Correlates and Outcomes of Low Physical Activity Post-Transplant: A Systematic Review and Meta-Analysis

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Abbreviations

BMI, body mass index

B-SERIOUS, Brocher Foundation-funded grant to develop a solid organ transplant endpoint model on relationships between influencing factors and outcomes of transplant self-management

CI, confidence interval

OR, odds ratio

PA, physical activity

Abstract

Background: Little is known about associations between low physical activity (PA) and its correlates and outcomes in solid organ transplant recipients. This systematic review with meta-analysis examined correlates and outcomes associated with low PA (i.e. not meeting individual study's definition of being physically active) following solid organ transplantation.

Methods: We searched PubMed, CINAHL, PsycINFO and EMBASE from inception to February 2016 to identify peer-reviewed data-based articles. Articles published in English, German, Spanish, French, Italian, Portuguese, or Dutch that examined correlates or outcomes associated with low PA in adult single, solid organ transplant recipients were included. Studies' quality was assessed using a 14-item checklist. Pooled odds ratios and 95% confidence intervals were computed for correlates and outcomes examined in ≥ 5 studies.

Results: Of 7,401 publications screened, 34 studies met inclusion criteria and were included in the overall synthesis with 15 included in the meta-analysis. Most focused on renal transplantation ($n=18$, 53%) and used cross-sectional designs ($n=26$, 77%). Of 30 correlates examined, [condition-related ($n=11$), social/economic-related ($n=9$), patient-related ($n=4$), healthcare system-related ($n=3$), and treatment-related ($n=3$)], only four were examined ≥ 5 times and included in meta-analyses. None were significantly related to low PA. Of 19 outcomes assessed, only physical health-related quality of life was examined ≥ 5 times. Low PA was significantly associated with low physical health-related quality of life (OR=0.172, 95% CI=0.08, 0.37).

Conclusions: We found few studies examining most correlates and outcomes related to low PA despite growing evidence that improving PA might be an effective intervention in improving post-transplant outcomes.

INTRODUCTION

With improvements in surgical methods and medical treatment for transplantation¹, clinical attention has shifted from maximizing short-term transplant recipient survival to optimizing long-term survival.² Given the organ shortage, transplant recipient self-care management is essential to foster patient and graft survival.³ Accordingly, transplant recipients need to undertake a complex post-transplant self-care regimen that involves healthy lifestyle and behavior modifications.

A major lifestyle recommendation entails engagement in sufficient physical activity (PA) post-transplant to prevent cardiovascular disease, and promote patient and graft survival. The primary cause of death for kidney recipients is cardiovascular disease.⁴⁻⁶ Reported 5-year mortality rates from cardiovascular disease in heart and kidney transplant recipients are 30% and 15% respectively.⁷ In hepatic and pancreatic transplant recipients, cardiovascular complications are the leading cause of death.⁸⁻¹¹ Regular PA and exercise can effectively lower lipid profiles, blood pressure and insulin sensitivity,¹² and are considered essential for cardiovascular risk prevention.¹³

Current international guidelines recommend at least 150 minutes of moderate intensity or 75 minutes at vigorous-intensity PA per week for healthy adults age 18-64 years.¹⁴ [ENREF 14](#) While official guidelines for PA in the transplant setting do not exist,⁴ guidelines for those with chronic diseases recommend similar levels of exercise guided by the individual's exercise capacity.¹⁵ While organ transplant recipients generally do not meet recommended levels of PA in the immediate post-transplant period secondary their post-surgical state, prolonged bedrest, and compromised overall status, most can engage in PA after recovering from surgery.

Yet, based on the U.S. Surgeon General's guidelines recommending moderate-intensity PA three or more times per week for at least 30 minutes, only 22% to 50% of transplant recipients report being regularly physically active at 1 to 2 years post-transplant.¹⁶⁻¹⁸

A systematic review and meta-analysis focusing on exercise training after transplantation found that exercise training, particularly programs of longer duration, can improve exercise capacity in cardiac transplant recipients.⁷ Another systematic review suggests improvement in functional exercise capacity, skeletal muscle function, and lumbar bone mineral density in lung transplant recipients after structured exercise treatment.¹⁹ While supervised, exercise programs were examined in these reviews, little research has focused on PA in daily life. Given the established benefits of physical activity, identifying modifiable factors associated with inadequate PA following transplantation is important for designing interventions to encourage PA. In addition, better understanding the associations between low PA and various post-transplant outcomes will provide evidence to encourage clinicians to discuss the importance of PA in daily life and may help to influence attitudes and increase patients' motivation to engage in PA following transplantation. This systematic review and meta-analysis aimed to examine the correlates and outcomes of low PA following solid organ transplantation in adult recipients.

MATERIALS AND METHODS

The systematic review was conducted following methodology described in the Center for Reviews and Dissemination handbook,²⁰ and data reporting follows the PRISMA guidelines.²¹ This review was part of the B-SERIOUS research project,

which aimed to assess the relationships between selected post-transplant behaviors (i.e., low PA, medication nonadherence, smoking, and alcohol use), and correlate and outcomes in kidney, liver, lung, and heart transplant recipients, to develop a solid organ transplant endpoint model on relationships between possible influencing factors and outcomes of post-transplant self-management behaviors. The B-SERIOUS review protocol was registered in the PROSPERO database (registration number: CRD42015003333)²².

Studies included in the review varied widely in their definition and measurement of PA. Thus, for the purpose of this review we defined low PA as not meeting the individual study's identified target for being physically active. For studies examining PA as a continuous variable and no specific cut-off was defined, lower physical activity was compared to higher physical activity.

Search strategy

We conducted systematic electronic literature searches of the PubMed, Embase, PsycINFO and Ebscohost CINAHL databases to identify relevant studies published from inception until February 3, 2016. A PubMed search string (Table 1) was initially designed in collaboration with a health science librarian (MLK) and was adapted to all databases searched (search strings are available from the researchers on request). All search strings combined controlled vocabulary (e.g., MESH terms) and free text words representing the concepts of physical activity and solid organ transplantation. In addition, the reference sections of all eligible articles were reviewed to identify additional articles. Four review authors (LB, AST, EG, CK) assessed titles and abstracts of all records retrieved. After consensus had been reached, three pairs of authors (LB/AST, EG/TG, and AR/CK) independently

reviewed all potentially relevant full-text articles using eligibility criteria described below. Disagreement was resolved by discussion between each pair of reviewers. A third author was consulted if consensus was not reached. No attempts were made to contact authors in instances of missing data.

--include Table 1 PubMed search string about here--

Eligibility criteria

After retrieving all references and eliminating duplicates, titles and abstracts were reviewed. Articles were eligible for full-text review if they: 1) reported the results of original quantitative research; 2) included adult (age 18+ years) kidney, liver, lung, or heart transplant recipients; 3) measured **PA** post-transplant; and 4) examined the associations between post-transplant **PA** and correlates/determinants and/or clinical, economic, or health-related quality of life or outcomes of post-transplant **PA**. Articles were excluded if they: 1) did not report results from an original quantitative study (e.g., case reports, reviews, books, consensus documents, letters to the editors); 2) focused on recipients undergoing combined transplants (e.g., kidney-liver), tissue transplantation, or vascularized composite allotransplantation (e.g., stem cell transplantation); 3) included children or adolescents (<18 years of age); or 4) examined physical activity that was part of a study intervention.

Next, full text of all potentially eligible articles (i.e., all articles judged by at least one reviewer to fulfill all initial inclusion criteria) were screened independently by two reviewers applying the following inclusion criteria: 1) reported in either English, Dutch, German, French, Portuguese, Italian, or Spanish; 2) full text article available; 3) reported original research (not book chapter, case study or case series with no descriptive data); 4) employed quantitative or mixed methods; 5) focused on adults

or reported results separately for adult subjects; 6) results were reported for single organ kidney, liver, lung, or heart transplant recipients; 7) measured post-transplant PA; 8) empirically assessed the associations between predictors, correlates, or determinants of post-transplant PA and/or empirically assessed the associations between post-transplant PA and clinical, economic outcomes and/or health-related quality of life; and 9) reported statistical data (e.g., mean, standard deviation, test-statistics, p-values) necessary to calculate an effect size (at a minimum, the sample size and a p-value less than or more than a specified value (e.g., $p < 0.05$). Articles were included if both reviewers agreed that the article fulfilled all inclusion criteria. Disagreements were resolved by consensus discussion or consultation by a third reviewer.

Data extraction

Using a standardized data extraction database developed in Access (version 2007, Microsoft Corp., Redmond, WA), the following data were extracted from each included article: general information (e.g., journal, year of publication, language of article, country and continent where the study was conducted, funding source, and organ type); study methodology (e.g., study design, sample size, participants' mean age, time since transplant, sex and race frequency distributions of participants); use of a theoretical framework; the method used to measure PA; the prevalence of low PA; and correlates and post-transplant outcomes examined in relation to PA or low PA. The World Health Organizations' taxonomy for classifying correlates of medication non-adherence (e.g., social/economic-related, patient-related, condition-related, treatment-related and healthcare system-related correlates)²³ was applied to classify the correlates of post-transplant low PA. Post-transplant outcomes included economic, clinical, and health-related quality of life outcomes. To be considered an

outcome, a clinical condition (e.g., diabetes, cardiovascular disease) needed to be diagnosed following transplant. Conditions known to be present prior to transplant were considered condition-specific correlates. Two reviewers independently extracted data from each study. Inconsistencies were resolved by discussion or through consultation with a third reviewer.

Quality assessment

To assess the quality of included studies, we used an adapted checklist of 14 criteria (Figure 1).^{24,25} Each criterion was rated as reported (yes), not reported (no), partially reported or not applicable. The study sample size was considered adequate if it was formally calculated and reported *a priori*, at least $104+m$ subjects for bivariate analysis where m is the number of independent variables evaluated, or $50+8m$ subjects for multivariate analysis.²⁶ A study was considered reproducible if the methods (i.e., sampling method, measurement of physical activity, outcomes and correlates, and data analysis) were described in enough detail that the study could be replicated. Two members of the research team independently rated the quality of all included studies. Any disagreements were resolved by discussion.

Data Analysis

Study and participant characteristics were analyzed descriptively (frequency counts and percentages, means, standard deviations, and ranges, as applicable). For characteristics such as age and time since transplant when the mean and standard deviation was reported in individual studies, a weighted mean and pooled standard deviation was calculated. Where there was sufficient number of studies (i.e., at least 5 independent studies) and with sufficient data to calculate an odds ratio (OR) and

its 95% confidence interval (CI) for at least one correlate or outcome, the pooled OR for low PA was calculated across the included studies using a random-effects model.²⁷ Comprehensive Meta-Analysis software (version 2.2, Biostat, Inc., Englewood, NJ)²⁸ was used for the meta-analysis. For each statistically significant pooled effect size, we estimated the impact of publication bias by calculating the classic fail-safe N²⁹. The fail-safe N is the number of non-significant studies that would need to be included to make a significant pooled effect size nonsignificant. We calculated the Q statistic to determine whether there was significant variability in effect sizes among studies. Since the Q test has limited power to detect significant heterogeneity when the number of studies is small, we also calculated the T² (the estimated variance of the true effect sizes) and I² (the percentage of variations across studies due to heterogeneity rather than chance) indices to summarize the heterogeneity in effect sizes across the independent studies.²⁹ Correlates and outcomes examined in fewer than five independent studies were excluded from the meta-analysis and the percentage of studies reporting statistical significance were summarized. Four of 11 studies that examined the relation between time since transplantation and low PA used single-group pretest-posttest design or repeated measures analysis. An OR and 95% CI could not be calculated for these studies. Consequently, they were not included in the meta-analysis, and their findings, along with the correlates and outcomes examined in fewer than five studies, were summarized in a tabular format.

RESULTS

Study selection

The electronic searches returned 9,888 references (Figure 1). After eliminating duplicates and adding one additional reference identified during screening of the reference list of included articles, 7,401 (74.8%) unique references were identified. After screening for initial eligibility by title and abstract, 924 (12.5%) articles were identified for full-text review. Finally, 34 studies (3.7% of the screened full-text articles) were included in the qualitative synthesis and 15 (1.6% of the screened full-text articles) were included in the quantitative synthesis (meta-analysis).

--INSERT FIGURE 1 (flow chart) ABOUT HERE--

Study and participant characteristics

Characteristics of included studies are described in Table 2. Two studies reported their findings in two different articles each.³⁰⁻³³ Consequently, we included 34 studies reported in 36 articles. Slightly more than half of the studies (n=18, 53%) were conducted among renal transplant recipients. Most studies were conducted in Europe (n=21, 62%), followed by North America (n=8, 24%). The mean sample size over all studies included was 99 (SD=100.9), ranging from 8 to 540. Across studies, most participants were male (60%). Among studies reporting the participants' ages, the weighted mean age was 50 years, ranging from 18 to 79 years. Eighteen studies reported the mean time since transplantation with the weighted mean across these studies being 53 months.

--INSERT TABLE 2 (study characteristics) ABOUT HERE--

Methods used to measure PA

A variety of subjective and objective methods were used to measure and quantify PA, including self-report questionnaires (n=27, 79.4%), objective measures

(accelerometer or pedometer (n=6, 17.6%), and a combination of self-report and objective measures (n=3, 8.8%). Given the diversity of methods used to assess PA and its definition, we were unable to calculate overall prevalence rates of low PA.

Quality assessment

Figure 2 reports the results of the quality assessment of the included studies. Most studies used and described appropriate data analysis methods (n=30, 88.2%), reported the eligibility criteria used to select participants (n=23, 67.6%), included a definition of low PA (n=14, 41.2%), and reported when PA was assessed (n=21, 61.8%). The quality criteria fulfilled by the fewest studies were comparison of the study sample to the overall transplant population (n=3, 8.8%) and reproducibility of the study based on the key criteria reported (n=6, 17.6%). No studies were excluded on the basis of the quality appraisal.

--INSERT FIGURE 2 about here--

Correlates of low PA

A total of 30 correlates of low PA were examined in the studies included in this systematic review. Correlates were classified as: condition- (n=11), social/economic- (n=9), patient- (n=4), healthcare system- (n=3), and treatment- (n=3) related. Only four correlates met our criteria for inclusion in a meta-analysis: age, post-transplant BMI, sex and time since transplantation. Their pooled odds ratios and 95% confidence intervals are reported in Table 3 and displayed in the forest plot in Figure 3. None of the correlates examined in the meta-analyses were significantly related to low PA following solid organ transplantation. Except for sex, substantial heterogeneity was detected for the correlates examined, as evidenced by an I^2 of

91.02% for age, 68.5% for **post-transplant** BMI and 76.8% for time since transplant. There was less heterogeneity for sex (male); I^2 was 33.9%. Time since transplantation (a treatment-related correlate) was examined in eight studies where an effect size could be calculated. The pooled effect size for these studies was not significant (OR=0.83; 95% CI 0.47, 1.47). However, this correlate was also examined in four single-group prospective studies that used pre-post or repeated measures analyses to examine its relationship with low **PA**. We were unable to identify a valid method to calculate an effect size estimate for these analytic approaches, thus, these studies were excluded from the meta-analysis. Three of the four found a significant inverse relationship between time since transplantation and low **PA** (i.e., as time since transplant increased), the level of low **PA** decreased.³⁴⁻³⁷

Most correlates were examined in only one or two studies (Table 4), and many of the relationships were not significant. An exception was post-transplant blood pressure/hypertension, which was significantly related to low **PA** in three of four studies examining this relationship.^{33,38-40}

--INSERT TABLE 3 (estimated pooled effect sizes)--

AND

--Figure 3 (Forest plot) ABOUT HERE--

Outcomes of low **PA**

Nineteen outcomes were reported. Only one outcome, physical health-related quality of life, was examined in 6 studies and, thus, had a pooled effect size calculated (Table 3 and Figure 3). There was a significant negative association

between low PA and physical health-related quality of life (OR=0.172, 95% CI 0.08, 0.37 ; $I^2 = 69.60\%$). Low PA was associated with worse physical health-related quality of life compared to being more physically active. Most of the other 18 outcomes were only examined in a single study and were significantly related to low PA (Table 4).

DISCUSSION

This systematic review examined the relationship between low PA correlates and outcomes following single kidney, liver, lung, and heart transplant in adults. Overall, relatively few studies examined correlates and outcomes associated with PA in post-transplant recipients. Among the 30 correlates that were investigated, only four were examined in a sufficient number of studies to perform meta-analyses – age, gender, post-transplant BMI, and time since transplant and none were significantly related to low PA. While we did not find a statistically significant relationship between time since transplant and low PA, we excluded four studies from the meta-analysis because we were unable to calculate an effect size. Inclusion of these studies in the meta-analysis may have changed the results. Most of the other correlates were examined in only one or two studies. Additional research is needed to examine the association between these characteristics and physical activity following solid organ transplantation.

Nineteen studies assessed the association between PA and post-transplant outcomes, but only one, physical health-related quality of life, was examined in enough studies to conduct a meta-analysis. There was a statistically significant association between physical-health related quality of life and PA. Low physical

activity was associated with poorer physical health related quality of life in comparison with higher levels of activity. This is consistent with the findings of systematic reviews in other chronically ill populations.⁴¹⁻⁴³ Most outcomes were not assessed in at least five studies, so no meta-analysis was performed. Although the number of studies most outcomes is small, based on this review there is some evidence that PA is associated with a lower likelihood of a metabolic syndrome, better cardiovascular fitness, and lower risk of osteoporosis and better mineral bone density^{33,44-48,39,49} in selected solid organ transplant recipients. These findings should be confirmed by further research.

A strength of this review is the focus on PA as part of individuals' normal daily activities. While structured exercise programs can play an important role in early post-transplant rehabilitation, and later care for select patients, they are generally of limited duration and potentially costly. Lifestyle change in terms of increased PA may not be sustained by such programs. Given that most beneficial effects of PA depend on sustained engagement, it is important to examine the effects of PA that is part of individuals' normal daily activities.

The methodological quality of the included studies varied widely. All studies were observational which is to be expected given that the focus of the review was on PA that participants engaged in during their daily lives. However, most studies used cross-sectional designs which further limits the ability to infer causal relationships between low PA and the correlates and outcomes measured. The methods used to measure PA varied across studies with the majority using self-report.

Limitations

There are limitations to this review. Despite the extensive and rigorous search process used to identify published studies, relevant papers may have been missed. We included published studies, and may have missed studies that were not published in peer-reviewed databases. While we included papers published in 7 languages, 17 papers were excluded because they did not meet our language-related criteria. Reported statistical data varied in completeness and some effect size estimates were highly estimated (e.g., based only on p-values and sample sizes). For most of the correlates and the outcome with sufficient studies to perform meta-analysis there was a substantial degree of heterogeneity based on I^2 values. While random-effects analysis was appropriately used during meta-analysis, the small number of studies available for each of the correlates and the outcomes examined precluded our ability to conduct sensitivity or sub-group analysis to identify potential sources of the heterogeneity. Most studies were conducted in European settings and most of the study participants were renal transplant recipients. This may limit the generalizability of our findings to other settings and other organ transplant recipients.

Recommendations for clinical practice

Transplant recipients should be encouraged to meet current **PA** guidelines for individuals with chronic disorders¹⁵ as their capacity permits. For patients whose exercise capacity is markedly limited, the best initial approach is a structured and monitored exercise program. Clinicians should assess the **PA** habits and capacity at follow-up visits, educate patients about the benefits of regular **PA**, and encourage regular **PA**.

Recommendations for future research

This systematic review has important implications for future research. This review points to the need for well-designed studies **using similar methodologic approaches** to examine correlates and outcomes of **PA** in the transplant population. More prospective research studies are needed to examine outcomes associated with **PA**. Objective measures of **PA** should be used when possible, and when self-report questionnaires are used there should be evidence to support their reliability and validity in the transplant population. Many of the correlates and outcomes examined in the studies included in this review were examined in only one or two studies. Identifying a core group of correlates and outcomes that should always be included when examining the effect of health behaviors such as **PA** and/or basing variable selection on theoretical models will foster understanding of the effects of engaging or not engaging in these behaviors following transplantation. Authors are urged to either report effect size estimates or to report sufficient statistical data (sample sizes for those with and without a correlate or outcome, and descriptive statistics) to permit an effect size estimate to be calculated. Following publication guidelines such as STROBE will facilitate standardization reporting of methods and findings in observational studies.

CONCLUSIONS

We found a relatively small number of studies examining correlates and outcomes associated with low **PA** in solid organ transplant recipients. Most studies were conducted in kidney transplant recipients. The vast majority of correlates and outcomes were assessed in only one or two studies. The combined effect size estimates for the meta-analysis of age, sex, **post-transplant BMI**, and time since transplantation were not significant. We were only able to perform meta-analysis of one of the outcomes, physical health-related quality of life. Transplant recipients with

low **PA** reported lower health-related quality of life than those who were more physically active.

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Reference List

1. Watson CJ, Dark JH. Organ transplantation: historical perspective and current practice. *Br J Anaesth*. 2012;108 Suppl 1:i29-42.
2. Lodhi SA, Lamb KE, Meier-Kriesche HU. Solid Organ Allograft Survival Improvement in the United States: The Long-Term Does Not Mirror the Dramatic Short-Term Success. *Am J Transplant*. 2011.
3. Gordon EJ, Prohaska T, Siminoff LA, Minich PJ, Sehgal AR. Can focusing on self-care reduce disparities in kidney transplantation outcomes? *Am J Kidney Dis*. 2005;45(5):935-940.
4. Gordon EJ, Prohaska T, Siminoff LA, Minich PJ, Sehgal AR. Needed: tailored exercise regimens for kidney transplant recipients. *Am. J. Kidney Dis*. 2005;45(4):769-774.
5. Briggs JD. Causes of death after renal transplantation. *Nephrol. Dial. Transplant*. 2001;16(8):1545-1549.
6. Pilmore H, Dent H, Chang S, McDonald SP, Chadban SJ. Reduction in cardiovascular death after kidney transplantation. *Transplantation*. 2010;89(7):851-857.
7. Didsbury M, McGee RG, Tong A, et al. Exercise training in solid organ transplant recipients: a systematic review and meta-analysis. *Transplantation*. 2013;95(5):679-687.
8. Diedrich DA, Findlay JY, Harrison BA, Rosen CB. Influence of coronary artery disease on outcomes after liver transplantation. *Transplant. Proc*. 2008;40(10):3554-3557.
9. Findlay JY, Wen D, Mandell MS. Cardiac risk evaluation for abdominal transplantation. *Curr Opin Organ Transplant*. 2010;15(3):363-367.

10. Lin K, Stewart D, Cooper S, Davis CL. Pre-transplant cardiac testing for kidney-pancreas transplant candidates and association with cardiac outcomes. *Clin. Transplant.* 2001;15(4):269-275.
11. Watt KD, Pedersen RA, Kremers WK, Heimbach JK, Charlton MR. Evolution of causes and risk factors for mortality post-liver transplant: results of the NIDDK long-term follow-up study. *Am J Transplant.* 2010;10(6):1420-1427.
12. Zelle DM, Corpeleijn E, Klaassen G, Schutte E, Navis G, Bakker SJ. Fear of Movement and Low Self-Efficacy Are Important Barriers in Physical Activity after Renal Transplantation. *PLoS One.* 2016;11(2):e0147609.
13. Thompson PD, Buchner D, Pina IL, et al. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). *Circulation.* 2003;107(24):3109-3116.
14. World Health Organization. *Global recommendations on physical activity for health.* Switzerland 2010.
15. Nelson ME, Rejeski WJ, Blair SN, et al. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. *Circulation.* 2007;116(9):1094-1105.
16. Painter PL, Hector L, Ray K, et al. A randomized trial of exercise training after renal transplantation. *Transplantation.* 2002;74(1):42-48.
17. Gordon EJ, Prohaska TR, Gallant M, Siminoff LA. Self-care strategies and barriers among kidney transplant recipients: a qualitative study. *Chronic illness.* 2009;5(2):75-91.

18. Krasnoff JB, Vintro AQ, Ascher NL, Bass NM, Dodd MJ, Painter PL. Objective measures of health-related quality of life over 24 months post-liver transplantation. *Clin Transplant*. 2005;19(1):1-9.
19. Wickerson L. Exercise training following lung transplant is now evidence-based practice. *Journal of Physiotherapy (Elsevier)*. 2013;59(1):58-58 51p.
20. Centre for Reviews and Dissemination. Systematic Reviews: CRD's guidance for undertaking reviews in health care. Accessed August 27, 2015.
21. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.
22. PROSPERO International prospective register of systematic reviews.
23. Sabaté E. *Adherence to long-term therapies: Evidence for action*. Geneva: World Health Organization;2003.
24. Harlein J, Dassen T, Halfens RJ, Heinze C. Fall risk factors in older people with dementia or cognitive impairment: a systematic review. *J Adv Nurs*. 2009;65(5):922-933.
25. Cho MK, Bero LA. Instruments for assessing the quality of drug studies published in the medical literature. *JAMA*. 1994;272(2):101-104.
26. Tabachnick BG, Fidell LS. *Using multivariate statistics*. Vol 5th edition. Boston, MA: Allyn & Bacon; 2006.
27. Fleiss JL. The statistical basis of meta-analysis. *Stat Methods Med Res*. 1993;2(2):121-145.
28. Comprehensive Meta-Analysis software.
29. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. *Introduction to meta-analysis*. West Sussex: John Wiley & Sons, Ltd; 2009.

30. Gordon EJ, Prohaska TR, Gallant MP, et al. Prevalence and determinants of physical activity and fluid intake in kidney transplant recipients. *Clin Transplant*. 2010;24(3):E69-81.
31. Gordon EJ, Prohaska TR, Gallant MP, et al. Longitudinal analysis of physical activity, fluid intake, and graft function among kidney transplant recipients. *Transpl Int*. 2009;22(10):990-998.
32. Zelle DM, Dorland HF, Rosmalen JG, et al. Impact of depression on long-term outcome after renal transplantation: a prospective cohort study. *Transplantation*. 2012;94(10):1033-1040.
33. Zelle DM, Corpeleijn E, Stolk RP, et al. Low physical activity and risk of cardiovascular and all-cause mortality in renal transplant recipients. *Clin J Am Soc Nephrol*. 2011;6(4):898-905.
34. van der Mei SF, van Son WJ, van Sonderen EL, de Jong PE, Groothoff JW, van den Heuvel WJ. Factors determining social participation in the first year after kidney transplantation: a prospective study. *Transplantation*. 2007;84(6):729-737.
35. Dontje ML, de Greef MH, Krijnen WP, et al. Longitudinal measurement of physical activity following kidney transplantation. *Clin Transplant*. 2014;28(4):394-402.
36. Jakovljevic DG, McDiarmid A, Hallsworth K, et al. Effect of left ventricular assist device implantation and heart transplantation on habitual physical activity and quality of life. *Am J Cardiol*. 2014;114(1):88-93.
37. Costa-Requena G, Cantarell MC, Moreso FJ, Parramon G, Seron D. Health-related behaviours after 1 year of renal transplantation. *Journal of health psychology*. 2015.

38. Evangelista LS, Dracup K, Doering L, Moser DK, Kobashigawa J. Physical activity patterns in heart transplant women. *J Cardiovasc Nurs*. 2005;20(5):334-339.
39. Painter P, Krasnoff J, Paul SM, Ascher NL. Physical activity and health-related quality of life in liver transplant recipients. *Liver Transpl*. 2001;7(3):213-219.
40. van den Ham EC, Kooman JP, Christiaans MH, van Hooff JP. Relation between steroid dose, body composition and physical activity in renal transplant patients. *Transplantation*. 2000;69(8):1591-1598.
41. Lahart IM, Metsios GS, Nevill AM, Carmichael AR. Physical activity for women with breast cancer after adjuvant therapy. *Cochrane Database Syst Rev*. 2018;1:CD011292.
42. Thilarajah S, Mentiplay BF, Bower KJ, et al. Factors Associated With Post-Stroke Physical Activity: A Systematic Review and Meta-Analysis. *Arch Phys Med Rehabil*. 2017.
43. Shephard RJ. The Case for Increased Physical Activity in Chronic Inflammatory Bowel Disease: A Brief Review. *Int J Sports Med*. 2016;37(7):505-515.
44. Anastacio LR, Ferreira LG, Ribeiro Hde S, Liboredo JC, Lima AS, Correia MI. Metabolic syndrome after liver transplantation: prevalence and predictive factors. *Nutrition*. 2011;27(9):931-937.
45. Armstrong K, Rakhit D, Jeffriess L, et al. Cardiorespiratory fitness is related to physical inactivity, metabolic risk factors, and atherosclerotic burden in glucose-intolerant renal transplant recipients. *Clin J Am Soc Nephrol*. 2006;1(6):1275-1283.

46. Kallwitz ER, Loy V, Mettu P, Von Roenn N, Berkes J, Cotler SJ. Physical activity and metabolic syndrome in liver transplant recipients. *Liver Transpl.* 2013;19(10):1125-1131.
47. Myers J, Gullestad L, Bellin D, Ross H, Vagelos R, Fowler M. Physical activity patterns and exercise performance in cardiac transplant recipients. *J Cardiopulm Rehabil.* 2003;23(2):100-106.
48. van den Ham EC, Kooman JP, Schols AMWJ, et al. Similarities in skeletal muscle strength and exercise capacity between renal transplant and hemodialysis patients. *American Journal of Transplantation.* 2005;5:1957-1965.
49. Grotz WH, Mundinger FA, Rasenack J, et al. Bone loss after kidney transplantation: a longitudinal study in 115 graft recipients. *Nephrol Dial Transplant.* 1995;10(11):2096-2100.
50. Lin SY, Fetzner SJ, Lee PC, Chen CH. Predicting adherence to health care recommendations using health promotion behaviours in kidney transplant recipients within 1-5 years post-transplant. *J Clin Nurs.* 2011;20(23-24):3313-3321.
51. Sanchez ZV, Cashion AK, Cowan PA, Jacob SR, Wicks MN, Velasquez-Mieyer P. Perceived barriers and facilitators to physical activity in kidney transplant recipients. *Prog Transplant.* 2007;17(4):324-331.
52. Rongies W, Stepniewska S, Lewandowska M, et al. Physical activity long-term after liver transplantation yields better quality of life. *Ann Transplant.* 2011;16(3):126-131.
53. Kotarska K, Wunsch E, Kempinska-Podhorodecka A, et al. Factors affecting health-related quality of life and physical activity after liver transplantation for

- autoimmune and nonautoimmune liver diseases: a prospective, single centre study. *J Immunol Res*. 2014;2014:738297.
54. Plonek T, Pupka A, Marczak J, Skora J, Blocher D. The influence of regular exercise training on kidney transplant recipients' health and fitness condition. *Adv Clin Exp Med*. 2013;22(2):203-208.
  55. Bossenbroek L, den Ouden ME, de Greef MH, Douma WR, Ten Hacken NH, van der Bij W. Determinants of overweight and obesity in lung transplant recipients. *Respiration*. 2011;82(1):28-35.
  56. van der Mei SF, van sonderen ELP, Van Son WJ, de jong PE, Groothoff JW, van den heuvel WJA. Social participation after successful kidney transplantation. *Disability and rehabilitation*. 2007;29(6):473-483.
  57. Bossenbroek L, ten Hacken NH, van der Bij W, Verschuuren EA, Koeter GH, de Greef MH. Cross-sectional assessment of daily physical activity in chronic obstructive pulmonary disease lung transplant patients. *J Heart Lung Transplant*. 2009;28(2):149-155.
  58. Flattery MP, Salyer J, Maltby MC, Joyner PL, Elswick RK. Lifestyle and health status differ over time in long-term heart transplant recipients. *Prog Transplant*. 2006;16(3):232-238.
  59. van den Berg-Emons R, Kazemier G, van Ginneken B, Nieuwenhuijsen C, Tilanus H, Stam H. Fatigue, level of everyday physical activity and quality of life after liver transplantation. *J Rehabil Med*. 2006;38:124-129.
  60. Carvalho EV, Reboredo MM, Gomes EP, et al. Physical activity in daily life assessed by an accelerometer in kidney transplant recipients and hemodialysis patients. *Transplant Proc*. 2014;46(6):1713-1717.

61. Langer D, Gosselink R, Pitta F, et al. Physical activity in daily life 1 year after lung transplantation. *J Heart Lung Transplant*. 2009;28(6):572-578.
62. Mazzoni D, Cicognani E, Mosconi G, et al. Sport activity and health-related quality of life after kidney transplantation. *Transplant Proc*. 2014;46(7):2231-2234.
63. Bengel FM, Ueberfuhr P, Schiepel N, Nekolla SG, Reichart B, Schwaiger M. Effect of sympathetic reinnervation on cardiac performance after heart transplantation. *N Engl J Med*. 2001;345(10):731-738.
64. Rubin S, Dale J, Santamaria C, Tomalty J. Weight change in cardiac transplant patients. *Can J Cardiovasc Nurs*. 1991;2(2):9-13.
65. Zelle DM, Kok T, Dontje ML, et al. The role of diet and physical activity in post-transplant weight gain after renal transplantation. *Clin Transplant*. 2013;27(4):E484-490.
66. Sarrias M, Diaz E, Escofet R. Lifestyle in patients with chronic kidney disease is associated with less arterial stiffness. *J Ren Care*. 2010;36(3):139-144.
67. Brzezinska B, Junik R, Kaminska A, Wlodarczyk Z, Adamowicz A. Factors associated with glucose metabolism disorders after kidney transplantation. *Endokrynologia Polska*. 2013;64(1):21-25.
68. Lai FC, Chang WL, Jeng C. The relationship between physical activity and heart rate variability in orthotopic heart transplant recipients. *J Clin Nurs*. 2012;21(21-22):3235-3243.

Table 1: PubMed search string

((("Muscle Strength"[Mesh]) OR ("Exercise"[Mesh:noexp]) OR ("Sports"[Mesh:noexp]) OR ("Actigraphy"[Mesh]) OR (exercise[tiab]) OR (muscle strength[tiab]) OR (accelerometer[tiab]) OR (accelerometers[tiab]) OR (accelerometry[tiab]) OR (pedometer[tiab]) OR (step counter[tiab]) OR (maximum oxygen uptake[tiab]) OR (activities of daily living[tiab]) OR (activity of daily living[tiab]) OR (habitual activity[tiab]) OR (physical activit*[tiab]) OR (physical function[tiab]) OR (physical inactivit*[tiab]) OR (activity monitor*[tiab]) OR (actigraphy[tiab]) OR (fitness[tiab]) OR (motor activity[tiab]) OR (walking[tiab]) OR (sport[tiab]) OR (training[tiab]) OR ("Sedentary Lifestyle"[Mesh]) OR (sedentary[tiab]) OR ("motor activity"[Mesh:NoExp]) OR ("walking"[Mesh:noexp]))) AND ((("Heart Transplantation"[Mesh:noexp]) OR (heart transplant*[tiab]) OR (cardiac transplant*[tiab]) OR (heart graft*[tiab]) OR (heart allograft*[tiab]) OR (cardiac allograft*[tiab]) OR (cardiothoracic transplant*[tiab]) OR (thoracic transplant*[tiab]) OR (Cardiac Graft* [tiab]) OR ("Kidney Transplantation"[Mesh]) OR (kidney transplant*[tiab]) OR (renal transplant*[tiab]) OR (kidney graft*[tiab]) OR (kidney allograft*[tiab]) OR (renal allograft*[tiab]) OR (Renal Graft* [tiab]) OR ("Liver Transplantation"[Mesh]) OR (liver transplant*[tiab]) OR (hepatic transplant*[tiab]) OR (liver graft*[tiab]) OR (liver allograft*[tiab]) OR (hepatic allograft*[tiab]) OR (Hepatic Graft* [tiab]) OR ("Lung Transplantation"[Mesh:noexp]) OR (lung transplant*[tiab]) OR (lung graft*[tiab]) OR (lung allograft*[tiab]) OR (pulmonary transplant*[tiab]) OR (Pulmonary Graft* [tiab]) OR ("Organ Transplantation"[Mesh:noexp]) OR (solid organ*[tiab]) OR (organ transplant*[tiab]))))

MeSH: Medical Subject Heading; noexp: no explode; tiab: Title/Abstract

Figure 1: PRISMA flowchart of the study selection and inclusion process

Table 2: Study and participant characteristics of 34 studies included in the systematic review

Study Characteristics (N=34 studies):		
Organ type, n (%)	Kidney	18 (52.9)
	Heart	7 (20.6)
	Liver	6 (17.6)
	Lung	3 (8.8)
Continent, n (%)	Europe	21 (61.8)
	North America	8 (23.5)
	Asia	2 (5.9)
	Other	3 (8.8)
Sample size ¹ , mean $\pm$ SD; range; median		99.2 $\pm$ 100.9; 8-540; 74.0
Study design, n (%)	Cross-sectional	26 (76.5)
	Prospective	8 (23.5)
Participant characteristics:		
Male participants, n (%)		1,966 (59.95)
Age in years: Weighted mean $\pm$ pooled SD ²		50.3 $\pm$ 11.6
Time since transplantation (in months): Weighted mean $\pm$ pooled SD ³		52.7 $\pm$ 35.6
¹ For repeated measures designed, if the sample size varied across the measurement time points, the sample size for the final time point was used. For one of the two studies reporting their findings in two different articles, the sample		

size was slightly larger in one of the articles than the other (540 vs. 527); the larger sample size was used

²Data available in 31 studies

³Data available in 18 studies

N = number/count, SD = standard deviation

Figure 2: Quality assessment of the included studies

Number in bars represent the number of studies

Table 3: Estimated pooled effect size estimates (odds ratios) generated under a random effects model: Low physical activity

Factor	N	Estimated Odds Ratio (OR)	95% Confidence Interval for the OR		Q sta-tistic	p-value	T ²	I ² (%)	Classic Fail-safe N
			Lower Limit	Upper Limit					
Socio/economic-related									
Older age 30,33,34,38,39,50-52	8	1.35	0.75	2.43	77.93	<0.001	0.55	91.02	--
Male gender 30,33,34,39,40,50-53	9	1.02	0.77	1.36	12.10	0.147	0.06	33.88	---
Condition-related									
Greater body mass index (BMI) 33,38,39,51,53-55	7	1.03	0.64	1.64	19.02	0.004	0.246	68.45	---
Treatment-related									
Longer time since transplant 50,51,53,56-60	8	0.83	0.47	1.47	30.19	<0.000 1	0.414	76.81	
Outcome									

Greater physical health-related quality of life (Physical HRQoL) 30,39,52,59,61,62	6	0.17	0.08	0.37	16.45	0.006	0.49	69.60	103

Figure 3: Forest plot of pooled effect size estimates for correlates and outcomes examined ≥ 5 times

¹Physical health related quality of life

²Low physical activity

Table 4: Correlates and outcomes examined in fewer than 5 studies or in studies where an effect size could not be calculated

Times Examined	Correlate (percentage of studies (of 4 or fewer independent studies) reporting a significant association)
Social/economic-related correlates (7 explored)	
2	Level of education ^{30,50} (0%); marital status ^{30,50} (50%); annual income/financial status ^{30,50} (0%)
1	Living arrangement ⁵⁶ (0%); social support ³⁰ (0%); ethnicity ³⁰ (0%); employment status ⁵³ (100%)
Patient-related correlates (4 explored)	
2	Motivators for physical activity ^{30,51} (50%)
1	Self-efficacy ³⁰ (100%); barriers to physical activity ⁵¹ (0%); smoking post-Tx ³³ (0%)
Condition-related correlates (10 explored)	
4	Post-Tx blood pressure/hypertension (including medication to treat hypertension) ^{33,38,39,51} (75%)
3	Post-Tx hyperlipidemia (including use of statins) ^{33,38,51} (33%)
2	Waist circumference/waist to hip ^{33,40} (50%); underlying cause for transplantation ^{30,53} (0%)
1	Lean body mass ⁴⁰ (100%); reinnervation vs denervation of the heart ⁶³ (100%); arthritis as co-morbidity ³⁹ (0%); weight change ⁶⁴ (0%); depression ³² (100%); body fat stability ⁶⁵ (100%)
Treatment-related correlates (2 explored)	

4	Time since transplantation (single group repeated measures) ³⁴⁻³⁷ (75%)
1	Steroid use ⁴⁰ (100%)
Healthcare system-related correlates (3 explored)	
1	Support from the healthcare provider ⁵⁰ (0%); state or country of transplant surgery ⁵⁰ (100%); travel time to transplant center ³⁰ (0%)
Outcomes (18 explored)	
4	Metabolic syndrome ^{33,44-46} (75%)
3	Cardiovascular disease ^{33,39,66} (0%); diabetes ^{33,39,51} (0%); cardiorespiratory fitness ^{45,47,48} (100%)
2	Kidney function ^{31,33} (0%*); osteoporosis/bone mineral density ^{39,49} (100%)
1	Patient survival time ³³ (100%); patient mortality ³³ (100%); cancer (non-skin malignancies) ³⁹ (0%); post-Tx infection ³³ (100%); lung function ⁵⁷ (100%); hepatitis C infection post-Tx ³⁹ (0%); quality of life ³⁸ (100%); body strength ⁵⁷ (100%); glucose intolerance ⁶⁷ (0%); heart rate variability ⁶⁸ (100%); self-reported health ⁵⁴ (100%); self-reported fitness ⁵⁴ (100%)
*One study ³³ examined kidney function with 4 measures. Three out of four measures were non-significant, one was significant (creatinine clearance), therefore categorized as non-significant	