Mean	2005	42	58%	13.6 (SD) 5.3	8.5 (SD) 5.1	3.2 (SD) 2.0			119	52%	11.3 (SD) 2.0		73%
SD	8	27	5%						145	1%			15%

Characteristics of included patients of all studies (N=32). Data are presented as mean ± SD for each study, and each type of transplant group. *tx: transplant; mo.: months; VO₂max: volume of oxygen consumption at maximal exercise; C: control group; N: normative values.*

Table 3-3 Characteristics of included patients – summary

	Heart N-studies = 13	**Kidney** N-studies = 11	**Liver** N-studies = 5	**Bone marrow** N-studies = 4
Tx patients				
N-participants	32 (SD) 34	24 (SD) 8	23 (SD) 7	42 (SD) 27
% male	61 (SD) 10	62 (SD) 14	50 (SD) 16	58 (SD) 5
Age (yrs)	12.9 (SD) 3.5	15.2 (SD) 3.4	12.3 (SD) 3.1	13.6 (SD) 5.3
Age at tx (yrs)	8.5 (SD) 3.4	8.7 (SD) 3.7	5.7 (SD) 3.8	8.5 (SD) 5.1
Time post-tx (yrs)	4.1 (SD) 2.1	6.0 (SD) 3.1	7.2 (SD) 3.8	3.2 (SD) 2.0
Controls				
N-participants	55 (SD) 60	164 (SD) 149	104 (SD) 90	119 (SD) 145
% male	61 (SD) 16	57 (SD) 11	55 (SD) 6	52 (SD) 1
Age (yrs)	12.4 (SD) 2.5	16.2 (SD) 2.7	11.3 (SD) 2.2	11.3 (SD) 2.0
Comparison				
Tx aerobic capacity (% control)	71 (SD) 12	75 (SD) 14	72 (SD) 10	73 (SD) 15

Characteristics of included patients presented as mean ± SD of all studies in each type of transplant group.

Figure 3-2 Forest plot of VO$_2$max – all types of transplant

Study or Subgroup	Transplant Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
1.1.1 BMT									
Hogarty et al.	24.7	5.1	33	40.1	5.9	33	8.1%	-15.40 [-18.06, -12.74]	2000
San Juan et al.	25.9	8.2	8	43	8	8	0.9%	-17.10 [-25.04, -9.16]	2007
Mathiesen et al.	37.4	8.5	63	44.6	6.5	33	6.1%	-7.20 [-10.25, -4.15]	2014
Subtotal (95% CI)			**104**			**74**	**15.1%**	**-12.18 [-14.12, -10.23]**	
Heterogeneity: Chi² = 17.32, df = 2 (P = 0.0002); I² = 88%									
Test for overall effect: Z = 12.27 (P < 0.00001)									
1.1.2 HTx									
Christos et al.	22	8	7	33	8	7	0.8%	-11.00 [-19.38, -2.62]	1992
Hsu et al.	20	6	31	32.8	10.8	31	3.0%	-12.80 [-17.15, -8.45]	1993
Felici et al.	28.5	4	11	52.8	5.8	9	2.9%	-24.30 [-28.77, -19.83]	1996
Calzolari et al.	33	7.9	14	36	2.2	14	3.1%	-3.00 [-7.30, 1.30]	1998
Marconi et al.	27	7.1	14	42.8	5.3	9	2.2%	-15.80 [-20.88, -10.72]	2002
Abarbanell et al.	32.3	5.6	24	36.8	5.5	25	5.9%	-4.50 [-7.61, -1.39]	2004
Davis et al.	25	6.7	28	42.2	6.5	28	4.8%	-17.20 [-20.66, -13.74]	2006
Dipchand et al.	30	8	58	44.4	6.5	58	8.1%	-14.40 [-17.05, -11.75]	2009
Giardini et al.	32	8.8	8	43.4	7.6	8	0.9%	-11.40 [-19.46, -3.34]	2013
Altamirano–Diaz et al.	29.6	7.2	128	40.5	7.2	160	20.5%	-10.90 [-12.57, -9.23]	2013
Subtotal (95% CI)			**323**			**349**	**52.2%**	**-11.89 [-12.94, -10.85]**	
Heterogeneity: Chi² = 84.16, df = 9 (P < 0.00001); I² = 89%									
Test for overall effect: Z = 22.26 (P < 0.00001)									
1.1.3 KTx									
Feber et al.	40.9	14	26	44.4	6.5	26	1.6%	-3.50 [-9.43, 2.43]	1997
Krasnoff et al.	30.1	8.8	25	47.8	4.8	25	3.7%	-17.70 [-21.63, -13.77]	2006
Tangeraas et al. A	36	10.3	22	53	6.2	22	2.3%	-17.00 [-22.02, -11.98]	2010
Tangeraas et al. B	37.9	11	31	44.4	9	36	2.4%	-6.50 [-11.36, -1.64]	2011
Lubrano et al.	26.6	2.8	16	37.8	4.3	36	14.9%	-11.20 [-13.16, -9.24]	2012
Subtotal (95% CI)			**120**			**145**	**24.9%**	**-11.74 [-13.25, -10.22]**	
Heterogeneity: Chi² = 25.21, df = 4 (P < 0.0001); I² = 84%									
Test for overall effect: Z = 15.16 (P < 0.00001)									
1.1.4 LiTx									
Krasnoff et al.	33.4	8.2	11	47.8	4.8	11	1.8%	-14.40 [-20.01, -8.79]	2006
Patterson et al.	37.5	9.3	28	44.1	8.8	28	2.5%	-6.60 [-11.34, -1.86]	2016
Vandekerckhove et al.	33.2	7.6	23	43.1	6.7	23	3.3%	-9.90 [-14.04, -5.76]	2016
Subtotal (95% CI)			**62**			**62**	**7.7%**	**-9.87 [-12.60, -7.14]**	
Heterogeneity: Chi² = 4.33, df = 2 (P = 0.11); I² = 54%									
Test for overall effect: Z = 7.10 (P < 0.00001)									
Total (95% CI)			**609**			**630**	**100.0%**	**-11.74 [-12.50, -10.98]**	
Heterogeneity: Chi² = 133.10, df = 20 (P < 0.00001); I² = 85%									
Test for overall effect: Z = 30.40 (P < 0.00001)									
Test for subgroup differences: Chi² = 2.08, df = 3 (P = 0.56), I² = 0%									

Favours [control] Favours [transplant]

Forest plot of VO$_2$max for bone marrow, heart, kidney, and liver transplant recipients and healthy participants (controls or normative values) for N=10 studies. Data are presented in units of ml/kg/min, as mean ± SD for individual groups, and mean difference with 95% confidence intervals for group comparisons.

Figure 3-3 Forest plot of VO$_2$max – heart transplant

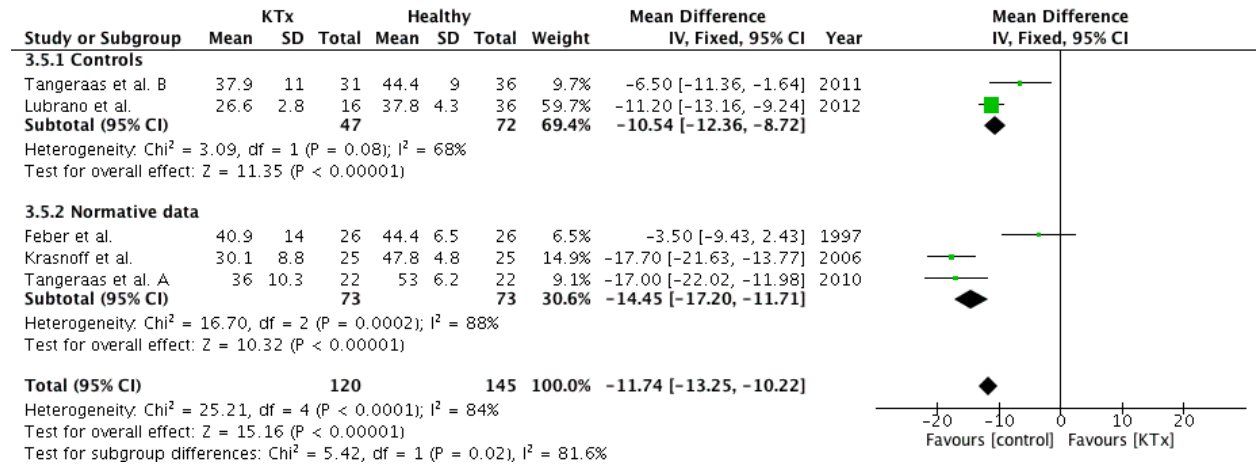| Study or Subgroup	HTx Mean	SD	Total	Healthy Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
2.2.1 Controls									
Christos et al.	22	8	7	33	8	7	1.6%	-11.00 [-19.38, -2.62]	1992
Felici et al.	28.5	4	11	52.8	5.8	9	5.5%	-24.30 [-28.77, -19.83]	1996
Calzolari et al.	33	7.9	14	36	2.2	14	5.9%	-3.00 [-7.30, 1.30]	1998
Marconi et al.	27	7.1	14	42.8	5.3	9	4.2%	-15.80 [-20.88, -10.72]	2002
Abarbanell et al.	32.3	5.6	24	36.8	5.5	25	11.3%	-4.50 [-7.61, -1.39]	2004
Giardini et al.	29.6	7.2	128	40.5	7.2	160	39.2%	-10.90 [-12.57, -9.23]	2013
Altamirano-Diaz et al.	32	8.8	8	43.4	7.6	8	1.7%	-11.40 [-19.46, -3.34]	2013
Subtotal (95% CI)			206			232	69.4%	**-10.55 [-11.81, -9.30]**	

Heterogeneity: Chi^2 = 67.14, df = 6 (P < 0.00001); I^2 = 91%
Test for overall effect: Z = 16.46 (P < 0.00001)

Study or Subgroup	HTx Mean	SD	Total	Healthy Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
2.2.2 Normative data									
Hsu et al.	20	6	31	32.8	10.8	31	5.8%	-12.80 [-17.15, -8.45]	1993
Davis et al.	25	6.7	28	42.2	6.5	28	9.2%	-17.20 [-20.66, -13.74]	2006
Dipchand et al.	30	8	58	44.4	6.5	58	15.6%	-14.40 [-17.05, -11.75]	2009
Subtotal (95% CI)			117			117	30.6%	**-14.94 [-16.83, -13.04]**	

Heterogeneity: Chi^2 = 2.73, df = 2 (P = 0.26); I^2 = 27%
Test for overall effect: Z = 15.45 (P < 0.00001)

| | | | 323 | | | 349 | 100.0% | **-11.89 [-12.94, -10.85]** | |
| **Total (95% CI)** | | | | | | | | | |

Heterogeneity: Chi^2 = 84.16, df = 9 (P < 0.00001); I^2 = 89%
Test for overall effect: Z = 22.26 (P < 0.00001)
Test for subgroup differences: Chi^2 = 14.28, df = 1 (P = 0.0002), I^2 = 93.0%
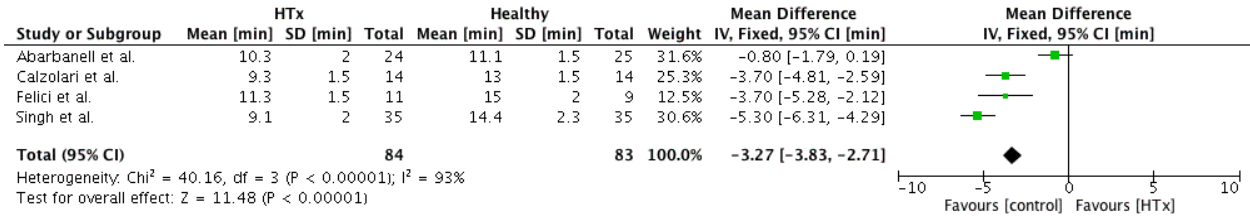
Favours [control]   Favours [HTx]

Forest plot of VO$_2$max for heart transplant recipients and either healthy controls (N=7) or normative data (N=3). Data are presented in units of ml/kg/min, as mean ± SD for individual groups, and mean difference with 95% confidence intervals for group comparisons.

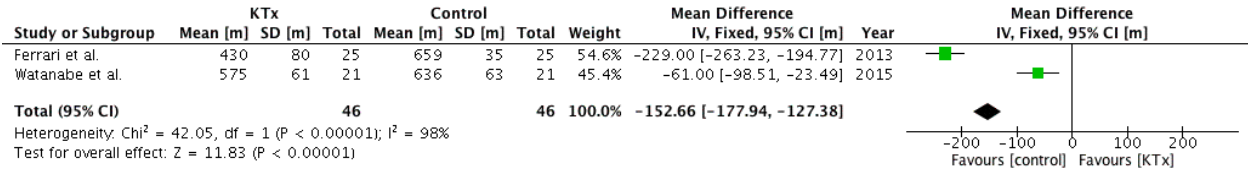**Figure 3-4** Forest plot of VO$_2$max – kidney transplant

Study or Subgroup	KTx Mean	SD	Total	Healthy Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Year	Mean Difference IV, Fixed, 95% CI
3.5.1 Controls										
Tangeraas et al. B	37.9	11	31	44.4	9	36	9.7%	−6.50 [−11.36, −1.64]	2011	
Lubrano et al.	26.6	2.8	16	37.8	4.3	36	59.7%	−11.20 [−13.16, −9.24]	2012	
Subtotal (95% CI)			47			72	69.4%	**−10.54 [−12.36, −8.72]**		
Heterogeneity: Chi^2 = 3.09, df = 1 (P = 0.08); I^2 = 68%										
Test for overall effect: Z = 11.35 (P < 0.00001)										
3.5.2 Normative data										
Feber et al.	40.9	14	26	44.4	6.5	26	6.5%	−3.50 [−9.43, 2.43]	1997	
Krasnoff et al.	30.1	8.8	25	47.8	4.8	25	14.9%	−17.70 [−21.63, −13.77]	2006	
Tangeraas et al. A	36	10.3	22	53	6.2	22	9.1%	−17.00 [−22.02, −11.98]	2010	
Subtotal (95% CI)			73			73	30.6%	**−14.45 [−17.20, −11.71]**		
Heterogeneity: Chi^2 = 16.70, df = 2 (P = 0.0002); I^2 = 88%										
Test for overall effect: Z = 10.32 (P < 0.00001)										
Total (95% CI)			120			145	100.0%	**−11.74 [−13.25, −10.22]**		
Heterogeneity: Chi^2 = 25.21, df = 4 (P < 0.0001); I^2 = 84%										
Test for overall effect: Z = 15.16 (P < 0.00001)										
Test for subgroup differences: Chi^2 = 5.42, df = 1 (P = 0.02), I^2 = 81.6%										

Favours [control]   Favours [KTx]

Forest plot of VO$_2$max for kidney transplant recipients and either healthy controls (N=2) or normative data (N=3). Data are presented in units of ml/kg/min, as mean ± SD for individual groups, and mean difference with 95% confidence intervals for group comparisons.

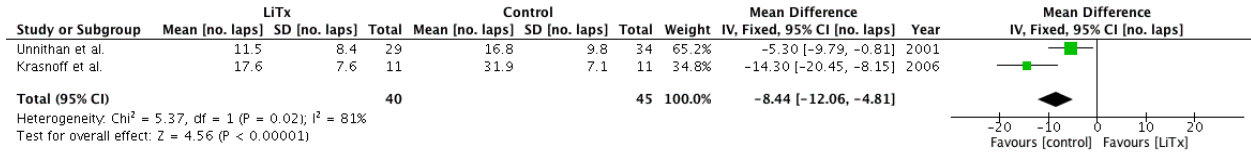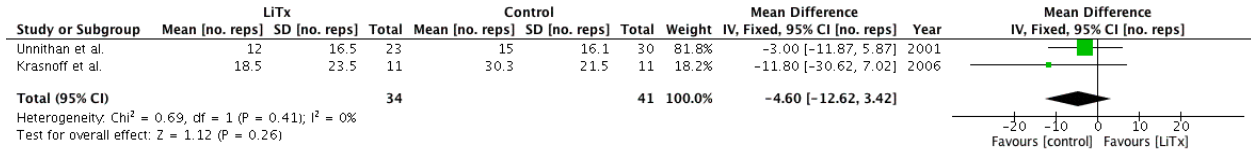**Figure 3-5** Forest plot of exercise time – heart transplant

Study or Subgroup	HTx Mean [min]	SD [min]	Total	Healthy Mean [min]	SD [min]	Total	Weight	Mean Difference IV, Fixed, 95% CI [min]
Abarbanell et al.	10.3	2	24	11.1	1.5	25	31.6%	−0.80 [−1.79, 0.19]
Calzolari et al.	9.3	1.5	14	13	1.5	14	25.3%	−3.70 [−4.81, −2.59]
Felici et al.	11.3	1.5	11	15	2	9	12.5%	−3.70 [−5.28, −2.12]
Singh et al.	9.1	2	35	14.4	2.3	35	30.6%	−5.30 [−6.31, −4.29]
Total (95% CI)			84			83	100.0%	−3.27 [−3.83, −2.71]

Heterogeneity: Chi² = 40.16, df = 3 (P < 0.00001); I² = 93%
Test for overall effect: Z = 11.48 (P < 0.00001)

Mean Difference IV, Fixed, 95% CI [min]
-10   -5   0   5   10
Favours [control]   Favours [HTx]

Forest plot of exercise time for heart transplant recipients and healthy participants (controls or normative values) for N=4 studies. Data are presented in units of minutes, as mean ± SD for individual groups, and mean difference with 95% confidence intervals for group comparisons.

Figure 3-6 Forest plot of 6MWT distance – kidney transplant

Study or Subgroup	KTx Mean [m]	SD [m]	Total	Control Mean [m]	SD [m]	Total	Weight	Mean Difference IV, Fixed, 95% CI [m]	Year	Mean Difference IV, Fixed, 95% CI [m]
Ferrari et al.	430	80	25	659	35	25	54.6%	−229.00 [−263.23, −194.77]	2013	
Watanabe et al.	575	61	21	636	63	21	45.4%	−61.00 [−98.51, −23.49]	2015	
Total (95% CI)			**46**			46	100.0%	**−152.66 [−177.94, −127.38]**		

Heterogeneity: Chi² = 42.05, df = 1 (P < 0.00001); I² = 98%
Test for overall effect: Z = 11.83 (P < 0.00001)

Favours [control]　Favours [KTx]

Forest plot of six-minute walk test distance for kidney transplant recipients and healthy participants (controls or normative values) for N=2 studies. Data are presented in units of meters (m), as mean ± SD for individual groups, and mean difference with 95% confidence intervals for group comparisons.

Figure 3-7 Forest plot of PACER laps – liver transplant

Study or Subgroup	LiTx Mean [no. laps]	SD [no. laps]	Total	Control Mean [no. laps]	SD [no. laps]	Total	Weight	Mean Difference IV, Fixed, 95% CI [no. laps]	Year	Mean Difference IV, Fixed, 95% CI [no. laps]
Unnithan et al.	11.5	8.4	29	16.8	9.8	34	65.2%	-5.30 [-9.79, -0.81]	2001	
Krasnoff et al.	17.6	7.6	11	31.9	7.1	11	34.8%	-14.30 [-20.45, -8.15]	2006	
Total (95% CI)			40			45	100.0%	-8.44 [-12.06, -4.81]		

Heterogeneity: Chi² = 5.37, df = 1 (P = 0.02); I² = 81%
Test for overall effect: Z = 4.56 (P < 0.00001)

Favours [control]   Favours [LiTx]

Forest plot of PACER laps for liver transplant recipients and healthy participants (controls or normative values) for N=2 studies. Data are presented in units of number of laps, as mean ± SD for individual groups, and mean difference with 95% confidence intervals for group comparisons.

Figure 3-8 Forest plot of curl-up repetitions – liver transplant

Study or Subgroup	LiTx Mean [no. reps]	SD [no. reps]	Total	Control Mean [no. reps]	SD [no. reps]	Total	Weight	Mean Difference IV, Fixed, 95% CI [no. reps]	Year	Mean Difference IV, Fixed, 95% CI [no. reps]
Unnithan et al.	12	16.5	23	15	16.1	30	81.8%	−3.00 [−11.87, 5.87]	2001	
Krasnoff et al.	18.5	23.5	11	30.3	21.5	11	18.2%	−11.80 [−30.62, 7.02]	2006	
Total (95% CI)			34			41	100.0%	−4.60 [−12.62, 3.42]		

Heterogeneity: Chi² = 0.69, df = 1 (P = 0.41); I² = 0%
Test for overall effect: Z = 1.12 (P = 0.26)

−20 −10 0 10 20
Favours [control] Favours [LiTx]

Forest plot of curl-up repetitions for liver transplant recipients and healthy participants (controls or normative values) for N=2 studies. Data are presented in units of number of repetitions, as mean ± SD for individual groups, and mean difference with 95% confidence intervals for group comparisons.

Chapter 4: Methods – Fitness Assessment

4.1 Study overview

This study is a cross-sectional design. Participants were recruited to complete a physical activity questionnaire, quality of life questionnaire, anthropometry, body composition measurements, and a fitness battery. The fitness battery consisted of three hand-held dynamometry measurements, a push-up test, a curl-up test, a timed wall sit and a six-minute walk test. The schedule for their test may be found in Table 4-1. The research team collected clinical information from patient charts after testing. All data were de-identified, assigned a code, and entered into a secure RedCap database before analysis(90).

4.2 Study population

4.2.1 Sample size

A sample size calculation was performed to determine the minimum sample size of the study. Twenty-two pediatric heart transplant (HTx) recipients, 6 pediatric kidney transplant (KTx) recipients, and 20 healthy controls participated in the study. The control group consisted of patient siblings, when possible, to minimize variability among groups due to lifestyle and genetic factors. To fill the control group, non-sibling, height-matched controls were selected and recruited from the Healthy Infants and Children Clinical Research Program (HICCUP) database.

4.2.2 Inclusion criteria

Patients who received a heart or kidney transplant between the ages of 0-17 were eligible for this study. At the time of the study, participants were at least 5 years of age, at least 1 after their transplant, and enrolled in a structured elementary or secondary school system. The minimum age was set to ensure that participants had the physical ability to perform the fitness assessment. The minimum time post-transplant was set to avoid confounding of fitness impairment from recovery from the surgical transplant procedure. School enrollment was a requirement for the validity of the physical activity questionnaire.

4.2.3 Exclusion criteria

Participants were excluded if they were not able to complete, or did not complete, 2 or more fitness tests for any reason. Sibling controls were excluded if they received a transplant or any heart surgery in their lifetime, since their fitness levels may have been affected by the same factors as their transplanted siblings.

4.3 Participant recruitment

Eligible patients were determined by their chart and the criteria for the study by the clinical team. All eligible HTx patients in the Edmonton and Calgary area, and all eligible KTx patients in the Edmonton area, were approached by the clinical staff from their respective hospital for consent to be contacted by the research team. All consenting families were then contacted by the research team via telephone to discuss participation in the research study. Both Tx patients and any healthy siblings they may have in the study age range were invited to participate in the study.

In addition, a recruiting presentation about the research study was given at a camp for pediatric heart transplant recipient families that are followed at Alberta transplant centers. Social media posts were used to recruit transplant recipients who may not receive frequent follow up, and did not attend the transplant camp.

Healthy controls were recruited from patient families and the HICCUP database. Participants were enrolled in the study until we reached our target of 22 HTx patients, 20 controls, and 6 KTx patients.

4.4 Chart data collection

A chart data collection tool was created, and coded into RedCap format. All data were de-identified and extracted directly into these forms in the RedCap database. For Calgary HTx patients, data was pulled from paper charts and filled in with data from the OTTR electronic database. For Edmonton HTx and KTx patients, data was pulled from the OTTR electronic database.

The following parameters were extracted from patient charts: type of transplant; pre-transplant diagnosis; type of disease leading to transplant (congenital heart or kidney disease, cardiomyopathy, autoimmune kidney disease, or other); date of diagnosis; date of transplant;

age at time of transplant (y); time post-transplant (y); time from diagnosis to transplant (days); hospital length of stay immediately pre- and post-transplant (days); pre- and post-transplant rehabilitation (weeks); hemoglobin level (most recent before the test date, mmol/L); date of hemoglobin measurement; creatinine level (most recent before the test date, umol/L); date of creatinine measurement; medication status (on/off) for tacrolimus, prednisone, statin, cyclosporine, mycophenolate mofetil, amlodipine, enalapril, and other medications or supplements; prednisone start and stop date; time on prednisone (days); history of stroke (y/n, date of stroke); exisitence of current neuromotor deficits (y/n); history of ventricular assist device (VAD, y/n, days on VAD); history of extracorporeal membrane oxygen (ECMO, y/n, days on ECMO); history of rejection (y/n, number of episodes); abo-compatability status; history of post-transplant lymphoproliferative disease (PTLD, y/n, number of episodes); history of previous cardiac or kidney surgery (number, type, date, and age at time of surgery); history of dialysis (start and stop dates, time on dialysis (days), and type of dialysis); and, a list of other medical conditions.

A copy of the chart data collection tool can be found in Appendix C.

4.5 Quality of life questionnaire

Quality of life was quantified using the Pediatric Quality of Life Questionnaire version 4.0 (PedsQL), which is a standardized questionnaire adapted for respective age groups in the 5- to 26-year range(86). This questionnaire has been used in the pediatric transplant population in the past, and its reliability, validity, and feasibility have been shown(86).

For this study, an electronic version of the questionnaire was created and coded into RedCap, and participants completed the questionnaire on the electronic form. For children aged 5-7 years, the researcher read the questions aloud, asking the kids to point to the PedsQL scale designed for their age group, and the researcher recorded answers on the electronic form.

4.6 Physical activity level questionnaire

The Physical Activity Questionnaire (PAQ) measures physical activity level in the last 7 days, and collects age, grade, and sex information(91). For this study, an electronic version of the questionnaire was created in RedCap, and participants completed the questionnaire on the electronic form. There are two versions of the questionnaire, given to different age groups. The

PAQ-C was used for school-aged children, up to grade 8. The PAQ-A was used for adolescents, from grades 9-12, who answered directly on the electronic form.

Physical activity of children in the 5- to 7-year age group was assessed with the PAQ-C questionnaire. Though this tool has not been validated in populations less than 8 years old, the PAQ-C was used in this study to remain consistent with the other age groups. For this age group, the researcher read the questions aloud to the child, who answered, and then the researcher input the answers in the online questionnaire. This approach was used, rather than letting the children read their own questionnaire, to mimic the success of this style of questioning with the PedsQL 4.0 quality of life questionnaire for ages 5-7 years(86). Because the actual level of physical activity was deemed more important than the child's perception of their level of physical activity, parents were consulted for answers when the child was unable to provide them.

4.7 Anthropometry and body composition

Height and weight were measured using digital scales before body composition or exercise testing. Clinic apparatus at each testing site was used for these measurements.

Fat-free mass (FFM) was measured by air-displacement plethysmography (BodPod)(92). The BodPod was warmed-up and calibrated each day before testing, including hardware analysis, mass calibration, practice mass (20.000 kg), autorun, and volume measurements. Autorun and volume measurements were performed using the calibration cylinder with a volume of 50.140 L. Before every test, the BodPod was further calibrated with the calibration cylinder.

To keep air conditions consistent, the BodPod room temperature was set to 22 ˚C, and the room door was kept shut whenever possible. Testing was done in a time-efficient manner, so that body heat would not increase the temperature in the testing room.

Lung volume was accounted for using a predicted value, based on participant height. The lung volume of participants was calculated using the Lohman equation, since participants were under the age of 18(93).

Participants were asked not to eat for 1-2 hours before testing, and they were encouraged to go to the washroom before testing, if they were able. For the test itself, participants were asked to wear spandex-like, tight clothing with maximal skin exposure, and a swim cap covering their hair. Participants were also asked to remove all jewelry. Once prepared, height was entered into the software program, and weight was measured again on the BodPod-integrated scale.

Then, participants were asked to enter the BodPod, sit very still, and breathe normally. Parents were asked to encourage their child to sit still during the testing. Two, one-minute tests were performed, and a third was performed if the first two results were inconsistent with each other, as per the owner's manual protocol(94). The BodPod uses the air displaced by the participant to calculate body volume, percent fat mass, absolute fat mass, percent fat-free ass, and absolute fat-free mass.

BodPod testing was always completed before exercise testing so that participants would not be in a volume-depleted state, which would affect the body composition results.

BodPod equipment was only available at the University of Alberta site, so a triceps skinfold test was performed on participants being tested at other sites to measure body fat percentage.

4.8 Six-minute walk test

The six-minute walk test (6MWT) was used to assess functional exercise capacity. The 6MWT measures the distance that participants can walk in six minutes, while going between two markers, set 30 meters apart. This test is safe for cardiorespiratory patients since it is a submaximal test, that correlates with aerobic capacity, without requiring participants to reach their VO_2max. The 6MWT has been validated in children, and is correlated with maximum oxygen uptake at peak exercise testing on a treadmill(95). The protocol described by the American Thoracic Society was followed for this test(96). Participants completed the test twice to account for the learning effect. The second test result was used for analysis. Raw values were compared to reference values to generate a percent predicted 6MWT distance. For children aged 5-6, reference values were taken from *Lammers et al. 2007*(97). For children and adolescents aged 7-16, the cohort from a study by *Li et al. 2007* was used(98). For adolescents aged 17-18, the equation from *Li et al. 2007* was used(98). The equations for predicted 6MWT distance are as follows:

$$Male\ 6MWT\ predicted\ distance\ (m) = 554.16 + (difference\ in\ HR \times 1.76) + (height\ (cm) \times 1.23)$$

$$Female\ 6MWT\ predicted\ distance\ (m) = 526.79 + (difference\ in\ HR \times 1.66) + (height\ (cm) \times 0.62)$$

To promote the validity of this test in children, some additions were made to the American Thoracic Society protocol. First, between the 30-meter markers, there were additional marks every 3-meters, to help young children stay on track. Next, for participants that often

missed the end of the track, or needed more motivation to perform their best (as determined by the performance on their trial run), parents remained at one end of the track. This served as a reminder for participants to turn around, and/or an incentive for participants to walk their fastest to reach their parent at the end of each repetition of the track. Last, motivation was provided to participants. If participants were being tested with their siblings, their results were shared to encourage some competition, and drive to beat their sibling's test score. In each case, participants were offered stickers if they beat their score from their trial run, while following the rules set out for the test.

4.9 Muscle endurance

4.9.1 90° push-ups and curl-ups

The FITNESSGRAM protocol for 90° push-ups and curl-ups was used for these measurements(10).

For a 90° push-up, the participant assumes a plank position, in which they are on their hands and toes, facing the floor, shoulders over hands, ankles over toes, and hips at the same or slightly lower level than the shoulders (Figure 4-1A). Then, the participant bends their arms, without moving the rest of their body until their arms make a 90° angle (Figure 4-1B). Then, the participant uses their strength to push themselves away from the floor to the starting position, and this counts as one repetition.

For a curl-up, the participant assumes a laying down position, with their legs bent and their feet flat on the mat, and their arms extended at their side (Figure 4-2A). A measuring strip is placed at the edge of their fingertips. Then, they lift their torso until their fingers reach the desired area on the measuring strip (Figure 4-2B). This roughly corresponds to lifting about half of their back off the mat. Then, they relax back down to the mat, and this corresponds to one repetition.

Participants were given standardized instructions, and then asked to perform 1-3 warm up repetitions. These warm up repetitions were used to provide form corrections so the first repetition would be correct on the test. There was a minimum rest of one minute between warm-up repetitions and test performance.

In this protocol, as in the FITNESSGRAM, participants performed a push-up or curl-up to a cadence of one repetition every 3 seconds. A standardized audio track provided the cadence.

The number of push-ups or curl-ups before the participants broke form twice, or reached volitional exhaustion, was counted.

4.9.2 Timed wall-sit

The timed wall-sit test is a new test to the pediatric transplant population, but it has been previously described in a sample of football players in the setting of injury prevention(30). To complete the timed wall-sit test, participants were asked to stand against a wall with their legs in a position that were extended slightly beyond what was comfortable for them, and squat into a position where their knees assumed a 90-degree angle (Figure 4-3). The position was demonstrated by the researcher, and then the participants were asked to get into the same position to practice. Forms corrections were made to the practice position, if necessary, and then participants were asked to relax. After a short break of at least one minute, they reassumed the wall sit position for the actual test. Once the participant was in the correct position, the timer was started. The time was stopped when the participant reached volitional exhaustion – when they could no longer hold the wall sit position – or broke form twice. Like the other muscle endurance tests (push-ups and curl-ups), the test was not repeated.

4.10 Hand-held dynamometry

Functional muscle strength was measured using a hand-held dynamometer (Lafayette Instruments). The quadriceps, deltoid, and abdominal muscle groups were tested using manual muscle testing positions to measure the strength of muscle groups corresponding to those used in the endurance tests(24). The researcher performing the HHD testing remained consistent among tests to provide the greatest degree of reliability.

To test the quadriceps, participants were sitting, and asked to extend their knee, then the researcher applied pressure through the HHD just proximal to the ankle, on the anterior side to oppose the patient's extension. This test was completed on the participant-identified dominant leg. To test the deltoid, patients were sitting, and asked to abduct their shoulder, while the researcher applied pressure through the HHD just proximal to the elbow, on the lateral side. This test was completed on the participant-identified dominant arm. To test the abdominal muscles, patients were laying down flat, and they were asked to flex their torso, while the researcher applied pressure through the HHD to the upper chest, inferior to the clavicles.

After one set of measurements, participants were given at least one minute of rest, and the cycle of testing and rest was repeated twice in each muscle group (quadriceps, deltoids, abdominals). The average of the first two measurements was used for analysis.

4.11 Encouragement

Encouragement was provided in a consistent manner to all participants. Each participant was given a name tag, and offered a sticker for each test completed to maximal effort. For tests where multiple tried were involved, such as the six-minute walk test and hand-held dynamometry measurements, participants were encouraged with earning a second sticker if they beat their initial score in subsequent tests.

For the six-minute walk test, the standardized encouragements were provided, as per the ATS guidelines(96). The only other verbal communication from the researcher was for safety reasons, which included reminding children not to run or play in the hallway.

For hand-held dynamometry, the words "lift" and "push" were used repeatedly with a loud, positive tone to encourage participants to exert their maximal force against the hand-held dynamometer.

For the curl-up and push-up tests, no encouragement was provided, as the participants had to listen and pay attention to the commands given by the cadence audio track. Only form feedback was given, as per the FITNESSGRAM protocol(10).

For the wall sit, the researcher provided an update on the time held in the wall-sit position every 30 seconds. In addition, before the test, participants were asked to let the researcher know when they were getting tired. When they gave the signal, the phrases "you got this", "keep holding", and "push, push, push" were used in that order to encourage participants to hold the position as long as possible.

No encouragement was provided for the remaining, non-effort dependent tests.

4.12 Data storage

Participants were given a study code to preserve confidentiality on all data collection files and forms. The key was handwritten and locked in a private area that only the research team could access using a single key. All data and electronic forms were stored in RedCap, which is a secure service provided through support from the Women and Children's Health Research

Network(90). RedCap operates on a password-protected, secure server. Only the research team was given the password to the data.

4.13 Statistical analysis

All data are reported as medians with range. All figures show individual patient data with medians. All analyses were non-parametric, including the Kruskal-Wallis test with Dunn's post-hoc test when three or more groups were being compared, the Mann-Whitney test when two unpaired groups were being compared, and the Wilcoxon signed rank test when two paired groups were being compared. Correlations were analyzed by Spearman correlation when the variables were continuous, and rank bivariate analysis when the variables were dichotomous. All tests were two-tailed. The significance level was set to $P=0.05$. Statistical significance was expressed as *$P<0.05$, **$P<0.01$, ***$P<0.001$ for all analyses.

GraphPad Prism (99) was used for all analyses, except the rank bivariate analysis that was used to assess correlations of clinical factors with wall-sit time and 6MWT percent predicted distance. The rank bivariate analysis was conducted using SPSS(100).

4.14 Tables and figures

Table 4-1 Schedule for research study after clinical visit.

Activity	Time required (minutes)
Walk from hospital clinic (Mazankowski building) to clinical research unit (Li Ka Shing building, 2nd floor)	6
Physical activity questionnaire	10
Quality of life questionnaire	10
Body composition and anthropometric measurements	10
Walk from clinical research unit (Li Ka Shing building, 2nd floor) to testing area (Li Ka Shing building, 6th floor)	2
Six-minute walk test 1	10
Rest	2
Hand-held dynamometry (incl. rest)	6
Rest	1
Push-up test	2
Rest	1
Curl-up test	2
Rest	1
Timed wall sit test	2
Rest	5
Six-minute walk test 2	10
Total	**80**

Schedule for research study after clinical visit. Times variable depending on how well the participants were able to follow the testing instructions, and their stage of development.

Figure 4-1 FITNESSGRAM 90˚ push-up test

A

PHOTO © Human Kinetics.   Starting position for the 90° push-up test.

B

PHOTO © Human Kinetics.   Student in the "down" position for the 90° push-up test.

FITNESSGRAM 90˚ push-up test starting position (**A**) and "down" position (**B**)(10).

Figure 4-2 FITNESSGRAM curl-up test

A   B

FITNESSGRAM curl-up test starting position (**A**) and "up" position (**B**)(10). Participant finger tips must be in the range indicated on the measuring position to ensure they are in the correct "up" position.

Figure 4-3 Wall sit test
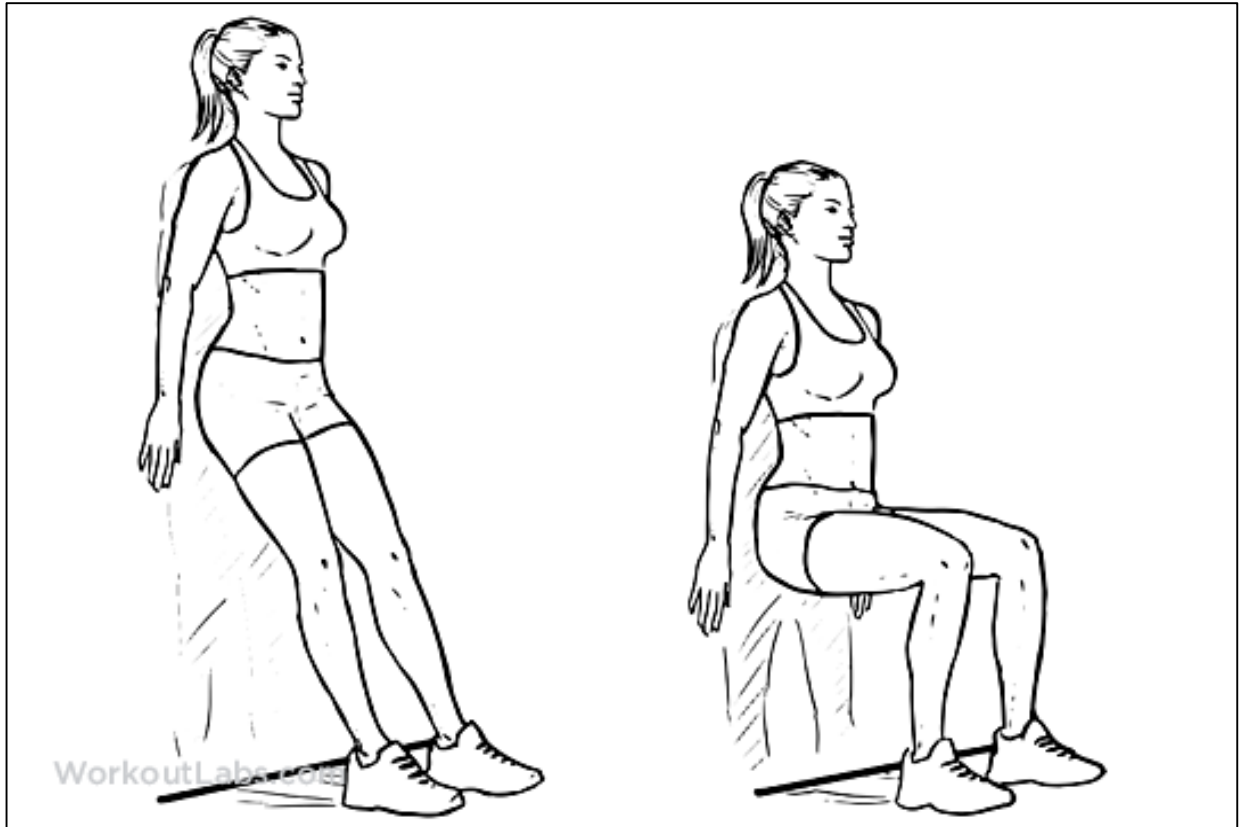
Instructions to the patient:
1. Stand tall against a wall with your head and back touching the wall.
2. Position your feet so that they are shoulder-width apart and a few inches away from the wall.
3. Rest your arms at your sides.
4. Bend your knees and lower into a squat position until your thighs are parallel to the floor and hold the position as long as you possibly can
5. Return to starting position by straightening your knees and standing tall again.

Wall-sit test visual aid and instructions.

Chapter 5: Results – Fitness Assessment

5.1 Cohort

5.1.1 Demographics

Both the control and HTx groups spanned the age of inclusion for this study (Table 5-1). The control group's median age was 11.1 (6.02-17.8) y, and the HTx group's median age was 10.7 (4.90-17.2) y. The KTx group had a similar median age (8.77 y), but the range spanned the lower end of the age of inclusion for this study (5.70-13.8 y). The height of the KTx group was significantly lower than the control group. All three groups varied significantly from each other in terms of weight.

5.1.2 Patient characteristics

Patient characteristic data are presented in Table 5-2. For the HTx group, the age at time of transplant was 2.5 (0.20-8.7) y, and the time post-transplant was 7.0 (1.9-15) y. For the KTx group, the age at time of transplant was 3.3 (1.5-8.6) y, and the time post-transplant was 3.3 (0.91-12) y. Both the age at time of transplant and time post-transplant were not significantly different between groups.

The blood pressure was not significantly different between HTx and KTx groups. KTx patients had significantly lower Hg level and higher creatinine level than HTx patients.

Four patients in the HTx group had persisting neuromotor deficits after having a stroke, whereas no KTx patients had a stroke or neuromotor deficits.

Most patients in the HTx group were taking tacrolimus, mycophenolate mofetil, a statin, blood pressure medication, and vitamin D. The blood pressure medication distribution is as follows: beta-blockers N=1, ACE inhibitors N=10, calcium channel blockers N=9. All HTx patients had taken prednisone at some point after their transplant, though only 2 HTx patients were taking prednisone at the time of testing. The median time on prednisone was 217 (31-2436) days for this group.

Most KTx patients were taking tacrolimus, prednisone, mycophenolate mofetil, blood pressure medication, vitamin D, and iron. The blood pressure medication distribution is as follows: beta-blockers N=1, ACE inhibitors N=3, calcium channel blockers N=3. The median

time on prednisone was 452 (1-1921) days for this group. There was no significant difference in the number of days on prednisone between the HTx and KTx groups.

5.2 Six-minute walk test

5.2.1 Distance walked

Aerobic capacity was assessed using the 6MWT, and the distance was compared with reference values to calculate a percent predicted 6MWT distance. The percent predicted 6MWT distance was 99.9 (80.4-120) % in healthy controls, 87.2 (69.9-118.6) % in HTx and 90.3 (78.6-114.9) % in KTx recipients. The percent predicted 6MWT distance was lower in HTx recipients, but not KTx recipients, as compared to healthy controls (Figure 5-1).

5.2.2 Heart rate

The percent increase in heart rate from the beginning to the end of the 6MWT for controls was 62.0 (9.00-143) %, HTx recipients was 23.1 (-15.3-71.9) %, and KTx recipients was 31.8 (2.90-55.1) % (Figure 5-2). The change in HR was significantly lower in HTx recipients than healthy controls.

Two patients in the HTx group had a decrease in HR after the 6MWT (-15.3 and -7.10 %). The change in rating of perceived exertion (RPE) of dyspnea in these individuals was -1 and 0, respectively. The change in RPE of leg fatigue in these individuals was 4 and 5, respectively.

There were 2 patients taking beta-blockers, one in the HTx and one in the KTx group. The percent change in HR for the HTx recipient was 12.7% and the KTx recipient was 34.4%. Both of these values were within their respective interquartile ranges.

5.2.3 Six-minute walk test 1 vs test 2

All participants (N=48) were analyzed together, comparing their results on test 1 with test 2. However, due to equipment problems, for the SpO_2 analysis, N=40, and for the blood pressure analysis, N=44. Several parameters from the second 6MWT were significantly higher than the first test, including pre-and post-test heart rate, RPE dyspnea, and RPE leg fatigue, and total distance walked (Table 5-3). Pre-test blood pressure, and both pre- and post-test SpO_2 were similar in tests 1 and 2.

5.3 Muscle function

5.3.1 Hand-held dynamometry reliability

The reliability data set (N=5) was analyzed to show the correlations between week 1 and week 2 of different sets of the 3 available measures for hand-held dynamometry (Table 5-4). All different sets of measures showed a strong correlation between week 1 and week 2 results. However, using the first two measures showed the strongest correlation (r=0.9), and the only correlation that approached significance (P=0.078). Therefore, the first two measures were used in the following strength analyses.

The absolute values of force (first 2 measures combined) for each muscle group were compared between week 1 and week 2 (Figure 5-3). Though none of the results differed significantly between weeks, there is variability in test results among individuals each week.

5.3.2 Hand-held dynamometry test results

Muscle strength differed among testing groups, in a different way for each muscle group. For upper body strength, the force to body surface area ratio was lower for HTx recipients (6.15 (4.35-11.3) kg/m²), as compared to controls (8.48 (4.80-10.8) kg/m²). The KTx recipient group (6.10 (4.25-8.30) kg/m²) did not differ from controls or HTx recipients. Core strength did not significantly differ between groups. The force to body surface area ratio for core strength was 4.95 (1.30-17.5) kg/m² for controls, 4.25 (0.00-14.0) kg/m² for HTx recipients, and 4.30 (0.00-10.3) kg/m² for KTx recipients. For lower body strength, the force to body surface area ratio was lower for KTx (9.27 (8.65-19.1) kg/m²) than controls (15.4 (11.7-21.3) kg/m²). The HTx group (13.1 (8.90-24.8) kg/m²) did not differ significantly from controls or KTx recipients.

5.3.3 Muscle endurance tests

Muscle endurance differed among testing groups, in a different way for each muscle group. For upper body endurance, the percent predicted number of push-ups was highest in controls (112 (48.9-400) %). As compared to controls, the percent predicted number of push-ups was lower in HTx recipients (28.6 (0.00-250) %) and KTx recipients (8.35 (0.00-150) %).

For core muscle endurance, the percent predicted number of curl-ups was significantly lower in HTx recipients (115 (0.00-450) %) than controls (167 (46.7-500) %). The KTx group percent predicted number of curl-ups (122 (0.00-217) %) did not significantly differ from controls or HTx.

For lower body muscle endurance, the wall-sit time was significantly shorter in the KTx group (18.5 (10.0-54.0) s) than in the control group (62.0 (11.0-203) s). The HTx group wall-sit time (36.5 (11.0-132) s) did not differ significantly from the control or KTx groups.

5.3.4 Wall-sit test correlations

The wall-sit test had weak to moderate and significant correlations with many variables in an analysis of all study participants (Table 5-5). These variables included quality of life (R=0.3596, P<0.05), body surface area (R=0.4562, P<0.01), lower body strength (R=0.3059, P<0.05), upper body muscle endurance (R=0.3857, P<0.01), and core muscle endurance (R=0.4313, P<0.01). In only the control group, some of these correlations were stronger (quality of life R=0.5196, body surface area R=0.5611, and core muscle endurance R=0.6191), and others were no longer significant (lower body strength, upper body muscle endurance). In the HTx group, none of the variables in the analysis correlated with wall-sit time.

5.4 Quality of life

5.4.1 Questionnaire results

Quality of life, as measured by the PedsQL 4.0 questionnaire, was not significantly different between groups (P=0.14, Figure 5-5). The total scale score of the control group was 78 (46-100), the HTx group was 64 (33-97), and the KTx group was 71 (50-91).

A similar pattern was observed in the physical health summary score, and the difference between groups approached significance (P=0.056, Figure 5-6). The physical health summary score of the control group was 81 (59-100), the HTx group was 69 (31-100), and the KTx group was 80 (50-100).

5.4.2 Correlates of quality of life

Quality of life total scale score correlated with wall-sit time in 2 groups (Table 5-6). There was a weak correlation between these two variables in the group with all participants (R=0.3595, P<0.05), and there was a moderate correlation between these two variables in the control group (R=0.5196, P<0.05). Though the correlation between quality of life total scale score and all measured fitness variables was analyzed, no other relationships were significant or showed a correlation above R=0.3000.

5.5 Physical activity level

The physical activity level, as measured by the Physical Activity Questionnaire, was not significantly different between groups (P=0.17, Figure 5-7). The PAQ score (/5) of the control group was 2.739 (1.509-4.265), the HTx group was 2.963 (1.730-4.172), and the KTx group was 2.363 (2.080-2.862).

5.6 Clinical factors

Clinical factors affecting patients in the HTx group were analyzed to examine their effect on the 6MWT percent predicted distance and wall-sit time. Since almost all HTx patients were on tacrolimus (N=19) and vitamin D (N=17), and few were on prednisone (N=2) or beta-blockers (N=1), these medications were excluded from the analysis (Table 5-2).

Six-minute walk test percent predicted distance was moderately correlated with stroke (R=-0.553, P<0.05), but not persisting neuromotor deficits from stroke (R=-0.283, P=0.271, Table 5-7). Also, the correlation between 6MWT percent predicted distance and number of previous surgeries was moderate and approached significance (R=-0.420, P=0.083). All other correlates with 6MWT percent predicted distance in our analysis were not significant.

None of the clinical factors in our analysis correlated with wall-sit time (Table 5-8).

5.7 Tables and figures

Table 5-1 Demographics

	Control	HTx	KTx	P-value
No. subjects	20	22	6	
Female, n (%)	7 (35)	11 (50)	2 (33)	
Age, yrs	11.1 (6.02-17.8)	10.7 (4.90-17.2)	8.77 (5.70-13.8)	ns
Height, cm	150.6 (116.5-187.9)	137.9 (110.0-180.7)	125.8 * (110.5-150.9)	**0.04**
Weight, kg	40.4 (18.7-81.5)	29.7 (15.1-67.1)	25.9 (21.0-40.3)	**0.04**

Demographics of controls, heart transplant recipients (HTx), and kidney transplant recipients (KTx). All data are expressed as median (range). Analyzed by Kruskal-Wallis non-parametric analysis with Dunn's post-hoc test for multiple comparisons *P<0.05.

Table 5-2 Patient characteristics

	HTx	KTx
Type of diagnosis	Congenital (N=11) Cardiomyopathy (N=9) Other (N=2)	Congenital (N=3) Other (N=3)
Age at tx, yrs	2.5 (0.20-8.7)	3.3 (1.5-8.6)
Time post-tx, yrs	7.0 (1.9-15)	3.3 (0.91-12)
Blood pressure, measured, mmHg	108 (90-148) / 68 (52-86)	111 (92-129) / 66 (44-82)
Hg level, most recent, mmol/L	129 (116-152)	112 (103-129) **
Creatinine level, most recent, umol/L	49 (5.5-110)	83 (36-152)
Other medical events	Stroke (N=7) Motor deficits (N=4) VAD (N=9) ECMO (N=7) Rejection (N=5) PTLD (N=4)	Stroke (N=0) Motor deficits (N=0) VAD (N=0) ECMO (N=0) Rejection (N=2) PTLD (N=0)
Previous cardiac or kidney surgeries	Fontan procedure (N=4) Glenn procedure (N=5) Norwood procedure (N=3) Other (N=7)	Nephrectomy (N=2) Other (N=4)
Dialysis, no. days	n/a	761 (220-1543) Peritoneal (N=3) Hemodialysis (N=0)
Prednisone, no. days	217 (31-2436)	452 (1-1921)

Medications, current	Tacrolimus (N=21)
	Prednisone (N=2)
	MMF (N=16)
	Statin (N=13)
	Blood pressure (N=18)
	    Beta-blocker (N=1)
	    ACEi (N=10)
	    CCB (N=9)
	Vitamin D (N=19)
	Iron (N=8)
		Tacrolimus (N=6)
		Prednisone (N=6)
		MMF (N=6)
		Statin (N=0)
		Blood pressure (N=6)
		    Beta-blocker (N=1)
		    ACEi (N=3)
		    CCB (N=3)
		Vitamin D (N=5)
		Iron (N=3)

Patient characteristics for HTx and KTx recipients. Data were analyzed by Mann-Whitney test, and are reported as median (range) *P<0.05, **P<0.01. tx: transplant, VAD: ventricular assist device, ECMO: extracorporeal membrane oxygenation, MMF: mycophenolate mofetil, ACEi: angiotensin-converting enzyme inhibitor, CCB: calcium channel blocker.

Figure 5-1 Six-minute walk test distance (% predicted)
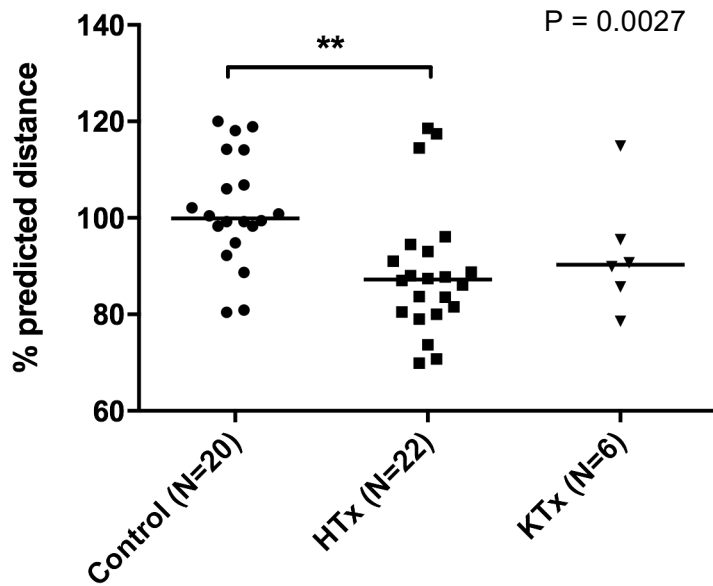
Six-minute walk test distance (% predicted) of healthy controls, heart transplant recipients (HTx), and kidney transplant recipients (KTx). Measured by six-minute walk test, and presented as percent of predicted normal values. Data are presented as individual patient data with medians. Analyzed by Kruskal-Wallis non-parametric test and Dunn's post-hoc test. ***P<0.01*

Figure 5-2 Heart rate
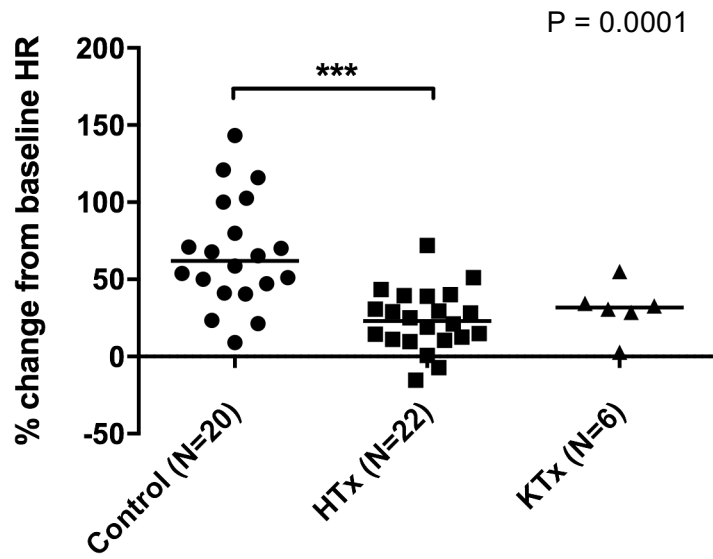
Percent change in heart rate from before to immediately after exercise ((post-6MWT HR – pre-6MWT HR)/pre-6MWT HR). Data for healthy controls, heart transplant recipients (HTx), and kidney transplant recipients (KTx) are presented as individual patient data with medians. Analyzed by Kruskal-Wallis non-parametric test and Dunn's post-hoc test ***$P<0.001$.

Table 5-3 Six-minute walk test 1 vs. test 2

	Test 1	Test 2	Test 2 – Test 1	P-value
Pre-test				
Blood pressure, mmHg	106 (82-142) / 67 (44-88)	108 (80-166) / 64 (42-88)	0 (-21-56)/ 0 (-28-14)	ns ns
SpO_2 (%)	97 (92-100)	98 (90-99)	0 (-6-3)	ns
Heart rate (bpm)	86 (44-126)	92 (64-126)**	2.5 (-12-57)	0.002
RPE dyspnea (Borg)	0 (0-6)	0.5 (0-6) ***	0 (-3-6)	<0.001
RPE leg fatigue (Borg)	0 (0-5)	0.75 (0-10) ***	0.5 (-2.5-9)	<0.001
Post-test				
SpO_2 (%)	98 (92-99)	98 (92-99)	0 (-6-3)	ns
Heart rate (bpm)	120 (68-174)	128 (83-190) **	4 (-33-61)	0.009
RPE dyspnea (Borg)	2 (0-10)	3 (0-10) *	1 (-9-10)	0.03
RPE leg fatigue (Borg)	3 (0-10)	5 (0-10) ***	1 (-6-10)	<0.001
Overall				
Distance (m)	540 (399-737)	610 (397-840) ***	47 (-55-163)	<0.001

Comparison of six-minute walk test parameters for each participant's first (Test 1) and second (Test 2) test. All participants, including healthy controls, HTx, and KTx (N=48) were included in the analysis. Due to equipment problems, for the SpO_2 analysis, N=40, and for the blood pressure analysis, N=44. All data are expressed as median (range). Analyzed by Wilcoxon matched-pairs signed rank test *P<0.05, **P<0.01, ***P<0.001. SpO2: oxygen saturation, RPE: rated perception of exertion.

Table 5-4 Hand-held dynamometry reliability correlations

	All 3 measures		First 2 measures		Last 2 measures	
Testing maneuver	R	P-value	R	P-value	R	P-value
Quadriceps extension (kg)	0.7	0.233	0.8	0.133	0.5	0.45
Trunk flexion (kg)	0.7	0.233	0.9	0.083	0.6	0.35
Deltoid extension (kg)	1.0 *	0.017	1.0 *	0.017	0.7	0.233
Mean	0.8	0.161	0.9	0.078	0.6	0.344

Reliability testing with a separate set of healthy volunteers (N=5). Relationship between duplicate (first, last) or triplicate (all) values for hand-held dynamometry testing of quadriceps extension, trunk flexion, and deltoid extension force. Analyzed by Spearman correlation *$P<0.05$.

Figure 5-3 Hand-held dynamometry reliability absolute values
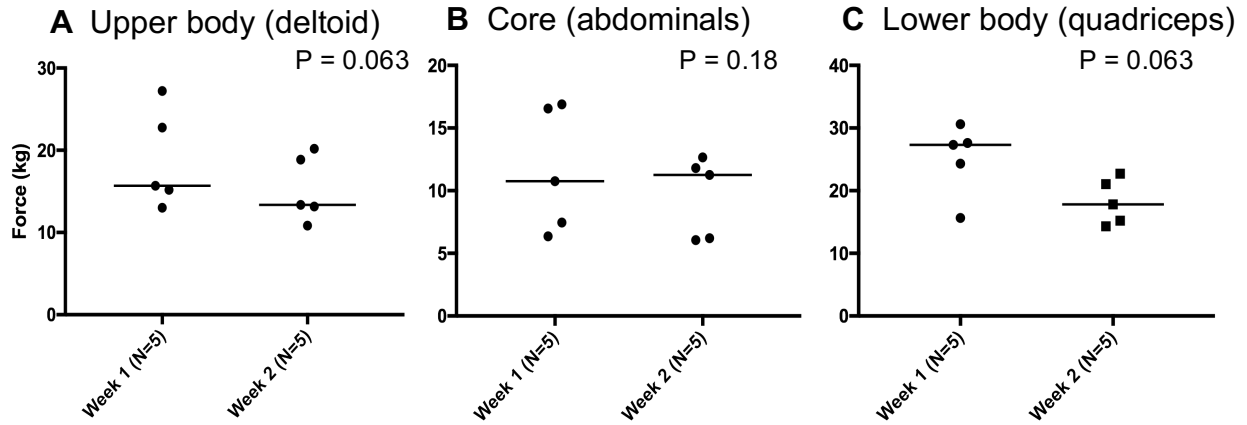
Reliability testing with a set of healthy volunteers, separate from the control group (N=5). Absolute difference in upper body (deltoid), core (abdominals), and lower body (quadriceps) strength measured by hand-held dynamometry between week 1 and week 2. Data are reported as individual participant data with medians. Analyzed by Wilcoxon matched-pairs signed rank test *P<0.05.*

Figure 5-4 Muscle strength and muscle endurance
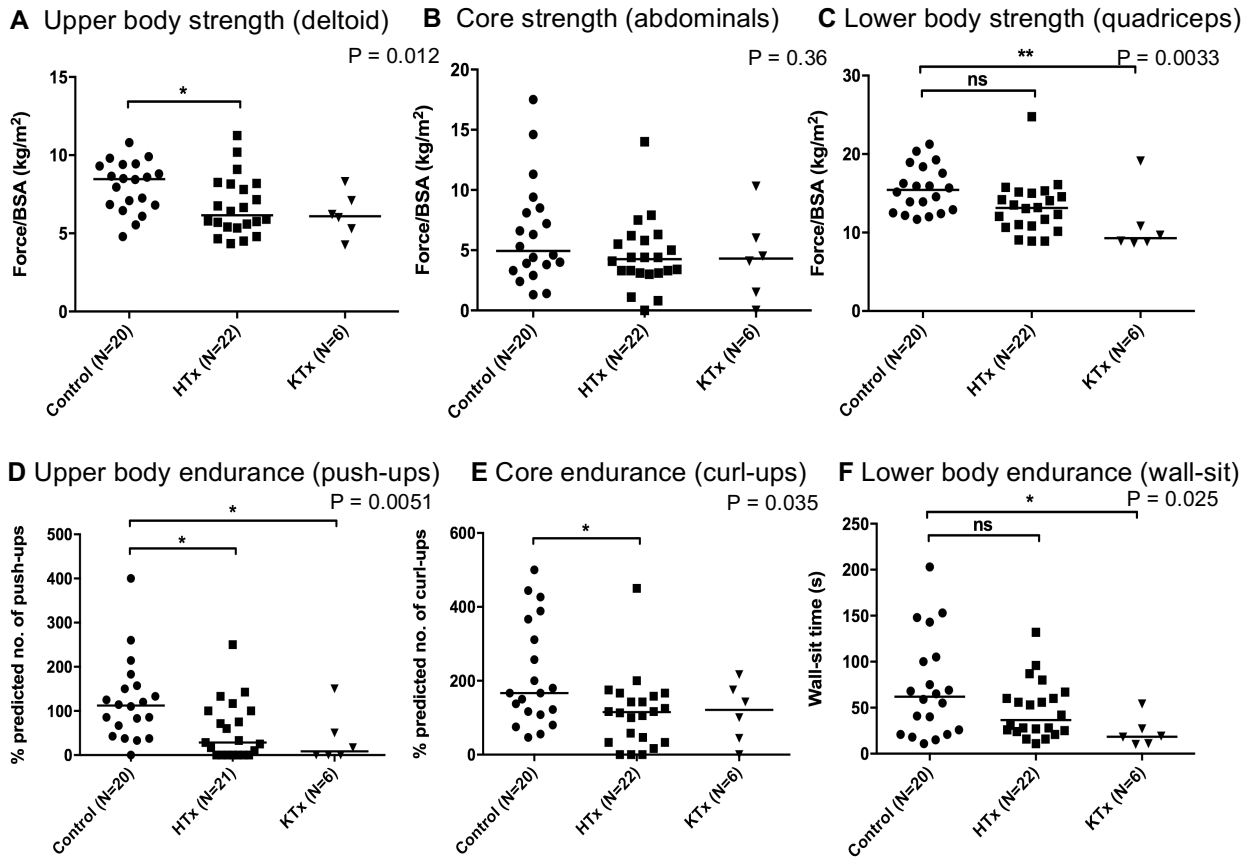
A-C Muscle strength and **D-F** muscle endurance of various muscle groups of controls (N=20), HTx (N=22), and KTx (N=6) recipients. Muscle strength was measured by hand-held dynamometry for **A** deltoid, **B** core, and **C** quadriceps muscle groups. Muscle endurance was measured by **D** push-ups, **E** curl-ups, and **F** wall-sit. Data are presented as individual patient data with medians. Analyzed by Kruskal-Wallis non-parametric test and Dunn's post-hoc test *P<0.05, **P<0.01.

Table 5-5 Wall-sit correlations

Wall-sit vs.	All (N=48)		Control (N=20)		HTx (N=22)	
	Spearman R	P-value	Spearman R	P-value	Spearman R	P-value
QOL (PedsQL score)	0.3596 *	0.0141	0.5196 *	0.0271	0.2460	0.2699
BSA (m^2)	0.4562 **	0.0011	0.5611 *	0.0101	0.3313	0.1321
Quad force/BSA (kg/m^2)	0.3059 *	0.0345	0.2833	0.2261	0.1510	0.5024
Push-ups (no.)	0.3857 **	0.0068	0.4180	0.0667	0.1993	0.3740
Curl-ups (no.)	0.4313 **	0.0022	0.6191 **	0.0036	0.3053	0.1671

Relationship between wall-sit time and quality of life, body surface area, lower body strength, and other muscle endurance tests. Analyzed by Spearman correlation of all participants (controls, HTx, KTx, N=48), controls (N=20), and HTx (N=22) *P<0.05, **P<0.01.

Figure 5-5 Quality of life total scale score
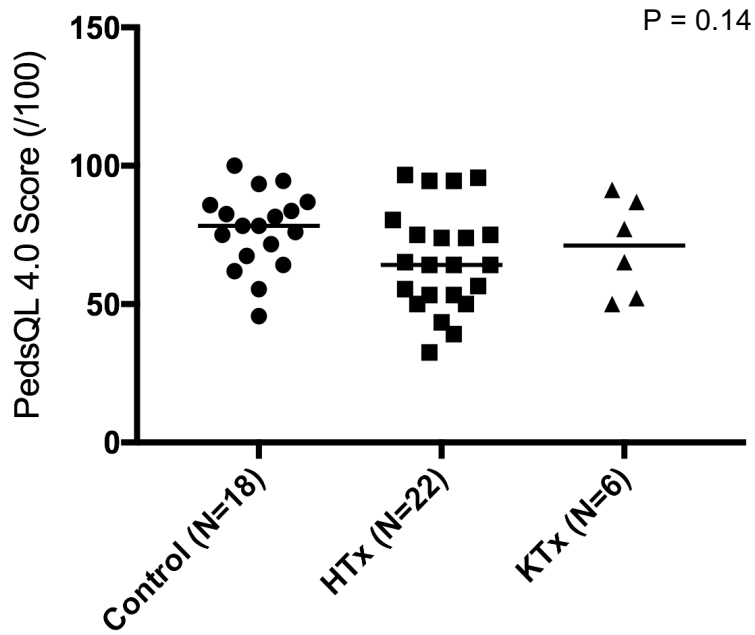
Quality of life of controls (N=18), HTx recipients (N=22), and KTx recipients (N=6), measured by PedsQL 4.0 questionnaire total scale score (/100). Data are presented as individual patient data with medians. Analyzed by Kruskal-Wallis non-parametric test and Dunn's post-hoc test *P<0.05.

Figure 5-6 Quality of life physical health summary score
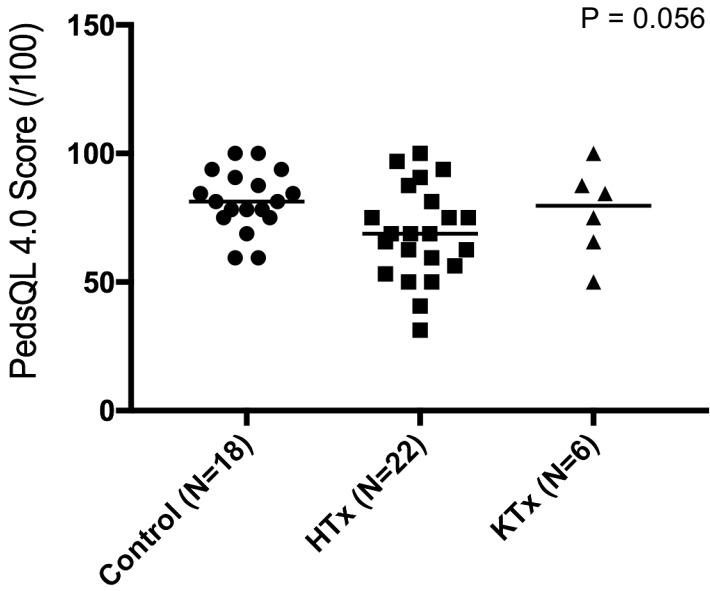
Physical functioning of controls (N=18), HTx recipients (N=22), and KTx recipients (N=6), measured by PedsQL 4.0 questionnaire physical health summary score (/100). Data are presented as individual patient data with medians. Analyzed by Kruskal-Wallis non-parametric test and Dunn's post-hoc test *P<0.05.

Table 5-6 Quality of life correlations

QOL (PedsQL score) vs.	All (N=46)		Control (N=18)		HTx (N=22)	
	Spearman R	P-value	Spearman R	P-value	Spearman R	P-value
6MWT (m)	0.2718	0.0677	0.2292	0.3602	0.2164	0.3335
Delt force/BSA (kg/m^2)	0.0645	0.6702	-0.1301	0.6069	-0.03453	0.8787
Ab force/BSA (kg/m^2)	0.1972	0.1891	0.127	0.6155	0.2562	0.2497
Quad force/BSA (kg/m^2)	0.06701	0.6581	0.1591	0.5283	0.05832	0.7965
Push-ups (no.)	0.147	0.3296	0.06535	0.7967	-0.1201	0.5944
Curl-ups (no.)	0.1027	0.4971	0.05168	0.8386	0.04892	0.8288
Wall-sit time (s)	0.3595 *	0.0141	0.5196 *	0.0271	0.246	0.2699

Relationship between quality of life and all measured fitness variables of all participants (controls, HTx, and KTx, N=46), controls (N=18), and HTx (N=22). Analyzed by Spearman correlation of *P<0.05.*

Figure 5-7 Physical activity level
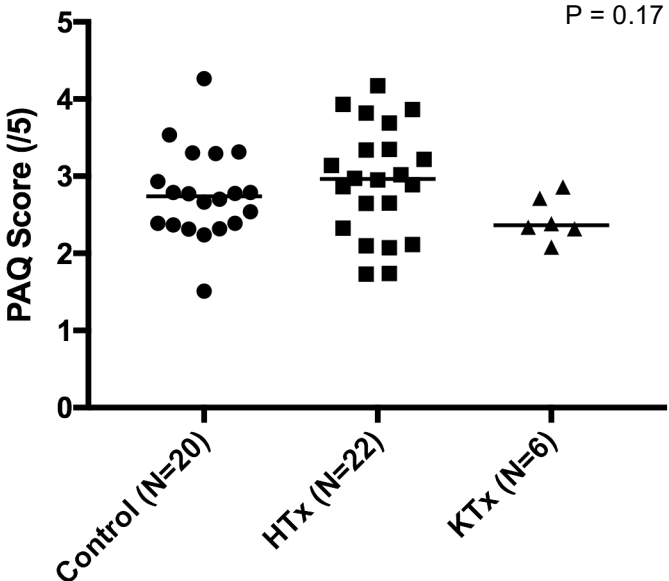
Physical activity level, measured by PAQ score (/5), for controls (N=20), HTx recipients (N=22), and KTx recipients (N=6). Data are presented as individual patient data with medians. Analyzed by Kruskal-Wallis non-parametric test and Dunn's post-hoc test *P<0.05.*

Table 5-7 Correlation of clinical risk factors with six-minute walk test percent predicted distance

6MWT distance (% predicted) vs.	R	P-value	Significant?
Continuous variables			
Age at tx (y)	-0.418	0.053	ns
Time post-tx (y)	-0.179	0.427	ns
Time from diagnosis to transplant (days)	-0.092	0.686	ns
Hg level (most recent mmol/L)	-0.075	0.740	ns
Creatinine level (most recent umol/L)	-0.389	0.073	ns
Previous surgeries (no.)	-0.213	0.342	ns
Prednisone (days)	-0.248	0.265	ns
Dichotomous variables (y/n)			
Prednisone	0.224	0.315	ns
Statin	-0.302	0.172	ns
ACE inhibitor	-0.117	0.605	ns
Calcium channel blocker	-0.071	0.747	ns
ECMO	-0.038	0.865	ns
VAD	-0.226	0.312	ns
PTLD	0.000	1.000	ns
Stroke	-0.562	0.007	**
Neuromotor deficits	-0.351	0.110	ns
Rejection episode(s)	0.111	0.622	ns

Correlation of clinical risk factors with six-minute walk test distance (% predicted) in the HTx population (N=22). Continuous variables analyzed by Spearman correlation, and dichotomous variables analyzed by rank bivariate analysis (*P<0.05, **P<0.01*).

Table 5-8 Correlation of clinical risk factors with wall-sit time

Wall-sit time (s) vs.	R	P-value	Significant?
Continuous variables			
Age at tx (y)	0.325	0.140	ns
Time post-tx (y)	0.174	0.438	ns
Time from diagnosis to transplant (days)	0.193	0.389	ns
Hg level (most recent mmol/L)	-0.280	0.208	ns
Creatinine level (most recent umol/L)	0.280	0.207	ns
Previous surgeries (no.)	-0.047	0.834	ns
Prednisone (days)	-0.194	0.387	ns
Dichotomous variables (y/n)			
Prednisone	-0.200	0.373	ns
Statin	0.194	0.386	ns
ACE inhibitor	-0.190	0.398	ns
Calcium channel blocker	0.306	0.166	ns
ECMO	-0.239	0.285	ns
VAD	-0.255	0.252	ns
PTLD	0.288	0.193	ns
Stroke	0.184	0.412	ns
Neuromotor deficits	0.026	0.910	ns
Rejection episode(s)	0.026	0.910	ns

Correlation of clinical risk factors with wall-sit time (s) in the HTx population (N=22). Continuous variables analyzed by Spearman correlation, and dichotomous variables analyzed by rank bivariate analysis (*P<0.05*).

Chapter 6: Discussion

6.1 Prospective study population

6.1.1 Population characteristics

Age was not significantly different between groups, but kidney transplant (KTx) recipients were shorter than both heart transplant (HTx) recipients and controls. This difference in height is consistent with other findings in the KTx population where growth is stunted, which may relate to delayed onset of puberty due to steroid treatment in this population(101). To address this difference in height, the six-minute walk test (6MWT) and muscle strength measures were controlled for height and body size, respectively. Muscle endurance tests are internally controlled for body size, since participant weight is the resistance for the test.

The HTx group had more female participants (50%) than the control (35%) and KTx (33%) groups. Since males can generate greater muscle strength(102) and generally have higher aerobic capacity(103), fitness values in the HTx group may have been lower than if the sex composition were the same as the control and KTx groups.

6.1.2 Patient characteristics

The patient characteristics are similar among HTx and KTx groups. In both groups, about half the patients had congenital disease leading to transplant, and age at transplant, time post-transplant, and blood pressure were not significantly different between transplant (Tx) groups. The KTx group, however, had a lower mean hemoglobin. It has been shown that hemoglobin level is associated with six-minute walk distance in pediatric KTx recipients(104). However, there was no correlation between the level of hemoglobin and 6MWT distance in the KTx group in our study (R=-0.075, P=0.740).

The medical conditions of the HTx group were different from the KTx group. The HTx group included 7 patients who had a stroke, of which 4 had persisting neuromotor deficits. Though this was unlikely to affect one-sided tests (hand-held dynamometry was performed on the dominant side), it may have played a role in the ability to complete other fitness tests like the 6MWT, push-ups, curl-ups, and wall-sit test. However, the presence of neuromotor deficits was not associated with 6MWT distance (R=-0.351, P=0.110) or wall-sit time (R=0.026, P=0.910).

Almost all patients were taking tacrolimus, mycophenolate mofetil, a blood pressure medication, and vitamin D at the time of the study. All KTx patients were also taking prednisone at the time of the study. Medication status (on/off) these medications was not correlated with 6MWT distance or wall-sit time ($P>0.05$).

6.2 Aerobic capacity

6.2.1 Heart transplant recipients

This is the first study to assess 6MWT distance in HTx recipients, as compared to healthy controls. In the prospective study, 6MWT percent predicted distance was 13% lower in HTx than controls ($P<0.05$). The difference in 6MWT distance in the prospective study is less than the difference in VO_2max versus in-study controls (26%) and exercise time versus healthy comparators (25%) in the meta-analysis. The difference in aerobic capacity between the prospective study and meta-analysis may be explained by the type of fitness test. The difference in aerobic capacity may be greater in a maximal test (VO_2max, exercise time), as opposed to a sub-maximal test (6MWT), because the difference in fitness level in HTx recipients occurs near the upper end of their aerobic reserve, which is not captured in sub-maximal tests.

Alternatively, it is possible that the age at transplant of the cohort in the prospective study affected the level of aerobic capacity. One of the review studies by Dipchand et al. (52) explored this relationship. Their study showed that younger age at transplant is associated with higher VO_2max. In the prospective study, the correlation between age at transplant and percent predicted 6MWT distance in HTx recipients was weak and approached significance (R=-0.418, P=0.053). This study included patients who were relatively young at the time of their transplant (median 2.5 years), as compared to the age at transplant of the meta-analysis group (mean 8.5 years). Therefore, it is possible that the younger age at transplant in this study resulted in a 6MWT distance closer to controls than the studies with older ages at transplant in the meta-analysis.

Last, it is possible that the cohort of HTx recipients in this study is simply more fit than other cohorts. In fact, this cohort of HTx recipients had a similar level of physical activity to controls, which is different from other studies where HTx recipients had lower physcial activity levels than controls(105, 106). The meta-analysis showed that there is a high level of heterogeneity among studies of aerobic capacity in HTx recipients ($I^2=89\%$). Two other studies showed similarly high levels of aerobic capacity (92% and 86% of healthy values) in their HTx

populations(74, 105). Upon review, there were no clear trends that may have set these studies apart from other studies that reported lower levels of aerobic capacity. Therefore, the differences among studies may be related to the fitness level of the cohort.

6.2.2 Kidney transplant recipients

The aerobic capacity of the KTx group was not significantly different from HTx or controls in the prospective study. The comparison between KTx and controls was not consistent with the meta-analysis. In the meta-analysis, VO_2max and 6MWT distance were significantly lower in KTx recipients than controls. There was a difference of 26% of healthy values in VO_2max, and 24% of healthy values of 6MWT distance between KTx recipients and healthy controls in the meta-analysis.

The age of KTx recipients in the studies included in the meta-analysis of VO_2max and the cohort in this study was different. Tangeraas et al. (107) included adult participants who were transplanted as children, and had an average age of 27 years. The study by Lubrano et al. (108) had an average age of 16 years. In this study, the mean age was 9 years. It has been shown that body-size controlled aerobic capacity is highest in younger children(109), which may explain the higher values of aerobic capacity in this study.

However, age of KTx recipients was similar in the 2 studies included in the meta-analysis of 6MWT distance and this study. Therefore, other factors may explain the difference in the findings of our study and the meta-analysis. The 6MWT percent predicted distance in the prospective study is similar to the results of Watanabe et al. (104), who found that 6MWT distance was only 8% different from control values. The prospective study was different from the study by Ferrari et al. (110), who found that 6MWT distance was 35% lower than the healthy comparator. The differences in 6MWT distance between these studies may be attributable to the difference in samples from the pediatric KTx population.

The similarity in KTx and HTx percent predicted 6MWT distance in the prospective study is consistent with the meta-analysis. The meta-analysis showed that VO_2max was not significantly different between types of transplant. This finding suggests that transplantation has a similar effect on aerobic capacity, regardless of the type of transplant performed. Therefore, factors that are common to all types of transplant are likely to be the main predictors of aerobic capacity in transplant populations. However, further studies are needed to investigate the underlying causes of impairment in aerobic capacity.

6.2.3 Liver transplant recipients

In the meta-analysis, VO$_2$max and number of PACER laps were significantly lower in LiTx than healthy controls or normative values. One study by Vandekerckhove et al. investigated correlates with VO$_2$max in LiTx recipients. There was no correlation between VO$_2$max and time post-transplant, age at transplant, history of rejection, or previous hospital admission, but VO$_2$max did correlate with maximal heart rate (R=0.64). LiTx recipients were not assessed in the prospective study, so further conclusions could not be drawn.

6.2.4 Bone marrow transplant recipients

In the meta-analysis, VO$_2$max was significantly lower in BMT than healthy controls or normative values. Hogarty et al. investigated the effect of time since BMT on aerobic capacity, and they found that VO$_2$max increased 4% per year after BMT. San Juan et al. did not investigate causes of impaired aerobic capacity after BMT. A study by Mathiesen et al. showed that VO$_2$max correlated with lung function and physical activity, but not diagnosis, donor type, or history of graft versus host disease. BMT recipients were not assessed in the prospective study, so further conclusions could not be drawn.

6.3 Meta-analysis

6.3.1 Control vs. normative data

When studies were divided according to type of healthy comparator (controls within the study vs. normative data), the mean difference in VO$_2$max differed. In fact, there was a significantly greater mean difference in VO$_2$max between Tx and healthy comparators when patient values were being compared to normative values, as opposed to in-study controls. On average, studies using normative data used reference studies from 15 ± 8.2 years before they were published. It has been shown that over recent years, physical activity level has decreased over time in different cohorts of healthy children(111). It is possible that using older, normative data results in transplant patients being compared to healthy children that were more active and fit than normal at the time of the study. It is encouraged that future studies use control groups

or more recent normative values to account for changes in normal fitness levels of healthy children.

6.3.2 Heterogeneity

The meta-analysis was designed to be inclusive, and capture all published studies in the field of fitness after pediatric transplantation. The limitation of this methodology is that a wide variety of types and sizes of studies were included, which resulted in high heterogeneity of the results ($I^2=84\%+$). In addition, some studies were weighted much more than others because they had considerably greater N-values, and thus the mean difference of the group may have represented one centre considerably more than others.

6.3.3 Treadmill vs. cycle ergometer

For VO_2max analysis, studies using both treadmills and cycle ergometers were included. It has been shown that cycle ergometry yields VO_2max about 8-10% lower than treadmill testing, due to utilization of less muscle mass(112). Therefore, VO_2max values reported in the meta-analysis may be up to 10% lower than participants' true VO_2max. However, within each study, the same method was used for both groups, so the mean difference should be largely unaffected.

6.4 Six-minute walk test

6.4.1 Heart rate

The percent change in heart rate (HR) during the 6MWT of HTx recipients was significantly lower than that of controls. This finding is consistent with other studies, and may reflect the denervation of the heart during the transplant procedure. The percent change in HR may be lower in HTx than controls because either the baseline HR is higher, the maximum HR is lower, or both. In fact, both of these effects on heart rate are observed in heart transplant recipients(48, 49). Though a reduced change in HR has the potential to affect aerobic capacity, it has been shown that pediatric HTx recipients compensate for the lower HR by increasing their stroke volume to maintain cardiac output during exercise(47, 74, 75).

Interestingly, the change in HR of the KTx recipient group was not different from controls or the HTx group. There is no change in innervation of the heart during the kidney transplant procedure, so other factors may explain the finding in the kidney group. One explanation is muscle weakness due to prednisone(40), which may limit the patient's ability to walk before heart rate increases to match oxygen demands. This effect may have been enhanced in the prospective study because the second 6MWT was performed after muscle testing, which may have weakened leg muscles. In fact, the pre-test rated perception of exertion (RPE) of leg fatigue was significantly higher in the whole cohort before the second test, as compared to the first test. However, the median RPE was 0.75, which corresponds to somewhere between an "extremely weak" amount of leg fatigue, and a "weak" amount of leg fatigue on the Borg scale. Though this rating of leg fatigue was quite minimal, a small change may have had a greater impact on patients taking steroids, like all the patients in the KTx group.

Two patients were taking beta-blockers: one in the HTx group, and one in the KTx group. Though beta-blockers can affect maximal heart rate, it is unlikely that such a small number of participants taking these medications affected the group's values.

6.4.2 Test 1 versus test 2

The second 6MWT was different from the first test in many ways. First, the pre-test HR, rated perception of exertion (RPE) of dyspnea, and RPE of leg fatigue were all higher in the second test than the first test. In this study, for the convenience of the participants, all tests were conducted on the same day. To follow the ATS guidelines (96) and allow for sufficient time between tests, one test was performed at the beginning of the fitness battery, while the other was done after all other fitness testing was complete. Though participants were given at least one minute, but up to as much time as required, to recover from previous testing, it appears that their physiology had not completely returned to resting values. Despite this incomplete recovery, the post-test HR, RPE of dyspnea, RPE of leg fatigue, and overall distance were higher in the second versus the first test. The increase in fatigue levels and HR would suggest that participants were still able to exert maximal effort during the test. The increase in distance walked from test 1 to test 2 also supports that participants were able to exert full effort on the second test.

6.4.3 Limitations

Since the 6MWT is a sub-maximal test, it is possible to observe a ceiling effect. This ceiling effect might occur if the participants have a fitness level that is not sufficiently challenged by the demands of the test, so they are limited by other factors, like their leg span. Though it is difficult to objectively evaluate whether participants reach a ceiling effect, it was observed that most controls and many patients experienced this phenomenon in this study. It is suggested that future studies in transplant recipients use maximal tests to subject pediatric participants to a greater challenge, in order to gain a better understanding of their aerobic fitness level.

For this study, two sets of data and one equation for the calculation of percent predicted 6MWT distance were used. One reference data set was used for children aged 5-7 years, and it was based on age. The other reference data set was used for children aged 7-16 years, and it was based on height. The equation was used for adolescents aged 17-18 years, and it was derived from that same data set that was used for children aged 7-16 years. This variability in reference data may have contributed to slight differences in percent predicted 6MWT distance among participants in each testing category. It would be helpful to generate a comprehensive reference data set for children of all ages, based on height, the main predictor of 6MWT distance apart from fitness level, for future studies.

6.5 Muscle function

6.5.1 Hand-held dynamometry

In this study, three measurements of hand-held dynamometry were taken for each muscle group. When analyzed in groups of either all three measurements, first two measurements, or last two measurements, the first two measurements had the highest correlation between testing sessions in healthy volunteers (R=0.9). This finding likely reflects the metabolism of strength-generating fast-twitch muscle fibers. Though fast-twitch fibers are able to produce energy quickly, they also tire quickly(20). This physiology is evidenced in this study by a less consistent third strength measurement. This muscle tiring appears to have more of an effect on muscle strength than the learning effect. If the learning effect was the main determinant of consistency in muscle strength testing, the last two measurements would likely have been more consistent between weeks. Perhaps this effect was mitigated by the practice repetition without resistance that participants were asked to perform before the actual test.

6.5.2 Heart transplant recipients

This is the first study to quantify muscle function in pediatric HTx recipients. In HTx recipients, both muscle strength and endurance were lower in the upper body, compared to controls. However, the difference in upper body muscle endurance (75%) was much greater than the difference in upper body muscle strength (27%). It is possible that upper body muscle endurance is affected to a greater extent in the HTx group because the aerobic muscle fibers are more affected than anaerobic muscle fibers in HTx recipients. However, it is important to consider the difference in load involved in each movement. In the deltoid strength test, the resistance was applied by the researcher, in proportion to the force generated by the participant. In the push-up test, the load was the participant's body weight, which may be a greater proportional load than the resistance in the strength test. For this reason, many participants were able to generate force in the strength test, but not perform even one push-up. This lack of strength in the push-up test is reflected by the number of zero scores in that test. Because of this limitation, it is difficult to draw meaningful conclusions about upper body muscle endurance in the HTx and KTx cohorts. Further, it is recommended that future studies utilize other measures of upper body muscle endurance, with less of a strength component, to truly analyze these parameters separately.

There was no difference in core strength between control and HTx groups, but core muscle endurance was lower in HTx recipients than controls. In part, there was an effect similar to the push-up test where some participants would get a score of zero because they lacked the strength to perform a curl-up. However, fewer participants were affected by this lack of strength, compared to HTx recipients in the push-up test.

Lower body muscle strength and endurance were not different between controls and HTx recipients. In the context of all muscle function tests, lower body function is the most similar to controls. Muscle strength has never been evaluated in pediatric HTx recipients, but in adult HTx literature, lower body muscle strength is lower in HTx recipients than controls(113). This difference may be due to the differences in course of disease pre-transplant in each population. In adults, patients with heart disease may have peripheral vascular dysfunction, which affects their ability to exercise(114). These differences in vascular function and lower body muscle strength persist after transplantation(115). In children, peripheral vascular function of the muscle blood supply may be in better condition before and after transplant, leading to better muscle strength, as compared to controls. However, vascular function, as it relates to muscle function, has not been investigated in the pediatric HTx population.

6.5.3 Kidney transplant recipients

This is the first study to measure and compare the muscle strength and endurance of multiple muscle groups in pediatric KTx recipients. Overall, KTx recipients had a different profile of muscle function than HTx recipients.

Upper body muscle endurance, but not upper body muscle strength was lower in the KTx group than controls. Like the results in the HTx population, it is suspected that this difference occurs because the push-up test has a greater load than the upper body muscle strength test, which results in many scores of zero in the KTx population. However, it is possible that muscle endurance is affected to a greater extent than muscle strength in the upper body of KTx recipients.

There was no difference in core muscle strength or muscle endurance in the KTx population. This finding is inconsistent with the study by Krasnoff et al. (116), which showed that KTx recipients attained only 68% of predicted values on the curl-up test. Further, it would be expected that abdominal muscle function would be affected since the incision made in the kidney transplant procedure goes through the abdominal muscles(117).

In contrast to HTx recipients, both lower body muscle strength and endurance were lower in KTx than controls. In adult KTx on prednisone, it has been shown that there is a decrease in myofibril volume per unit of muscle fiber, as compared to healthy controls(40). Because this difference is relative to body size, it may explain the difference in muscle strength, even when controlled for body size, as in this study. Another explanation for reduced lower body muscle strength and endurance in the KTx population is muscle wasting pre-transplant that persists after transplant. It has been shown that there is significant skeletal muscle wasting in children with chronic kidney disease(118). Without sufficient rehabilitation, physiotherapy, nutrition, moderate to high intensity physical activity, or other factors, it is possible that KTx recipients never regain normal muscle function after transplantation. Or, perhaps their long-term prednisone treatment prevents them from regaining muscle function after transplantation, as opposed to HTx recipients. Further studies are needed to investigate potential causes for lower body muscle function in KTx recipients.

6.5.4 Liver transplant recipients

The number of curl-up repetitions was measured in three LiTx studies, but only two provided a healthy comparison for the meta-analysis. The number of curl-ups was not

significantly different between LiTx recipients and controls or normative values. This finding would suggest that LiTx recipients have better muscle function after transplant than HTx and KTx. However, these findings are from small studies (N=27, N=11), so further studies are needed to confirm these results. LiTx were not assessed in the prospective study, so this study cannot add to the findings of the meta-analysis.

6.5.5 Bone marrow transplant recipients

Though the muscle function of BMT recipients was measured in one study in the systematic review, there was no comparison to healthy values. BMT recipients were not included in the prospective study, so no conclusions can be drawn about muscle function in these patients.

6.6 Wall-sit test

In all participants (controls, HTx and KTx), there was a significant, but weak correlation between wall-sit time, and quality of life (R=0.36), body surface area (R=0.46), lower body muscle strength (R=0.31), upper body muscle endurance (R=0.39), and core muscle endurance (R=0.43). However, these relationships were not maintained when these correlations were analyzed in only the HTx group. It is suspected that the correlations were not maintained in the HTx group because the wall-sit test values were distributed less evenly than the control group.

The wall-sit test requires less strength to perform than push-ups and curl-ups, because participants may use gravity to position themselves for the test, rather than having to work against it to perform repetitions. Also, it was observed that participants understood the instructions for this test more easily, since there are less requirements for proper form to perform a wall-sit.

Because of the correlations with muscle function tests and quality of life in the whole cohort, and the simple methodology of this test, the wall-sit test could be used as a quick and easy tool for longitudinal assessments of both muscle function and quality of life in children.

6.7 Quality of life

Quality of life (QOL) was not different between controls, HTx, and KTx recipients in the prospective study, and it was not assessed in HTx and KTx studies in the meta-analysis. This

finding is inconsistent with the literature, which shows that QOL is lower in both HTx (119, 120) and KTx (121, 122) recipients. It was found that the difference in physical functioning score in this study approached significance (P=0.056), so it is possible that with more participants, a difference in QOL may have been observed in this study's population.

The relationship between QOL total score and fitness parameters was investigated in this study. There was a weak but significant correlation between QOL total score and wall-sit time in the whole cohort (controls, HTx and KTx), and the control group. There were no significant correlations between QOL and fitness variables in the HTx group. This finding would suggest that fitness level does not determine quality of life. However, fitness level may be important to HTx recipients in other ways, like the extent to which they can participate in sport, and long-term health outcomes.

In the systematic review, three studies measured QOL, but only one study compared their results statistically to healthy or normal values. This study, by Vandekerckhove et al. (123) measured QOL in LiTx recipients using the same PedsQL generic scale as in this study. They found that total score was significantly lower in LiTx than controls. No assessment of the relationship between quality of life and fitness level was made in that study.

6.8 Physical activity level

Physical activity (PA) level was not different between controls, HTx, and KTx recipients in this study. This finding is inconsistent with the literature that reports that PA level is lower in heart and kidney transplant recipients than controls(60, 105-108, 116, 124). The inconsistency in the findings in this study with the literature could be a reflection of the cohort in this study. This cohort does have a similar QOL to controls, which suggests they are functioning similarly to healthy children in their daily life. Perhaps their PA patterns resemble healthy children in a similar manner.

However, it is possible that this similarity in PA level is due to limitations in the Physical Activity Questionnaire (PAQ) used in this study. First, this questionnaire has been validated in children of age 8 years and older. In this study, the questionnaire was also administered to children and parents aged 5-7 years. Though parents were good at recalling physical activities after school, it was difficult for young children to recall their activity level during school in the last 7 days. Further, one of the 9 or 10 questions (child vs. adolescent version) asked about a variety of physical activities to gauge diversity of activity, but many activities were seasonally-dependent. Though this was good to ensure that all types of activities were captured, there may

have been differences in physical activity scores among seasons. Overall, it would be recommended to use the PAQ only in children age 8 years or older, and try to collect data in the same season for the tool to be more effective.

In the systematic review, most studies that investigated the relationship between PA level and fitness level reported that these two variables did not correlate with each other(107, 108, 125). The exception was one study in KTx recipients by Tangeraas et al. (124) that found a correlation between moderate to vigorous physical activity time and VO_2max. The findings from the prospective study are consistent with the review, since physical fitness level was reduced in pediatric transplant recipients, despite similar PA levels. This could be explained by inconsistent PA patterns in children. Often, PA in children is sporadic, and of varying intensity, which may or may not be enough to affect their fitness level(126). It is suggested that future studies use PA tools that assess the intensity of PA as well as level of PA to capture types of activity that have an impact on fitness level.

6.9 Clinical factors affecting fitness level

In HTx recipients in this study, age at transplant, time post-transplant, time from diagnosis to transplant, hemoglobin level, creatinine level, number of previous surgeries, days on prednisone, current use of statin, current use of angiotensin-converting enzyme inhibitor, current use of calcium channel blocker, history of extracorporeal membrane oxygenation, history of ventricular assist device, history of post-transplant lymphoproliferative disease, presence of neuromotor deficits, and history of rejection did not correlate with wall-sit time or percent predicted 6MWT distance. There was a significant, moderate correlation between history of stroke and percent predicted 6MWT distance (R=-0.562, P<0.01), but this correlation was not maintained when only those stroke patients with neuromotor deficits were analyzed (R=-0.351, P=0.110). Therefore, any relationship between history of stroke and fitness level is likely either coincidental, or relates to other, non-neuromotor deficits persisting after stroke.

6.10 Limitations

There are two general ideologies regarding inclusivity in meta-analyses: to be as inclusive as possible to avoid exclusion bias, or to be strict with inclusion criteria to avoid bias from confounding factors. In this study, the aim was to be as inclusive as possible with the meta-analysis. Though exclusion bias was reduced by following this methodology, the results yielded

high levels of heterogeneity. Though this limits the confidence of the findings, it also highlights how samples of pediatric transplant recipients vary by study, and the truly heterogeneic nature of these populations.

To gather as much data as possible from the meta-analysis, data extrapolation equations were used. Some of these data extrapolation equations have been used in the literature(80), but others were created for this study. The logic of these formulas was reviewed by a statistics mathematician, but these formulas have not been validated previously. Therefore, these equations may have introduced bias into the study.

In this study, the groups were not normally distributed, and they were different in size (control n=20, HTx n=22, KTx n=6). When the Kruskal-Wallis (KW) test was used, the ability to detect differences in the KTx group may have been impaired. When groups of 5 or less are analyzed with the KW test, the statistic H does not follow its Chi distribution, and the analysis becomes less accurate(127). Though this study sample had n=6 in the KTx group, which is higher than the required n=5, there are likely some effects on the distribution of the statistic H. The limited ability of the KW test in detecting differences in smaller groups may have resulted in type 2 errors, or false negatives, in this study(128). With a greater sample size of the KTx group, it may have been possible to detect true differences in the KTx group versus controls and HTx.

There was an attempt to quantify fat-free mass, as an indicator of muscle mass, using the BodPod in this study. However, due to the limited availability of this equipment at testing sites in Calgary and Vancouver, and technical difficulties with the equipment in Edmonton, the gathered data were insufficient for analysis. Therefore, body surface area was used as an indicator of body size and muscle mass, which was controlled for in the muscle strength analysis.

In children, the gold standard for physical activity measurement is direct observation, and other useful tools include heart rate monitors and accelerometers(129). However, in this study, for convenience to the participants, a questionnaire was used. When measuring physical activity using questionnaires, it is important to consider recall bias. Some participants may not fully or correctly remember their physical activity in the period of time specified by the questionnaire, which may affect the results(130).

The timed wall-sit test was introduced in the pediatric transplant population in this study. Though the wall-sit test is internally controlled for body size by test resistance being the participant's body weight, there was a moderate and significant correlation between wall-sit time and body surface area (R=0.4562, P<0.01). Therefore, groups with larger body size, like the controls and HTx as compared to KTx in this study, may perform better on the wall-sit test

because of their size and not their muscle function. However, this study did not have the power to distinguish which factor was the cause of reduced wall-sit time in the KTx group.

Correlations between the wall-sit test and both anatomical (BSA) and functional (quadriceps strength, push-ups, curl-ups) parameters of muscle function were investigated. However, these investigations were not sufficient to show validity of the wall-sit test as an isolated measure reflecting overall fittness. Future studies could study the correlation between wall-sit time and gold standard tests of muscle function, like electromyography(131).

6.11 Significance

This is the first study to provide a comprehensive assessment of muscle strength and endurance in the pediatric heart transplant population as compared to healthy controls. This is the first study to directly compare fitness level between heart and kidney transplant recipients. This is the first meta-analysis in the field of fitness after pediatric transplantation, and the first study to summarize aerobic capacity level in pediatric heart, kidney, liver, and bone marrow transplant recipients, and compare them to one another.

The main findings of this study are that fitness level is reduced in pediatric transplant recipients, and that recipients of different types of transplant have similar changes in aerobic capacity, but different changes in muscle function as compared to healthy children. This would suggest that the process of transplantation has a similar effect on overall fitness level, but different types of transplant have different effects on muscle function in the long-term after transplantation. Further studies are needed to identify the differences in muscle strength and endurance in different types of pediatric transplant.

Current tests for muscle function in pediatric transplant recipients have significant limitations, and the wall-sit test was introduced as a solution to these limitations. The wall-sit test correlates with other muscle function parameters, and it is easier for children to perform. These findings suggest that the wall-sit test could be a useful tool for future assessments of muscle function both in the clinic and in research studies.

6.12 Future studies

Though the meta-analysis contained large amounts of data regarding aerobic capacity after pediatric transplantation, there was very high heterogeneity among studies. Therefore, it is recommended to conduct larger-scale studies evaluating aerobic capacity in each type of

transplant. Because of the difference in using control and normative values as the healthy population, it is recommended to use a control group, which may be a better representation of the fitness level of the population as it is at the time of the study.

This study provided useful information about muscle function in pediatric heart and kidney transplant recipients, but further, larger studies, in all types of transplant would be helpful to understand how muscle function is affected in transplantation, and perhaps start to understand what factors are driving changes in muscle function.

Once there is more information about the changes in aerobic capacity, muscle strength, and muscle endurance in all types of transplant, physical therapy interventions or physical activity recommendations specific to transplant could be developed, and their effects evaluated in randomized controlled trials. The goal would be to develop an effective strategy to help pediatric transplant recipients improve their fitness level after transplantation, which may improve their long-term health outcomes.

In the interim, physical therapy or physical activity interventions are needed for children living with transplants to achieve a normal fitness level. All types of pediatric transplant recipients would likely benefit from both aerobic and resistance training to improve both aerobic capacity and muscle function. It is recommended that transplant centres fund physical therapy programs for their pediatric transplant recipients, and that moderate to vigorous physical activity is recommended in this population.

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126.   Dencker M, Bugge A, Hermansen B, Andersen LB. Objectively measured daily physical activity related to aerobic fitness in young children. Journal of Sports Sciences. 2010;28(2):139-45.

127.   Chan Y, Walmsley RP. Learning and understanding the Kruskal-Wallis one-way analysis-of-variance-by-ranks test for differences among three or more independent groups. Phys Ther. 1997;77(12):1755-61.

128.   Banerjee A, Chitnis U, Jadhav S, Bhawalkar J, Chaudhury S. Hypothesis testing, type I and type II errors. Industrial psychiatry journal. 2009;18(2):127.

129.   Sirard JR, Pate RR. Physical activity assessment in children and adolescents. Sports medicine. 2001;31(6):439-54.

130.   Sallis JF, Saelens BE. Assessment of physical activity by self-report: status, limitations, and future directions. Research quarterly for exercise and sport. 2000;71(sup2):1-14.

131.   Chaffin DB, Lee M, Freivalds A. Muscle strength assessment from EMG analysis. Medicine and Science in Sports and Exercise. 1980;12(3):205-11.

Appendix A

Literature Search — *Physical fitness after pediatric transplantation*

Searcher: Robin Featherstone, MLIS
Requestor: Chantal Allan & Karen Hunter for the Alberta Transplant Institute and SPOR
SPOR Program Coordinator: Meghan Sebastianski
Files Submitted: Allan-Transplant_Sept2016.xlsx
Proceedings available on Google Drive:
https://drive.google.com/open?id=0BzDxLT4TpP5TMzNwaFFvVFBxaTg

Review Question(s): What is the effect of each type of pediatric transplant on aerobic and muscle fitness after transplantation? How is quality of life affected by fitness after pediatric transplantation? Which factors affect fitness after pediatric transplantation?

Search Summary:

Databases	Date Searched	Number Retrieved	After Duplicate Removal
1. Medline	21 Sept 2016	2691	2686
2. Embase	21 Sept 2016	3249	1563
3. CINAHL	21 Sept 2016	486	104
4. ProQuest Dissertations & Theses	22 Sept 2016	50	41
Total Database:		**6476**	**4394**
Proceedings (last 2 years only)	**Date Searched**	**Number Retrieved**	**After Duplicate Removal**
1. CST-CNTRP	22 Sept 2016	4	4
2. International Society of Heart and Lung Transplantation	22 Sept 2016	2	2
3. International Congress of the Transplant Society	22 Sept 2016	2	2
Total Proceedings:		**8**	**8**
Total:		**6484**	**4402**

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R)

Daily and Ovid MEDLINE(R) 1946 to Present

Search Title: Allan_Transplant

Strategy:

1. Bone Marrow Transplantation/
2. exp Heart Transplantation/
3. Kidney Transplantation/
4. Liver Transplantation/
5. exp Lung Transplantation/
6. Organ Transplantation/

7. exp Stem Cell Transplantation/
8. (bone marrow* adj2 (graft* or transplant*)).tw,kf.
9. ((cardiac or heart*) adj5 (graft* or transplant*)).tw,kf.
10. ((graft* or transplant*) adj2 (hepatic or liver)).tw,kf.
11. ((graft* or transplant*) adj2 (lung* or respirator*)).tw,kf.
12. ((graft* or transplant*) adj3 organ*).tw,kf.
13. ((graft* or transplant*) adj2 (kidney* or renal*)).tw,kf.
14. stem cell transplant*.tw,kf.
15. or/1-14 [Combined MeSH & text words for organ transplantation]
16. exp Adolescent/
17. exp Child/
18. exp Infant/
19. exp Minors/
20. exp Pediatrics/
21. (baby* or babies or infant* or infancy or neonat* or newborn* or postmatur* or prematur* or preterm*).tw,kf.
22. (boy* or girl* or teen*).tw,kf.
23. (child* or kid or kids or preschool* or school age* or schoolchild* or toddler*).tw,kf.
24. (elementary school* or high school* or highschool* or kindergar* or nursery school* or primary school* or secondary school*).tw,kf.
25. minors*.tw,kf.
26. p?ediatric*.tw,kf,jw.
27. or/16-26 [Combined MeSH & text words for pediatric patients]
28. and/15,27 [Combined concepts for transplantation and pediatric patients]
29. Exercise Test/
30. exp Muscle, Skeletal/ph [Physiology]
31. exp Muscle Strength/
32. exp Oxygen Consumption/
33. exp Physical Endurance/
34. Physical Fitness/
35. Quality of Life/
36. (("6" or six) adj min* walk*).tw,kf.
37. ((aerobic or anaerobic) adj1 (capacit* or endurance or function or threshold*)).tw,kf.
38. ((body or physical or musc*) and flexib*).tw,kf.
39. (BOT-2 or Bruininks-Oseretsky).tw,kf.
40. Bruce protocol*.tw,kf.
41. ((capacity or endurance or test* or threshold* or toleran*) adj2 exercis*).tw,kf.
42. ((capacity or endurance or strength) adj2 physical*).tw,kf.
43. (cardi* adj2 (capacit* or endurance or function or threshold*)).tw,kf.
44. (CHQ or child health questionnaire*).tw,kf.
45. ((consum* or uptake) adj2 (O2 or oxygen)).tw,kf.
46. (DCGM-37 or DISABKIDS*).tw,kf.
47. dynamomet*.tw,kf.
48. ((endurance or mass or size or strength) adj2 musc*).tw,kf.
49. fitness*.tw,kf.
50. kidscreen*.tw,kf.
51. kindl-r*.tw,kf.
52. PACER*.tw,kf.

53. pedsQL*.tw,kf.
54. (QoL or QoML or (quality adj2 life)).tw,kf.
55. shuttle run*.tw,kf.
56. sit-up*.tw,kf.
57. ((step or treadmill* or walk*) adj1 test*).tw,kf.
58. (VO2 max* or VO2max*).tw,kf.
59. wall sit*.tw,kf.
60. or/29-59 [Combined MeSH & text words for physical fitness]
61. and/28,60 [Combined concepts for pediatric transplantation and physical fitness]
62. exp Animals/ not Humans/
63. 61 not 62 [Animal studies excluded]
64. (comment or editorial or letter or news or newspaper article).pt.
65. 63 not 64 [Opinion pieces excluded]
66. case reports.pt.
67. (case report* or case stud*).ti.
68. 65 not (66 or 67) [Case studies excluded]
69. limit 68 to yr="1990-Current"
70. remove duplicates from 69

Database: Ovid Embase 1988 to 2016 Week 38

Search Title: Allan_Transplant_1

Strategy:

1. bone marrow transplantation/
2. exp heart transplantation/
3. exp kidney transplantation/
4. exp liver transplantation/
5. exp lung transplantation/
6. organ transplantation/
7. exp stem cell transplantation/
8. (bone marrow* adj2 (graft* or transplant*)).tw,kw.
9. ((cardiac or heart*) adj5 (graft* or transplant*)).tw,kw.
10. ((graft* or transplant*) adj2 (hepatic or liver)).tw,kw.
11. ((graft* or transplant*) adj2 (lung* or respirator*)).tw,kw.
12. ((graft* or transplant*) adj3 organ*).tw,kw.
13. ((graft* or transplant*) adj2 (kidney* or renal*)).tw,kw.
14. stem cell transplant*.tw,kw.
15. or/1-14 [Combined Emtree & text words for organ transplantation]
16. exp adolescence/
17. exp adolescent/
18. exp child/
19. exp newborn/
20. exp pediatrics/
21. adoles*.mp.
22. (baby* or babies or infant* or infancy or neonat* or newborn* or postmatur* or prematur* or preterm*).mp.
23. (boy* or girl* or teen*).mp.

24. (child* or kid or kids or preschool* or school age* or schoolchild* or toddler*).mp.
25. minors*.mp.
26. p?ediatric*.tw,kw,jx.
27. or/16-26 [Combined Emtree and text words for pediatric patients]
28. and/15,27 [Combined concepts for transplantation and pediatric patients]
29. anaerobic threshold/
30. endurance/
31. exp exercise test/
32. fitness/
33. motor performance/
34. exp muscle strength/
35. oxygen consumption/
36. physical capacity/
37. physical performance/
38. exp "quality of life"/
39. (("6" or six) adj min* walk*).tw,kw.
40. ((aerobic or anaerobic) adj1 (capacit* or endurance or function or threshold*)).tw,kw.
41. ((body or physical or musc*) and flexib*).tw,kw.
42. (BOT-2 or Bruininks-Oseretsky).tw,kw.
43. Bruce protocol*.tw,kw.
44. ((capacity or endurance or test* or threshold* or toleran*) adj2 exercis*).tw,kw.
45. ((capacity or endurance or strength) adj2 physical*).tw,kw.
46. (cardi* adj2 (capacit* or endurance or function or threshold*)).tw,kw.
47. (CHQ or child health questionnaire*).tw,kw.
48. ((consum* or uptake) adj2 (O2 or oxygen)).tw,kw.
49. (DCGM-37 or DISABKIDS*).tw,kw.
50. dynamomet*.tw,kw.
51. ((endurance or mass or size or strength) adj2 musc*).tw,kw.
52. fitness*.tw,kw.
53. kidscreen*.tw,kw.
54. kindl-r*.tw,kw.
55. PACER*.tw,kw.
56. pedsQL*.tw,kw.
57. (QoL or QoML or (quality adj2 life)).tw,kw.
58. shuttle run*.tw,kw.
59. sit-up*.tw,kw.
60. ((step or treadmill* or walk*) adj1 test*).tw,kw.
61. (VO2 max* or VO2max*).tw,kw.
62. wall sit*.tw,kw.
63. or/29-62 [Combined Emtree & text words for physical fitness]
64. and/28,63 [Combined concepts for pediatric transplantation and physical fitness]
65. animals/ not (animals/ and humans/)
66. 64 not 65 [Excluded animal studies]
67. (conference* or editorial or letter or note or proceeding).pt.
68. (conference* or comment* or editorial* or letter* or proceeding*).ti.
69. 66 not (67 or 68) [Opinion pieces & proceedings excluded - Note: will search for conference proceedings separately]
70. (case report* or case stud*).ti.

71. 69 not 70 [Excluded case studies]
72. limit 71 to yr="1990-Current"
73. remove duplicates from 72

S1. (MH "Bone Marrow Transplantation+")
S2. (MH "Heart Transplantation+")
S3. (MH "Hematopoietic Stem Cell Transplantation")
S4. (MH "Kidney Transplantation")
S5. (MH "Liver Transplantation")
S6. (MH "Lung Transplantation+")
S7. (MH "Organ Transplantation")
S8. "bone marrow*" N2 (graft* or transplant*)
S9. (cardiac or heart*) N5 (graft* or transplant*)
S10. (graft* or transplant*) N2 (hepatic or liver)
S11. (graft* or transplant*) N2 (lung* or respirator*)
S12. (graft* or transplant*) N3 organ*
S13. (graft* or transplant*) N2 (kidney* or renal*)
S14. "stem cell transplant*"
S15. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 [Combined CINAHL Headings & text words for organ transplantation]
S16. (MH "Adolescence+")
S17. (MH "Child+")
S18. (MH "Infant+")
S19. (MH "Minors (Legal)")
S20. (MH "Pediatrics+")
S21. adolescen* or babies or baby or boy* or child* or girl* or infan* or kid or kids or minors* or neonat* or "new born*" or newborn* or paediatric* or pediatric* or postmatur* or prematur* or preschooler* or preterm* or "school age*" or schoolchild* or teen* or toddler* or youth or youths
S22. S16 OR S17 OR S18 OR S19 OR S20 OR S21 [Combined CINAHL Headings and text words for pediatric patients]
S23. S15 AND S22 [Combined concepts for transplantation and pediatric patients]
S24. (MH "Exercise Test+")
S25. (MH "Muscle, Skeletal+/PH")
S26. (MH "Muscle Strength+")
S27. (MH "Oxygen Consumption+")
S28. (MH "Physical Endurance+")
S29. (MH "Physical Fitness+")
S30. (MH "Quality of Life")
S31. ("6" or six) W1 "min* walk*"
S32. (aerobic or anaerobic) N1 (capacit* or endurance or function or threshold*)
S33. (body or physical or musc*) and flexib*
S34. BOT-2 or Bruininks-Oseretsky

S35. "Bruce protocol*"
S36. (capacity or endurance or test* or threshold* or toleran*) N2 exercis*
S37. (capacity or endurance or strength) N2 physical*
S38. cardi* N2 (capacit* or endurance or function or threshold*)
S39. CHQ or "child health questionnaire*"
S40. (consum* or uptake) N2 (O2 or oxygen)
S41. DCGM-37 or DISABKIDS*
S42. dynamomet*
S43. (endurance or mass or size or strength) N2 musc*
S44. fitness*
S45. kidscreen*
S46. kindl-r*
S47. PACER*
S48. pedsQL*
S49. QoL or QoML or (quality N2 life)
S50. "shuttle run*"
S51. sit-up*
S52. (step or treadmill* or walk*) N1 test*
S53. "VO2 max*" or VO2max*
S54. "wall sit*"
S55. S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 [Combined CINAHL Headings & text words for physical fitness]
S56. S23 AND S55
S57. (MH "Vertebrates+") NOT (MH "Human")
S58. S56 NOT S57
S59. PT (commentary or editorial or letter)
S60. TI (conference* or comment* or editor* or letter* or news*)
S61. S58 NOT (S59 OR S60) [Opinion pieces excluded]
S62. PT (Case Study)
S63. TI ("case report*" or "case stud*")
S64. S61 NOT (S62 OR S63) [Case reports excluded]
S65. S61 NOT (S62 OR S63) Limiters - Published Date: 19900101-20161231

Database: ProQuest Dissertations & Theses Global (1861 to present)

Search Title: Allan_Transplant

Strategy:

S1. su.Exact("transplants & implants") OR AB,TI(("bone marrow*" OR cardiac OR heart* OR hepatic OR kidney* OR liver OR lung* OR organ* OR respirator* OR renal* OR "stem cell") N/2 (graft* OR transplant*))

S2. su.Exact("Children & youth" OR "Pediatrics") OR AB,TI(adoles* OR baby* OR babies OR child* OR infant* OR neonat* OR newborn* OR paediatric* OR pediatric* OR preschool* OR "school age*" OR schoolchild* OR teen* OR toddler*)

S3. S1 AND S2

S4. su.Exact("physical fitness" OR "quality of life") OR AB,TI((("6" or six) N/1 ("minute walk")) OR ((aerobic OR anaerobic) N/1 (capacit* OR endurance OR function OR threshold*)) OR ((body or physical or musc*) AND flexib*) OR BOT-2 OR Bruininks-Oseretsky OR "Bruce protocol*" OR ((capacity OR endurance OR test* OR threshold* OR toleran*) N/2 exercis*) OR ((capacity OR endurance OR strength) N/2 physical*) OR (cardi* N/2 (capacit* OR endurance OR function OR threshold*)) OR CHQ OR "child health questionnaire*" OR ((consum* OR uptake) N/2 (O2 OR oxygen)) OR DCGM-37 OR DISABKIDS* OR dynamomet* OR ((endurance OR mass OR size OR strength) N/2 musc*) OR fitness* OR kidscreen* OR kindl-r* OR PACER* OR pedsQL* OR QoL OR QoML OR (quality N/2 life) OR "shuttle run*" OR sit-up* OR ((step OR treadmill* OR walk*) N/1 test*) OR VO2 max* OR VO2max* OR "wall sit*")

S5. S3 AND S4

RF Note: 1990-current limit applied to all searches

Known item test: Medline search finds 26/26 ; Final results retains all 26

Known items: (15607660 or 22607632 or 22042340 or 1640305 or 22116577 or 16730567 or 25039300 or 23050737 or 24483258 or 19481019 or 9031264 or 9770574 or 19497018 or 8222160 or 16858284 or 7734874 or 21825306 or 7750327 or 11079265 or 18435609 or 19667944 or 17372771 or 11737767 or 20676694 or 11244161 or 18184856).ui.

Abarbanell G, Mulla N, Chinnock R, Larsen R. Exercise assessment in infants after cardiac transplantation. The Journal of heart and lung transplantation. 2004 Dec 31;23(12):1334-8. PMID: 15607660

Banks L, Dipchand AI, Manlhiot C, Millar K, McCrindle BW. Factors associated with low physical activity levels following pediatric cardiac transplantation. Pediatric transplantation. 2012 Nov 1;16(7):716-21. PMID: 22607632

Chiu HH, Wu MH, Wang SS, Lan C, Chou NK, Chen SY, Lai JS. Cardiorespiratory function of pediatric heart transplant recipients in the early postoperative period. American Journal of Physical Medicine & Rehabilitation. 2012 Feb 1;91(2):156-61. PMID: 22042340

Christos SC, Katch V, Crowley DC, Eakin BL, Lindauer AL, Beekman RH. Hemodynamic responses to upright exercise of adolescent cardiac transplant recipients. The Journal of pediatrics. 1992 Aug 31;121(2):312-6. PMID: 1640305

Clark CG, Cantell M, Crawford S, Hamiwka LA. Accelerometry-based physical activity and exercise capacity in pediatric kidney transplant patients. Pediatric Nephrology. 2012 Apr 1;27(4):659-65. PMID: 22116577

Davis JA, McBride MG, Chrisant MR, Patil SM, Hanna BD, Paridon SM. Longitudinal assessment of cardiovascular exercise performance after pediatric heart transplantation. The Journal of heart and lung transplantation. 2006 Jun 30;25(6):626-33. PMID: 16730567

da Silva MR, Brunow de Carvalho W, Johnston C, Borba de Castro M, Manta Ferreira I, Patti CL, Anthero de Azevedo R, Miziara Gonzalez A, Moura Linhares M, Augusto Salzedas-Netto A. Functional capacity after pediatric liver transplantation: A pilot study. Pediatric transplantation. 2014 Sep 1;18(6):586-93. PMID: 25039300

Deliva RD, Hassall A, Manlhiot C, Solomon M, McCrindle BW, Dipchand AI. Effects of an acute, outpatient physiotherapy exercise program following pediatric heart or lung transplantation. Pediatric transplantation. 2012 Dec 1;16(8):879-86. PMID: 23050737

Derakhshan A, Derakhshan D, Amoozgar H, Shakiba MA, Basiratnia M, Fallahzadeh MH. Exercise test in pediatric renal transplant recipients and its relationship with their cardiac function. Pediatric transplantation. 2014 May 1;18(3):246-53. PMID: 24483258

Dipchand AI, Manlhiot C, Russell JL, Gurofsky R, Kantor PF, McCrindle BW. Exercise capacity improves with time in pediatric heart transplant recipients. The Journal of Heart and Lung Transplantation. 2009 Jun 30;28(6):585-90. PMID: 19481019

Ekstrand A, Schalin-Jäntti C, Löfman M, Parkkonen M, Widén E, Franssila-Kallunki A, Saloranta C, Koivisto V, Groop L. The effect of (steroid) immunosuppression on skeletal muscle glycogen metabolism in patients after kidney transplantation. Transplantation. 1996 Mar 27;61(6):889-93.

Feber J, Dupuis JM, Chapuis F, Braillon P, Jocteur-Monrozier D, Daudet G, So S, Levrey H, Hadj-Aissa A, Martin X, Bellon G. Body composition and physical performance in children after renal transplantation. Nephron. 1997;75(1):13-9. PMID: 9031264

Giordano U, Calzolari A, Matteucci MC, Pastore E, Turchetta A, Rizzoni G. Exercise tolerance and blood pressure response to exercise testing in children and adolescents after renal transplantation. Pediatric cardiology. 1998 Nov 1;19(6):471-3. PMID: 9770574

Hamiwka LA, Cantell M, Crawford S, Clark CG. Physical activity and health related quality of life in children following kidney transplantation. Pediatric transplantation. 2009 Nov 1;13(7):861-7. PMID: 19497018

Hsu DT, Garofano RP, Douglas JM, Michler RE, Quaegebeur JM, Gersony WM, Addonizio LJ. Exercise performance after pediatric heart transplantation. Circulation. 1993 Nov;88(5 Pt 2):II238-42. PMID: 8222160

Krasnoff JB, Mathias R, Rosenthal P, Painter PL. The comprehensive assessment of physical fitness in children following kidney and liver transplantation. Transplantation. 2006 Jul 27;82(2):211-7. PMID: 16858284

Krull F, Schulze-Neick I, Hatopp A, Offner G, Brodehl J. Exercise capacity and blood pressure response in children and adolescents after renal transplantation. Acta Paediatrica. 1994 Dec 1;83(12):1296-302. PMID: 7734874

Lubrano R, Tancredi G, Bellelli E, Gentile I, Scateni S, Masciangelo R, De Castro G, Versacci P, Elli M. Influence of physical activity on cardiorespiratory fitness in children after renal transplantation. Nephrology Dialysis Transplantation. 2011 Aug 8:434. PMID: 21825306

Nixon PA, Fricker FJ, Noyes BE, Webber SA, Orenstein DM, Armitage JM. Exercise testing in pediatric heart, heart-lung, and lung transplant recipients. CHEST Journal. 1995 May 1;107(5):1328-35. PMID: 7750327

Pahl E, Sundararaghavan S, Strasburger JF, Mitchell BM, Rodgers S, Crowley D, Gidding SS. Impaired exercise parameters in pediatric heart transplant recipients: comparison of biatrial and bicaval techniques. Pediatric transplantation. 2000 Nov 1;4(4):268-72. PMID: 11079265

Painter P, Krasnoff J, Mathias R. Exercise capacity and physical fitness in pediatric dialysis and kidney transplant patients. Pediatric Nephrology. 2007 Jul 1;22(7):1030-9. PMID: 17372771

Pastore E, Turchetta A, Attias L, Calzolari A, Giordano U, Squitieri C, Parisi F. Cardiorespiratory functional assessment after pediatric heart transplantation. Pediatric transplantation. 2001 Dec 1;5(6):425-9. PMID: 11737767

Patel JN, Kavey RE, Pophal SG, Trapp EE, Jellen G, Pahl E. Improved exercise performance in pediatric heart transplant recipients after home exercise training. Pediatric transplantation. 2008 May 1;12(3):336-40. PMID: 18435609

Sethna CB, Salerno AE, McBride MG, Shults J, Paridon SM, Sharma N, Meyers KE, Leonard MB. Cardiorespiratory fitness in pediatric renal transplant recipients. Transplantation. 2009 Aug 15;88(3):395. PMID: 19667944

Sun YN, McKay LI, DuBois DC, Jusko WJ, Almon RR. Pharmacokinetic/pharmacodynamic models for corticosteroid receptor down-regulation and glutamine synthetase induction in rat skeletal muscle by a receptor/gene-mediated mechanism. Journal of Pharmacology and Experimental Therapeutics. 1999 Feb 1;288(2):720-8.

Tangeraas T, Midtvedt K, Fredriksen PM, Cvancarova M, Mørkrid L, Bjerre A. Cardiorespiratory fitness is a marker of cardiovascular health in renal transplanted children. Pediatric Nephrology. 2010 Nov 1;25(11):2343-50. PMID: 20676694

Unnithan VB, Veehof SH, Rosenthal P, Mudge C, O'Brien TH, Painter P. Fitness testing of pediatric liver transplant recipients. Liver transplantation. 2001 Mar 1;7(3):206-12. PMID: 11244161

Weaver DJ, Kimball TR, Knilans T, Mays W, Knecht SK, Gerdes YM, Witt S, Glascock BJ, Kartal J, Khoury P, Mitsnefes MM. Decreased maximal aerobic capacity in pediatric chronic kidney disease. Journal of the American Society of Nephrology. 2008 Mar 1;19(3):624-30. PMID: 18184856

Appendix B

Secondary Screening Form – *Physical fitness after pediatric transplantation inclusion/exclusion criteria*

Reviewer ID:	Date: / /2016	Record ID:

Criteria	Yes	No	Unclear/ Comments
1. PUBLICATION TYPE			
a. Report of primary research	☐	☐	☐
2. STUDY DESIGN			
a. At least one cross-sectional assessment of fitness parameters (including cross-sectional studies and cross-section assessments before intervention)	☐	☐	☐
3. POPULATION			
a. Patients received transplant during age 0-17	☐	☐	☐
4. SETTING			
a. Fitness assessment in hospital or university-sanctioned facility	☐	☐	☐
5. INTERVENTION			
a. Received one of the following types of transplant:			
i. Heart	☐	☐	☐
ii. Lung	☐	☐	☐
iii. Liver	☐	☐	☐
iv. Kidney	☐	☐	☐
v. Stem cell	☐	☐	☐
vi. Any combination of the transplant types in I-V	☐	☐	☐
6. COMPARATOR			
a. Healthy children (age-matched to transplant group)	☐	☐	☐
b. Normative values	☐	☐	☐
7. OUTCOME			
a. Assessment of one of the following fitness parameters:	☐	☐	☐
i. Aerobic capacity (including Bruce protocol, six-minute walk, etc.)	☐	☐	☐
ii. Muscle strength (including dynamometry, weight lifted, etc.)	☐	☐	☐
iii. Muscle endurance (including push-ups, curl-ups, pull-ups, etc.)	☐	☐	☐
iv. Flexibility (including toe reach, etc.)	☐	☐	☐

REVIEWER'S DECISION : Include ☐ Exclude ☐ Unsure ☐

FINAL DECISION: Include ☐ Exclude ☐ Unsure ☐
NOTE: Must clearly identify at least one of the above reasons for exclusion.

Non-English report needing translation ☐   Language _____

Appendix C

Chart data collection tool

TRANSPLANT 1	
What type of transplant?	○ Heart ○ Kidney ○ Liver ○ Lung ○ Bone marrow
Pre-transplant diagnosis	————————————
Type of disease leading to transplant	☐ Congenital heart disease ☐ Cardiomyopathy ☐ Other
Type of disease leading to transplant	☐ Congenital kidney disease ☐ Autoimmune kidney disease ☐ Other
Date of diagnosis	————————————
Date of transplant	————————————
Age at time of transplant	————————————
Time post-transplant (years)	————————————
Time from diagnosis to transplant (days)	————————————
Hospital length of stay pre-transplant, for transplant-related illness (days)	————————————
Hospital length of stay post-transplant (days)	————————————

TRANSPLANT 2	
Have you had any other transplants?	○ Yes ○ No
What type of transplant?	○ Heart ○ Kidney ○ Liver ○ Lung ○ Bone marrow
Pre-transplant diagnosis	————————————

Type of disease leading to transplant	☐ Congenital heart disease ☐ Cardiomyopathy ☐ Other
Type of disease leading to transplant	☐ Congenital kidney disease ☐ Autoimmune kidney disease ☐ Other
Date of diagnosis	_____
Date of transplant	_____
Age at time of transplant	_____
Time post-transplant (years)	_____
Time from diagnosis to transplant (days)	_____
Hospital length of stay pre-transplant, for transplant-related illness (days)	_____
Hospital length of stay post-transplant (days)	_____

REHABILITATION

Pre-transplant rehab (wk)	_____
Post-transplant rehab (wk)	_____

LABS

Hg level (most recent, mmol/L)	_____
Date of Hg measurement (Y-M-D)	_____
Creatinine (umol/L)	_____
Date of creatinine measurement (Y-M-D)	_____

MEDICATION

Please complete the following medication history for time POST-transplant

Have you ever taken the following medications?

	Yes	No
Tacrolimus	○	○
Prednisone	○	○
Statin	○	○
Cyclosporine	○	○
Mycophenolate mofetil/cell-cept	○	○
Amlodipine	○	○
Enalapril	○	○
Other medications or supplements	○	○

Please list all other medications and supplements that you are currently taking (include name, start date, and stop date in Y-M-D)

(E.g. Tacrolimus: 2016-01-30 to 2017-01-30)

Prednisone - Start Date

Prednisone - Stop Date

Prednisone time (days)

OTHER MEDICAL CONDITIONS

Have you ever had a stroke?
○ Yes
○ No

When was the stroke? (Y-M-D)

Persisting neuromotor deficit(s)?
○ Yes
○ No

Please describe the neuromotor deficit(s)

Have you ever had a ventricular assist device (VAD)?
○ Yes
○ No

How long did you have the VAD? (days)

Have you ever had extracorporeal membrane oxygen support (ECMO)?
○ Yes
○ No

How long were you on ECMO? (days)	
	_____

Have you ever had a rejection episode?	○ Yes ○ No

No. of episodes	
	_____

ABO-compatible?	○ Yes ○ No

ABO type (donor into recipient)	
	_____

Have you ever had post-transplant lymphoproliferative disease (PTLD)?	○ Yes ○ No

No. of episodes	
	_____

Have you had any previous cardiac or kidney surgery?	○ Yes ○ No

Type of surgery	
	_____

Date of surgery	
	_____

Age at time of surgery	
	_____

Have you had other cardiac or kidney surgery?	○ Yes ○ No

Type of surgery	
	_____

Date of surgery	
	_____

Age at time of surgery	
	_____

Have you had other cardiac or kidney surgery?	○ Yes ○ No

Type of surgery	
	_____

Date of surgery	
	_____

Age at time of surgery

_____

Have you had other cardiac or kidney surgery?   ○ Yes
                                                ○ No

Type of surgery

_____

Date of surgery

_____

Age at time of surgery

_____

Have you ever had dialysis?   ○ Yes
                                                ○ No

Dialysis start date

_____

Dialysis stop date

_____

Dialysis time (days)

_____

Type of dialysis   ○ Peritoneal
                                                ○ Hemodialysis

Please list any other medical conditions:

_____