Transplantation is a life-saving intervention for individuals with end-stage solid organ disease and often the optimal treatment of the disease.¹ The number of people that receive an organ transplantation has been rather stable over the past decade, however, as short term survival has been significantly improved and long-term survival is increasing, the total population of recipients of a solid organ transplantation continues to grow. With increasing long term survival, new areas of medical and psychosocial attention arise in the population. New onset diabetes after transplantation, medication adherence, quality of life, and the level of physical activity have gained increasing attention especially because they are likely modifiable and amenable for intervention to prolong long-term survival after transplantation.

In this thesis, physical activity and factors associated with the level of physical activity in recipients of solid organ transplantation were the main focus. As current evidence suggests that greater physical functioning in transplant recipients is associated with improved outcomes¹, physical activity in the transplant population is highly relevant. The level of physical activity is indicated to be positively associated with the capacity to perform activities of daily life², experience quality of life³–⁷, and survival⁸–¹² However, only little is known about the level of physical activity in various groups of recipients of solid organ transplantation and the factors associated with this level. This knowledge is required in order to justify the need for rehabilitation programs or physical therapy interventions and to compose the appropriate content and focus areas in program development. Therefore, the main objectives of this thesis were to gain additional insight into the physical activity level of recipients of solid organ transplantation and into factors that are associated with this level.

This chapter summarizes the primary findings of the studies in this thesis, and their methodological considerations are discussed. Finally, the implications and future directions in healthcare and research are provided.

**Main findings**

**Level of physical activity**

One of the main aims of this thesis was to investigate the level of physical activity of recipients of solid organ transplantation. The study in Chapter 3 showed that 58% of recipients of a lung transplantation did not reach the cut-off point of the six-minute walk test at 12 months after transplantation, indicating impairment of functional exercise capacity. This study remarkably showed an initial steep increase in submaximal exercise performance between discharge and six months after discharge, however, this increase was reduced in the second half of the first year following transplantation. In line with these findings the study described in Chapter 6, showed that, in a study population of diverse types of transplantation, less than 60% of recipients complied with the general physical activity guidelines. Comparing the level of compliance to the physical activity guideline in the transplant population with that of the average Dutch population indicated that the percentage in those with a transplantation were exceedingly below reported levels in the
general population (75%). These results on the level of physical activity in recipients of solid organ transplantation taken together demonstrated that the average level of physical activity in this population is considerably lower than that of the non-transplanted population and can be considered inadequate.

On the other hand, the results of Chapter 7 indicated that a select group of recipients of diverse solid organ transplantations can perform strenuous physical activity and that even a high-altitude expedition is a possibility after transplantation. This subgroup was highly active and were performing physical activities at a level that is above the level of the general population. This illustrates that there are recipients of a solid organ transplantation that are capable of fulfilling the general physical activity guidelines. Several factors are likely to influence the level of physical activity performed after transplantation, some of which are studied in this thesis.

**Understanding physical activity in recipients of solid organ transplantation**

Understanding why one recipient of organ transplantation is active and another is not is a complex and multidimensional question. Gaining knowledge on the wide spectrum of associated factors of physical activity is needed for developing and improving interventions that will increase the level of physical activity in these recipients. The associated factors that were studied in this thesis can be divided into physiological associates, on the one hand, and patient reported barriers and facilitators on the other. As is also depicted in Figure 1, there is an overlap between categories of associates, i.e., a physiological associate such as reduced peripheral muscle function can also be a patient reported barrier to being physically active.

**Figure 1.** Schematic representation of associated factors of physical activity in recipients of kidney, liver, lung, and heart transplantation.
Physiological associates of physical activity
In the study described in Chapter 2, it was shown that the level of the cardiac markers and physical activity were associated in recipients of renal transplantation. Cardiac markers were highest in the most inactive group and lowest in the most active one. This does not make cardiac function a direct physiological determinant of the level of physical activity, however, it does indicate that cardiac function and level of physical activity are associated factors.

Peripheral muscle strength was indicated as an associate of functional exercise capacity in recipients of lung transplantation (Chapter 3). In the analysis of the longitudinal change of six-minute walking distance, quadriceps strength was indicated as the only directly amendable variable that predicted the distance and thereby functional exercise capacity. Quadriceps strength in combination with the forced expiratory volume in one second was also predictive of recipients reaching the lower threshold of 82% of the predicted six-minute walking distance, an indication of experienced impairment in functional exercise capacity.14 Another variable that was associated with functional exercise capacity and reaching the indicated threshold was recipients’ grip strength. Grip strength on its own, however, is not a variable that is easily intervened on, but it is a factor that is associated with general well-being, mortality, health related quality of life, the metabolic syndrome, and frailty.15–19

Recipients’ reported barriers to and facilitators of physical activity
Besides being influenced by physiological associates, the level of physical activity in recipients of solid organ transplantation is influenced by the experienced barriers to and facilitators of physical activity, though it should be noted that perceived barriers and facilitators are not consistently associated with the actual level of physical activity.20,21

The barriers to and facilitators of physical activity for all types of solid organ transplant recipients were studied in Chapter 4. Semi structured, in-depth interviews in diverse groups of solid organ transplant recipients revealed the barriers and facilitators that were the most salient. The most important indicated barriers were ‘physical limitations’, ‘insufficient energy level’, ‘fear’, and ‘comorbidities’. The most frequently mentioned facilitators included ‘motivation’, ‘coping’, ‘consequences of (in)activity’, ‘routine/habit’, ‘goals/goal priority’, and ‘responsibility for the transplanted organ’. Neutral factors acting as a barrier or facilitator were ‘self-efficacy’ and ‘expertise of personnel’. Several of these barrier and facilitators were similar to those common in the general population, however, specific barriers and motivators were indicated as well (‘responsibility for the transplanted organ’/ ‘fear of damaging the new organ’/ ‘side-effect of medication leading to physical limitations’). Remarkably, a comparison of barriers and facilitators between transplant recipient groups yielded no overt differences.

The barrier and motivator components that were identified in the study as described in Chapter 5 were analyzed together with additional potential predictors in a large cohort study on the level of physical activity and sedentary time in recipients of solid organ transplantation (Chapter 6). Factors associated with the level of physical activity were ‘education level’, ‘exercise self-efficacy’, ‘employment status’, the barrier components ‘fear of
negative effects’ and ‘physical limitations’, and the motivator component ‘health and physical outcomes’. Associated factors of the amount of sedentary time were ‘gender’, ‘age’, ‘employment status’, and the barriers ‘physical limitations’ and ‘low expectations and self-confidence’. In rehabilitation programs and physical therapy interventions, the following key items should be addressed: ‘exercise self-efficacy’, the barriers ‘fear of negative effects’, ‘physical limitations’ and ‘low expectations and self-confidence’, and the motivator component ‘health and physical outcomes’. A reduction of physical limitations by treatment and training in combination with an increase in experience with physical activity and training will lead to an increase of knowledge and becoming aware of new physical limits. A rehabilitation program thereby will likely induce a reduction in fear of negative effects and an increase in self-confidence. Clinical experience demonstrates that recipients often do not know what their capabilities are after transplantation which is endorsed by the low levels of exercise self-efficacy that were discussed in Chapter 6. Recipients, therefore, are likely to retain physical activity patterns of the pre-transplantation phase. Insight into realistic goals and adjusting their expectations accordingly will likely result in higher levels of exercise self-efficacy and an increase of expectations.

The results for factors that were associated with the level of physical activity are reinforced by a recent qualitative study in recipients of lung transplantation in which it was indicated that physical complaints, fear of organ rejection and infections, adverse effects of medication, and restrictions in daily life were the primary concerns early after transplantation. Another recent study in recipients of renal transplantation indicated experienced fear of movement and low self-efficacy as important barriers to physical activity.

**Type of transplantation**

Although it is often assumed that the type of organ transplantation that is received influences the level of physical activity and its associated factors, the results of this thesis showed that this ‘organ effect’ is limited. The experienced barriers to and facilitators of physical activity as described in Chapter 4 indicated no overt differences between the transplant groups. The case was the same in the study described in Chapter 6 whereby the type of organ received was not of significant influence on fulfilling the activity guidelines, the amount of physical activity, or the amount of sedentary time. In an additional analysis of the study on the multidimensional structure of the barriers and motivators questionnaire (Chapter 5), potential differences between the organ transplantation groups were studied. This analysis revealed a number of minor differences between groups (when corrected for age and gender) for all barrier components, and two out of the four indicated motivator components. However, the indicated differences were very minimal and clinically negligible. Considering the relatively small differences indicated between organ transplant groups, the components appear to be generic for transplant recipients in general rather than organ group specific. The indicated barriers to and facilitators of physical activity that can be addressed in the development of rehabilitation programs or physical therapy interventions and, therefore, do not need to be organ specific. Where the initial figure (Figure 1) representing the components that influence physical activity contained the
different types of solid organs, these organs can be replaced by ‘organ transplantation’ in general (Figure 2). Aspects that could be taken into account in the specification of programs are gender and age. Recipients being female and older tended to score higher on the barrier ‘fear of negative effects’, and recipients being female and younger tended to score higher on the motivator ‘group activities’. Younger recipients were also inclined to score higher on the barrier ‘lack of motivation or time’. These aspects could be addressed in the development of specific modules or to target a specific subgroup.

**Figure 2.** Adjusted schematic representation of associated factors of physical activity in recipients of solid organ transplantation.

### Methodological considerations

**Measuring the level of physical activity and exercise capacity**

Inextricably linked to the assessment of fulfilling the physical activity guidelines is the method of measuring the physical activity level that is performed. The instrument should provide information on the intensity, frequency, duration, type, and total amount of activities that are executed. Adequate measurement is key to study the associations between the level of physical activity and health outcomes in epidemiological studies and in the formulation of recommendations on the appropriate level and type of physical activity to be performed. Three types of assessment methods of physical activity levels are commonly indicated: (1) criterion methods; (2) objective methods; and (3) subjective methods. Examples of criterion methods are the use of doubly labeled water or indirect calorimetry. These criterion methods are the most reliable and valid methods but are expensive and logistically challenging when performing studies with a large number of participants. Objective assessment methods include activity monitors such as pedometers and accelerometers as well as heart rate monitoring, however, just as with the criterion methods,
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aspects such as the expenses, availability, and logistics creates limitations for its application. The most frequently used, especially in more comprehensive studies, are subjective methods of assessment such as questionnaires and activity diaries. In this thesis, questionnaires were utilized for the physical activity level assessment in Chapter 2 and Chapter 6. The use of different assessment methods to measure physical activity, different outcome measures, and variety in what is being reported in publications limits the comparability between studies.

Although questionnaires have been utilized broadly and already for over 50 years, they still show limited reliability and validity. Validation studies have showed that questionnaires, however, can be used for classifying a (large) population into categories of physical activity behavior (i.e., inactive/moderate active/active) but are not to be used to assess the energy expenditure at the individual level. Under- and overestimation of physical activity can occur due to several factors including social desirability, perception, cultural factors, age, complexity of the questionnaire, memory of the respondent, seasonal variation, and length of the period surveyed. A recent review regarding the measurement properties of self-reported questionnaires to measure physical activity concluded that ambiguity in terminology, persons' reporting of actual physical activity, and the variable nature of physical activity between the seasons and seven days makes daily physical activity difficult to assess with self-reported questionnaires. Further validation and assessment of responsiveness and interpretability of physical activity questionnaires would be valuable for specifying the level of physical activity required to decrease the risk for chronic diseases or conditions. However, in order to obtain insight into an individual's level of physical activity for possible intervention, measures that are more accurate are necessary. Information that is more detailed is worthwhile from the professional's perspective so as to aggregate data to be employed in coaching or setting up a treatment plan. For the recipient, it will assist in obtaining insight into their actual physical activity level and monitoring their longitudinal change.

One of the methods to obtain information that is more accurate is by not only assessing the level of physical activity but also the level of physical fitness. Physical fitness refers to the attributes that people possess or achieve that relate to their ability to perform physical activity. Several components of physical fitness such as cardiorespiratory endurance, muscle strength and endurance, body composition, and balance are associated with health and functional capacity. Physical fitness was measured in the studies described in Chapter 3 (functional exercise capacity) and Chapter 7 (maximal exercise testing). Assessment of physical fitness can provide important diagnostic and prognostic information in a wide variety of clinical and research settings. It can be performed with laboratory or field assessment methods. A well-known method of laboratory testing is maximal incremental exercise testing that determines a recipient's maximal or peak oxygen uptake. Although the information generated with a maximal incremental exercise test is worthwhile to determine factors that limit a recipient's exercise performance (i.e., pulmonary limitations, cardiovascular, or peripheral muscle limitations) and can provide specific information to be used in composing a training schedule, unfortunately, it is not widely applied in the rehabilitation or transplantation settings. The insufficient number of adequate testing facilities, the need of a physician being present, and the costs of testing are
known barriers for an extensive application. However, as maximal exercise capacity is a strong and independent predictor of cardiovascular disease and mortality, investing in the testing of maximal exercise capacity in recipients of solid organ transplantation would be of substantial value. It would generate strong (intermediate) outcome measurements with relative ease and provides information to be used in adequate activity or training advice.

In addition to laboratory testing, field tests are often used which, depending on the aim of the test, focus on the morphological component (body mass index, waist to hip ratio), muscular component (handgrip, sit-up and stand), motor component (balance testing), or cardiovascular component (submaximal exercise testing). Although outcomes are usually surrogates of strong outcome measures such as organ function, graft survival, and mortality, results can be beneficial in an assessment of functional capacity. Because most daily physical activities do not require maximal effort, a submaximal test or endurance test can be beneficial while strength testing or other functional tests can provide insight into limiting factors of physical activity in recipients of solid organ transplantation. Field tests are usually easy to perform, do not need supervision of a medical doctor, and are low in cost. Therefore, these tests are useful in cohort studies as well as in the evaluation of intervention studies. However, as stated, field tests are utilized preferably in addition to maximal exercise testing in order to also generate strong outcome measures.

**Physical activity guidelines and reference values**

The leading recommendation on the amount and type of physical activity to promote or maintain health is composed by the American College of Sports Medicine (ACSM) and the American Heart Association (AHA). The ACSM/AHA guidelines recommend adults to accumulate at least 30 minutes of moderate to vigorous intensity physical activity at least five days per week. This guideline corresponds to the guideline adopted as the Dutch norm for health enhancing physical activity. The adult population with a clinically significant chronic condition or physical limitation is advised to comply with the general recommendations for healthy adults to the extent that their abilities and conditions allow. The formulation of the general guideline and the specific advice for persons with a chronic condition affords ample opportunity for interpretation. How is moderate to vigorous intensity defined and measured, and how is the ‘extent of a person’s abilities and conditions’ determined? Furthermore, thus far, no studies have been performed that specifically investigate the appropriateness of applying the general guidelines to populations with a chronic disease or chronic condition and, therefore, it is not known whether the general physical activity guidelines also apply for recipients of solid organ transplantation.

Possibly fulfilling the general physical activity guidelines is a goal that is set too high for recipients of solid organ transplantation. However, it is also possible that ‘just’ fulfilling the general guidelines is not enough to increase physical activity levels in the early stages after transplantation. Due to usually prolonged periods of inactivity in the end-stage disease phase, a higher frequency, duration, and/or intensity of activities may possibly be
necessary in order to develop the prerequisite functions to develop and maintain a healthy and active lifestyle with a sufficient amount of physical activity. Increasing physical activity levels in daily life (usually on a light to moderate intense level) is potentially not enough to regain a normal exercise capacity and, therefore, training or exercise on a higher intensity level seems mandatory.

The use of immunosuppressive medication after transplantation and the associated risks of this medication on the development of cardiovascular diseases might also positively support guidelines that are more elaborate for transplant recipients to prevent the development of secondary diseases, however, further studies are needed. Considering the amount of physical activity in the general population, it was stated by Powell et al. in 2011 that ‘some activity is better than none, and more is better than some’. However, it is unclear if this is also the case for cardiovascular risk reduction in the transplant population; potentially complying with the guidelines is necessary to achieve positive effects. Future studies should provide more insight into the amount and intensity of physical activity that is required to generate cardiovascular health benefits. As is already known, aerobic exercise enhances endothelial-dependent vasodilatation in healthy adults, patients with hypertension, and patients with coronary artery disease and chronic heart failure. Moderate-intensity physical activity has been shown to augment endothelial-dependent vasodilatation through increased production of nitric oxide where high intensity aerobic exercise potentially leads to oxidative stress. The optimal frequency and intensity of physical activity for generating the maximal positive effect in recipients of organ transplantation is unknown.

Related to the guidelines not being specific, reference values that are available are also not specific for the transplant population. As an example, the SQUASH questionnaire that is used in Chapter 6 provides information on the amount and intensity of physical activities performed in daily life and utilizes a compendium of metabolic equivalents of tasks to determine the intensity of activities. The metabolic equivalent of tasks (MET) is a unit of measurement within physiology that expresses the amount of energy that a certain physical effort requires when compared to the amount of energy required at rest. One MET corresponds to the resting metabolic rate, the amount of energy consumed during sitting or lying supine. This one MET unit is specified at 3.5 milliliters of oxygen per kilogram body weight per minute. Complying with the physical activity guidelines would lead to 150 MET minutes of physical activity per week in which moderate to vigorous physical activities are defined as activities of at least 4.0 MET (adult population). To calculate the intensity of indicated activities, a compendium of physical activities is used. This broadly employed compendium, however, is based on the energy expenditure of the average American population when performing specific tasks or sports. It is questionable if these values are one to one transferable to a European population and even more questionable if persons with a chronic disease or condition have the same metabolic rate and movement efficiency. Furthermore, the transformation of absolute data to a relative intensity of an activity can only be performed accurately if a subject’s maximal oxygen intake is known and, therefore, questionnaire data will always result in a gross estimation.
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Taken together, with the guidelines and reference values not being specific for the transplant population, it is difficult to assess if this population is active enough. Population specific physical activity guidelines and reference values which are concrete and tailored to this population are needed in order to guide recipients of solid organ transplantation adequately.

**Associated factors of physical activity**

The selection of associated factors studied in this thesis was aimed at indicating factors that are amendable in rehabilitation settings or indicating subgroups within the population that should be targeted due to the highest need of intervention. The indicated barriers and motivators should be considered in intervention development to increase physical activity levels in recipients of solid organ transplantation. The factors studied in this thesis, however, do not provide an inclusive overview of potentially associated factors of physical activity. Due to the multidimensionality of physical activity behavior, several behavioral theories and models can be utilized to describe the diversity of associated factors of physical activity behavior. Over the past decade, the use of ecological models to capture all aspects influencing physical activity behavior and to incorporate concepts from several theories (i.e., trans-theoretical model and theory of planned behavior) is becoming rather common. With this approach, a comprehensive framework incorporating determinants on a personal, social, environmental, and policy level can be studied. Further extension of the bio-psychosocial model in the future seems worthwhile in order to include all potential influencers of physical activity behavior to identify amendable aspects.

**Future directions in healthcare and research**

The findings of this thesis have several implications for clinical practice. The findings in combination with developments in the field also provide direction for future research. The most important implications are discussed in the following sections.

**Directions in health care**

**Clinical practice**

As it was indicated that the level of physical activity in recipients of solid organ transplantation is limited, there is a need to develop intervention strategies that improve this. However, inextricably linked to this is the improvement of assessment and monitoring of the level of physical activity and physical fitness within this population. Including exercise testing as standard care would be valuable for monitoring development, indicating the limiting factors, and generating training schedules. As was indicated previously in literature, a prescription of physical activity is indicated as an undervalued intervention, and physical activity should be prescribed and encouraged as a component of routine post transplantation care.

As there are currently no adequate and specific guidelines for physical activity and exercise in recipients of solid organ transplantation, it is recommended to develop an
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evidence based or best practice guideline on exercise testing and training in recipients of solid organ transplantation. In accordance with this, information for recipients should be updated to include the current knowledge about physical activity levels, consequences of inactivity, often experienced barriers to physical activity, and other associated factors of physical activity. Insight into commonly experienced barriers and associated factors will likely help recipients in recognizing their own.

The indicated barriers and other associated factors of physical activity and sedentary time should be taken into account in physical activity assessment and rehabilitation programs. Part of the indicated associated factors could be included in educational modules, however, rehabilitation programs or physical activity interventions should especially employ well guided training to provide recipients the experience of how exercise should feel, what signals to keep in mind, and how to adjust training.

Health care professionals in transplantation

After transplantation, all recipients are monitored or treated by a physical therapist in the hospital setting, however, as the geographical area of recipients is wide, recipients’ physical therapy treatment is usually not followed up at the transplant center. After discharge, referral to treatment by a physical therapist in the community is provided in most cases. However, as the results of the studies in this thesis indicate, the results on improving exercise capacity and the physical activity level appear to be limited. One factor that, from clinical experience, seems to contribute to this limited improvement is the insufficient knowledge on the training of recipients of solid organ transplantation. This lack of knowledge was substantiated by the fact that ‘expertise of personnel’ was an important factor that emerged in the qualitative study on barriers to and facilitators of physical activity among recipients of solid organ transplantation (Chapter 4). Inadequate knowledge of the local physical therapist was indicated as a factor that could incite a negative feeling about being physically active and even result in recipients discontinuing training.

A factor that is likely to contribute to the insufficient amount of knowledge on this specific population of physical therapists and other exercise specialists is the relatively small population of recipients of solid organ transplantation and the geographically wide distribution of them. As a consequence, therapists do not become familiar with the population as they rarely have recipients under treatment. Furthermore, assessment and treatment of this specific population is not an element of the educational program in any university of applied sciences, as far as we know. Improving knowledge, information material, and education in physical therapists and other exercise specialists is key for achieving the goal of improving the physical activity level in recipients of solid organ transplantation. A situation in which expert centers on physical activity for this population are established could provide a potential alternative or a worthwhile addition to increasing information and training. Assessment, initial set-up of schedules, and follow-up could be performed in the expert center and execution of the program could be performed by the recipients’ local physical therapist with guidance from the expert center.

In general, physical therapists should not only be focused on and employed in the treatment of acute problems in a person’s ability to move and perform functional activities
of daily life. Developments in the health care system require physical therapists to be involved along the continuum of health care settings and coach patients and their surrounding system in lifestyle management. In that way, it is most likely that long-term goals to sustain and improve functional status are reached. In accordance with this, physical therapists and exercise specialists as well as all other health care providers in the field of organ transplantation should not only specialize in their individual profession but should also be capable of identifying issues in adjacent areas as well. All healthcare professionals should be able to provide basic information and referral to the appropriate discipline when necessary. A professional should possess in-depth knowledge and expertise in a single field but should also have the ability to collaborate between disciplines and apply knowledge in areas of expertise outside of their own. This is also referred to as a T-shaped professional. A combination of T-shaped will result in the optimal specialized interdisciplinary team. A collaboration in interdisciplinary teams directed at holistic, patient centered care is required to optimize chronic diseases or chronic condition management. Furthermore, it would be most valuable if one team could manage the same patients across the continuum of the disease.

**Rehabilitation programs and physical therapy interventions**

Little knowledge is available concerning existing rehabilitation programs for recipients of solid organ transplantation. What is known is that there are large differences between the different organ transplantation programs nationally and maybe even more internationally. In some transplantation programs, it is common for an individual to be referred to a rehabilitation setting directly after discharge from the hospital after transplantation; in some programs, it is common to refer to a community practice and, in some programs, no referral at all is provided. In this latter case, follow-up on physical activity is usually not provided.

A recent systematic review and meta-analysis on exercise training regarding recipients of solid organ transplantation showed that exercise training including aerobic, resistance, or combined training improves physical functioning and quality of life for these recipients.43 Exercise capacity is notably increased after exercise training in recipients of a heart transplantation, however, results for the other transplantation groups is too limited for concise conclusions to be drawn. Structured exercise training in transplant recipients has been indicated to have the potential to reduce cardiovascular risk factors such as hypertension and percent body fat and increase aerobic fitness.1 The trials up to today are small, of relative short duration, and focused on surrogate outcomes instead of hard endpoints (i.e., heart rate, blood pressure, and body composition instead of cardiovascular risk factors, and survival). Furthermore, follow-up time is limited and, therefore, the long-term effects of physical activity interventions in the populations are unknown. From the recipients’ perspectives, rehabilitation is indicated to be important. A recent study on patients’ expectations and experiences of rehabilitation following lung transplantation indicated that post-transplantation rehabilitation was perceived as highly valuable.44 Group exercise was expressed as being motivational, offering peer support, and assistive in patients achieving their desired level of physical performance after transplantation.44
In the systematic review on exercise training in recipients of solid organ transplantation, it was also demonstrated that, for the described interventions, there was a substantial variation in the length of time between the transplantation and the initiation of the exercise program. For recipients of a heart transplantation, it was indicated that exercise training that began within one year after transplantation was associated with significant improvements in the overall maximal oxygen uptake compared to standard care whereas those who started the exercise program 12 months after transplantation exhibited no significant improvement in functional capacity. Based on several observations in clinical practice and from the described research findings, we hypothesize that starting rehabilitation between three and nine months after transplantation would be optimal. First, it is expected that natural recovery will occur in the period after discharge from the hospital. Being at home and becoming familiar with functioning of the new organ will likely provide sufficient stimulation to resume activities of daily life and generate an initial increase in the level of physical activity compared to the pre-transplantation phase. Second, the results of our study as described in Chapter 3 and another study on the longitudinal recovery after transplantation showed that there is an initial steep increase in recovery in the first six months after transplantation, but this recovery does not continue in the second half of the first year. Third, to be able to perform sufficient maximal exercise testing to be used in establishing an adequate training schedule, participants should be able to perform a maximal exercise test of a duration between eight and 12 minutes. This combination of factors makes us believe that intervening between three to nine months after the transplant would be optimal.

The geographical distribution of recipients of a solid organ transplantation is wide and, therefore, centralized outpatient rehabilitation programs are difficult to realize. Travel time and the burden it places on recipients is likely to be detrimental to the expected profit of exercise training. Alternatives to full hospital or rehabilitation center based and supervised rehabilitation programs, therefore, should be developed. As indicated in several studies in this thesis, there are no overt differences between transplantation groups in physical activity level, sedentary time, and its associated factors, therefore, we would propose that rehabilitation programs are designed generically to include all types of recipients of organ transplantation. Based on the findings of this thesis, a rehabilitation program designed as an assessment week after transplantation was proposed. In this proposition, we have assumed that an expert center will take the lead in the program and be in charge of assessment and setting up the rehabilitation program. In that program, the physical component is the primary element, but a broader lifestyle assessment is also performed [Box 1]. Currently, the proposed program is being performed in a pilot setting to generate experience and preliminary results in order to investigate whether the program can be broadly applied or should be adapted.
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Box 1. Proposed key items rehabilitation assessment week after transplantation

**Population**
- All recipients of solid organ transplantation with stable organ function and no signs of rejection.

**Timing**
- Between three and nine months after transplantation

**Duration**
- One-week inpatient setting in an expert rehabilitation center

**Assessment**
- Questionnaires
  - Physical activity level and sedentary behavior
  - Barriers to and facilitators of physical activity
  - Exercise self-efficacy
  - Nutritional diary and malnutrition
  - Anxiety and depression
  - Sleep quality
  - Quality of life
- Activity monitoring in the week before the inpatient phase
- Physical functioning
  - Assessment by physical therapist (history, barriers, general physical functioning)
  - Maximal cardiopulmonary exercise test
  - Submaximal exercise capacity (six-minute walking distance)
  - Endurance capacity (70% constant work-rate test)
  - Peripheral muscle strength (grip strength, quadriceps strength, and one repetition maximum major muscle groups)
- Dietary assessment by dietician
- Psychosocial status and work assessment by psychologist or social healthcare worker
- Lab values blood and 24-hour urine samples

**Content**
- Training modules
  - Endurance training (cycle ergometer and circuit training)
  - Interval training
  - Strength training (gym and circuit training)
- Educational modules
  - Exercise and physical activity
  - Psycho-education
  - Medication and side-effects
  - Nutrition
- Workshop nutrition (shopping and cooking)
- Movement activities (walking/ cycling/ swimming)

**Transfer**
- Training schedule based on the assessment and experiences with trial training session in the assessment week
- Transfer of schedule, additional information, and contact information to local physical therapist
- Possible continuation of psychological or dietetic therapy

**Evaluation**
- Phone contact with treating local physical therapist three months after the assessment week
- Follow-up measurement (repetition of assessment measurements) at six months after the assessment week combined with regular outpatient check-up after transplantation.
Directions in research

The results of this thesis contribute to the further development of interventions to increase physical activity and reduce sedentary time in recipients of solid organ transplantation. However, additional research is needed in this field in order to obtain more insight into the effectiveness of interventions and newly arising themes in the physical activity and transplantation field.

- Effectiveness of rehabilitation and physical therapy interventions:
  Clinical decisions and rehabilitation programs should be supported by accurate, timely, and up-to-date clinical information and reflect the best available evidence. Relying on randomized controlled trials in this field of study will likely not be sufficient as the population is small and diverse. Furthermore, with the use of randomized controlled trials with a control group that receives no intervention, half of the study population is omitted from an intervention that is very likely to have several positive effects. Therefore, it might even be considered as unethical to exclude half of the population from the intervention as there is strong evidence of the positive effects of higher levels of physical activity in the general population and subgroups of the transplantation population. I would, therefore, recommend an evaluation of the effectiveness of programs that are introduced in regular care. Comparing results of a population that begins with an intervention with an historical cohort of recipients would be more practical and time-efficient. A pragmatic approach that will accumulate and disseminate new knowledge through innovation in local rehabilitation settings will be required. It was recently recommended to form a small group of innovative institutions or expert centers to join around a shared set of clinical questions to achieve this knowledge and innovation in a timely manner. This requires a common set of advanced process and outcome measures in order to aggregate and analyze sufficient data that will enable answering questions of interest. In achieving this goal, international collaborations are recommended. Future studies should also focus on the effects of targeting the indicated and amendable aspects associated with the level of physical activity and sedentary time in this population.

- Development of transplant specific physical activity guidelines and reference values:
  As indicated, the physical activity guidelines are not specific for recipients of solid organ transplantation and further research is needed to specify them. The same is valid for reference values. A good starting point would be to investigate the differences in the resting metabolic rate and energy expenditure during regular activities when compared to the non-transplant population. This data could be used in the development of a transplantation specific table of metabolic equivalents of tasks values for activities.

- Muscle wasting and frailty in the transplant population:
  Muscle wasting and frailty are concepts that are gaining attention in the transplant population. Muscle wasting has been linked to negative pre- and post-transplant outcomes when compared to recipients with preserved muscle mass, and frailty is emerging as an...
important risk factor in recipients of solid organ transplantation and clearly linked to functional exercise capacity. The mechanism of muscle wasting in the transplant population is not completely understood, and it is unknown if the process is reversible. Frailty is described as a state of functional decline and increased vulnerability to adverse health outcomes. It is associated with increased inflammation and a dysregulation of the immune system. The indicated prevalence in recipients of solid organ transplantation varies by organ type and measurement method but seems to be notably higher than in the community dwelling elderly population (average prevalence of ~25% in recipients of transplantation vs. ~7% in the community dwelling elderly). However, literature is sparse and limited by different definitions of muscle wasting (sarcopenia/cachexia) and frailty and as well as by different measurement methods to assess these concepts. No standardized treatment is described, however, adequate nutrition and resistance training appear to be key for reducing or preventing muscle wasting and frailty.

Exercise and the immune system in recipients of solid organ transplantation:
Although a number of initial studies have been performed, such as the example provided in Chapter 7 of the current thesis, there continues to be insufficient knowledge regarding the effects of strenuous exercise on transplant recipients. Especially regarding the interaction between exercise and the immunosuppressive effect of medication in recipients of solid organ transplantation. Research has shown that the immune system of healthy individuals benefits from regular moderate-intensity physical activity. This effect, however, can be transiently suppressed by prolonged exhaustive exercise. Acute and chronic exercise alter the number and function of circulating cells of the innate immune system and, therefore, it has been speculated that recipients of transplantation who engage in regular physical activity may require less maintenance immunosuppressive medication. The plus side of this decrease in medication would be that the short and long-term adverse drug effects of the use of immunosuppressive medication would be reduced.

Concluding remarks
Based on this thesis, it can be concluded that, although there is wide variability in the level of physical activity in recipients of solid organ transplantation and measurement methods have their limitation, the majority of recipients do not meet the recommended level of physical activity. No significant and overt differences in physical activity and factors associated with the level of physical activity were ascertained between the different transplant groups. Therefore, the relevance of intervention development and the majority of the content of rehabilitation or physical therapy interventions is equal for all transplantation groups. The experienced barriers, facilitators and psychological components and not the type of transplantation are suggested to influence the level of physical activity. Given the interdisciplinary approach in healthcare in transplantation, all healthcare providers should work together to increase the level of physical activity in this population. Healthcare providers should take responsibility in sufficiently assessing the level of physical activity and physical fitness. Additionally, assessment of potential barriers to physical activity and psychological characteristics should receive substantial attention as the association with the level of physical activity is evident, and these factors are likely to be intervened on in rehabilitation or physical therapy programs. Healthcare providers should guide or refer recipients with an inactive lifestyle to increase their physical activity levels and reduce the negative effect of inactivity. Working together to achieve this goal will give expression to the slogan of the Groningen Transplant Center: Shared care for shared organs.
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Chapter 8

References


Physical activity in recipients of solid organ transplantation

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