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The association of physical function and physical activity with all-cause mortality and adverse clinical outcomes in non-dialysis chronic kidney disease: a systematic review

Running title: The importance of being active in chronic kidney disease

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Abstract

Objective: People with non-dialysis dependent chronic kidney disease (CKD) and renal transplant recipients (RTR) have compromised physical function and reduced physical activity (PA) levels. Whilst established in healthy older adults and other chronic diseases, this association remains underexplored in CKD. We aimed to review the existing research investigating poor physical function and PA with clinical outcome in non-dialysis CKD.

Data sources: Electronic databases (PubMed, MEDLINE, EMBASE, Web of Science, Cochrane Central Register of Controlled Trials) were searched until December 2017 for cohort studies reporting objective/subjective measures of PA/physical function and the associations with adverse clinical outcomes/all-cause mortality for patients with non-dialysis chronic kidney disease stages 1 to 5 and RTR. The protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42016039060).

Review methods: Study quality was assessed using the Newcastle-Ottawa Scale and the Agency for Healthcare and Research Quality (AHRQ) standards.

Results: 29 studies were included; 12 reporting on physical function and 17 on PA. Only 8 studies were conducted with RTR. The majority were classified as "Good" according to the AHRQ standards. Although not appropriate for meta-analysis due to variance in the outcome measures reported, a coherent pattern was seen with higher mortality rates and/or prevalence of adverse clinical events associated with lower PA and physical function levels, irrespective of the measurement tool used. Sources of bias included incomplete description of participant flow through the study and over-reliance on self-report measures.

Conclusions: In non-dialysis CKD, survival rates correlate with greater PA and physical function levels. Further trials are required to investigate causality and the effectiveness of physical function/physical activity interventions in improving outcomes. Future work should identify standard assessment protocols for PA and physical function.

Key words: “kidney diseases”, “kidney transplantation”, “physical activity”, “mortality”, “physical function”

Introduction

Chronic kidney disease (CKD) is a long term condition affecting approximately three million people in the UK and >61,000 people have end stage renal disease and require dialysis or a renal transplant(1). Research into kidney disease has historically tended to concentrate on patients with severe renal impairment requiring renal replacement therapy, however there is a significant proportion of the UK population living with earlier stage CKD and interventions to promote a healthy lifestyle with this group are starting to emerge.

People living with *non-dialysis* CKD experience a high symptom burden with progressively impaired physical function and low levels of physical activity (PA). These negatively affect quality of life (QoL) and independence(2, 3). In *non-dialysis* CKD patients, even a small increase in regular PA levels can improve self-reported quality of health and life, as well as improving exercise tolerance and cardiovascular reactivity(4). In older adults(5), and in other chronic disease populations such as diabetes(6, 7), it is well-established that both reduced physical function and PA are associated with an increased risk of cardiovascular disease (CVD) and all-cause mortality(8, 9). Whilst evidence is limited in *non-dialysis* chronic kidney disease populations, it is well established in patients undergoing dialysis that both self-reported(10-13) and objective(13-15) physical function is a significant and independent predictor of all-cause mortality and future hospitalisation. Notably, regularly physically-active dialysis patients have a decreased risk of CVD and death(16), however the physiological and social impact of dialysis is such that findings in this group are not directly transferable to a patient population that does not require renal replacement therapy. Although renal transplant recipients (RTR) generally report improved physical function, PA, and QoL following transplantation, it often remains poor(17, 18), and patients who have undergone transplantation remain at high risk of CVD(19).

Physical function and PA are two key ‘modifiable’ lifestyle factors that may reduce mortality and clinical adverse events and have a positive impact on quality of life in *non-dialysis* CKD and RTR. Furthermore, early identification, using simple physical function or physical activity measures, of patients at risk of clinical adverse events may focus interventions (e.g., exercise or nutrition) designed to improve such outcomes.

Physical function and PA should be viewed as two independent concepts. Physical function is the ability to perform activities of daily living, and is assessed using simple tests to reflect these tasks (e.g. getting out of a chair) or by subjectively rating competency in completing different tasks(13). PA is any bodily movement produced by contraction of skeletal muscle that increases energy expenditure above a basal level(20). PA and physical function correlate significantly and both concepts are important to clinicians and patients, hence this review will explore the relationship of each with clinical outcomes.

We performed a systematic review to identify the association between physical function and PA with all-cause mortality and other adverse clinical outcomes in *non-dialysis* CKD (i.e. including RTR). No systematic review of the current literature has been performed on this association in this patient group. We hypothesised that patients with *non-dialysis* CKD who are functionally limited or less physically active will demonstrate a higher risk of all-cause mortality and adverse clinical outcomes.

Methods

Protocol and registration

The protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42016039060). Data is reported in line with the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) guidelines(21).

Search strategy and selection criteria

We aimed to identify observational studies that explored the link between physical function, PA, and adverse clinical outcomes and all-cause mortality in *non-dialysis* CKD. The primary question of interest was the association between objective and subjective measures of physical function, PA, and the likelihood of death (i.e. all-cause mortality) and adverse clinical outcomes in patients with CKD *not currently requiring dialysis therapy*. For the purpose of this review, an 'adverse clinical outcome' was defined as one (or more) of the following events: end-stage renal disease (i.e. the need for/time to dialysis), unforeseen hospital admission, or non-fatal cardiovascular event (e.g., myocardial infarction, stroke, etc.). The primary outcome of interest was all-cause mortality.

Data sources and search strategy

The following electronic databases were searched from their date of establishment to July 2016 and a further search was performed in December 2017 to gather any new literature. National Centre for Biotechnology Information (NCBI) PubMed (which includes the Medical Literature Analysis and Retrieval System Online (MEDLINE)), Excerpta Medica dataBASE (EMBASE), Web of Science (WOS) (which includes the KCI-Korean Journal Database, MEDLINE, Russian Science Citation Index, and SciELO Citation Index), and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy was tailored to each database and used a combination of key words and medical subject headings (MeSH). MeSH search terms were: "kidney diseases", "kidney

transplantation", "physical activity", "mortality", "death", "cardiovascular event". Other non-MeSH search terms used were: "renal impairment", "physical function", "physical performance", "disability", "all-cause mortality", "cardiovascular diseases"; "adverse event", "hospital admission".

As per the PRISMA statement, an example full electronic search strategy can be found for the NCBI PubMed database in supplementary material 1.

Article eligibility criteria

The eligibility for full text review of each citation was independently evaluated by two authors (HJM, TJW) on the basis of title and abstract. Any article deemed potentially relevant was retrieved for full-text review. The reference lists of any relevant articles were also screened to identify studies which may have been missed in the search.

Inclusion criteria:

1. Human adults (aged 18 years or over);
2. CKD (any stage) or RTR;
3. Cohort studies including secondary analysis of randomised control trials and abstracts;
4. Reporting physical function or PA outcome measures;
5. Reporting association with adverse clinical outcomes and all-cause mortality in either unadjusted or adjusted terms.

Specific exclusion criteria:

1. Renal failure - any dialysis modality;
2. Review articles;
3. Animal trials;

4. Non-English articles.

Data extraction

Following a preliminary pilot search in NCBI PubMed, a data extraction form was created to capture relevant information from included studies. Each article was reviewed by two independent members of the research team during the data extraction process. The following information was extracted for each study:

1. Study characteristics: such as the year of publication, study design, and sample size;
2. Patient characteristics, such as mean age, sex distribution, race, and comorbidities;
3. Definitions and incidences of: CKD, physical function (or its associated domains), PA, clinical adverse events, and all-cause mortality;
4. Reported association of physical function or PA with adverse clinical outcomes and/or all-cause mortality in either unadjusted or adjusted terms (e.g., hazard or odds ratio).

Evaluation of quality and risk of bias

Each study was evaluated for quality and risk of bias using the Newcastle-Ottawa Scale (NOS)(22) independently by two reviewers. Discrepancies in scoring were settled by mutual agreement. Primary authors HJM and TJW had the final verdict decision. The NOS is a quality evaluation method for non-randomized studies which uses three criteria: Selection, Comparability, and Outcome. Each study is designated a number of stars for each section, based on predetermined queries(22). The NOS has been extensively used to evaluate quality and bias for systematic reviews and meta-analyses and is recommended by the Cochrane Collaboration(23). Scores from the NOS were transformed into Agency for Healthcare Research and Quality (AHRQ) standards (‘Good’, ‘Fair’, and ‘Poor’ quality)(22).

Results

Study selection

A total of 6299 records were identified by systematic searching and 249 were deemed appropriate based upon the title and abstract alone. Upon removal of 211 duplicates, 38 records were assessed against the full eligibility criteria and 14 records were removed. One additional source was identified during the original review process. In December 2017, a re-search found 4 additional studies. A total of 29 trials were reviewed (see PRISMA diagram, **Figure 1**).

Study characteristics

Overall, the articles demonstrated a range of follow-up times (median follow-up = 7.0 years; range 1(24)- 15.9 years(25)) and sample sizes (median = 719; range 26(26)- 50,620(27)). Studies were conducted in the USA(25, 28-41),Taiwan(27, 42-44), Estonia(26), the Netherlands(45), Korea(46), the UK(47, 48), Italy(24), Hungary(49), Brazil(50), Finland(51), and Slovakia(52) ensuring data from a variety of cultures are included which, although increasing generalisability, may mean culturally specific behaviour trends are masked. Studies included single- (25, 26, 38, 42-45, 47, 49, 50, 52) and multi-centre investigations(24, 30, 33-37, 39-41, 48, 51), and population-wide surveys(27-29, 31, 32, 46). The majority of these studies are observational except Pechter et al(26) who described a 10 year programme of supervised hydrotherapy exercise, and Chen et al(30) who reported observational data collected as part of an RCT investigating effects of different diets in kidney disease.

The disease populations studied varied with 19 investigations conducted in non-dialysis CKD(24, 26-29, 31-33, 35, 37, 39, 40, 42, 43, 46, 47, 50, 53, 54), seven with RTR(36, 38, 41, 45, 48, 49, 52), and Tikkanen-Dolenc et al(51) studied both CKD and RTR. Some studied all five stages of CKD(24, 26-28, 34, 39, 43, 44, 46, 47, 51), whilst others studied a fixed eGFR range(29-34, 37, 40,

42, 50). Gulati et al(25) studied a female only population with no pre-existing diagnosis of CKD, however the mean eGFR of the study population was 53.7 ml/min/1.73m² and 79% were found to have an eGFR <60ml/min/1.73m². Further, Robinson-Cohen et al(34) conducted a general population study but calculated HR for stratified eGFR bands and, henceforth, both of these papers have been included in the review. Two papers(39, 50) investigated physical function as a subset of another concept: Delgado et al(39) investigated frailty in CKD, whilst Periera et al(50) studied the incidence of sarcopenia. Similarly Chang et al(43) measured hand-grip strength (HGS) to investigate the effects of protein-energy wasting.

The association between physical function and all-cause mortality or adverse clinical outcomes are summarised in **Table 1**, and studies reporting the association between PA and outcomes can be found in **Table 2**. Ten papers investigated physical function, whilst 15 studied PA. Two papers used cumulative measures using both PA and physical function(34, 38), however these have been included in the table corresponding to the main emphasis of the individual trial. Tsai et al(44) investigated physical function as "indices" of the person's ability to engage in PA in addition to reporting PA behaviour.

Outcomes reported

The majority of the papers studied mortality, either as all-cause(24-33, 36, 38-43, 45-52) or cardio-vascular mortality(37, 45). Other outcomes reported included prevalence of frailty(39), sarcopenia(50), protein-energy wastage(43), major adverse cardio-vascular event(44), first hospitalisation(44), rate of decline of renal function(34, 35), or risk of requiring dialysis(26, 42-44). One study reported an odds ratio of developing diabetic nephropathy(27).

Overall, the results showed that poorer physical function and lower PA was associated with increased mortality rates, however differing methodologies preclude meta-analysis. Hazard ratios

were reported in some studies (summarised in **Table 1**) varying from 1.04(52) to 5.7(24) dependent on measurement type and population studied.

Only four papers(36, 38, 45, 51) reviewed the importance of being active with a renal transplant and four(41, 48, 49, 52) of the 10 papers investigating physical function studied renal transplant recipients. Outcomes studied were all-cause mortality(36, 38, 41, 45, 48, 49, 51, 52), cardio-vascular mortality(45), graft failure(38, 45, 48, 49), and death with a functioning transplant(36, 49). Higher PA levels both prior to transplantation(36) and post-transplant(38, 45) were associated with lower mortality rates. Similarly lower physical function levels were associated with increased mortality hazard ratios(48, 49, 52).

Objective physical function

Six papers used objective measures of physical function including the Short Physical Performance Battery (SPPB)(24, 41), HGS(43, 44, 50), using a Bruce protocol treadmill test to determine cardiorespiratory fitness(25), the 'timed-up-and-go' (TUAG)(40), the 6 minute walk test (6MWT)(40), 30 second chair stands(44), 2 minute step(44) and gait speed(40). The Short Physical Performance Battery (SPPB), TUAG, the 6MWT, and gait speed were independently associated with increased all-cause mortality(24, 40, 41). Greater scores in the 2 minute step were correlated with a reduced risk of commencing dialysis(44). The number of chair stands achieved in 30 seconds was shown to correlate with reduced risk of a major adverse cardio-vascular event and with all-cause hospitalisation(44). Since both TUAG and the SPPB include measured of a person's gait speed and ability to stand from a chair, it may be inferred that a measure of physical function utilising walking and standing provides a useful measure of physical function in CKD when outcomes are to be studied.

HGS was measured in three studies(40, 43, 50), with inconsistent results. Pereira et al(50) measured HGS as a marker of saropaenia which was demonstrated to correlate with mortality risk; Roshanravan et al(40) found HGS was relatively preserved compared to lower limb strength, as 6MWT, gait speed, and TUAG had greater area under the ROC values than HGS. However, Chang et al(43) found that HGS was an independent outcome predictor in CKD.

Cardiorespiratory fitness was found to modify the association between eGFR and mortality(25). A maximum cardiorespiratory fitness level of <5 METS (Metabolic Equivalent of Task ~17.5 ml/kg/min) combined with an estimated glomerular filtration rate (eGFR) of <45 mL/min/1.73 m² was associated with increased mortality rates compared to those with better fitness and higher eGFR(25).

Objective physical activity

Only one study(29) used an objective PA measure (i.e. accelerometry), whilst another(34) combined gait speed with a questionnaire to give a cumulative PA score.

Subjective physical function

Self-report measures of physical function were used by six papers(39, 46-49, 52). The 36-item Short Form survey 'SF-36' was used in three of these(48, 49, 52) and a significant relationship between the 'Physical Component Score' (PCS) and outcomes was consistently demonstrated. The other subjective methods used included 'Modification of Diet in Renal Disease (MDRD) Quality of Wellbeing measure'(39), 'Korean version of ADL's'(46), 'Instrumental ADL'(46), 'Health Related Quality of Life (HRQoL)'(48) and 'Kidney Disease Quality of Life measure (KDQoL)'(49) which included 'HRQoL', 'SF-36' and 'Center for Epidemiologic Studies Depression Scale' (CES-D). Similar trends were seen between poorer outcomes and lower physical function.

Subjective physical activity

Thirteen studies which explored PA associations used questionnaires including 'Household Adult' questionnaire(28, 32) (a translated version was used by Tsai et al(44)), 'Leisure Time Physical Activity Questionnaire'(31), 'Modified Diet in Renal Disease Leisure Time Physical Activity Questionnaire' (MDRD-LTPAQ)(30), 'Four-Week Physical Activity History Questionnaire (FWH)'(35), 'Multi-Ethnic Study of Atherosclerosis (MESA) Typical Week Physical Activity Survey'(33), 'Physical Activity Scales for the Elderly' (PASE)(36), 'Minnesota Leisure Time PA' questionnaire(37, 45) (a translated version was used by Tikkanen-Dolenc et al(51)), and 'Tecumseh Occupational Activity Questionnaire'(45). One study(27) failed to report which method was used and two used clinician judgement to classify PA(38, 42). Questionnaires were frequently used in conjunction with a compendium of activities to give MET score for further analysis(27, 28, 31-33, 36, 44, 45, 51).

The most common PA reported was walking, with data showing that increasing walking duration and intensity correlates with favorable health benefits. The dose-response relationship remains unclear. Navaneethan et al(31) and Ricardo et al(33) demonstrated reduced mortality risk only when guideline PA levels were achieved (i.e. >150mins/week moderately-vigorous PA) whilst Beddhu et al(29) found replacing sedentary time with light activity resulted in a lower mortality risk but upgrading to moderate/vigorous PA did not reduce the risk further. Robinson-Cohen et al(35) found the risk of developing end stage renal disease decreased with every 60 min/week increase in PA with the largest reduction when >150minutes was achieved. Similarly, Tikkanen-Dolenc et al(51) stratified HR's according to intensity, duration and frequency of PA and demonstrated increased HR's when each of these differed from the guideline amounts, with the greatest increase in risk when target duration of PA was not achieved. In contrast, Tsai et al(44) found no change in hazard ratios with PA levels as measured by questionnaires, but found that various functional measures were significant. Whilst these studies demonstrate interesting, although conflicting, conclusions,

despite large sample sizes, the *P* values reported are often not significant(35) or not specified(29, 31, 33).

Risk of bias

Each study was evaluated for quality and risk of bias using the Newcastle-Ottawa Scale and Agency for Healthcare Research and Quality (AHRQ standards. These results are summarised in **Table 3**. Overall the quality of these papers was mixed, with 20 classed as 'Good', 7 as 'Fair' and 2 determined to be 'Poor' quality. Sources of potential bias identified included not fully describing the participant flow through the study and the use of self-report measures.

Discussion

Summary of review findings

Overall, our review has shown that, in patients with *non-dialysis* CKD, reduced physical function and PA levels are associated with increased mortality and adverse clinical events, including decline in renal function, increased risk of requiring renal replacement therapy, and poor renal graft survival (RTR only). Similar observations have been observed in dialysis patients(16) and in other chronic populations(6, 7). This has important clinical implications, potentially providing an opportunity to improve outcomes. The concepts of PA and physical function have significant overlap and although engagement in functional tasks can be considered a category of PA, function can also be considered an antecedent of activity. The two concepts are also frequently intertwined in the literature which necessitated the consideration of the two ideas in the same review.

Bias was assessed in this review using the NOS. Interestingly, the papers studying disease progression were scored negatively by the NOS as the outcome, i.e. CKD, was present at the start of the trial and this represents a weakness for this scoring system. Hazard ratios were reported in many, but not all, papers, however, some studies reported mortality risk whilst others reported survival analysis, making the data unsuitable for meta-analysis. Studies which yielded hazard ratios were calculated both as unadjusted models and adjusted for confounding variables, such as age, body mass index (BMI), gender, depression, and kidney function levels; however sensitivity analysis to confirm these findings was poorly reported.

It is important to state the difficulty deducing causality from the data presented, as patients with greater illness burden are often less active and have a reduced functional level. Further longitudinal studies are needed whereby interventions increase PA or physical function to assess resultant changes in outcomes. Further research is needed into the potential dose-response of PA, and whilst

it appears that being active on most days, in line with the current PA recommendations, is beneficial, even low levels of PA may confer some benefit in renal patients. It is also important to consider that there is a physical function minima, below which PA is impossible. Whilst in principle, encouraging patients to be more active may be a straightforward suggestion, the complexity of successful behaviour change interventions should not be underestimated.

The data was not appropriate for meta-analysis due to the variance in the measurement outcomes and the analysis methods used. This demonstrates the need to identify accepted norm assessments of physical function and PA to use in the renal community to allow comparison between interventions. The paucity of research in the transplant population is also demonstrated in regard to both PA and physical function.

Physical function and outcome

Reduced physical function was found to correlate with frailty, sarcopenia, and protein-energy wastage which, in turn, are associated with mortality. Despite the potential confounders introduced by investigating these wider concepts, the value of maintaining functional ability and activity levels remained clear. Only one paper(49) assessed depression as a co-variant when exploring the relationship between physical function and mortality. Once the hazard ratio analysis was adjusted, the significance of the model dropped. Due to the frequent concomitance of depression and functional loss, further investigations are required to determine whether this is a trend as yet uncharted, or a coincident pattern.

Doyle et al.(47) assessed physical function using the Barthel score, where ability to engage in activities of daily living is assigned an ordinal score, and demonstrated a higher score on hospital discharge was associated with a lower risk of all-cause mortality. Whilst this score is frequently used by clinicians as an objective measure, it is unclear in this paper whether it was used objectively

or as a self-report tool. Ricardo et al(32) calculated a 'healthy lifestyle score', based on BMI, PA levels, dietary intake, and smoking behaviour. Their results demonstrated a positive relationship between a 'healthy' lifestyle and mortality rates but it is difficult to isolate the effect of PA.

Objective tests were more commonly used to measure physical function. A gait speed reduction of 0.1m/s was associated with a 26% increased mortality risk, whilst a 1-second longer TUAG score correlated with an 8% increased risk of death(40). Thus these objective tests could be useful prognostic tools in chronic kidney disease, and may provide interventional targets yielding direct patient benefit. HGS measurements generated inconsistent results and hence requires further investigation before recommendations can be made about its use as an outcome measure in non-dialysis CKD.

Physical activity and outcome

Interestingly, Pechter et al(26) found a 100% survival in patients who maintained engagement in a 10 year hydrotherapy programme, compared to 55% in the control group (no exercise) who either died or required renal replacement therapy. However it may be argued that only the patient group with a low co-morbidity burden are able to engage continuously in this type of intervention which may confound these results. It must be considered that financing such supervised exercise for the entire CKD population is untenable under modern health systems. Conversely, Chen et al(30) reported no change in mortality risk with higher PA levels, although the authors acknowledge the data's wide confidence intervals. Also, the sample studied was generally more active than a general CKD cohort with 50% walking or exercising regularly.

Measurement of PA should be conducted using objective accelerometry where possible, however only one paper utilised this outcome measure. This diversity of PA measures also means that cut-

offs determining ‘activity’ or ‘inactivity’ vary widely, and as such, different constructs are being compared. This also limits exploration of dose-response effects and potential benefits.

Outcome measure use

A key finding from this review was the large breadth of measures used to assess both physical function and PA. Both objective and subjective measures were used, and whilst each confer their own strength and limitations, the heterogeneity makes it difficult to compare effects and prevents meta-analysis. In many instances, questionnaire-based assessments were used, particularly in the measurement of PA level. This has substantial limitations in regard to recall bias and desirable responses and for some of these questionnaires validity in the renal population remains undemonstrated. Some questionnaires were administered by interviewers(30-32, 37, 45) which may have increased completion rates and corrected one of the common criticisms of questionnaire use. In Yango et al(38), retrospective clinician judgement on patient PA level was used, and such subjectivity means minimal conclusions can be drawn from this trial. Methodological flaws were also demonstrated by Chen et al(42) who asked participants and their care-givers to recall a 3 month history of PA. The ‘Minnesota Leisure Time Physical Activity’ questionnaire, used by three studies(37, 45, 51), has been criticised as it requires a full year’s recall which has been previously demonstrated to be limited by recall bias(55). We propose future researchers should use commonly reported and validated measures to aid synthesis of data between clinical trials. The SF-36 was used by 3 papers(48, 49, 52) and a 1 point increase in the Physical Component Score correlated with between a 1.8%(49) and 4%(52) decrease in mortality risk in renal transplant recipient and hence this subjective outcome measure is recommended for further use.

Despite a consensus among nephrologists that PA is important for patients, assessment of physical function or PA advice is not a part of the routine management of CKD. Efforts to improve both physical function and PA by intervention should be actively encouraged in this group. In regard to

physical function, it appears simple objective tests, such as the TUAG and gait speed, (but perhaps not hand-grip strength), and self-reported measures, in particular the SF-36 (Physical Component Score), are useful prognostic tools in CKD. As such, research or clinical practice should use these physical function tests when assessing intervention effects. Complex and 'laboratory'-based measures, such as those measuring VO_2 or using an accelerometer or isokinetic dynamometer, provide high quality and reliable data, however these assessments are often impractical in a clinical setting and poorly tolerated by patients. More pragmatic measures of physical function and physical activity, such as the TUAG, gait speed, or via self-report, can be quickly and cheaply conducted in a clinic waiting room and hence provide a real-world method of assessing the patient's functional status which correlates with morbidity and mortality. When assessing either physical functioning or activity, a researcher or healthcare professional should be aware of the relative strengths and limitations of each assessment.

Conclusions

This is the first systematic review elucidating the relationship between physical function and PA with clinical outcomes in the under-explored area of *non-dialysis* CKD. Better physical function and greater PA levels both correlate with improved outcomes including both reduced all-cause and cardio-vascular mortality risk, reduced risk of rapid decline in renal function, reduced prevalence of frailty and sarcopenia, and graft survival in transplant recipients. However, causality as yet remains unproved and further research is needed.

Clinical Messages

- Reduced physical function and PA levels are associated with increased mortality risk and increased risk of adverse clinical outcomes in both non-dialysis CKD and in RTR.
- Further work is needed to investigate causality within this relationship.
- Consistent use of outcome assessments is critical to allow meta-analysis.

Conflict of Interest Statement.

The authors declare that there is no conflict of interest.

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Table 1. Summary of findings; association between *physical function* with all-cause mortality or adverse clinical outcomes

Study	Patient characteristics N; CKD stage or RTR; mean age(years); % male; mean eGFR [SD]	Mean follow-up duration (years)	Comparison, control, or comparator	Outcome measure(s)/ intervention	Main findings	Mortality Hazard ratio (HR) [95CI]
Chin et al 2014(46)	984 CKD 1-5; 76.0 years [9.1];44%; 72.3 [17.0]	5	eGFR groups	**Self-report:** Korean version of ADLs, Instrumental ADL	↓renal function associated with 29.5% ↓ADL/IADL scores. ↓ADL/IADL scores associated with ↑MR	eGFR ≥60 HR=1.87[c] [1.10–3.20] eGFR <59 HR= 2.53[c] [1.57–4.09]
Delgado et al 2015(39)	812 CKD; 52 years (median); 60.5%, mGFR=33.1 [11.7]	17 (median)	Sample divided into 3 categories: Not Frail, Immediate Frail, Frail.	**Self-report:** MDRD LTPAQ; MDRD quality of well-being measure	↓eGFR correlates with ↑levels of self-report frailty and ↑MR	Intermediate Frail HR=1.47[1.14-1.90][b,c,d,f] Frail: HR:1.71[1.26-2.30] [b,c,d,f] Intermediate Frail HR=1.43 [1.11-1.83] [b,c,d,e,f] Frail HR=1.48 [1.08-2.00] [b,c,d,e,f]
Griva et al 2013(48)	347 RTR; 46.55 years [13.96]; 54.2%; 38.54 [14.07]	8.57 [6.55]	n/a	**Self-report:** HRQoL and SF-36	↓Physical HRQoL and ↓PF associated with ↑MR and graft failure.	All-cause mortality: HR=4.3 [2.72-6.78][a] *p*<0.001. HR=1.82 [1.04-2.86][b,f] p=0.04 Graft failure: HR=2.99 [2.08-4.3][a] p<0.001 HR=1.57 [1.04-2.38][b,f] p=0.03
Molnar-Varga et al 2011(49)	879 RTR's; 49years [13]; 58%; 50 [22]	7.83 (median)	n/a	**Self-report:** KDQoL-including HRQoL, SF-	PCS and PF independently associated with mortality or graft loss. However, associations were not	SF-36 PCS: HR= 0.66 [0.59-0.75][a] p<0.001 HR=0.8 [0.7-0.91][b,c,e,f] p=0.001

				36 and CES-D scale.	significant after adjustment for depression. 10-point ↑PCS yields 18%↓MR; 10-point ↑ PF associated with 11% ↓MR.	Adjusted for depression score HR= 0.82 [0.71-0.95][b,c,e,f] p=0.008 PF score HR=0.84 [0.80-0.87][a] p<0.001 HR=0.88 [0.83-0.93] [b,c,e,f] p<0.001 Adjusted for depression score HR=0.89 [0.84-0.94] [b,c,e,f] p<0.001
Prihodova et al 2014(52)	151 RTR; 47.09 years [13.2]; 56.3%; 51.16 [15.6]	7.1 [2.2]	N/A	**Self-report**: SF-36	↑survival with ↑eGFR (2% per point), ↑PCS (4% per point)	Survival analysis: PCS HR=1.04 p<0.05[a]
Doyle et al 2015(47)	3012 CKD 1-5; 84 years; 41%	12	Comparison across eGFR groups	**Self-report/objective:** Barthel score	↑discharge Barthel Score (i.e. ↑PF) were associated with ↓ all-cause MR	Barthel Score ≥10, eGFR <30 HR=7.0 eGFR HR=3.0 Barthel Score 19-20, eGFR <30 HR: 1.5 eGFR 45-90 HR=1.25
Chang et al 2011	128 CKD1-5; 60.7 years [14.8]; 46.8%; 46.6 [28.2]	2.825	eGFR groups	**Objective**: HGS	HGS used as measure of protein-energy wasting. HGS is independent predictor of outcome.	Risk of all-cause mortality or dialysis initiation: HR=0.9 p=0.004 (CKD1-5) HR=0.91[0.83-0.99] p=0.031 CKD3b-5
Gulati et al 2012(25)	5716; 52.5years [10.8]; 0%; 53.7 [8.3]	15.9	n/a	**Objective**: Treadmill test using Bruce protocol to measure cardiorespiratory fitness	Cardiorespiratory fitness significantly modified the association between eGFR and mortality (p < 0.001). eGFR< 45 + fitness level < 5 METs: MR=7.6 deaths/1000 person-years	

					eGFR ≥ 60 + fitness level of > 8 METs MR=0.56 deaths/1000 person-years	
Lattanzio et al 2015(24)	487 CKD post-hospital discharge; 80.1 years [6.0]; 45.8%; 50.4 [14.7]	1	none	**Objective**: SPPB	↑MR with older age, hypoalbuminemia, cognitive impairment, impaired ADL's, eGFR <30, anemia and SPPB < 5.	SPPB=5-8 HR = 1.96, [0.63-6.07][b,c] SPPB: 0-4 HR = 5.70, [1.98-12.4][b,c] SPPB= 5-8: HR = 1.45 [0.53-4.27][b,c,d,f] SPPB: 0-4: HR = 2.93 [1.07-8.63] [b,c,d,f]
Nastasi et al 2017(41)	719 RTR; 51.6 years [14.2]; 62.3%;	2 (median)	N/A	**Objective:** SPPB	1 point reduction in chair stand or walking speed score correlates with 1.21 and 1.5 fold increase in mortality risk	SPPB <10 HR=3.57 [1.83-6.98][a] p<0.001 HR=2.3 [1.12-4.74][b,c,d,f] p=0.02
Pereira et al 2015(50)	287 CKD 3-5; 59.9 years [10.5]; 62%; 25.0 [15.8]	Up to 3.33	N/A	**Objective**: Sarcopenia measured using HGS and Bioelectrical Impedance Analysis	Presence of sarcopenia significantly predicts all-cause mortality.	HR=2.89 [1.4-5.96][a] p=0.004 HR=3.58 [1.43-8.31][b,c,d] p=0.003
Roshanravan et al 2013(40)	385 CKD2-4; 61 years [13]; 84%; 41 [19]	3 (median)	N/A	**Objective**: TUAG; HGS; 6MWD;Gait speed	PF measures reliant on lower limb strength ↓ 30-39% compared to normative values but grip strength relatively preserved. MR=47 deaths per 1000person-years.	Gait speed ≤ 0.8m/s HR=2.45 [1.09–5.54][b,c,d,e,f] (per 0.1m/s slower HR=1.26) TUAG ≥12s HR=1.81 [0.92–3.56] [b,c,d,e,f] (HR=1.08 increases per 1s slower)

					0.1m/s ↓gait speed associated with 26% ↑risk of death; 1s longer TUAG associated with ~8% ↑MR	6-min walk distance <350m HR=2.82 [1.17–6.92] [b,c,d,e,f] (HR=1.15 per 50m reduction)

CKD = chronic kidney disease; RTR = renal transplant recipients; ADL = activities of daily living; eGFR = estimated glomerular filtration rate [ml/min/1.73m²]; HR = hazard ratio; PA = physical activity; PF = physical function; MDRD LTPAQ = Modification of Diet in Renal Disease Leisure Time Physical Activity Questionnaire; HRQoL= health related quality of life; SF-36 = 36-item Short Form survey; KDQoL= Kidney Disease Quality of Life; CES-D = Centre for Epidemiologic Centres Scale for Depression; PCS = physical composite score; SPPB = Short Physical Performance Battery; MR = mortality rate; MET = metabolic equivalent task; TUAG = Timed- Up-and-Go; HGS = hand grip strength; 6MWD = 6 minute walk distance

[a] = unadjusted model; [b] = adjusted for age; [c] = adjusted for gender; [d]= adjusted for BMI; [e] = adjusted for eGFR; [f] = adjusted for additional co-variants (see reference for full analysis)

Table 2. Summary of findings; association between *physical activity level* with all-cause mortality or adverse clinical outcomes

Study	Patient characteristics N; CKD stage or RTR; mean age(years); % male; mean eGFR [SD]	Mean follow-up duration (years)	Comparison, control, or comparator	Outcome measure(s)/ intervention	Main findings	Mortality Hazard ratio (HR) [95CI]
Beddhu et al 2009(28)	15368 in full study; Non-CKD: Inactive: 48years;37%;95.6 Insufficiently Active; 42years;47%;94.9 Recommended Activity: 43years;54%;92.9 CKD n=907; (eGFR<60); Inactive: 73years;27%male;46.9 Insufficiently Active: 66years; 40%male;50.8 Recommended Activity: 68years;43%male;49.8	7 for CKD group (8.8 years for non-CKD group)	Non-CKD population. Divided into: Inactive: Insufficiently Active; Recommended Activity	**Self-report:** interviewer administered HAQ	CKD was associated with a ↑prevalence of low PA (odds ratio 1.30[1.03-1.64]).	CKD: Insufficiently Active HR=0.58 [0.42-0.79][b,c,d,e,f] Recommended Activity HR=0.44 [0.33-0.58] [b,c,d,e,f] Non-CKD group: Insufficiently Active HR=0.6 [0.45-0.81] [b,c,d,e,f] Recommended Activity HR=0.59 [0.45-0.77] [b,c,d,e,f]
Chen et al 2008(30)	811 CKD 3-4;52 years, 61% ;32.5	Not explicitly stated.	Nil	**Self-report**: interviewer administered MDRD-LTPAQ	No change in MR with PA category	Indoor activity HR=0.94 [0.77-1.14][b,c,e,f] exercise HR=1.01 [0.84-1.10] [b,c,e,f] Outdoor activity HR=0.94 [0.80-1.10] [b,c,e,f]
Chen et al 2014(42)	6363 CKD 3-5; 70.1years;57%;	10		**Self-report**: exercise activity with 3month recall; confirmed by	↓MR in groups that walked regularly. ↑frequency of walking correlated with ↓MR.	Walking HR=0.65;[0.51-0.81]; *P*<0.001 RRT risk (HR=0.75; [0.69-0.80] *P*<0.001

				family/care-giver		↑duration of exercise HR=0.77 [0.70-0.85] *P*<0.001) RRT risk HR=0.89; [0.86-0.92]; *p*<0.001for each 30min increase. ↑frequency of exercise HR=0.83[0.78-0.90] p<0.001 RRT risk HR=0.92; [0.90-0.94]; *p*<0.001 for each category increase.
Navaneetha n et al 2014(31)	11,586 9,433 non-CKD; 43.9years [0.3]; 50.6%; 96.8 (0.4) 2,153 CKD; 60.7years [0.7]; 43.1% [1.0]; 72.9 [0.9]	4.5	Non-CKD	**Self-report**: Interviewer administered PA questionnaire		PA below recommended levels mortality HR=1.36 [1.00-1.85][b,c,d,e,f] For each log unit ↑METS/week HR=0.97[0.95-1.00] [b,c,d,e,f] PA <450 METS/week CKD HR= 1.34 [0.98-1.84] [b,c,d,e,f] Non-CKD HR=1.65 [1.19-2.28] [b,c,d,e,f] PA <450 METS/week CKD HR= 1.36 [1-1.85] [b,c,d,e,f] Non-CKD =1.65 [1.21-2.26] [b,c,d,e,f]
Ricardo et al 2013(32)	2288 CKD 1-4; 59 years; 40%; 78	13		**Self-report** - interviewer	Individuals in the highest eGFR strata	Insufficient PA HR=0.76 [0.6-0.96][b,c]

				administered HAQ	were less likely to adhere to the recommended level of PA than those in the lowest eGFR strata (42% v 34%)	HR = 0.86 [0.67–1.10][b,c,e,f] p = 0.22 Recommended PA HR=0.73 [0.57-0.92][b,c] HR = 0.80 [0.65–0.99] [b,c,e,f] p = 0.04
Ricardo et al 2015(33)	3006 CKD eGFR20-70;58years [11]; 52%; 43[14]	4 (median)	N/A	**Self-report**: MESA.		Less than ideal PA HR=0.74 [0.57-0.96][b,c,f] Ideal PA HR 0.60 [0.49-0.74] [b,c,f]
Robinson-Cohen et al 2014(35)	256 CKD3-4; 82%; 0 min/wk - 61.8[11.3] years; 37.8[20.1] 1-60 min/wk- 58.8[12.8] years: 41.0[18.6] 60-150 min/wk- 61.7[12] years; 37.4[18.2] >150 min/wk- 61.7[12.5] years; 40.5[14.0]	3.7 (median)	Subdivided into groups based on min/week PA;	**Self-report**: Four-Week Physical Activity History Questionnaire	↓annual decline in eGFR (2.8%) in highest PA categories Each ↑60-min PA associated with ~0.5%/yr slower decline.	HR for incident ESRD Any PA HR=0.59[b,c] [0.28-1.24] p=0.19 Per 60min/week increment HR=0.9[b,c] [0.74-1.10] p=0.32
Rosas et al 2012(36)	507 RTR;47.8 years[12.8]; 61%	8.4		**Self-report**: Physical Activity scales for the Elderly	Inactive: MR 36.3% Moderate: MR 23.3% Active: MR: 16.3%	METS (per 10 unit change) HR=0.91[a] [0.87-0.96] p<0.001 HR=0.93[b,c] [0.88-0.97] p=0.002 Moderate tertile HR=0.81[a] [0.55-1.2]; p=0.3 HR=0.91[b,c,f] [0.61-1.36]; p=0.7 Active tertile

						HR=0.45[a] [0.29-0.72]; p=0.001 HR=0.53[b,c,f] [0.33-0.84]; p=0.01
Shlipak et al 2005(37)	6495 CKD group (eGFR<60) 1249;75[6]years;47%;50[1.73] Non CKD group 4559;772[5]years;41%;87[20]	8.6	Non-CKD	**Self-report**: MLTPAQ	CV MR = 32 deaths per 1000person-years in CKD; 16 deaths per 1000person-years in non-CKD.	CKD: Low PA HR=1.58[b,c,f] [1.25-2.01]; p<.001; non-CKD: low PA HR=1.31[b,c,f] [1.10-1.57] p.003;
Tikkanen-Dolenc et al 2017	310 CKD, including RTR (n=64) and dialysis-dependent patient (n=36) (2639 in full study)	11.4		**Self-report:** Finnish version of MLTPAQ		**HR for CKD & RTR (excluding dialysis-dependent)** **LTPA** (moderate/high LTPA used as reference) Low HR=1.99 [0.95-4.15] [a] Low HR=2.12 [0.99-4.57] [c,f] **Exercise Intensity** (moderate/high intensity used as reference) Low HR=3.11 [1.31-7.38] [a] Low HR=2.4 [0.99-5.81][c,f] **Exercise Frequency** (moderate/high freq used as reference) Low HR=2.85 [1.4-5.8] [a] Low HR=2.6 [1.15-5.84] [c,f] **Exercise duration** (high duration used as reference)

						Low HR=4.03 [1.8-9.01] [a] Low HR=2.87 [1.21-6.84] [c,f]
Wang et al 2013(27)	445,075; 41.1years[13.8];50% 42,757 CKD, no DM; 49.4years[16.5];52.3%;69.4 7863 CKD + DM; 59.3years[11.8];54.9%;66.2	Up to 12	Healthy population; CKD; CKD + DM	**Self-report**: questionnaire (not specified)	MR per 100,000 person-years: Healthy population: inactive: 362 [352-372] Low-active: 314 [300–328] Fully active: 281.4 [269–295] CKD+DM Inactive: 1,317.2 [1,191–1,456] Low-active: 912.2 [744-1118] Fully active:871 [745–1018]	DM/CKD: low-active HR= 0.78[b,c] [0.65 – 0.92] fully active HR=0.63[b,c] [0.55 – 0.73]
Yango et al 2006(38)	402 RTR however data only presented for n=64 >60years 64years[4];65%	3	Retrospective Cohort study	**Self-report**: PA level assessed based on history obtained by the examining physician.	1 year survival rate: Overall 78% Active 94% Inactive 24% 3 year survival rate: Overall 71% Active 24% Inactive 24%	None calculated
Zelle et al 2011(45)	540 RTR patients: 51years [12]; 54%	5.3 [4.7-5.7]	N/A	**Self-report:** Interviewer-led Tecumseh Occupational Activity Questionnaire; MLTPAQ		HR=0.58 [0.4- 0.70][a] p<0.001 HR=0.67 [0.54-0.83][b,c] p<0.001

Robinson-Cohen et al 2009(34)	4011 PA score 2-3: 896;72.8years [5.4]; 30.7%; 75.1[18.3] PA score 4-6: 2137; 72.0 years [5.1]; 40.3%;78.9[17.2] PA score 7-8: 896;71.2 years [4.4];56.7%; 81.1[16.2]	7 (median)	Divided into categories based on PA score	**Objective and self-report:** Gait speed used in combination with PA questionnaires to give cumulative PA score.	Lower risk of RDKF was found with increased PA score[b,c,d,f] Same relationship could be seen when the results were stratified into groups using eGFR	HR of developing RDKF[b,c,d,f] eGFR<60 PA score 4-6 HR=0.75 [1.45-1.27] PA score 7-8 HR=0.78 [1.4-1.51] p=0.44 eGFR 60-89 PA score 4-6 HR=0.88 [0.71-1.09] PA score 7-8 HR=0.63 [0.47-0.85] p=0.02 eGFR90-119 PA score 4-6 HR=0.72 [0.56-0.92] PA score 7-8 HR=0.69 [0.51-0.94] P=0.04
Beddhu et al 2015(29)	3626 in full study; 383 CKD	2.86 [0.64]	Non-CKD population	**Objective**: Accelerometry	↑sedentary duration was associated with ↑mortality	Non CKD: HR 1.18 [1.09-1.28][b,c,f] CKD subgroup: HR 1.16 [1.04-1.13] [b,c,f]
Pechter et al 2014(26)	26 CKD; Intervention: 7; 52years; 42%;50.9[9.2] Control group; 9; 48 years; 50%; 51.6[7.1]	10	Sedentary control group who did not consent to exercise	**Intervention**: regular aquatic exercise for 10 years (>32 weeks a year, 30 mins, 2x a week)	Active group: 0% MR; 0% commenced dialysis Control group: 55% MR; 22% commenced dialysis	Not reported.

Tsai et al 2017(44)	161 CKD1-5; 67.2 years [7.8]; 54%; 34.5[28.8]	2.425	CKD1-3 v CKD4-5 comparison	**Objective:** HGS 30s chair stand 2min step **Subjective:** Taiwan version of the WHO QoL-BREF Interviewer administered HAQ	**COMBINED PA & PF** No relationship between PA and outcomes	Risk of initiation of dialysis: High HGS HR=0.89[0.84-0.96] High 2min step HR=0.304[0.01-0.95]

eGFR = estimated glomerular filtration rate; RTR = renal transplant recipient; HR = hazard ratio; PA = physical activity; PF = physical function; HAQ = Household Adult Questionnaire; MDRD LTPAQ = Modification of Diet in Renal Disease Leisure Time Physical Activity Questionnaire; MESA= Multi-Ethnic Study of Atherosclerosis Typical Week Physical Activity Survey; MLTPAQ = Minnesota Leisure Time Physical Activity Questionnaire; MR = mortality rate; RRT risk = risk of requiring renal replacement therapy; CV = cardiovascular; RDKF = rapid decline in kidney function;

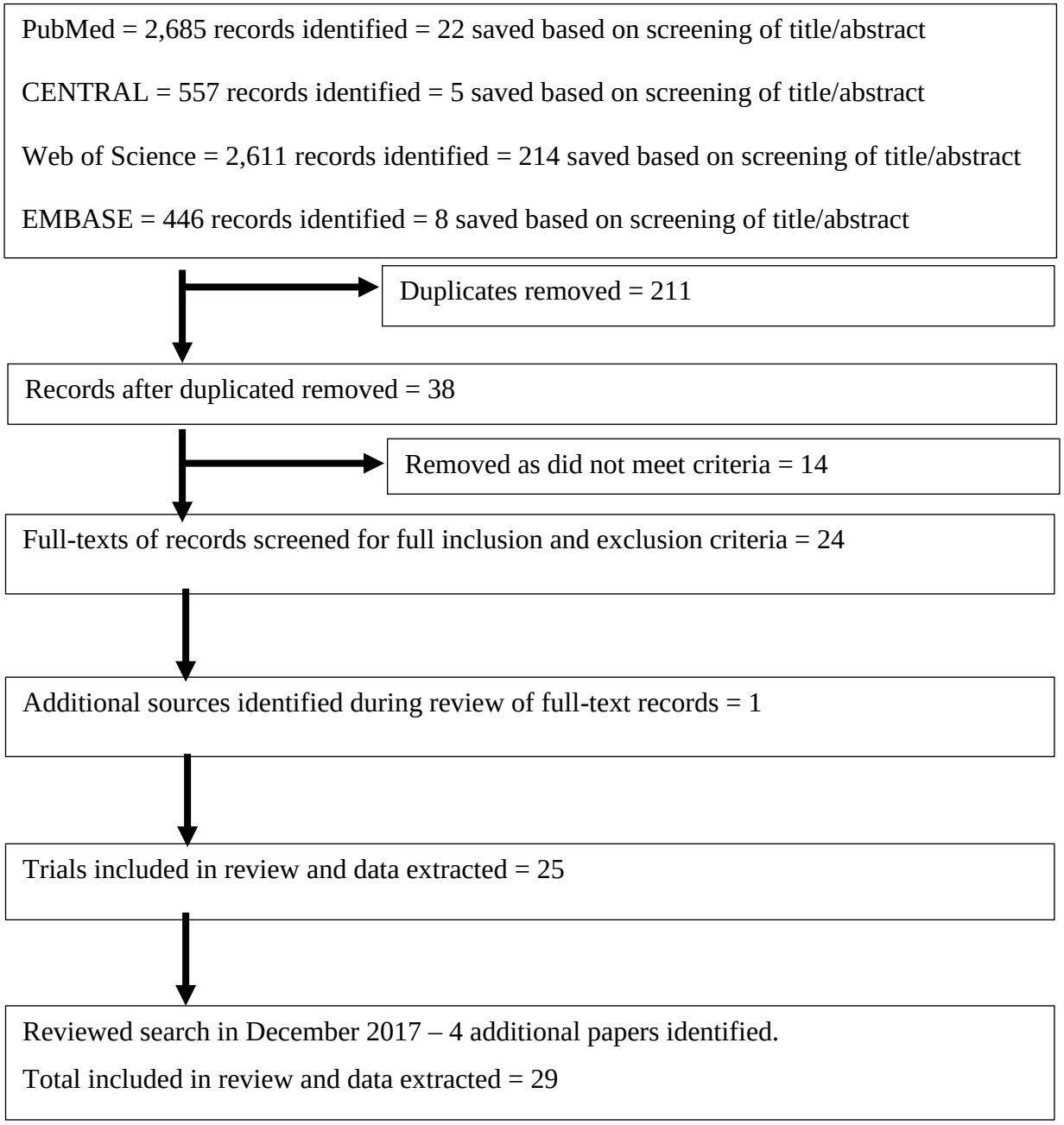
[a] = unadjusted model; [b] = adjusted for age; [c] = adjusted for gender; [d] = adjusted for BMI; [e] = adjusted for eGFR; [f] = adjusted for plus additional co-variants (see reference for full analysis)

Table 3. Papers reviewed, Newcastle-Ottawa Scale score, and bias criteria

	Study	Selection /4	Comparability /2	Outcome /3	AHRQ criteria
1	Beddhu et al 2009(28)	★★★	★★	★★	Good
2	Beddhu et al 2015(29)	★★★	★★	★★★	Good
3	Chang et al 2011(43)	★★★	★★	★★★	Good
4	Chen et al 2008(30)	★★	★★	★★	Fair
5	Chen et al 2014(42)	★★	★★	★★★	Fair
6	Chin et al 2014(46)	★★	★★	★	Poor
7	Delgado et al 2015(39)	★★	★★	★★★	Fair
8	Doyle et al 2015(47)	★★★	★★	★★	Good
9	Griva et al 2013(48)	★★★	★★	★★★	Good
10	Gulati et al 2012(25)	★★★	★★	★★★	Good
11	Lattanzio et al 2015(24)	★★★	★★	★★★	Good
12	Molnar-Varga et al 2011(49)	★★	★★	★★	Fair
13	Nastasi et al 2017	★★★	★★	★★	Good
14	Navaneethan et al 2014(31)	★★★★	★★	★★★	Good
15	Pechter et al 2014(26)	★★★	-	★	Poor
16	Pereira et al 2015(50)	★★★	★★	★★★	Good
17	Prihodova et al 2014(52)	★★★	★★	★★	Good
18	Ricardo et al 2013(32)	★★	★★	★★	Fair
19	Ricardo et al 2015(33)	★★	★★	★★★	Fair
20	Robinson-Cohen et al 2009(34)	★★★	★★	★★★	Good
21	Robinson-Cohen et al 2014(35)	★★★	★★	★★ ★	Good
22	Rosas et al 2012(36)	★★★	★★	★★★	Good

23	Roshanravan et al 2013(40)	★★★★	★★	★★	Good
24	Shlipak et al 2005(37)	★★★	★★	★★	Good
25	Tikkanen-Dolenc et al 2017	★★★	★★	★★	Good
26	Tsai et al 2017(44)	★★★	★★	★★★	Good
27	Wang et al 2013(56)	★★★	★★	★★★	Fair
28	Yango et al 2006(38)	★★★	★★	★★★	Good
29	Zelle et al 2011(45)	★★★	★★	★★	Good

Figure 1. PRISMA flow diagram



PubMed = National Centre for Biotechnology Information (NCBI) PubMed (which includes the Medical Literature Analysis and Retrieval System Online (MEDLINE)); CENTRAL = Cochrane Central Register of Controlled Trials; WoS = Web of Science (which includes the

KCI-Korean Journal Database, MEDLINE, Russian Science Citation Index, and SciELO Citation Index); EMBASE = Excerpta Medica database

Supplementary material 1.

Example search strategy from NCBI PubMed

User query using pre-defined search terms

“kidney diseases” AND “physical activity” AND “mortality” AND (Clinical Trial[ptyp] AND Humans[Mesh])

Query Translation

("kidney diseases"[MeSH Terms] OR ("kidney"[All Fields] AND "diseases"[All Fields]) OR "kidney diseases"[All Fields]) AND ("exercise"[MeSH Terms] OR "exercise"[All Fields] OR ("physical"[All Fields] AND "activity"[All Fields]) OR "physical activity"[All Fields]) AND ("mortality"[Subheading] OR "mortality"[All Fields] OR "mortality"[MeSH Terms]) AND (Clinical Trial[ptyp] AND "humans"[MeSH Terms])

Individual translations

kidney diseases	"kidney diseases"[MeSH Terms] OR ("kidney"[All Fields] AND "diseases"[All Fields]) OR "kidney diseases"[All Fields]
physical activity	"exercise"[MeSH Terms] OR "exercise"[All Fields] OR ("physical"[All Fields] AND "activity"[All Fields]) OR "physical activity"[All Fields]
mortality	"mortality"[Subheading] OR "mortality"[All Fields] OR "mortality"[MeSH Terms]
Humans[Mesh]	"humans"[MeSH Terms]

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4,5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6,7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	See Supp. material 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 1 and 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15-19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	19,20

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097