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# Does physical exercise affect cognition in patients living with Chronic Kidney Disease?

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# Does physical exercise affect cognition in patients living with Chronic Kidney Disease?

Submission for postgraduate degree of Master of Science by Research

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## Declaration

‘I hereby declare that this thesis is the results of my own investigations, except where otherwise stated. All other sources are acknowledged by bibliographic references. This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree unless, as agreed by the University, for approved dual awards.

I confirm that I am submitting this work with the agreement of my Supervisor(s).’

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‘Yr wyf drwy hyn yn datgan mai canlyniad fy ymchwil fy hun yw’r thesis hwn, ac eithrio lle nodir yn wahanol. Caiff ffynonellau eraill eu cydnabod gan droednodiadau yn rhoi cyfeiriadau eglur. Nid yw sylwedd y gwaith hwn wedi cael ei dderbyn o’r blaen ar gyfer unrhyw radd, ac nid yw’n cael ei gyflwyno ar yr un pryd mewn ymgeisiaeth am unrhyw radd oni bai ei fod, fel y cytunwyd gan y Brifysgol, am gymwysterau deuol cymeradwy.

Rwy'n cadarnhau fy mod yn cyflwyno'r gwaith hwn gyda chytundeb fy Ngoruchwyliwr (Goruchwylwyr)

## Contents

## Thesis Abstract

This thesis is submitted for the postgraduate degree of a Master of Science by Research. It was undertaken as part of an Academic Foundation Year 2 junior doctor post in Ysbyty Gwynedd, Wales. As well as answering a novel research question, the Academic Foundation programme was designed to allow me to develop both my academic research skills and to develop my clinical skills as a junior doctor. Thus, I completed three sequential clinical rotations of three days per week for four months each, and in parallel one academic rotation of two days per week for a period of one year.

This thesis answers the question, “Does physical exercise affect cognition in patients living with Chronic Kidney Disease?” It comprises of a brief general introduction to provide background and context, a single chapter describing the research carried out, and a brief general conclusion.

Cognitive impairment is a significant burden on health and social systems globally. Those with Chronic Kidney Disease are more likely to have cognitive impairment than those without. Regular physical activity has shown a correlation with maintaining cognitive function, both in the general population and in people living with Chronic Kidney Disease. Many trials have investigated a link between exercise and improving cognition, but with varying results. This thesis summarises this existing research, using a systematic review and meta-analysis of randomised controlled trials.

The thesis findings suggest there is no clear evidence of beneficial effects of exercise on cognition in Chronic Kidney Disease, though there may be benefit in pre-dialysis patients and in those with kidney transplants, who can complete aerobic exercise at higher intensities than those patients receiving dialysis. These findings are based on subgroup analyses which include subgroups of n = 1 studies.

Future research would benefit from further investigating those patients who do not require dialysis, those who have undergone kidney transplantation, and using exercise interventions at higher intensities. It would also be useful for studies to have a longer follow-up period post-intervention, to investigate whether there is lasting benefit from said interventions.

# General Introduction

## Background

Cognitive impairment (CI) and dementia are growing significant health problems globally. With an aging global population, more people are living to see a decline in their cognitive function. There is to be an expected loss of cognitive function as we age; the clinical states of CI describe a spectrum of dysfunction beyond this expected decline.[1] Mild cognitive impairment (MCI) is loss of cognition, or subdomains of cognition, which does not affect a person's ability to carry out activities of daily living (ADLs), whereas dementia is loss to the point that people are unable to independently carry out ADLs.[1] For example, someone with MCI may take a while to remember where they left their clean socks, whereas someone with dementia may be unable to dress themselves due to an inability to comprehend the process.

The effects of CI are wide-ranging, impacting individuals, their families, carers, and social and healthcare systems. In 2015, dementia cost approximately $818 billion US dollars globally, and it is estimated to rise to $2 trillion by 2030.[2] Worldwide, the burden of dementia has more than doubled from 2000 to 2019 in terms of disability-adjusted life years (DALYs)[3] and it is estimated that unpaid carers spend 5 hours a day providing care for someone with dementia. Alzheimer's disease and other dementias were the 7$^{th}$ leading cause of death in 2019.[3]

It is important to note that age alone does not cause CI. There are multiple modifiable and non-modifiable risk factors which increase the likelihood of an individual's progression to CI. Non-modifiable risk factors include advancing age, family history, genetics, race, and sex. Modifiable risk factors include inactivity, cardiovascular disease, diabetes, hypertension, and smoking. These risk factors particularly influence vessel health and subsequently affect the delivery of oxygenated blood to the brain. In addition, Chronic Kidney Disease (CKD) has been found to be an independent risk factor for CI.[4]

The term CKD covers a spectrum of chronic decline in renal function, defined as abnormalities in the structure or function of kidneys, present for >3 months, with implications for health.[5] It is classified into five stages (see table 1). CKD 1 – 4 is generally managed medically. Stage 5, also known as end stage renal failure (ESRF), is when patients are considered for renal replacement therapy (RRT). RRT consists of kidney transplant, haemodialysis (HD), and peritoneal dialysis (PD). Not all patients who have ESRF will be on

RRT, but all patients on dialysis are considered to have stage 5 disease, regardless of Glomerular Filtration Rate (GFR).

With the exception of smoking, the presence of all risk factors for CI is greater in the CKD population than the general population.[6,7] Diabetes and hypertension are particularly high, with around 20% of people with diagnosed diabetes having CKD; diabetes is the leading cause of end stage renal failure.[8] Between 60 and 90% of people with CKD are hypertensive, depending on the stage of their disease.[9] These comorbidities contribute to cardiovascular disease, including damage to the cerebral vasculature. In addition to this, there are several proposed mechanisms for the CKD-specific causes of CI. These include a high blood concentration of uraemic toxins, chronic inflammation, anaemia, and the dialysis process.[4,10,11] Furthermore, those with CKD are likely to have depression, be less physically fit and functioning than healthy peers, and have polypharmacy, all of which may contribute to cognitive decline.[10,12] These risk factors are summarised in figure 1.

**Exercise for risk factors of cognitive decline**

Regular physical activity has been linked with preserved cognitive function, in healthy populations[13] and in CKD[14]. Therefore, research has been carried out to investigate whether exercise interventions will improve, or slow decline of, cognitive function in these populations. One of the challenges with the CKD population is that they are more sedentary than healthy counterparts, and so it is difficult to reach clinically meaningful targets for exercise.[5] However, existing evidence has shown some changes in outcomes relating to risk factors for CI in this patient group, as summarised below:

Chronic inflammation is a hallmark of CKD, and known to contribute to atherosclerosis and arterial stiffness, which in turn are associated with worsening cognition.[15] Initial exercise studies suggest that exercise has an anti-inflammatory effect,[16] and may reduce arterial stiffness.[17]

Regular exercise training significantly reduced blood pressure at rest in patients with CKD stage 2 – 5 disease who were not on RRT,[18] but it is unclear if it makes a difference in dialysis patients.[19]

Insulin resistance is associated with cognitive decline. It is currently unclear whether exercise plays a role in decreasing insulin resistance in CKD. A single-group study in 11 participants undergoing HD found no improvement in insulin resistance after 3 months of

aerobic exercise,[20] but a randomised controlled trial (RCT)[21] and a single-group study[22] of dialysis patients, undergoing aerobic and resistance exercise respectively, both found improvements in insulin resistance after the intervention periods.

Exercise also improves depressive symptoms in dialysis patients,[19] and when patients are exercising for longer durations.[12]

**Challenges of cognition research**

Research into cognition can be difficult, as there are many varied assessments which measure different aspects of cognition. Some tests are used as screening tools for CI (for example, the Montreal Cognitive Assessment (MoCA)),[23] and some are designed to measure changes in cognition (for example, the Alzheimer's Disease Assessment Scale – Cognitive section (ADAS-Cog)).[24] Cognition can be measured using objective tools with right and wrong answers (such as the Mini-Mental State Examination (MMSE)),[25] and subjective tools which ask patients to reflect on their own experiences (for example the Kidney Disease Quality of Life questionnaire (KDQOL)).[26] Some objective tests are delivered by an assessor who asks questions and records answers (for example, the MMSE),[25] whilst others are computer-based to attempt to remove human bias (for example, at www.cogstate.com). Different tools may also measure global cognition or measure specific domains such as memory, attention, and executive function. Across the literature there is inconsistency in which tests are used and for what purpose.

The recent systematic review and meta-analysis of Vanderlinden *et al.* found that the MMSE is the most commonly used assessment of global cognition in CKD research.[27] Whilst a recommended single measure of global cognition, it is well known to be insensitive to changes in cognition.[28] Currently the gold standard for assessing anti-dementia treatments is the ADAS-Cog, but again there is evidence that it is not optimised to detect change in MCI populations.[29] Within exercise studies, Shu *et al.* found that type of outcome measurement did not moderate the effect of exercise on global cognition in patients with cerebrovascular disease.[30]

**Exercise for cognition in CKD**

So far there have been several reviews into the effect of exercise on cognition in CKD. The systematic review of Kaltsatou *et al.* examined the mechanisms for the proposed benefits of exercise on cognition, but at the time there were only two trials which had examined this

relationship.[31] The first was a non-randomised trial in which volunteers undertook a combined exercise intervention and had cognition measured at the end of the intervention period.[32] Researchers found a significant positive correlation between participants' activity levels and cognition. The second trial completed a single-group aerobic exercise programme, with repeated measures of cognition.[33] No improvement in cognition was observed across the course of the study.

Other authors have subsequently carried out further systematic reviews. A 2019 review quoted three RCTs which demonstrated either an improvement or a lack of decline in cognitive function following intradialytic exercise, when compared to non-exercising controls.[34] Those three RCTs will be discussed later in Chapter 1. Subsequently Murtaza *et al.*[35] also carried out a qualitative review of the evidence, coming to the same subjective conclusion as the previous reviews (of an improvement or a lack of decline in cognitive function following an exercise intervention). They also flagged the need for researchers to conduct trials in the pre-dialysis population, as much of the work so far was in patients on dialysis. The conclusions of the above qualitative reviews are supported by a recent meta-analysis of the effect of exercise on cognition in HD patients.[36] The authors included eight reports of RCTs which examined cognition using any measure and found that exercise significantly improved cognition in this patient group. In particular, they found that exercise of at least 30 minutes duration, thrice weekly, over at least 16 weeks improved cognitive outcomes.

In contrast, the Cochrane review of Bernier-Jean *et al.* investigated the effect of exercise on multiple outcomes in patients on either form of dialysis.[19] As part of their review, they examined the effect on QoL and its subdomains, as measured by the KDQOL. Their meta-analysis of the effect of exercise training of any type (aerobic, muscle strengthening, combined aerobic and resistance, or yoga) *versus* control on the cognition subdomain included five trials and found no effect. However, a secondary analysis which compared each type of exercise separately showed aerobic exercise alone improved cognitive function compared to controls; neither resistance nor combined exercise interventions had any effect.

The systematic search for this review also found additional non-RCT trials which contribute further evidence. A 1998 non-randomised controlled trial examined the effects of a 12-week aerobic exercise intervention in 13 continuous ambulatory peritoneal dialysis (CAPD) patients, with 7 other CAPD patients who underwent usual care as controls.[37] Using the Kidney Disease Quality of Life – Short Form (KDQOL-SF), they did not find any improvement in cognition across time in either group. More recently, Yamamoto *et al*.

compared a prospective active cohort of transplant patients with a historic inactive cohort of transplant patients.[38] Active patients underwent a 2-month supervised and home-based aerobic exercise intervention following renal transplantation. Cognition was measured two months post-transplant surgery in all participants using the KDQOL-SF. They reported no significant difference in cognition scores between groups at the end of the study period.

Taken together, these previous empirical studies and reviews suggest that exercise may play a role in the cognition of patients with CKD, though it is unclear which patients, undergoing which type of exercise, will benefit the most. This meta-analysis collates the existing evidence to summarise the effect of exercise across the spectrum of CKD, expanding upon the work of Liu *et al.*[36] by including all patients with CKD and analysing more studies. It further investigates some aspects of the exercise prescription, the methods of measuring cognition, and which patient groups may benefit most.

**Exercise for cognition in other populations**

The effect of exercise on cognition in CKD has been discussed above, but it is relevant to look at the research in other populations. Like in CKD, the existing evidence is conflicting. A Cochrane review into global cognition in dementia[39] and a meta-analysis in cerebrovascular disease[30] found no improvement following any type of exercise intervention. Other similar reviews have investigated specific domains of cognition rather than global cognition. Cooke *et al.*[40] and Wang *et al.*[41] concluded that in patients with type 2 diabetes, a patient group with significant overlap with CKD, exercise did not improve executive function or memory. Another Cochrane review in participants with normal cognition also found no effect of aerobic exercise on multiple specific domains of cognition[42] (although in this population one may not expect to see any clinical improvements due to high levels of baseline functioning).

However, other meta-analyses in the same populations as above have found contrasting results. For example, Northey *et al.* investigated the effect of exercise on any test of cognition in participants with any level of cognition and found that exercise improves cognition in adults over 50 years old, regardless of baseline cognitive function.[43] Wang *et al.,* using a different analysis to that reported above, found a significant difference in change in cognition scores between exercising participants with type 2 diabetes and controls.[41] Likewise, the umbrella review of Demurtas *et al.* in dementia and MCI,[44] that reviewed meta-analyses including Zheng *et al.*[45] and Groot *et al.,*[46] in MCI and dementia respectively, all found that exercise had some beneficial impact on cognition.

One possible reason for these disparate results is the different types of exercise intervention utilised in previous studies. In terms of type of exercise, Hoffman *et al.* found that aerobic exercise improved memory and executive function in sedentary adults with normal cognition[47] and Colcombe & Kramer found an improvement in global function in adults >55.[48] In patients with MCI, Demurtas *et al.* found aerobic exercise had a small beneficial effect on delayed memory.[44] They also showed that mixed interventions were beneficial to global cognition in both dementia and MCI. Landrigan *et al.* found that generally, resistance exercise improves cognition in adults.[49] Young *et al.* found no effect of aerobic exercise across multiple domains of cognition in apparently healthy adults of any baseline activity level, with no CI.[42] Furthermore, they also investigated whether the duration of the intervention moderated the effect. The average length of trial in their work was 15.6 weeks, which they felt to be too short and recommended that longer-term intervention trials be undertaken. Whilst Smith *et al.* found that aerobic exercise improved multiple domains of cognition in non-demented adults, neither duration of intervention nor exercise intensity moderated the result.[50] The qualitative review of Chen *et al.* attempted to classify exercise interventions according to the FITT-VP principle (frequency, intensity, time, type, volume and progression of the prescription).[51] They found that moderate – vigorous intensity exercise is likely to improve brain function and that vigorous intensity exercise led to increased brain volume, both of which are likely to influence cognition. They also found that the frequency of an intervention does not moderate either outcome, but that the length of an intervention and duration of each session may. However, there was insufficient evidence for them to recommend an overall optimal exercise prescription.

## Context to this thesis

I began this Master's degree as part of my work as an Academic Foundation Year 2 (FY2) junior doctor in the NHS. My contract included two days a week in which I could attend university and conduct research, alongside my usual role as a clinical doctor. The aim of this academic FY2 year was to enhance my medical training by completing a research project, developing my skills as a researcher and as a clinician practicing evidence-based medicine. The research and write-up periods were planned to take two years in total. This meant that at the end of my FY2 year I went back into full-time clinical work, with the research running alongside.

The original plan for this thesis was to carry out a feasibility study and pilot RCT asking "does physical exercise affect cognition and/or cerebrovascular reactivity in patients with

CKD 3 – 4 and MCI?" This was based in Prifysgol Bangor University with participants recruited from the CKD clinic of Ysbyty Gwynedd Hospital, Wales.

The pilot trial required 10 patients with CKD stage 3 – 4 and MCI. Potential participants were to be screened for MCI using a single-question screening tool in clinic, and then formally reviewed by a neurologist. Once patients were confirmed to have MCI, and were consented, they were randomly allocated to an exercise or control group. All patients would undertake baseline testing of a cognitive battery, exercise testing, and functional MRI. The exercise group were to undergo a 10-week exercise programme, with 3 sessions a week, led by researchers in the University gymnasium. Each session was to last 45 minutes plus a warm-up, include a combination of cardiovascular and resistance exercises, with target intensity based on the Borg scale, and increase as time went on as per individual achievement. The control group were to only receive usual care. At end of trial period, all participants would repeat the same set of tests.

Throughout the whole research period, information was to be gathered from researchers and participants regarding feasibility outcomes of process, resources, management, and scientific outcomes.

The primary outcome of the pilot trial was the feasibility of running a full-scale version of the trial. Secondary outcomes were changes to baseline tests (fitness, cerebrovascular reactivity, and cognition) – this thesis was to focus on cognitive outcomes.

My role, with another FY2 colleague, was to finalise the trial protocol, be involved in all stages of data collection and intervention, and to co-ordinate the running of it. When taking on the project, the trial protocol had been outlined and planned by another student, and outline ethical approval had been obtained. We helped to finalise the MRI protocol, including the delivery of gases to participants in the scanner, updated the ethical approval, learnt how to run exercise intervention sessions, introduced oxygen and glucose to the emergency trolley in the gym, and acted as the main point of contact between the university and the hospital. We guided the renal physicians on which patients would be suitable for recruitment and contacted these patients to ascertain interest in participation. We also collected data on each of these steps – what went well, what didn’t, and suggestions of how to improve. We successfully recruited one participant who completed all baseline testing, but sadly dropped out before randomisation.

A main finding in terms of the feasibility of the trial was issues with the recruitment process. As stated, participants were recruited from hospital-based renal clinics. However, most patients with CKD stage 3 – 4 are not frequently seen in clinic. Instead, they are managed by their general practitioner in the community. Those who do attend renal clinics regularly tend to be frailer, with more comorbidities, or with more advanced disease. This meant that we were not able to recruit patients with less severe cognitive decline, who would be more enthusiastic about participation and better able to complete a research trial. Indeed, the recruit who dropped out did so because they found the exercise testing too intense. In addition, they experienced a fall not long after testing which reduced their confidence. However, they did report that the enjoyed the cognitive testing, and that the MRI was not as distressing as they expected.

Another limiting factor was the availability of the doctors to run the trial – a medical rota does not provide much free time during the day or evenings, when it would be better to run the exercise intervention, particularly one which was face to face three times a week. This was planned to be mitigated by hiring Sports Science students to run the exercise sessions, and with the flexibility of other university-based members of the research team.

Partway into the recruitment period, the novel coronavirus (COVID-19) pandemic started, and the UK went into a national lockdown. At the onset of this period, the entire country was to remain at home, with minimal face to face contact with anyone for a minimum of three months. These same restrictions were extended and altered multiple times. Once restrictions started easing, there remained uncertainty around the nature of COVID-19. Patients with CKD were classed as high risk and the university took a cautious approach, preventing any further research with this group. At the time, there was no certainty regarding how long the pandemic would last. We were unable to continue with our two study days a week and had to go back to full time clinical work. After the dedicated FY2 year finished, there were still significant strains on the healthcare workforce, meaning it was extremely difficult to get any study leave approved. I made the decision to take 6 months absence from clinical work to focus solely on my research. Following this hiatus, I again went back to full time clinical work.

In light of the above, it was decided to change this thesis to a systematic review and meta-analysis asking, "do exercise interventions affect cognition in patients with CKD?" The original question was broadened due to lack of data in the CKD 3 – 4 group, as found by a scoping review. Carrying out both a qualitative systematic review and a quantitative meta-analysis allows a greater exploration of the current evidence. It allows the author(s) to

summarise the existing published thoughts and interpretations of evidence, then test these interpretations in a substantive manner, thus attempting to remove the existing biases of researchers. This piece of research was primarily conducted by me. I learnt and carried out each stage of the review process, including: how to conduct a systematic search, data extraction and manipulation, which statistical tests to use and how to run the appropriate software, and how to assess for other risks of bias within studies and publication bias. Advice was sought from a librarian on carrying out a systematic literature search. Systematic review training was provided by Bangor University via its virtual learning environment. This thesis is thus an account of this piece of research. There is a single chapter which details the systematic review and meta-analysis, followed by a short summary. The chapter is formatted to fit publication in the Clinical Journal of the American Society of Nephrology, to which it will be submitted for peer review, with the exception of having a longer word count herein. In addition, table 3 has been formatted to be similar to the more detailed tables typically included in Cochrane reviews.

Although the pandemic required a change of study design, I believe I have succeeded in meeting the aims of the academic FY2 role. I have learnt many technical and non-technical skills involved in the process of research. This includes developing my leadership skills and assertiveness, particularly when working with other members of the university with different backgrounds and skills to me. I attended a series of lectures on statistics and now have a grasp of many routinely used tests, and when to use them (such as analysis of variance (ANOVA), repeated-measures ANOVA, standardised mean difference, Hedge's *g*, random-effects *vs* fixed-effects analyses). I have learnt how to set-up and run an RCT and learnt about the principles of exercise interventions and prescriptions. My knowledge of the mechanism and interpretation of MRI has improved, including reaching level 1 safety certification. I have learnt the process of and completed a systematic review and meta-analysis of RCTs, and finally I have prepared and will submit a research paper for peer review and publication.

## Chapter 1: Does Physical Exercise Affect Cognition in Patients Living with Chronic Kidney Disease? A Systematic Review and Meta-analysis


### Abstract

**Background and objectives:** Cognitive impairment is a major health problem worldwide, affecting individuals, their families, and their wider communities. People with Chronic Kidney Disease (CKD) are more likely to develop cognitive impairment than those without. Exercise has been proposed to improve cognitive function and/or slow down cognitive decline in both CKD and non-CKD populations. We carried out a systematic review and meta-analysis of randomised controlled trials, investigating whether exercise influences cognition in people living with CKD.

**Design, setting, participants and measurements:** We undertook a systematic search of published and grey literature. Papers were screened at title/abstract level, before researchers read whole papers and selected those for inclusion. We included any randomised controlled trials of patients with any stage of CKD whose intervention exercised large-muscle groups, and measured cognition using a variety of outcome measures. A random-effects meta-analysis was carried out and subsequent planned subgroup analyses were used to investigate heterogeneity. Papers were also assessed for risk of the inclusion of bias.

**Results:** Fifteen trials were included in the analysis, which included 760 participants. All included trials were found to be at high risk of the inclusion of bias. Our primary analysis found that exercise did not have any effect on cognition in CKD (effect size (ES) = 0.21; 95% confidence intervals ($CI_{95}$) = -0.05, 0.47; $p$ = 0.12). Subgroup analyses found a positive effect of exercise in patients with CKD stages 1 – 4 (ES = 1.2; $CI_{95}$ = 0.45, 1.95; $p$ = 0.002) and when doing aerobic exercise (ES = 0.55; $CI_{95}$ = 0.12, 0.97; $p$ = 0.01), albeit the former subgroup analysis included subgroups consisting of a single study.

**Conclusions:** This study revealed that across the spectrum of CKD, exercise interventions do not affect cognition. However, certain subgroups may benefit from exercise, namely those with pre-dialysis CKD and if undertaking aerobic exercise. Furthermore, exercise did not appear to be harmful in this patient group. Due to the finding of minimal risk and possible benefit, clinicians may choose to recommend aerobic exercise to prevent cognitive decline, particularly to patients who do not require dialysis. Researchers may choose to focus their future studies on patients with CKD stage 1 – 4 and with renal transplants.

## Introduction

Dementia and cognitive impairment are common and increasing health burdens affecting more than 50 million people worldwide.[52] Cognitive impairment (CI) describes a range of worsening cognitive function from mild CI (which does not influence a person's ability to carry out activities of daily living (ADLs)), to dementia (which does influence ADLs). The burden of the effects of dementia and CI are felt from an individual to a national level, impacting on health, working life, care burden and cost to the nation.

People living with Chronic Kidney Disease (CKD) (GFR < 60 ml/min) are at higher risk of CI than those without CKD.[4] Estimates of prevalence range from 20 – 60% depending on degree of renal impairment and treatment[53,54] and may be as high as 70 – 80% in patients on HD.[10] Changes to cognitive function occur early on in the progression of CKD, and different domains of cognition are affected at different rates.[55]

There are many risk factors for CI, the presence of which increase the risk of, but do not guarantee, cognitive decline. Within the CKD population there is a high prevalence of risk factors for CI that may be both a cause and a consequence of their CKD. Of these, diabetes and hypertension are the most common.[10] In addition, CKD itself has been found to be an independent risk factor for CI.[4] Some suggested causes for this are due to the pathophysiology of CKD itself, such as chronic inflammation, anaemia, and increased blood concentrations of urea and its metabolites.[4,10] Associated clinical problems such as depression and polypharmacy are also likely to contribute.[4,10] Within the dialysis population, the process of HD appears to influence the progression of CI more than in PD.[11]

In the general population, the World Health Organisation (WHO) recommends physical exercise, as well as management of diabetes and hypertension (to which exercise can contribute) as a means to reduce the risk of cognitive decline and dementia.[52] The 2018 Physical Activity Guidelines for Americans also recommend habitual exercise to reduce the risk of dementia in all adults, and to improve cognition in adults over 50 years old.[56] These recommendations and guidelines are based upon studies suggesting that that physical activity has a protective effect against the development of cognitive decline, even at very low levels of exercise.[13]

Exercise has also been proposed to improve cognition in people living with CKD. This is because there is evidence for positive effects of exercise on multiple risk factors for cognitive decline. Across the spectrum of CKD, exercise has been shown to improve blood

pressure,[12,18] decrease arterial stiffness,[57] improve quality of life (QoL),[12,18,19] decrease BMI,[58,59] and improve symptoms of depression.[19,57] It may also decrease insulin resistance.[60] Many of these findings were consistently observed, regardless of the stage or treatment of CKD. Overall, exercise is considered a safe non-pharmacological intervention for this population, recommended by multiple expert bodies as an adjunct to medical therapy.[5,61,62]

Additionally, there are some observational data of CI and exercise in CKD. A cross-sectional study of 102 HD patients found a significant association between activity levels (as measured by the International Physical Activity Questionnaire) and cognitive function, even when adjusted for confounding variables.[63] Likewise, a recent analysis of cross-sectional data of older adults found that among patients with lower activity levels, those with CKD had significantly worse global cognitive function than those without CKD; among patients with higher levels of physical activity, there was no difference in global cognition between those with CKD and without.[14] In contrast, another cross-sectional study in HD patients found no difference in cognition between participants classified as active and inactive, apart from in the fluency subdomain.[64]

So far there have been several systematic reviews of studies including patients living with CKD which specifically investigated cognition as a primary outcome.[31,34,35] There has also been one meta-analysis of RCTs investigating cognition as a primary outcome in haemodialysis patients,[36] and one Cochrane review which analysed cognition as a secondary outcome.[19] The qualitative reviews largely concluded that exercise caused an improvement in cognition or prevented further decline, as did the meta-analysis of Liu *et al.*[36] Within the Cochrane review, the meta-analysis of the effect of exercise training of any type (aerobic, muscle strengthening, combined aerobic and resistance, or yoga) *versus* control on the cognition subdomain included five trials and found no effect. However, a secondary analysis which compared each type of exercise individually to controls showed aerobic exercise alone improved cognitive function.

This meta-analysis collates the existing evidence for the effect of exercise on cognition in patients living with CKD. It expands upon the existing meta-analyses by investigating cognition as a primary outcome across all stages of CKD and includes more empirical data.

**Outcomes**

This systematic review and meta-analysis asked the question: do exercise interventions affect cognition, when compared to controls, in people living with CKD? It comprises of a

systematic literature search and meta-analysis of RCTs. To enhance generalisability, the search terms broadly covered people with all stages and treatments of CKD, undergoing any large muscle group exercise intervention. Outcome measures were any objective or subjective measurement of cognition. Secondary outcomes via subgroup analysis looked at the effect of CKD stage and treatment, the type of exercise intervention, and the modality of outcome measure. Further planned meta-regressions investigated the relationship between intensity of exercise and length of intervention on cognition.

## Materials and methods

Each stage of this review was carried out independently by a single reviewer (EJB) whose work was then reviewed by a second person (JHM). Disagreements were discussed until consensus was reached.

### Eligibility criteria

The following criteria were used to identify studies suitable for review:

Participants: adults with CKD undergoing any treatment.

Intervention: Any exercise intervention which exercised large muscle groups was included. Exercise could be in combination with another intervention if the control group also received the additional intervention. Education could be part of the intervention if it was related to exercise. Respiratory muscle training alone, electrical nerve stimulation without associated repeated movement by the participant, and complex interventions, for example exercise plus diet/employment/lifestyle advice, were excluded.

Whilst the current guidelines recommend a minimum of 150 minutes of moderate intensity exercise per week,[5,65] it is recognised that CKD patients have lower baseline levels of physical activity than healthy counterparts.[5] The WHO 2020 guidelines recommend that adults with chronic conditions should partake in exercise to their best ability, commencing with small amounts of physical activity and gradually increasing the frequency, intensity and duration over time.[65] There is also evidence that any level of activity is beneficial for other health-related outcomes in CKD.[66] Therefore, all levels of exercise intensity have been included in this study.

Control: usual care, attention control (including sham exercise), brain training or diet change.

Outcomes: cognition measured by any means. Whilst quality of life (QoL) assessments are not gold standard measurements of cognition, they were considered appropriate for the purpose of this review.

Studies: RCTs reported in English.

**Information sources**

A scoping search was carried out beforehand to aid planning of feasible analyses. There was no limit on publication source. The final search of four databases (Medline, PubMed, CINAHL and Web of Science) was completed on the 4th February 2021. A further search of grey literature was carried out using the OpenGrey database (opengrey.eu) on 9th March 2021. The search terms used were more limited because the search engine does not have an "advanced search" option.

The references of relevant studies were reviewed to identify any further studies not identified by the database searches.

**Search strategy**

The full search strategy used is detailed in Supplementary Information S1. The same search terms were used for each of the four major databases, with alterations made to truncation symbols. Medical Subject Headings (MeSH terms) were used where available. Generally, the search combined themes of CKD, exercise, control, and cognition.

**Selection process**

The list of retrieved studies was manually screened at title/abstract level to identify papers suitable for analysis. This screening was carried out multiple times by one reviewer (EJB). The full texts of these papers were then reviewed. All included and borderline papers were discussed between two reviewers to confirm or veto their inclusion (EJB & JHM).

**Data collection process**

Data on each study setting, population, intervention, control group and outcome measures were extracted and input into pre-defined tables, which had been piloted before final data extraction. For studies which had not reported all required data, the authors were contacted with requests for information. A maximum of two authors per publication were contacted and given a month to respond.

Regardless of the number of measurements taken during the trial, only the mean cognition score from the end of the intervention period, and standard deviation (SD) of this score, were collected along with the number of participants in each group. Where data varied between

text and tables, they were taken from tables. Where baseline data were presented as separate groups, the values were combined using the formulae presented in the Cochrane Handbook for Systematic Reviews of Interventions.[67] Some studies used more than one measure of cognition. The results chosen for analysis followed these priorities: 1) primary outcome, or if not stated, 2) test of global cognition.

**Risk of bias in individual studies**

The risk of bias in each study was assessed using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2).[68] This tool assesses the risk of bias across five domains within trials, with "high" pertaining to high risk of bias and "low" corresponding to a low risk of bias. "Some concerns" was assigned to those where there was insufficient evidence to make a firm judgement. The five domains assess risk of bias due to the randomisation process, due to deviations from the intended interventions, arising from missing outcome data, from the measurement of the outcome, and from selective reporting of results.

For the global assessment of risk of bias, papers were designated high risk if they scored "high" in any one domain, or "some concerns" in at least three domains. They were considered low risk if they scored "low" in all five domains. These assessments were planned to later inform a sensitivity analysis.

Where flowcharts detailing randomisation, dropouts and analyses were included, they were used as evidence for or against deviations from the study protocol. A conservative approach was taken to the bias assessment, with reviewers tending to overestimate bias whenever uncertainty was present.

**Summary measures**

The primary outcome measure was the difference in cognitive test scores post-intervention, comparing exercise intervention groups to control groups. Interpretation of results followed Cohen's effect sizes of 0.2 = small effect, 0.5 = moderate effect, and 0.8 = large effect.[69]

**Synthesis of results**

Where there were multiple interventions, the exercise groups were combined into one, using the methods suggested by Higgins, Li & Deeks.[67] Where data were presented as medians (range or interquartile range), sample means and SD were estimated using the method

suggested by Wan *et al*.[70] If there was any confusion or missing values, clarification was sought from the authors. Where 95% confidence intervals were presented and n < 60, SD was estimated using the t-distribution look-up function of Microsoft Excel. If n > 60, the t-statistic was presumed to be 3.92.

Results are presented as effect estimate (effect size) (ES) and 95% confidence intervals ($CI_{95}$). P-value for significance was set at $p \leq 0.05$. Forest plots were used to visualise the effect outcomes, generated by the RevMan[71] and JASP[72] software.

Due to the heterogeneity of the included studies, the analyses were synthesised using the random-effects model (DerSimonian-Laird method) with standardised mean difference (Hedges' *g*) to calculate the effect size. The primary outcome and subgroup analyses were synthesised using the RevMan software.[71] The meta-regression and funnel plot were synthesised using JASP software.[72] This was due to ease of use of the software for the authors. $\chi^2$ was used as a test of heterogeneity, with the $I^2$ statistic as an indicator of the proportion of variance being due to true heterogeneity. Values for $I^2$ were interpreted in line with Cochrane advice.[73]

To further investigate heterogeneity between studies, as indicated by a statistically significant $\chi^2$ test, the following five analyses were conducted:

i) Subgroup analysis of *objective versus subjective measures of cognition*.
Here, 'objective' means tests with right and wrong answers, as marked by an assessor with a standard set of answers and corresponding scores. 'Subjective' means assessments where a participant gives a self-rated judgement based on a Likert scale. These judgements are then converted to an overall score via a standardised scoring. The two types of tests may vary in their detection of changes in cognition. In this and all other subgroup analyses, differences between subgroups were assessed using $\chi^2$, and subgroups within studies adopted the moniker given by the original authors.

ii) Meta-regression investigating *the relationship between intensity of exercise and effect size*.
Exercise intensity is known to affect the body's physiological response to exercise;[74] it may therefore also predict the effect, if any, on cognition. Interventions were classified as low, moderate, or high intensity based on the definitions given by the American College of Sports Medicine (ACSM),[75] and the National Strength and Conditioning Association (NSCA)[76] (table 2). The classification was based on the reported intensities achieved during the intervention

or was estimated using the target intensities for the intervention. In this and all other meta-regressions, the Q-test was used to assess the strength of any association and examine data for residual heterogeneity.

iii) Meta-regression exploring *the association of length of intervention period with effect size.*
The cognitive changes associated with mild cognitive impairment and dementia, by definition, occur chronically. It is therefore reasonable to expect that an exercise intervention would need to last for several weeks before it would have any effect on cognition. Heiwe & Jacobson stated that exercise programmes should last a minimum of 8 weeks in order to affect clinically important outcomes in this patient group.[12] The length of the intervention may correlate to the size of the effect, if any. Where the length of intervention was reported in months, it was converted to weeks (see Supplementary Information 2).

iv) Subgroup analysis comparing *stage and treatment of CKD and effect size*.
The severity of CKD is classified into 5 stages depending on GFR.[1] As GFR decreases, the risk of cognitive impairment increases.[4] In addition, treatment varies dependent on stage of CKD: patients with stage 1 – 4 disease are typically controlled with medical treatment. Stage 5 requires either renal replacement therapy (RRT) or conservative management. RRT consists of kidney transplant and dialysis (either HD or PD). Patients who have undergone renal transplant have been found to have lower mortality, lower risk of cardiovascular events, and higher QoL than their counterparts on dialysis.[77] Thus this analysis split participants into the subgroups of stage 1 – 4, renal transplants, and dialysis patients. For this analysis, HD and PD were classified as one group.

v) Subgroup analysis comparing *type of exercise intervention and effect size*.
Current evidence of the impact of the type of exercise on cognition is mixed; studies have shown that aerobic exercise improves[48] or has no effect on cognition in dementia[39] and healthy populations,[42] and that resistance exercise improves[49] or has no clear effect[39] on cognition in cognitively impaired or healthy adults. Thus, this analysis grouped participants by type of exercise: aerobic, resistance, flexibility, or combined (at least two of the above).

Finally, a sensitivity analysis was planned to reanalyse the primary outcome without the studies which were felt to have a high risk of bias.

**Risk of publication bias assessment**

To assess risk of publication bias a funnel plot was created, with asymmetry of the plot indicating a higher risk that non-significant experimental findings were not published, and therefore unavailable for inclusion in the meta-analysis. A visual assessment of the plot and Egger's regression test were used to assess asymmetry.[78]

The Outcome Reporting Bias In Trials (ORBIT) guidelines[79] were used to judge risk of bias arising from non-reporting of outcomes in papers which would otherwise have been included in the analysis.

## Results

### Study selection

The search strategy identified 1236 studies, 724 when duplicates were removed. After screening the abstracts, 95 full texts were retrieved and screened. In total, 15 studies were included in the meta-analysis. Figure 2 shows the decision-making process and reasons for exclusion for the studies identified.

Among the studies excluded, there were six which would have been included were it not for a lack of available data. These include the study of Bennett *et al.* which planned to measure KDQOL-SF at baseline and post-intervention, but which found the assessment too taxing for participants so did not repeat post-intervention.[80] Three studies presented aggregated KDQOL-SF scores but did not provide the cognition domain score on its own.[81–83] One study had not commented on the change in cognition or provided data due to non-significant results.[84] A sixth study had reported a significant improvement in the cognition domain in the intervention group but had not presented any comparative data for the control group.[85] These authors were contacted with requests for cognitive domain data for both groups but no further data were obtained.

### Study characteristics

A summary of included study characteristics can be found in table 3. There were data available from 760 participants across 15 studies. The number of participants randomised in each studied ranged from 16 [86] to 296.[87] In total there were 386 participants in intervention groups and 374 in control groups.

Three studies were multicentre trials,[87–89] nine were single centre trials,[90–98] and three did not specify.[86,99,100] All were RCTs; all were pre-test, post-test designs, albeit one study used a pre-test, mid-test, post-test design[100]. Of these, two were pilot RCTs.[94,95] There were no conflicts of interest in any of the included studies.

Generally, inclusion criteria consisted of adults with mild renal impairment, on dialysis, or with kidney transplants.

Exclusion criteria were patients with severe comorbidities which would prevent them from participating in exercise. For example, severe heart disease, musculoskeletal problems,

uncontrolled hypertension or angina, chronic obstructive pulmonary disease, cerebrovascular disease, or diabetic eye disease.

**Participant characteristics**

The weighted mean age of participants at baseline was 55. The proportion of women in each study ranged from 15 [98] to 60%.[89]

One study included patients with renal transplants[86] and one study included patients with stage 3 – 4 disease.[97] All other studies included dialysis patients; Uchiyama *et al.*[96] included only patients using peritoneal dialysis, Manfredini *et al.*[87] included both those on haemodialysis and peritoneal dialysis, and the remaining twelves studies included only those on haemodialysis.[88–95,98–100]

One study required participants to be literate,[100] but none of the studies required a minimum level of cognition. Seven of the included studies excluded patients with dementia[94,95] or a cognitive disturbance which would affect their ability to participate.[90,91,98–100] All studies included participants with diabetes. The most common reported comorbidities were diabetes, hypertension, smoking, coronary artery disease, and heart failure.

Only four studies reported education levels[89,93,94,98]; the proportion of participants who had less than a secondary school/high school education ranged from 20 [94] to 60%.[93]

Five studies explicitly included those who were sedentary or not undertaking any regular physical activity.[86,90,91,93,99] An additional two studies found all their participants to be relatively inactive at baseline when compared to other chronically ill patients, or less fit than healthy patients when measured by the 6 Minute Walking Test.[89,92] One further study reported 55% of their participants were inactive at baseline.[100] Conversely, three studies excluded patients undertaking regular exercise or deemed to have an existing high level of fitness.[87,88,95]

**Interventions**

Details of each study's exercise prescription are summarised in table 3. Duration, number of repetitions, and number of sets are reported as the maximum target by the end of the intervention period.

Frequency of activities ranged from 2 sessions per week[86,91,99] to 28 per week.[97] The mode frequency was 3 sessions per week and nine studies performed intradialytic interventions.[88,90,91,93–95,98–100]

According to the classifications of this review, three studies or subgroups used low intensity interventions.[87,88,90] Eleven studies or subgroups used moderate intensity interventions.[86,88,89,91–93,95–99] One study utilised a high intensity intervention.[100] One study did not report an intensity prescription.[94]

Seven studies or subgroups used aerobic exercise interventions,[87,90,91,94,97,98,100] six used resistance exercise interventions,[86,88,90–92,99] and four studies used combined interventions.[89,93,95,96] No studies used flexibility exercise as their main intervention. Three studies used stretching as a control.[88,92,98] Two studies used an additional oral nutritional supplement which both the intervention and control groups received.[91,99]

The duration of exercise sessions varied from 10 to 75 minutes. The shorter interventions were intended to be completed multiple times a day in order to meet a target of 20,[87] 30,[89] or 40 [97] minutes daily activity.

Four interventions were home-based,[87,89,96,97] two were supervised in a gym or rehab environment,[86,92] and the remaining nine were supervised at the dialysis unit. Two studies specified that participants were supervised by a trained physiotherapist,[86,92] one home home-based study began with 4 weeks supervision[97] and one study was supervised by a dietician trained in exercise for dialysis.[91]

Ten studies used individualised targets for exercise prescription.[86–92,95,96,98] Nine studies used progressive exercise prescriptions which increased in intensity or duration across the intervention period.[86–88,90,91,93,95,96,100]

**Adherence**

Adherence was measured in a variety of ways across studies. Three studies reported adherence as proportion of studies performed out of those offered; mean adherence was reported between 52 – 100%.[86,87,96] Within these there was a high amount of variance in adherence. Uchiyama *et al.* reported 52% ± 40% of the walking exercise and 76% ± 37% of resistance exercise was completed.[96] In the trial of Manfredini *et al.,* 44% of participants reported doing more than the prescribed intervention and 28% reported doing less than

10%.[87] Van Craenenbroeck *et al.* reported 100% of participants completed 70 or more training days with at least 40 mins exercise (out of a total possible 84 days).[97] Tawney *et al.* measured self-reported time doing activities and found that participants in the intervention group increased their moderate intensity activity by an hour per week.[89] Four studies reported adherence of 75 – 100% but did not report how it was measured.[88,91,95,99] One study measured adherence as completion of a minimum of 80% of the goal exercise time for all sessions but did not report how many participants achieved this.[93] Five studies did not report adherence to the intervention.[90,92,94,98,100]

**Adverse events**

Of the fifteen included studies, nine reported adverse events in the text of the report,[87–89,91–94,98,99] although Manfredini *et al.* did not record events in the control group.[87] These adverse events are summarised in table 4. Two studies reported that there were no adverse events related to the intervention group; again they did not comment on events in the control group.[86,96] However, there were additional adverse events noted in the flowcharts of some papers which were not mentioned in the text (table 5).

**Risk of bias in studies**

Overall, all studies were found to be at high risk of bias. Table 6 and figure 3 give a summary of the risk of bias assessments for all studies.

Across studies there were several common themes for sources of potential bias. The most frequent was assessments being conducted by unblinded assessors, either the participants themselves or an unblinded researcher (domain 4). Secondly, there was a large amount of missing data which could be due to the value of the missing data itself (domain 3). For example, patients who have worse cognitive function may be more likely to drop out of studies or to not complete assessments of cognitive function due to confusion or cognitive fatigue. In addition, many studies failed to report the method of allocation concealment, if any (domain 1).

**Main outcome**

The meta-analysis found that in patients living with CKD, the effect of exercise on cognition did not differ from that of controls (ES = 0.21; $CI_{95}$ = -0.05, 0.47; $p$ = 0.12) (figure 4). As can be seen in the forest plot there was a large degree of variability within most studies. The test

for heterogeneity indicated a substantial degree of difference between the studies, which was unlikely to all be attributable to chance ($I^2$ = 62%).

**Subgroup analysis by type of outcome measurement (objective *vs* subjective)**

Four studies used objective measurements of cognition: MMSE [95,100] and the Modified Mini-Mental State examination (3MS).[92,94] The remaining twelve studies used the KDQOL[88] or KDQOL-SF[86,87,89–91,93,96–99]. The KDQOL-SF is a condensed version of the KDQOL. Both contain three questions targeting cognitive function which are worded slightly differently but ask about the same aspects of cognition (concentration, becoming confused, and reacting slowly to stimuli).

Although a significant moderate positive effect size was obtained for objective measures (ES = 0.66; $CI_{95}$ = 0.02, 1.29; $p$ = 0.04), and a non-significant negligible effect was obtained when measured using a subjective assessment (ES = 0.09; $CI_{95}$ = -0.17, 0.35; $p$ = 0.51), the tests for subgroup differences revealed that outcome measure did not significantly moderate the relationship between exercise and cognition ($\chi^2$ = 2.62, $p$ = 0.11) (figure 5).

**Meta-regression investigating intensity of exercise as a covariate**

As per the classifications of this review, three studies or subgroups used low intensity interventions. [87,88,90] Eleven studies or subgroups used moderate intensity interventions[86,88,89,91–93,95–99] and one used a high intensity intervention.[100] One study did not report an intensity prescription so was not included in the meta-regression.[94]

The meta-regression found no effect of low intensity exercise on cognition (ES = 0.02; $CI_{95}$ = -0.49, 0.53; $p$ = 0.94) (table 7 and figure 6). In relation to low intensity exercise, moderate intensity exercise did not have any significant different effect (coefficient = 0.12; $CI_{95}$ = -0.47, 0.71; $p$ = 0.69). In relation to low intensity exercise, high intensity exhibited a significant difference, showing a strong beneficial impact on cognition (coefficient = 1.29; $CI_{95}$ = 0.14, 2.44; $p$ = 0.028). The test of the relationship between intensity and cognition was non-significant, indicating that the relationship could be explained by chance ($Q$ = 5.043 and $p$ = 0.08) (table 8). The test for residual heterogeneity indicated that there are remaining unexplained differences between the groups ($Q$ = 28.2, $p$ = 0.005) (table 8).

**Meta-regression examining length of intervention as a covariate**

The length of the interventions ranged from 8 weeks[90] to 6 months[89] across studies. The mode length was 12 weeks.[88,91–93,96,98,99]

The meta-regression demonstrated no relationship between the length of the intervention in weeks and the effect on cognition (coefficient = 0.004; $CI_{95}$ = -0.04, 0.05; $p$ = 0.86) (table 9 and figure 7).

**Subgroup analysis by CKD stage and treatment (kidney transplant *vs* dialysis *vs* stage 1 – 4)**

One study included patients with stage 3 – 4 kidney disease[97] and one study included those who had undergone kidney transplantation.[86] The remaining thirteen studies included patients managed with dialysis – Uchiyama *et al.* included only patients using peritoneal dialysis,[96] Manfredini *et al.* included both those on haemodialysis and peritoneal dialysis,[87] and the remaining eleven studies included only those treated with haemodialysis. [88–95,98–100]

Subgroup analyses revealed a significant strong positive relationship between exercise and cognition within patients with stage 1 – 4 disease (ES = 1.20; $CI_{95}$ = 0.45, 1.95; $p$ = 0.002) (figure 8), though it should be noted that this subgroup contained a single study. No effect of exercise was demonstrated in the stage 5 – dialysis group (ES = 0.12; $CI_{95}$ = -0.13, 0.38; $p$ = 0.35). Furthermore, cognition was not improved within the stage 5 – kidney transplant group, albeit the effect size was moderate (suggestive of lack of power for this analysis given the single study in this subgroup) (ES = 0.49; $CI_{95}$ = -0.51, 1.49; $p$ = 0.34). Moderation analyses revealed that CKD stage and treatment did significantly predict the relationship between cognition and exercise in CKD patients ($\chi^2$ = 7.31, $p$ = 0.03).

**Subgroup analysis by type of exercise**

Seven studies or subgroups used an aerobic exercise intervention.[87,90,91,94,97,98,100] Six studies or subgroups used a resistance exercise intervention.[86,88,90–92,99] Four studies used combined interventions.[89,93,95,96]

Aerobic exercise alone had a moderate positive effect on cognition (ES = 0.55; $CI_{95}$ = 0.12, 0.97; $p$ = 0.01) (figure 9). Neither resistance exercise nor combined interventions had any effect on cognition, with effect estimates of -0.06 ($CI_{95}$ = -0.38, 0.25; $p$ = 0.69) and -0.09 ($CI_{95}$

= -0.52, 0.34; $p = 0.70$) respectively (figure 9). Moderation analysis suggested that the type of exercise did predict the effect on cognition ($\chi^2 = 6.04$; $p = 0.05$).

**Sensitivity analysis**

As mentioned above, all included studies were felt to be at high risk for potential introduction of bias. Therefore, it was not possible to run the planned sensitivity analysis.

**Reporting biases**

A funnel plot of the included studies, charting standardised treatment effect by standard error is shown in figure 10. Visually there is little asymmetry, and Egger's test gave a result of $p = 0.17$, indicating that there was no asymmetry of the plot. These analyses suggest there was no effect of publication bias on this meta-analysis.

As seen in figure 2, six studies were excluded from the synthesis due to incomplete datasets. Based on the ORBIT classification system for missing or incomplete outcome reporting,[79] these partial reports largely present a low risk of bias from the lack of inclusion of non-significant results (table 10).

Overall, the primary finding of this meta-analysis was of no effect of exercise on cognition, and the majority of individual studies found no effect (as opposed to a mixture of significant positive and negative effects). This, together with the above findings, suggests that there was little evidence of publication bias affecting the overall result.

## Discussion

### Overall synthesis

This meta-analysis found that in patients living with CKD, the effect of exercise on global cognition did not differ from that of controls. Consequently, there is currently insufficient evidence to support implementing exercise interventions to improve cognitive function at a whole CKD population level.

However, exercise has multiple benefits for patients living with CKD[12] and is generally considered safe in this population.[5] Furthermore, analysis of adverse events in the present meta-analysis was consistent: exercise did not cause obvious harm. Combined with findings from pre-planned subgroup analyses reported herein, kidney care teams may wish to consider exercise intervention for maintenance of cognitive function in certain CKD patients. Specifically, we suggest exercise interventions in patients with CKD stages 1 – 4, who can exercise using aerobic exercise modes. In addition, there may be benefit for patients who have undergone renal transplantation, and who can exercise at higher intensities.

Two other similar systematic reviews and meta-analyses have been carried out investigating the effect of exercise on cognition, albeit in strictly dialysis populations. As mentioned previously, Bernier-Jean *et al.* conducted a meta-analysis of the effect of exercise on cognition as a secondary outcome in their Cochrane study.[19] Their finding that any exercise did not affect cognition is in keeping with our results. In contrast, Liu *et al.* found the opposite – that exercise significantly improved cognition.[36] This difference in findings may be due to a number of reasons: firstly that Bernier-Jean *et al.*'s analysis only used KDQOL-SF data,[19] whereas Liu *et al.*[36] and this review included any measure of cognition. Secondly, Bernier-Jean *et al.* included any dialysis patients,[19] Liu *et al.* included only HD patients,[36] and this study included all CKD patients. Thirdly, the two meta-analyses included different trials, with only one trial[87] in common between the two; the analysis herein shared 8 trials with the above two analyses.[87,91,92,94–96,98,99] Furthermore, Liu *et al.*[36] included two reports of participants from the EXCITE trial,[87,101] which found in favour of exercise, and included PD patients, and so may have exaggerated the effect size.

In many cognition trials in different populations, there are clear inclusion and exclusion criteria relating to participants' baseline cognition. In contrast, the trials included herein were heterogenous in terms of exclusion criteria based on cognitive function. Roughly half of the studies excluded participants with dementia or cognitive impairment, but the remainder did

not. Furthermore, there was no reporting in these studies regarding the proportion of the trial who had cognitive impairment at baseline. The possible variability in baseline cognition of the participants in the included studies may have had an influence on our results, and due to a lack of reporting within the reviewed trials, we were unable to include baseline cognitive function as a subgroup analysis.

**Type of exercise**

The type of exercise performed had differing effects on cognition, with only aerobic exercise having any effect (which was of a moderate improvement). These findings are in keeping with those of Bernier-Jean *et al.* who showed that aerobic exercise significantly improved cognition in dialysis patients, with no effect found with resistance or combined exercises.[19]

**Stage and treatment of CKD**

Patients with ESRF are more likely to have CI than those in earlier stages, and this study suggests that exercise does not affect cognition in patients on dialysis. This is in keeping with the recent findings of Bernier-Jean *et al.*, who found that any exercise did not affect self-rated cognition in patients undergoing maintenance dialysis.[19]

This finding may be due to an irreversible nature of cognitive impairment in this patient group. Alternatively, it may reflect limitations in the types and modes of exercise available during dialysis, particularly HD. Given that the process of HD requires users to be sat down and connected to a haemodialysis machine, participants are unable to move freely whilst undergoing the treatment. Intradialytic aerobic exercise interventions in this setting mostly consist of seated cycling (as found in this review and the 2022 Cochrane review[19]), limiting it to the lower body. Furthermore, patients with ESRF are known to experience high levels of fatigue[19] and low levels of physical fitness,[12] which could hinder their ability to exercise to prescription targets. That is, due to the type of symptoms they experience, they are not able to reach adequate levels of intensity or duration of exercise, thus limiting the dose received.

The fact that the effect estimate crossed the null line in the kidney transplant group may also indicate no effect in this population too, but note the small sample size of this subgroup analysis (n = 16) which included only one study. As such we would not yet rule out the possibility of effect in this patient group. In contrast, there was a strong effect of exercise in pre-dialytic patients, but again the results must be interpreted cautiously due to the small sample size (n = 40) from a single study. Notwithstanding this concern, it has been shown

that exercise improved blood pressure in non-RRT patients, with no effect in HD or transplant patients,[18] which is consistent with the findings reported on cognition herein, and of interest as early blood pressure control may preserve cognitive function.[28] Additionally, it has been found that MCI begins in the earlier stages of CKD, and around 10 – 20% of these patients progress to dementia within 12 months.[102] Therefore, exercise may be important in the earlier stages of CKD to prevent progression to severe CI.

**Exercise intensity**

The findings of this analysis suggested that high intensity exercise alone improved cognition; there did not appear to be any effect of low or moderate intensity exercise. Similarly, Northey *et al.* showed that moderate and high intensity, but not low intensity, exercise had a small but significant effect on cognition in older adults.[43] Furthermore, Wilund *et al.* argued that exercise interventions often fail to produce clinically significant improvements in the health and QOL of HD patients, primarily because the volume and intensity of the exercise prescribed is insufficient.[103] However, the omnibus test for subgroup differences completed herein, which determined if there was an overall significant difference between the different intensity groups, was non-significant, suggesting the finding that high intensity exercise improved cognition should be interpreted with caution. Indeed there was only one study which provided a high intensity intervention.[100] This study included a small number of participants who were allocated unevenly to the intervention and control groups and had a high risk of bias across multiple domains. Evidently, more research into high intensity exercise programmes is required.

A challenge for future studies will be to ensure compliance to exercise interventions, particularly if exercise intensity needs to be high to elicit an effect. It should be noted that, within the included RCTs, adherence to the intervention was poorly reported. Poor compliance (number of sessions attended, and intensity of exercise achieved) to exercise interventions is common in patients living with CKD, particularly in haemodialysis patients, due to intercurrent medical events and fatigue.[104] Thus, poor compliance may have reduced the efficacy of the exercise interventions analysed herein.

**Outcome measure**

When measured with objective tests, exercise showed a moderate positive effect on cognition. In contrast, there was no effect seen when cognition was measured using the KDQOL or KDQOL-SF assessments. This may suggest that objective measurements of

cognition are more sensitive to detect changes in cognition in response to exercise than subjective measurements. However, the omnibus test for differences showed that there was no significant difference between the two subgroups, that is, that outcome measurement did not moderate the relationship between exercise and cognition. This is in keeping with the finding of Liu *et al.* who found no difference in the effect of exercise on cognition when measured with 3MS, KDQOL-SF and MoCA.[36] Assuming that type of outcome measurement is not merely a reflection of some other unaccounted-for difference between studies, further discussion on outcome measures is thus warranted.

Research into the validity of the KDQOL-SF as a measure of cognition is conflicting. Kurella *et al.* compared the Kidney Disease Quality of Life Cognitive Function scale (KDQOL-CF), which is purely the three cognition questions of the KDQOL, to the 3MS.[105] They found a small correlation between the summary KDQOL-CF score and 3MS score, concluding that their findings support the use of KDQOL-CF as a screening tool for cognitive impairment. In contrast, Sorensen *et al.* compared the KDQOL-CF to a battery of established neurocognitive tests including MMSE, Trail Making Test (TMT), and the Digit Symbol-Coding test.[106] They concluded that the KDQOL-CF was a poor determinant of neurocognitive performance in haemodialysis patients, with very limited sensitivity for identifying individuals with poor performance on neurocognitive tests.

All of the aforementioned assessments vary in length and, in practice, it may be pragmatic to choose a shorter assessment in order to avoid cognitive fatigue and missing data, particularly where participants are subject to multiple rounds of testing.

**Length of intervention**

There was no relationship found between the length of exercise intervention and the effect on cognition. This finding is in keeping with the meta-analysis of Sanders *et al.*, who found that the duration of an exercise programme did not moderate the effect size in older adults without CKD, both with and without cognitive impairment.[107]

Most trials included herein were only 12 weeks in length, which may be too short to see an effect. Indeed Liu *et al.* found that interventions lasting 12 weeks had no effect on cognition and only those lasting over 16 weeks had any effect in HD patients.[36] It may also be that fixed duration exercise interventions are ineffective after they stop; instead patients may require sustained lifestyle change in order to have a significant effect on cognition, such as found by Sofi *et al.*[13] Sanders *et al.* also concluded that other aspects of the exercise

prescription, including duration of each session, and frequency of sessions, moderate the effect size of exercise in cognitively impaired older adults.[107] To avoid completing too many subgroup analyses, these characteristics of the exercise intervention were not analysed herein.

**Risk of bias in included studies**

In the assessment of the risk of bias within individual studies, all studies were found to be at high risk of being influenced by bias, albeit using a conservative approach to the risk of bias assessment. For any of these papers, this was due to the nature of the intervention and assessment itself, that is, in an exercise intervention blinding is impossible, and participants will know if they have exercised or not which may affect their self-rated cognition scores. Furthermore, in those studies which used an objective cognitive assessment, it was not clear that the researchers delivering these tests were blinded to which intervention the participants were allocated. Pragmatically, the authors acknowledge that in a real-world setting, it may not be possible to blind the researchers to group allocation due to financial or personnel restraints on the trial, but researcher effects could have affected outcome assessment.

Another potential source of bias was due to missing data due to non-completion of tests. This could have been caused by the poor cognition of the participants undertaking those tests, therefore overestimating any effect of the exercise interventions. Whilst this would not have changed the null finding of this analysis, it may have missed a negative effect, or would give more weight to the null result. In studies in non-CKD populations, there is a higher chance of non-completion of follow-up tests in those with deficits in executive function compared to those with memory or global cognitive deficits;[108] patients with CKD are known to lose executive function before other cognitive domains.[108]

**Limitations of evidence in the review**

Within the evidence collected for this review there are several limitations, the first of which is due to the high risk of bias, as discussed above.

Secondly, seven of the fifteen included studies excluded patients with diagnosed dementia, or cognitive changes which would affect study participation. The remaining eight studies did not exclude patients due to levels of cognition. It is known that CI is under-recognised in CKD[54,109,110] so we cannot be sure how many participants ‘fell through the net’, that is, had undiagnosed dementia or MCI and were included. In contrast, exclusion of those with known

dementia will have excluded a large proportion of CKD patients who may benefit from the intervention. It is possible that the effects and benefits of exercise may be exacerbated or potentiated in those with CI, given the differences between findings of other reviews in normal cognition[42] versus CI.[44]

Furthermore, the missing data surrounding adherence to the exercise prescription in the reviewed studies means that it is not clear if null fundings are due to a lack of efficacy of exercise or due to poor patient compliance. If many participants do not complete a substantial part of the prescribed exercise intervention, then there needs to be research into how to motivate participants into engaging with the intervention. One such study which aimed to increase adherence by using a more engaging intervention sadly did not report on said adherence.[93]

**Limitations of review process**

There were also some limitations with the process of this review itself. Firstly, the inclusion criteria were very broad, which resulted in a very heterogenous participant and intervention pool. This decision was made following a scoping review, to maximise the use of existing data. Patients with early CKD (stages 1 – 4) are physiologically very different from those with stage 5 disease. Likewise, interventions were varied, including aerobic, resistance, and combined, across a range of modalities. The subgroup analyses herein were carried out to somewhat mitigate this heterogeneity.

Secondly, the review was carried out by a small (two person) review team. One reviewer carried out all stages of the review, and the second researcher reviewed and offered opinions on each stage until consensus was found. While each stage of the review was checked by the second reviewer to minimise individual bias, a larger research team would more effectively mitigate this.

Thirdly, both PD and HD patients were combined into one group in the subgroup analysis investigating effect size and stage of CKD/type of treatment. Patients who are on PD are slightly more active than those on HD[111] and this may affect their participation in, and outcomes arising from, exercise interventions. However, for the purposes of this review it was decided to group them as there were very few trials identified in the scoping review which only included PD patients, and the trial which included both HD and PD patients did not present data for each treatment group separately.[87] Subsequent systematic reviews and

meta-analyses may wish to investigate these as individual groups, depending on the availability of evidence.

Finally, the interpretation of the results of the risk of bias assessment meant that it was not possible to run a sensitivity analysis. The categorical approach taken (that is, if one domain was classified as high risk then the study was overall classed as high risk) was intended to standardise the assessment of the risk of bias but also contributed to the finding that every paper was high risk. There were many instances of under-reporting of methods so, at times, clear judgement was difficult to reach. Additionally, in exercise studies where participants cannot be blinded to their intervention, coupled with the use of self-rated outcome measures (domain 4), there will always be a risk of bias and our approach did not account for this. Whilst a sensitivity analysis could have been executed based on the other four domains of the RoB 2 tool,[68] the result would have to be interpreted with caution and may have promoted findings which were otherwise not reflected in the other analyses. This limitation is a challenge faced by many authors of systematic reviews of exercise interventions, regardless of the risk of bias tool used.

**Implications of the results for practice, policy, and future research**

Whilst this review found that exercise did not affect cognition in CKD, the authors would still recommend kidney care teams consider exercise for this population. Such an approach is recommended because of other known benefits of exercise[18] and no evidence that exercise causes harm. Exercise may be particularly helpful to preserve cognition in patients with CKD stages 1 – 4 providing it can be aerobic in nature. There may also be benefit in those with kidney transplants and completed at higher intensities.

Surprisingly, the SONG initiative, which provides standardised recommended outcomes for research in nephrology, does not highly prioritise cognition as an outcome.[112] Currently, they recommend that cognition is *considered* as an outcome in trials of dialysis patients (low priority) and may be reported in *some* trials for transplant patients (intermediate priority).[113] There are no SONG recommendations yet for patients with CKD stages 1 – 4. It may be that as of yet, CI and its poor outcomes are still under-recognised by patients with CKD, their clinicians, and researchers.

We argue that more research is needed to examine pre-dialysis patients living with CKD, because they are most likely to see cognitive benefit from exercise interventions, and patients with kidney transplants as we cannot rule out that they will benefit. Currently, there

are several published protocols for ongoing trials which either specifically look at the effect of exercise on cognition,[114,115] or use a QoL questionnaire which includes cognitive domains.[116–118] Two of these experiments are in patients with renal transplants,[116,117] but unfortunately none of these planned trials include patients with CKD stages 1 – 4.

Furthermore, we suggest that in trials studying cognition, the following are considered:

1. an objective outcome measure is used, with blinded assessors carrying out the test
2. pre-dialysis and transplant patients
3. record and report fully on compliance (proportion of sessions undertaken and amount that intensity targets were met)
4. a follow-up period to investigate whether cognition is maintained

**Summary**

Overall, whilst this review and meta-analysis found no positive effect of exercise interventions on cognition in patients with CKD, it did not find any evidence of harm from these interventions. We found promising evidence of benefit from aerobic exercise and in patients with CKD stages 1 – 4, and the possibility of benefit from high intensity exercise or for patients with renal transplants.

**Other information**

This study was registered in the Prospero Registry (www.crd.york.ac.uk/prospero), number CRD42021271184. Funding was received by EJB from the Ysbyty Gwynedd Kidney Patients Association for an MScRes. There are no conflicts of interest.

## General Conclusion

This thesis has collated the existing evidence for the effect of exercise on cognition in patients living with CKD, and found that overall there is no clear effect. However, this finding is largely based on evidence in dialysis patients. Exercise appears to provide cognitive benefit to patients with CKD 1 – 4 and undergoing aerobic exercise. There is a necessity for further research into this cohort, and that of patients with renal transplants. Furthermore, care needs to be taken in the design and implementation of these studies to increase transparency and reduce the risk of bias as much as possible.

Notwithstanding the limitations of the research, there is no evidence to suggest that exercise is harmful in CKD and, given the other known beneficial effects, should continue to be recommended to the whole spectrum of these patients.

As evidenced above, this thesis involved learning and carrying out a substantial number of new skills for myself. Whilst the process was difficult at times, I believe it has already and will continue to inform my practice as a clinician. I have deepened my understanding of scientific method and the balanced interpretation of evidence which has affected my clinical decision-making. I am also able to share my understanding with colleagues, enabling them to take part in discussion of research. The development of my team-working and leadership skills has translated directly to my hospital work and allowed me to recognise both my own strengths and weaknesses as well as that of my colleagues. This has enabled me to both take the lead when needed, and to ask for help as appropriate. I believe the whole process and undertaking of this MScRes has benefitted me and that I have successfully completed the aims of the academic FY2 programme.

## Glossary and list of abbreviations

3MS – Modified Mini-Mental State examination.

ADAS-Cog – Alzheimer's Disease Assessment Scale – Cognitive subscale, the gold standard tool used to measure the effects of treatments on cognitive function in trials involving patients with dementia.

ADLs – activities of daily living.

Borg scale – a tool used to subjectively quantify the intensity of an exercise or activity.

CAPD – continuous ambulatory peritoneal dialysis, a form of peritoneal dialysis in which patients are able to go about their daily lives whilst undergoing treatment with dialysis fluid in their abdomens, in order to imitate the role of the kidney.

CI – cognitive impairment.

CKD – chronic kidney disease. Classified into 5 stages from least severe (stage 1) to most severe (stage 5).

DALYs – disability-adjusted life years. One DALY represents the loss of the equivalent of one year of full health. DALYs for a disease or health condition are the sum of the years of life lost to due to premature mortality and the years lived with a disability due to prevalent cases of the disease or health condition in a population.[119]

ESRF – end stage renal failure, also known as CKD stage 5.

FY2 – Foundation Year 2, the second year of working life for a newly qualified doctor within the NHS.

GFR – glomerular filtration rate. Rate at which the kidney filters blood, used as a marker of function.

HD – haemodialysis. Procedure whereby an external machine is used to filter the blood of a patient, replicating the work of the kidney.

KDQOL(-SF) – Kidney Disease Quality of Life (-Short Form), a series of questionnaires which measure patients' quality of life across a number of general and kidney disease-specific outcomes.

MCI – mild cognitive impairment.

MMSE – Mini-Mental State Examination, a tool which measures global cognitive function.

MoCA – Montreal Cognitive Assessment, a tool to screen for cognitive impairment.

MRI – magnetic resonance imaging.

MScRes – degree of Master of Science by Research.

NHS – National Health Service.

PD – peritoneal dialysis. Procedure whereby the peritoneum (the lining of the abdominal cavity) is used to filter the blood of a patient, to replicate the role of the kidney.

QoL – quality of life.

RCT – randomised controlled trial.

RRT – renal replacement therapy. Treatment which aims to replicate the function of the kidneys in people whose own kidneys no longer work. RRT includes haemodialysis, peritoneal dialysis, and kidney transplantation.

SONG - Standardised Outcomes in Nephrology. An international initiative that aims to establish core outcomes in chronic kidney disease research.

## Tables

| Classifications of CKD as per ICD-11 | |
|---|---|
| **Stage** | **Definition** |
| 1 | Kidney damage with normal or increased GFR > 90 |
| 2 | Kidney damage and GFR 60-89 |
| 3a | GFR 45-59 |
| 3b | GFR 30-44 |
| 4 | GFR 15-29 |
| 5 | GFR <15 |

*Table 1 - Classification of CKD as per the International Classification of Diseases – 11.*[1] *CKD = Chronic Kidney Disease. ICD-11 = International Classification of Diseases 11th Revision. GFR = Glomerular Filtration Rate, measured in ml/min/1.73m²*.

| Relative intensity of cardiorespiratory and resistance exercise | | | | | | |
|---|---|---|---|---|---|---|
| **Assigned Intensity** | **RPE as per Borg scale** | **%$HR_{max}$** | **%$\dot{V}O_2$max** | **%1RM** | **Repetitions** | **HR** |
| Low | 9-11 | 57-<64 | 37-<45 | <50 | 15 | Below anaerobic threshold |
| Moderate | 12-13 | 64-<76 | 46-<64 | 50-<70 | 12 | |
| High | 14-17 | 76-<96 | 64-<91 | >70 | <=10 | Above anaerobic threshold |

*Table 2- Relative Intensity of Cardiorespiratory and Resistance Exercise. Adapted from ACSM*[75] *& NSCA.*[76] *Assigned intensity = by authors using the following information taken from each paper: RPE = Rating of Perceived Exertion. $HR_{max}$ = maximal heart rate. $\dot{V}O_2$max = maximum oxygen consumption. %1RM = percentage of load of 1 repetition maximum. Repetitions = where no load was given, but number of repetitions was reported, an estimate of intensity was made based on the NSCA guidance.*[76] *HR = heart rate.*

| Characteristics of included studies | |
|---|---|
| **Study** | **Characteristics** |
| De Lima 2013 | Title: Effect of Exercise Performed during Hemodialysis: Strength versus Aerobic<br>Location: Brazil<br>Funding: NG<br>Study design: Single centre pre-test post-test RCT<br>Participants' stage of CKD and treatment: 5, HD<br>Number randomised (IG/CG analysed) (n): 33 (10/11/11)<br>Proportion of participants with dementia* (%): 0<br>Intervention (G2):<br>• Mode: Intradialytic lower limb resistance exercise<br>• Type: Resistance<br>• Target intensity: Modified Borg 2 – 3<br>• Intensity as per this review: Low<br>• Progressive: Yes<br>• Individualised: Yes<br>• Time (mins/session): NA<br>• Frequency (sessions/week): 3<br>• Length of intervention (weeks): 8<br>• Location: Dialysis unit<br>Intervention (G3):<br>• Mode: Intradialytic ergometric cycling<br>• Type: Aerobic<br>• Target intensity: Modified Borg 2 – 3<br>• Intensity as per this review: Low<br>• Progressive: Yes<br>• Individualised: Yes<br>• Time (mins/session): 20<br>• Frequency (sessions/week): 3<br>• Length of intervention (weeks): 8<br>• Location: Dialysis unit<br>Control: Usual care<br>Outcome: QoL<br>Measurement: KDQOL-SF<br>Primary or secondary outcome: Primary<br>Finding (re: cognition): No change in cognition domain in any group |

| | |
|---|---|
| Hernández Sánchez 2021contin | Title: Effects of a resistance training program in kidney transplant recipients: A randomized controlled trial.<br>Location: Spain<br>Funding: None<br>Study design: Pre-test post-test RCT<br>Participants' stage of CKD and treatment: 5, renal transplant<br>Number randomised (IG/CG analysed) (n): 16 (8/8)<br>Proportion of participants with dementia* (%): NG<br>Intervention:<br>• Mode: upper and lower limb resistance exercises<br>• Type: Resistance<br>• Target intensity: 3 – 4 sets of 10 RM<br>• Intensity as per this review: Moderate<br>• Progressive: Yes<br>• Individualised: Yes<br>• Time (mins/session): 60<br>• Frequency (sessions/week): 2<br>• Length of intervention (weeks): 10<br>• Location: Gymnasium<br>Control: NG "control"<br>Outcome: QoL<br>Measurement: KDQOL-SF<br>Primary or secondary outcome: Primary<br>Finding (re: cognition): No significant group by time interaction |
| Lopes 2019 | Title: Intradialytic Resistance Training Improves Functional Capacity and Lean Mass Gain in Individuals on Hemodialysis: A Randomized Pilot Trial |

| | |
|---|---|
| | Location: Brazil<br>Funding: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior scholarship<br>Study design: Multi-centre pre-test post-test RCT<br>Participants' stage of CKD and treatment: 5, HD<br>Number randomised (IG/CG analysed) (n): 80 (16/14/20)<br>Proportion of participants with dementia* (%): NG<br>Intervention (HLG):<br>• Mode: Intradialytic lower limb resistance exercise<br>• Type: Resistance<br>• Target intensity: 4 sets of 10 – 12 RM<br>• Intensity as per this review: Moderate<br>• Progressive: Yes<br>• Individualised: Yes<br>• Time (mins/session): 20 – 40<br>• Frequency (sessions/week): 3<br>• Length of intervention (weeks): 12<br>• Location: Dialysis unit<br>Intervention (MLG):<br>• Mode: Intradialytic lower limb resistance exercise<br>• Type: Resistance<br>• Target intensity: 3 sets of 18 – 20 RM<br>• Intensity as per this review: Low<br>• Progressive: Yes<br>• Individualised: Yes<br>• Time (mins/session): 20 – 40<br>• Frequency (sessions/week): 3<br>• Length of intervention (weeks): 12<br>• Location: Dialysis unit<br>Control: Intradialytic stretching<br>Outcome: QoL<br>Measurement: KDQOL<br>Primary or secondary outcome: Secondary<br>Finding (re: cognition): No significant group by time interaction |
| Manfredini 2017 | Title: Exercise in Patients on Dialysis: A Multicenter, Randomized Clinical Trial<br>Location: Italy<br>Funding: NG |

| | |
|---|---|
| | Study design: Multi-centre pre-test post-test RCT<br>Participants' stage of CKD and treatment: 5, HD or PD<br>Number randomised (IG/CG analysed) (n): 296 (104/123)<br>Proportion of participants with dementia* (%): NG<br>Intervention:<br>• Mode: Walking<br>• Type: Aerobic<br>• Target intensity: "low intensity"<br>• Intensity as per this review: Low<br>• Progressive: Yes<br>• Individualised: Yes<br>• Time (mins/session): 10<br>• Frequency (sessions/week): 6<br>• Length of intervention (weeks): 24<br>• Location: Home<br>Control: Usual care<br>Outcome: QoL<br>Measurement: KDQOL-SF<br>Primary or secondary outcome: Primary<br>Finding (re: cognition): CG had a significant decrease in cognition whereas IG did not - this difference in change was significant |
| Martin-Alemañy 2016 | Title: The effects of resistance exercise and oral nutritional supplementation during hemodialysis on indicators of nutritional status and quality of life<br>Location: Mexico<br>Funding: NG |

| | |
|---|---|
| | Study design: Pre-test post-test RCT<br>Participants' stage of CKD and treatment: 5, HD<br>Number randomised (IG/CG analysed) (n): 44 (17/19)<br>Proportion of participants with dementia* (%): 0<br>Intervention:<br>• Mode: Intradialytic upper and lower body resistance exercise plus oral nutritional supplement<br>• Type: Resistance<br>• Target intensity: Borg 12 – 13<br>• Intensity as per this review: Moderate<br>• Progressive: No<br>• Individualised: No<br>• Time (mins/session): 40<br>• Frequency (sessions/week): 2<br>• Length of intervention (weeks): 12<br>• Location: Dialysis unit<br>Control: Oral nutritional supplement<br>Outcome: QoL<br>Measurement: KDQOL-SF<br>Primary or secondary outcome: Primary<br>Finding (re: cognition): No significant change in cognition domain in either group |
| Martin-Alemañy 2020 | Title: Effect of Oral Nutritional Supplementation With and Without Exercise on Nutritional Status and Physical Function of Adult Hemodialysis Patients: A Parallel Controlled Clinical Trial (AVANTE-HEMO Study)<br>Location: Mexico<br>Funding: NG<br>Study design: Single centre pre-test post-test RCT |

| | |
|---|---|
| | Participants' stage of CKD and treatment: 5, HD<br>Number randomised (IG/CG analysed) (n): 45 (12/9/13)<br>Proportion of participants with dementia* (%): 0<br>Intervention (AE+ONS):<br>• Mode: Intradialytic ergometric cycling plus oral nutritional supplement<br>• Type: Aerobic<br>• Target intensity: Borg 12 – 13<br>• Intensity as per this review: Moderate<br>• Progressive: Yes<br>• Individualised: Yes<br>• Time (mins/session): 20 – 30<br>• Frequency (sessions/week): 2 or 3 (depending on number of dialysis sessions per week)<br>• Length of intervention (weeks): 12<br>• Location: Dialysis unit<br>Intervention (RE+ONS):<br>• Mode: Intradialytic upper and lower body resistance exercise plus oral nutritional supplement<br>• Type: Resistance<br>• Target intensity: Borg 12 – 13<br>• Intensity as per this review: Moderate<br>• Progressive: Yes<br>• Individualised: Yes<br>• Time (mins/session): 40<br>• Frequency (sessions/week): 2 or 3 (depending on number of dialysis sessions per week)<br>• Length of intervention (weeks): 12<br>• Location: Dialysis unit<br>Control: Oral nutritional supplement<br>Outcome: QoL<br>Measurement: KDQOL-SF<br>Primary or secondary outcome: Secondary<br>Finding (re: cognition): No significant group by time interaction |
| Matsufuji 2015 | Title: Effect of Chair Stand Exercise on Activity of Daily Living: A Randomized Controlled Trial in Hemodialysis Patients<br>Location: Japan<br>Funding: None<br>Study design: Single centre pre-test post-test RCT |

| | |
|---|---|
| | Participants' stage of CKD and treatment: 5, HD<br>Number randomised (IG/CG analysed) (n): 27 (6/11)<br>Proportion of participants with dementia* (%): NG<br>Intervention:<br>• Mode: Pre-dialytic chair stand exercise<br>• Type: Resistance<br>• Target intensity: Half of maximum duration of chair stand to fatigue<br>• Intensity as per this review: Moderate<br>• Progressive: No<br>• Individualised: Yes<br>• Time (mins/session): 15<br>• Frequency (sessions/week): 3<br>• Length of intervention (weeks) 12:<br>• Location: Hospital rehabilitation room<br>Control: Pre-dialytic stretching<br>Outcome: Global cognition<br>Measurement: 3MS<br>Primary or secondary outcome: Secondary<br>Finding (re: cognition): No difference in change in cognition between groups |
| Maynard 2019 | Title: Effects of Exercise Training Combined with Virtual Reality in Functionality and Health-Related Quality of Life of Patients on Hemodialysis<br>Location: Brazil<br>Funding: None<br>Participants' stage of CKD and treatment: 5, HD<br>Number randomised (IG/CG analysed) (n): 45 (20/20) |

| | |
|---|---|
| | Proportion of participants with dementia* (%): NG<br>Intervention:<br>• Mode: Intradialytic combined aerobic, resistance, balance, coordination, stretching using video games (Wii sports and Wii fit plus), cycle ergometer, and ankle weights.<br>• Type: Combined<br>• Target intensity: Borg 12 – 14<br>• Intensity as per this review: Moderate<br>• Progressive: Yes<br>• Individualised: No<br>• Time (mins/session): 30 – 60<br>• Frequency (sessions/week): 3<br>• Length of intervention (weeks) 12:<br>• Location: Dialysis unit<br>Control: Usual care<br>Outcome: QoL<br>Measurement: KDQOL-SF<br>Primary or secondary outcome: Primary<br>Finding (re: cognition): No significant change in cognition across groups |
| McAdams-DeMarco 2018 | Title: Intradialytic Cognitive and Exercise Training May Preserve Cognitive Function<br>Location: USA<br>Funding: Johns Hopkins Faculty Innovation Fund, National Institutes of Health Grants, the Johns Hopkins Bloomberg, School of Public Health Faculty Innovation Fund, National Institute on Aging.<br>Study design: Single centre pilot pre-test post-test RCT<br>Participants' stage of CKD and treatment: 5, HD<br>Number randomised (IG/CG analysed) (n): 23 (6/7) |

| | |
|---|---|
| | Proportion of participants with dementia* (%): 0<br>Intervention:<br>• Mode: Intradialytic foot peddling<br>• Type: Aerobic<br>• Target intensity: NG<br>• Intensity as per this review: NA<br>• Progressive: No<br>• Individualised: No<br>• Time (mins/session): as long as able to<br>• Frequency (sessions/week): NG<br>• Length of intervention (weeks): 13<br>• Location: Dialysis unit<br>Control: Usual care<br>Outcome: Global cognition, executive function, and psychomotor speed<br>Measurement: 3MS, TMTA, TMTB<br>Primary or secondary outcome: Primary<br>Finding (re: cognition): Significant decline in psychomotor speed in CG not seen in IG |
| Poorsaadet 2018 | Title: The effects of aerobic exercise on cognitive performance and sleep quality haemodialysis patients.<br>Location: Iran<br>Funding: Arak University<br>Study design: Repeated measures RCT<br>Participants' stage of CKD and treatment: 5, HD<br>Number randomised (IG/CG analysed) (n): 38 (27/11)<br>Proportion of participants with dementia* (%): 0<br>Intervention: |

| | |
|---|---|
| | • Mode: Intradialytic cycling<br>• Type: Aerobic<br>• Target intensity: Borg 12 – 15<br>• Intensity as per this review: High<br>• Progressive: Yes<br>• Individualised: No<br>• Time (mins/session): 75<br>• Frequency (sessions/week): 3<br>• Length of intervention (weeks): 24<br>• Location: Dialysis unit<br>Control: NG "control"<br>Outcome: Global cognition, executive function, and psychomotor speed<br>Measurement: MMSE, TMTB, SDT<br>Primary or secondary outcome: Primary<br>Finding (re: cognition): Significant improvement in all cognition domains in IG, with no significant change observed in CG. |
| Stringuetta Belik 2018 | Title: Influence of Intradialytic Aerobic Training in Cerebral Blood Flow and Cognitive Function in Patients with Chronic Kidney Disease: A Pilot Randomized Controlled Trial<br>Location: Brazil<br>Funding: São Paulo Research Foundation<br>Study design: Single centre pilot pre-test post-test RCT<br>Participants' stage of CKD and treatment: 5, HD<br>Number randomised (IG/CG analysed) (n): 35 (15/15)<br>Proportion of participants with dementia* (%): 0<br>Intervention:<br>• Mode: Intradialytic cycle ergometer and stretching exercise |

| | |
|---|---|
| | • Type: Combined<br>• Target intensity: 65 – 75% $HR_{max}$<br>• Intensity as per this review: Moderate<br>• Progressive: Yes<br>• Individualised: Yes<br>• Time (mins/session): 45<br>• Frequency (sessions/week): 3<br>• Length of intervention (weeks): 17<br>• Location: Dialysis unit<br>Control: Usual care<br>Outcome: Global cognition<br>Measurement: MMSE<br>Primary or secondary outcome: Primary<br>Finding (re: cognition): Improvement in IG compared to CG |
| Tawney 2000 | Title: The Life Readiness Program: A Physical Rehabilitation Program for Patients on Hemodialysis<br>Location: USA<br>Funding: Amgen grant<br>Study design: Multi-centre pre-test post-test RCT<br>Participants' stage of CKD and treatment: 5, HD<br>Number randomised (IG/CG analysed) (n): 99 (39/43)<br>Proportion of participants with dementia* (%): NG<br>Intervention:<br>• Mode: Physical activity-based counselling encouraging a mix of aerobic, strength, flexibility exercises<br>• Type: Combined<br>• Target intensity: "mild-moderate" |

| | |
|---|---|
| | • Intensity as per this review: Moderate<br>• Progressive: No<br>• Individualised: Yes<br>• Time (mins/session): 30<br>• Frequency (sessions/week): 7<br>• Length of intervention (weeks): 26<br>• Location: Home<br>Control: Usual care<br>Outcome: QoL<br>Measurement: KDQOL-SF<br>Primary or secondary outcome: Primary<br>Finding (re: cognition): No difference in change in cognition between groups |
| Uchiyama 2019 | Title: Home-based Aerobic Exercise and Resistance Training in Peritoneal Dialysis Patients: A Randomized Controlled Trial<br>Location: Japan<br>Funding: NG<br>Study design: Single centre pre-test post-test RCT<br>Participants' stage of CKD and treatment: 5, PD<br>Number randomised (IG/CG analysed) (n): 47 (24/23)<br>Proportion of participants with dementia* (%): NG<br>Intervention:<br>• Mode: Walking and upper and lower limb resistance training<br>• Type: Combined<br>• Target intensity: Borg 11 – 13 for walking and 70% of 1RM for resistance exercises<br>• Intensity as per this review: Moderate<br>• Progressive: Yes |

| | |
|---|---|
| | • Individualised: Yes<br>• Time (mins/session): 30 for walking, NG for resistance<br>• Frequency (sessions/week): 3 times walking, 2 times resistance<br>• Length of intervention (weeks): 12<br>• Location: Home<br>Control: Usual care<br>Outcome: QoL<br>Measurement: KDQOL-SF<br>Primary or secondary outcome: Primary<br>Finding (re: cognition): No significant change in cognitive subscale in either group |
| Van Craenenbroeck 2015 | Title: Effect of Moderate Aerobic Exercise Training on Endothelial Function and Arterial Stiffness in CKD Stages 3-4: A Randomized Controlled Trial<br>Location: Belgium<br>Funding: University of Antwerp & Research Foundation Flanders<br>Study design: Single centre pre-test post-test RCT<br>Participants' stage of CKD and treatment: 3 – 4, medical<br>Number randomised (IG/CG analysed) (n): 48 (16/17)<br>Proportion of participants with dementia* (%): NG<br>Intervention:<br>• Mode: Ergometric cycling<br>• Type: Aerobic<br>• Target intensity: 90% of HR at anaerobic threshold<br>• Intensity as per this review: Moderate<br>• Progressive: No<br>• Individualised: No |

| | |
|---|---|
| | • Time (mins/session): 10<br>• Frequency (sessions/week): 28<br>• Length of intervention (weeks): 13<br>• Location: Initially supervised then home<br>Control: Usual care<br>Outcome: QoL<br>Measurement: KDQOL-SF<br>Primary or secondary outcome: Secondary<br>Finding (re: cognition): Improvement in cognition in IG in comparison to CG |
| Wu 2014 | Title: Effect of individualized exercise during maintenance haemodialysis on exercise capacity and health-related quality of life in patients with uraemia<br>Location: China<br>Funding: None<br>Study design: Single centre pre-test post-test RCT<br>Participants' stage of CKD and treatment: 5, HD<br>Number randomised (IG/CG analysed) (n): 69 (32/33)<br>Proportion of participants with dementia* (%): 0<br>Intervention:<br>• Mode: Intradialytic recumbent cycling<br>• Type: Aerobic<br>• Target intensity: Borg 12 – 16<br>• Intensity as per this review: Moderate<br>• Progressive: No<br>• Individualised: Yes<br>• Time (mins/session): 15 – 20 |

| | |
|---|---|
| | • Frequency (sessions/week): 3<br>• Length of intervention (weeks): 12<br>• Location: Dialysis unit<br>Control: Intradialytic stretching<br>Outcome: QoL<br>Measurement: KDQOL-SF<br>Primary or secondary outcome: Primary<br>Finding (re: cognition): Improvement in cognition within IG but no difference in comparison to CG |

*Table 3- Characteristics of included studies. Subgroups are named as in the original study. NG = Not Given. RCT = Randomised Controlled Trial. CKD = Chronic Kidney Disease. HD = Haemodialysis. IG = intervention group. CG = control group. G2 = Group 2. G3 = Group 3. Borg = Borg CR20 Rating of Perceived Exertion (RPE) scale. Modified Borg = Borg CR10 RPE scale. NA = Not Applicable. QoL = Quality of Life. KDQOL(-SF) = Kidney Disease Quality of Life assessment (-Short Form). RM = rep max weight. HLG = High Load Group. MLG = Moderate Load Group. PD = Peritoneal dialysis. AE = Aerobic Exercise. RE = Resistance Exercise. ONS = Oral Nutritional Supplement. 3MS = Modified Mini-Mental State Examination. TMT (-A or -B) = Trail Making Test (part A or part B). MMSE = Mini-Mental State Examination. SDT = Symbol Digit Test. HR = heart rate. $HR_{max}$ = maximal HR. * based on exclusion criteria and/or reported numbers.*

| Adverse events referred to in the text | | | | | |
|---|---|---|---|---|---|
| **Paper** | **Total in IG (n)** | **Total in CG (n)** | **Event (quote from text)** | **Events in IG (n;%)** | **Events in CG (n;%)** |
| Lopes 2019 | 54 | 26 | Hypotension | 2 (4) | 0 (0) |
| | | | Angina | 2 (4) | 0 (0) |
| | | | Tachycardia at rest | 1 (2) | 0 (0) |
| | | | Access problems | 2 (4) | 1 (4) |
| Manfredi 202017 | 104 | 123 | Moderate fatigue | 31 (30) | NR |
| | | | Heavy legs or leg pain | 35 (34) | NR |
| | | | Moderate dyspnea | 29 (28) | NR |
| | | | Other symptoms including joint pain | 17 (16) | NR |
| | | | Angina | 0 (0) | NR |
| Matsufuji 2015 | 12 | 15 | Surgery for lung cancer | 1 (8) | 0 (0) |
| | | | Haemorrhage from renal cysts | 1 (8) | 0 (0) |
| | | | Hospitalisation for duodenal ulcer | 1 (8) | 0 (0) |
| | | | Knee joint pain | 1 (8) | 0 (0) |
| | | | Sudden cardiac death | 0 (0) | 1 (7) |
| | | | Surgery for cervical spondylosis | 1 (8) | 1 (7) |
| | | | Fall/head banging | 0 (0) | 1 (7) |
| Maynard 2019 | 22 | 23 | Death | 0 (0) | 1 (4) |
| | | | Adverse events unrelated to the intervention | 1 (5) | 0 (0) |
| McAdams-DeMarco 2018 | 9 | 7 | Nil | 0 (0) | 0 (0) |
| Wu 2014 | 34 | 35 | Headache | 3 (9) | 5 (14) |
| | | | Nausea/vomiting | 5 (15) | 4 (11) |

| | | | | | |
|---|---|---|---|---|---|
| | | | Hypotension | 5 (15) | 7 (20) |
| | | | Cramps | 3 (9) | 4 (11) |
| | | | Chest pain | 4 (12) | 5 (14) |
| | | | Palpitations | 1 (3) | 3 (9) |
| | | | Cognitive disturbance | 0 (0) | 1 (3) |
| Martin-Alemañy 2016 | 22 | 22 | Reports of adverse events | 0 (0) | 0 (0) |
| Martin-Alemañy 2020 | 30 | 15 | Reports of adverse events | 0 (0) | 0 (0) |
| Tawney 2000 | 51 | 48 | Death | 3 (6) | 1(2) |

*Table 4- Adverse events referred to in the text of studies. IG = Intervention Group; CG = Control Group. NR = Not Recorded.*

| Adverse events from flowcharts | | | | | |
|---|---|---|---|---|---|
| **Paper** | **Total in IG (n)** | **Total in CG (n)** | **Event (quote from flowchart)** | **Events in IG (n;%)** | **Events in CG (n;%)** |
| De Lima 2013 | 22 | 11 | Hospital admission | 1 (5) | 0 (0) |
| Lopes 2019 | 54 | 26 | Lost to follow up due to medical reason | 4 (7) | 2 (8) |
| Manfredini 2017 | 151 | 145 | Death | 2 (1) | 3 (2) |
| | | | Poor deambulation/poor clinical conditions | 16 (11) | 4 (3) |
| Martin-Alemañy 2016 | 22 | 22 | Death by bacteraemia | 1 (5) | 0 (0) |
| Martin-Alemañy 2020 | 30 | 15 | Parapneumonic pleural effusion | 0 (0) | 1 (7) |
| | | | Death | 1 (3) | 0 (0) |
| | | | Pericardial effusion | 1 (3) | 0 (0) |
| Uchiyama 2019 | 24 | 23 | Discontinued intervention due to illness unrelated to the study | 2 (8) | 1 (4) |
| Van Craenenbroeck 2015 | 25 | 23 | Illness unrelated to the study | NG | 1 (4) |
| Wu 2014 | 34 | 35 | Death from unrelated cause | 0 (0) | 1 (3) |

*Table 5 - Additional adverse events reported in the flowcharts of studies. *Note that the flowchart of De Lima* et al*. 2013 was not clear but was understood by the authors to mean that one participant from the aerobic group was hospitalised. IG = Intervention Group. CG = Control Group. NG = Not Given.*

| Assessment of risk of bias within studies | | | | | | |
|---|---|---|---|---|---|---|
| **Paper** | **Domain 1** | **Domain 2** | **Domain 3** | **Domain 4** | **Domain 5** | **Overall** |
| De Lima 2013 | Low | Low | Low | High | Some concerns | High |
| Hernández Sánchez 2021 | Low | Low | Low | High | Some concerns | High |
| Lopes 2019 | Low | High | High | High | Low | High |
| Manfredini 2017 | Low | Low | High | High | Low | High |
| Martin-Alemañy 2016 | Some concerns | Low | Low | High | Some concerns | High |
| Martin-Alemañy 2020 | Some concerns | Low | Low | High | Low | High |
| Matsufuji 2015 | Low | High | Low | High | Low | High |
| Maynard 2019 | Low | Low | High | High | Low | High |
| McAdams-DeMarco 2018 | Some concerns | Low | Low | High | Low | High |
| Poorsaadet 2018 | High | High | High | High | Some concern | High |
| Stringuetta Belik 2018 | Some concerns | Some concerns | Low | High | Low | High |
| Tawney 2000 | Some concerns | Low | High | High | Some concerns | High |
| Uchiyama 2019 | Some concerns | Low | Low | High | Low | High |
| Van Craenenbroeck 2015 | Low | Low | High | High | Low | High |
| Wu 2014 | Some concerns | Low | Low | High | Some concerns | High |

*Table 6- Assessment of risk of bias within studies. Domain 1 assesses risk of bias due to the randomisation process. Domain 2 assesses risk of bias due to deviations from the intended interventions. Domain 3 assesses risk arising from missing outcome data. Domain 4 assesses risk from the measurement of the outcome. Domain 5 assesses the risk from selective reporting of results. 'High' risk was assigned to those whose methods or reporting have a high potential for introducing bias. 'Low' risk was assigned to those with transparent reporting and methods which do not have a high risk of introducing bias. 'Some concerns' was assigned to those where there was insufficient evidence to make a judgement either way.*

| Coefficients | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | 95% Confidence Interval | |
| | Estimate | Standard Error | z | p | Lower | Upper |
| intercept | 0.019 | 0.260 | 0.073 | 0.942 | -0.491 | 0.529 |
| Intensity (2) | 0.121 | 0.300 | 0.405 | 0.686 | -0.466 | 0.709 |
| Intensity (3) | 1.286 | 0.586 | 2.195 | 0.028 | 0.138 | 2.435 |

*Note.* Wald test.

*Table 7 - Meta-regression by intensity of exercise. Intercept corresponds to the effect of low intensity exercise. Intensity (2) = moderate intensity exercise in relation to intercept. Intensity (3) = high intensity exercise in relationship to intercept. These values are displayed graphically in figure 6.*

| Fixed and Random Effects | | | |
|---|---|---|---|
| | Q | df | p |
| Omnibus test of Model Coefficients | 5.048 | 2 | 0.080 |
| Test of Residual Heterogeneity | 28.199 | 12 | 0.005 |

*Note.* *p* -values are approximate.

*Table 8 - ANOVA table for intensity regression. df = degrees of freedom*

| Coefficients of length of intervention in weeks | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | 95% Confidence Interval | |
| | Estimate | Standard Error | z | p | Lower | Upper |
| intercept | 0.152 | 0.392 | 0.388 | 0.698 | -0.616 | 0.919 |
| Length of intervention (weeks) | 0.004 | 0.024 | 0.178 | 0.858 | -0.042 | 0.051 |

*Note.* Wald test.

*Table 9- Meta-regression using length of intervention in weeks to predict effect on cognition.*

| Assessment of the risk of bias for missing or incomplete reporting of outcomes | | | | |
|---|---|---|---|---|
| **Excluded study** | **Sample size** | | **ORBIT classification for primary outcome: measure of cognition** | **Risk of bias*** |
| | **Intervention** | **Control** | | |
| Bennett 2016 | 112 | 59 | I | No risk |
| Kheirkhah 2016 | 30 | 30 | F | Low risk |
| Suhardjono 2019 | 81 | 39 | F | Low risk |
| Rahimimoghadam 2018 | 25 | 25 | F | Low risk |
| Pellizzaro 2013 | 30 | 15 | A | High risk |
| Paluchamy 2018 | 10 | 10 | B | No risk |

*Table 10- Assessment of the risk of bias for missing or incomplete outcome reporting in benefit outcomes, based on the ORBIT classification (Kirkham et al., 2018). A = Trial report states that outcome was analysed but only reports that result was not significant (typically stating P>0.05). B = Trial report states that outcome was analysed but only reports that result was significant (typically stating P<0.05. F = Clear that the outcome was measured. Judgment says outcome unlikely to have been analysed. I = Clear that the outcome was not measured. *Risk of bias arising from the lack of inclusion of non-significant results when a trial was excluded from a meta-analysis or not fully reported in a review because the data were unavailable.*

## Figures

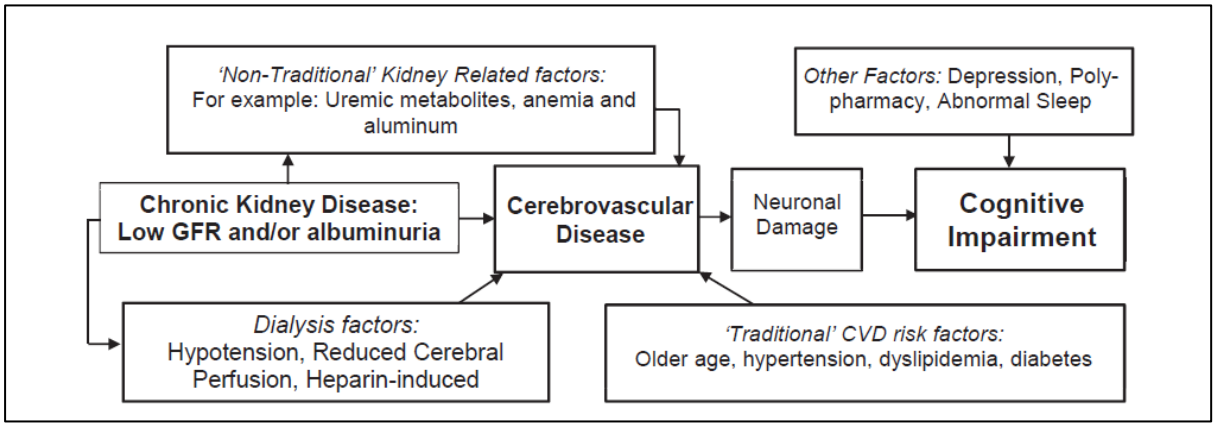


*Figure 2 - Proposed pathophysiology of chronic kidney disease–related cognitive impairment. Taken from Drew* et al.*, 2019.*[10] *CVD = cardiovascular disease, GFR = glomerular filtration rate.*

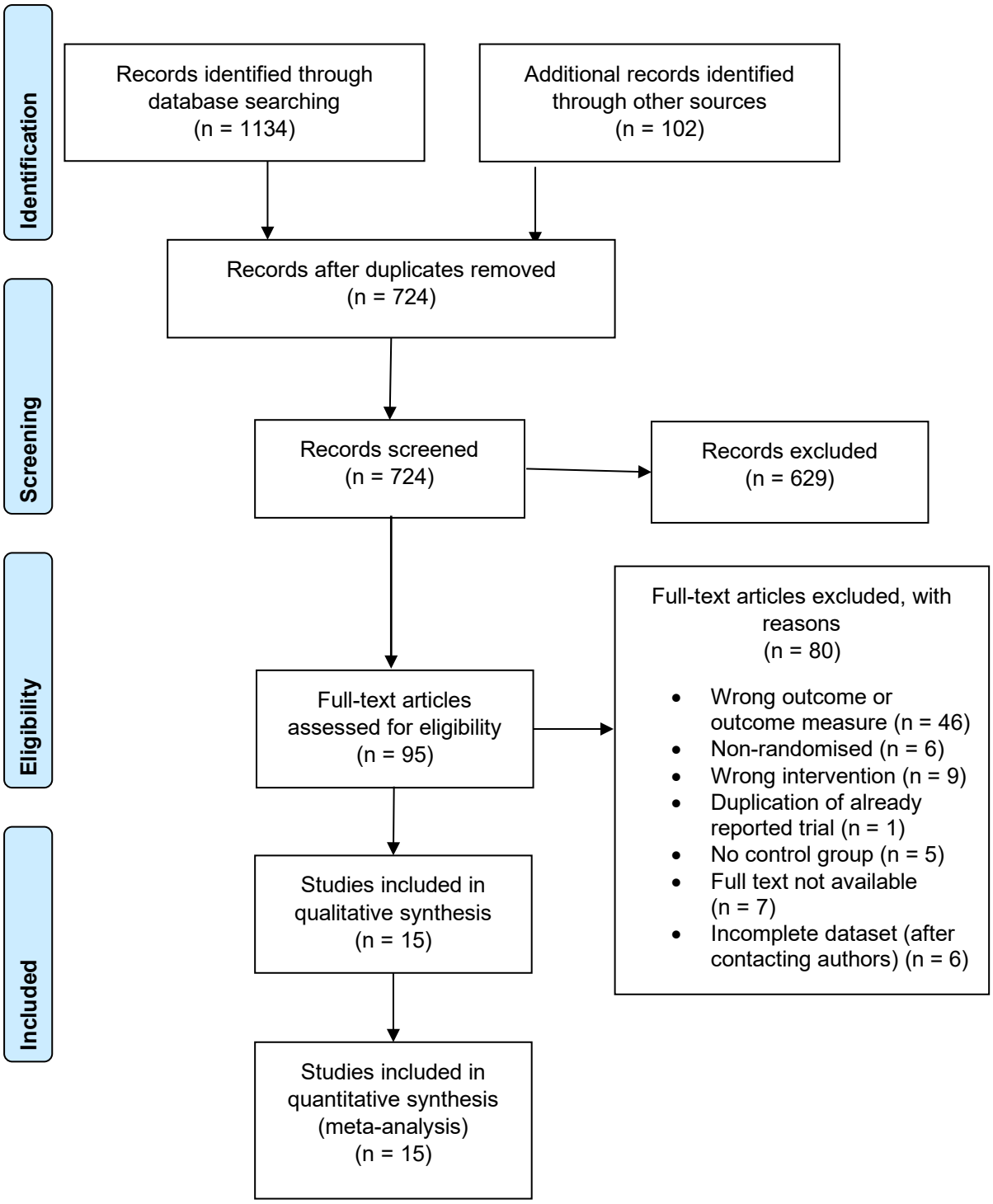


*Figure 2- Flowchart demonstrating study selection.*

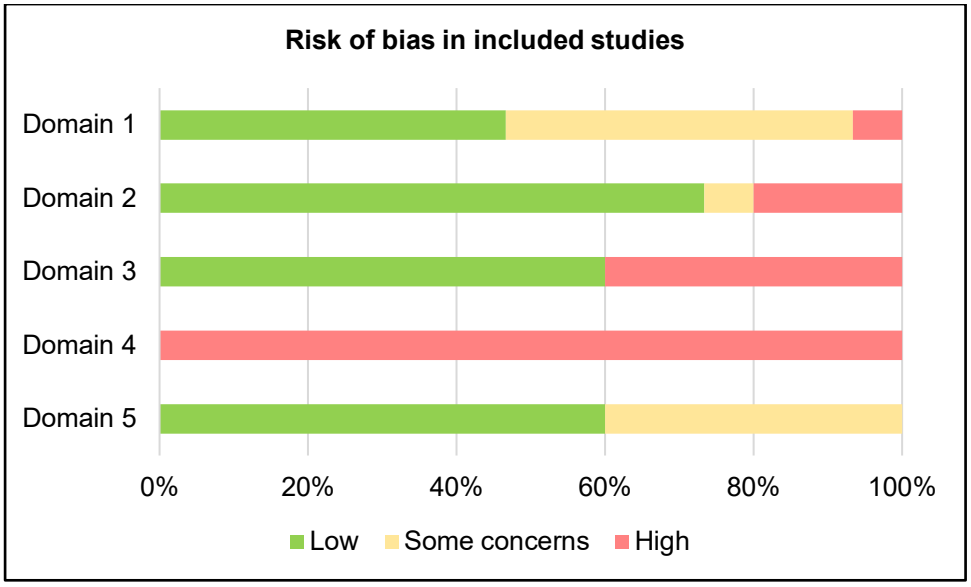


*Figure 3- Assessment of risk of bias within studies. Domain 1 assesses risk of bias due to the randomisation process. Domain 2 assesses risk of bias due to deviations from the intended interventions. Domain 3 assesses risk arising from missing outcome data. Domain 4 assesses risk from the measurement of the outcome. Domain 5 assesses the risk from selective reporting of results. 'High' risk was assigned to studies whose methods or reporting have a high potential for introducing bias. 'Low' risk was assigned to those with transparent reporting and methods which do not have a high risk of introducing bias. 'Some concerns' was assigned to those where there was insufficient evidence to make a judgement either way.*

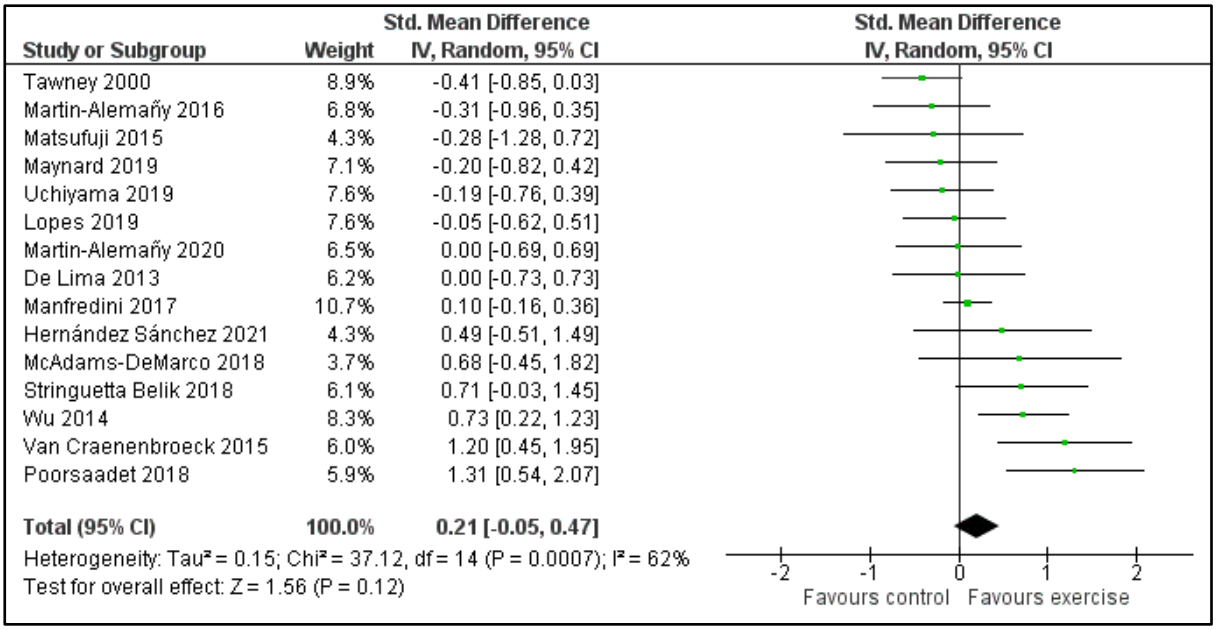


*Figure 4 - Forest plot of individual studies and overall effect estimate for effect of exercise on cognition, vs control. IV = Inverse Variance.*

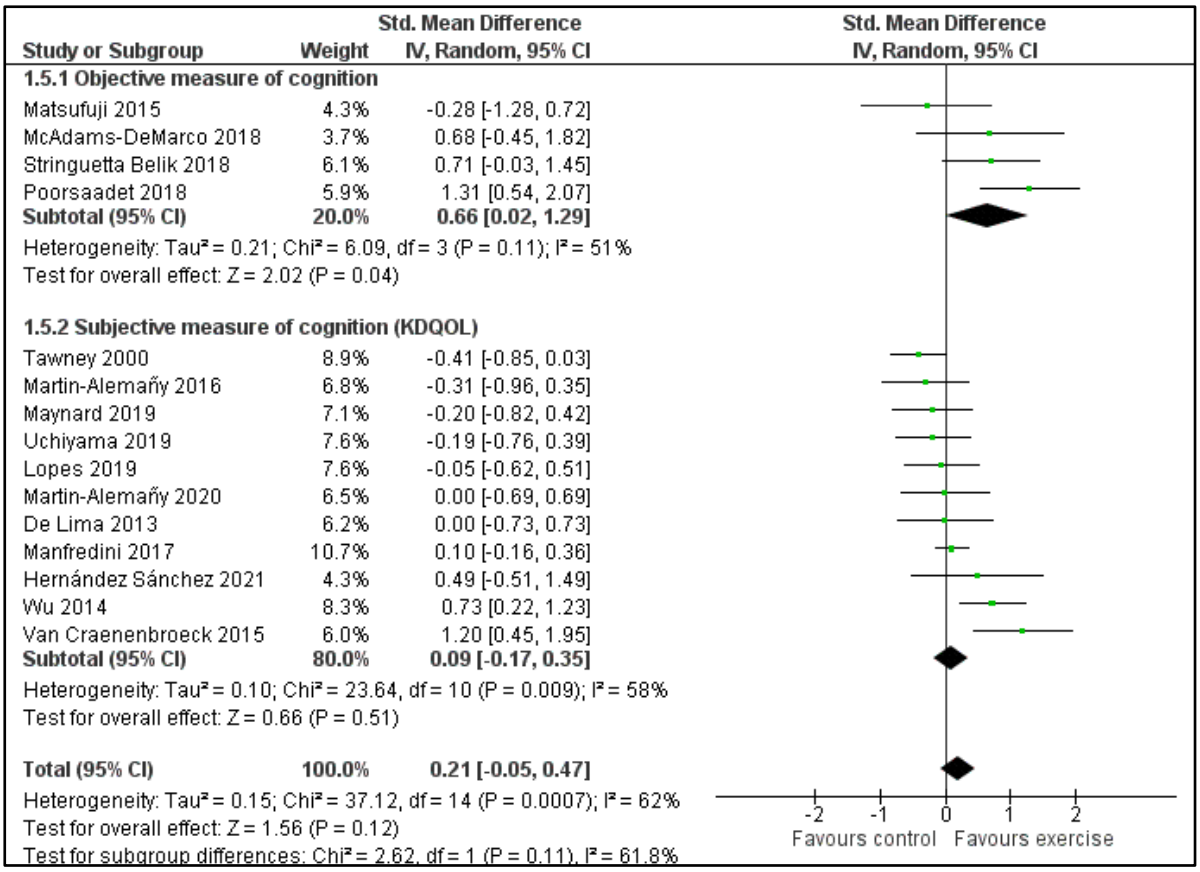


*Figure 5- Subgroup analysis by type of outcome measurement.*

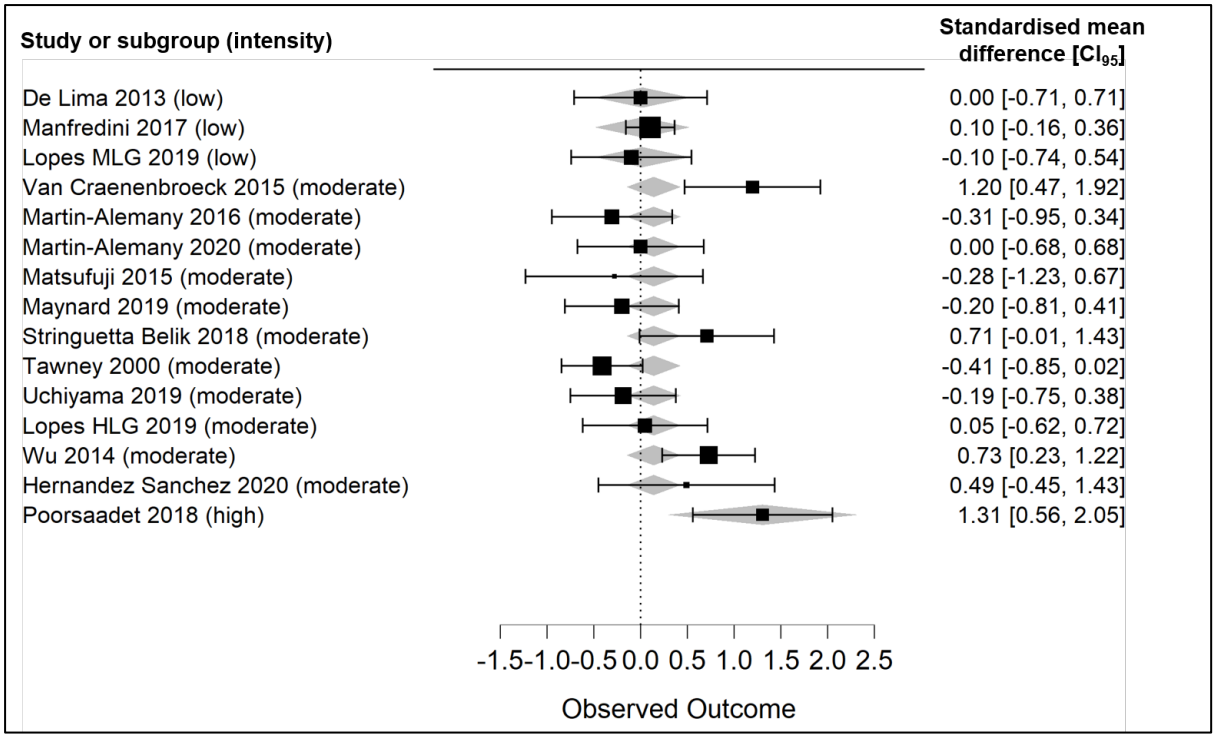


*Figure 6- Forest plot of meta-regression to investigate effect of intensity of exercise on cognition. Grey diamonds represent the expected effect for that intensity. MLG = moderate load group, HLG = high load group, both as named by Lopes* et al.[88] *Coefficient for low intensity exercise = 0.019, for moderate intensity exercise in relation to low = 0.121, for high intensity exercise in relation to low = 1.286.*

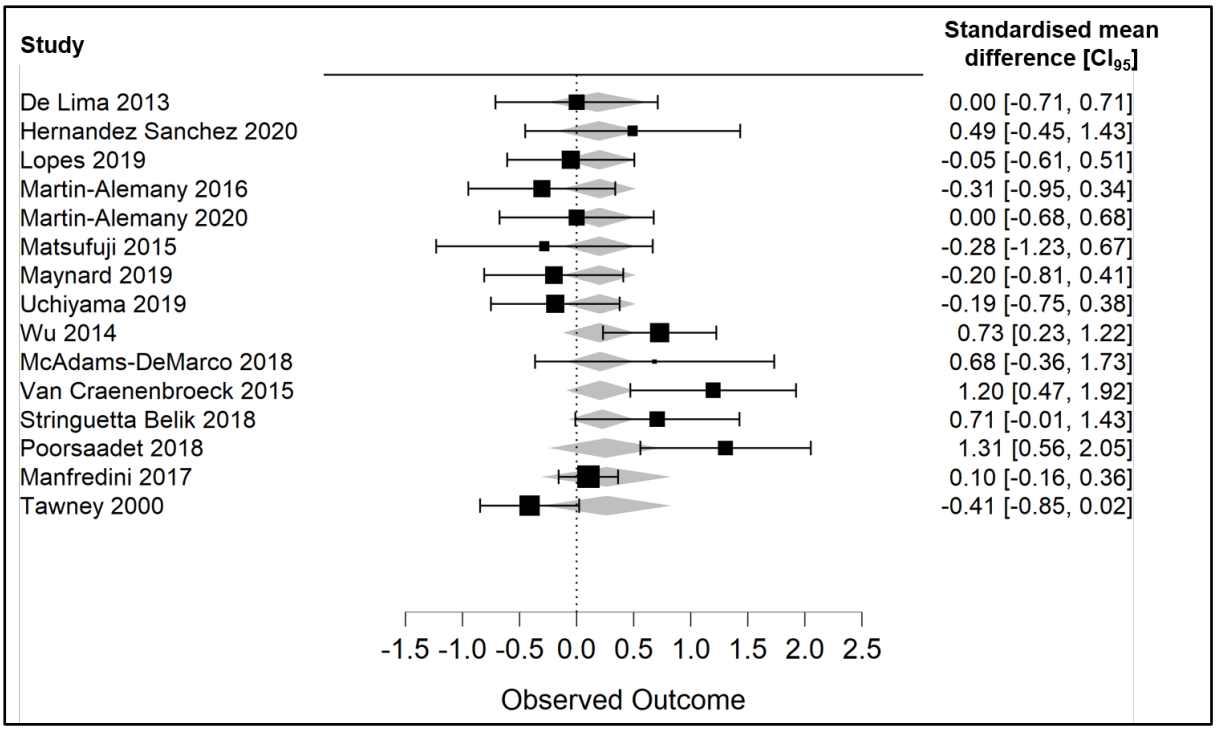


*Figure 7 - Forest plot of meta-regression to predict effect on cognition by length of intervention. Studies are presented from shortest to longest (top to bottom). Grey diamonds represent the effect estimate for each duration.*

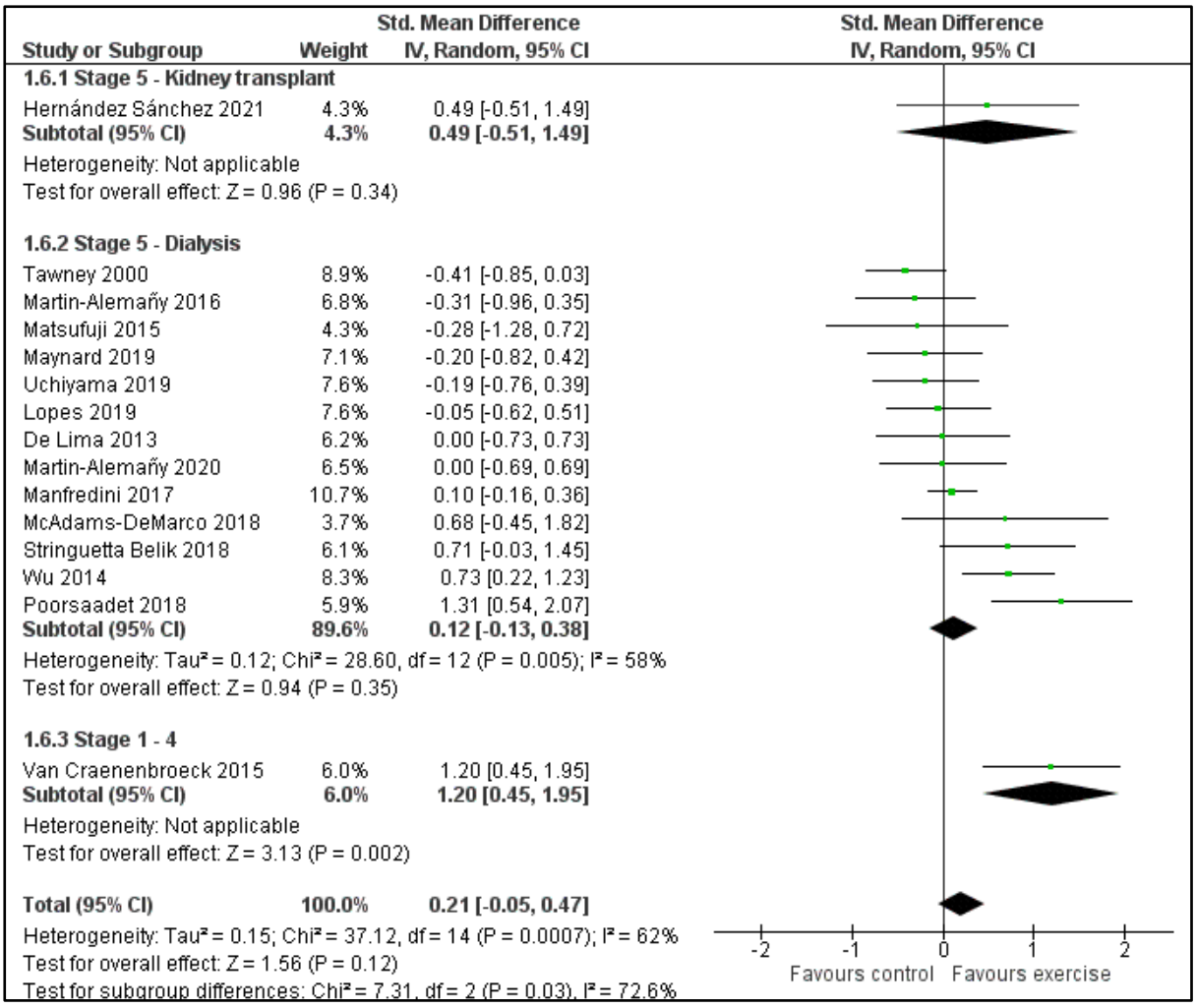


*Figure 8- Subgroup analysis by stage and treatment of CKD.*

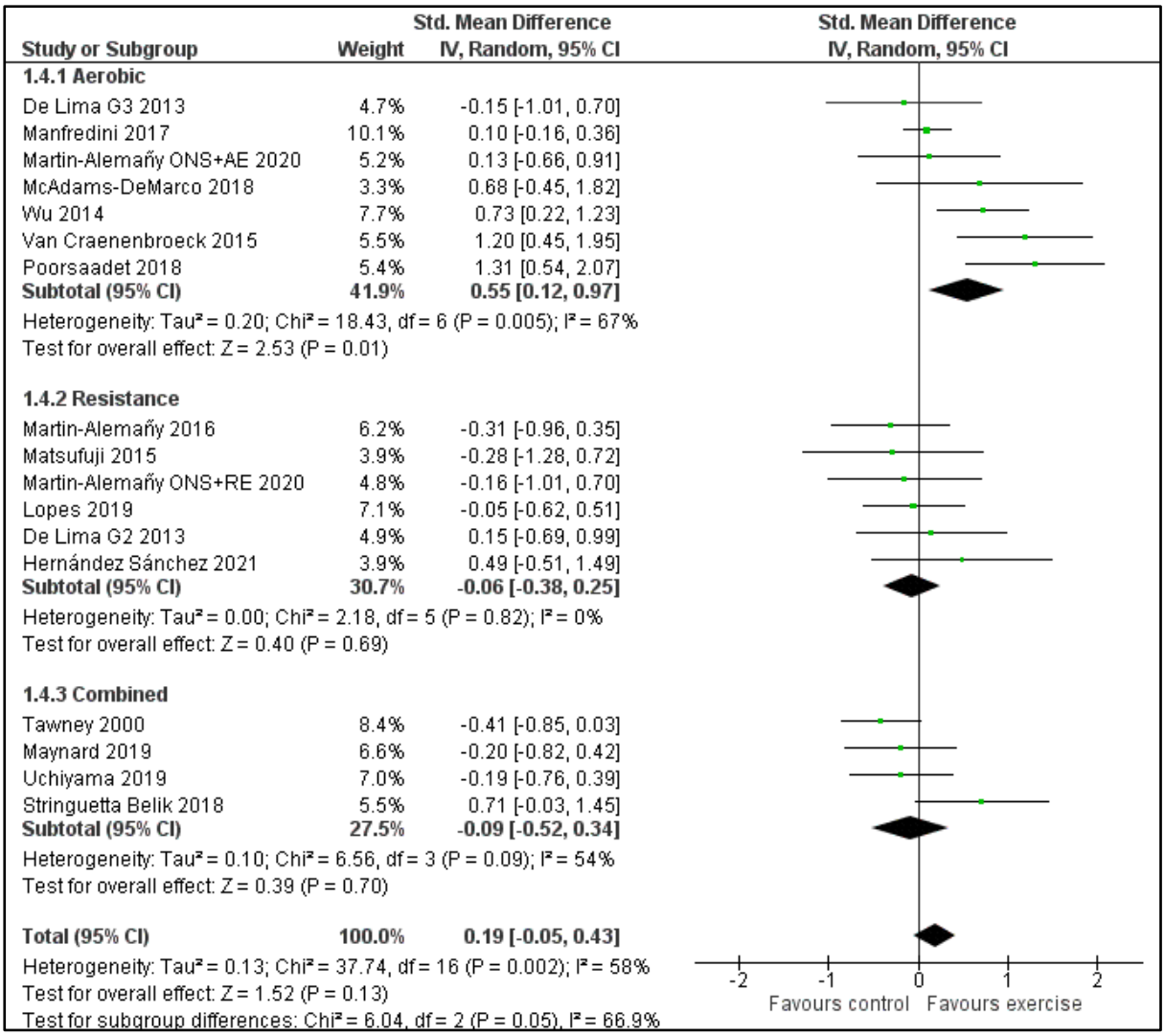


*Figure 9- Subgroup analysis by type of exercise. Subgroups are named as they were in the original papers.*

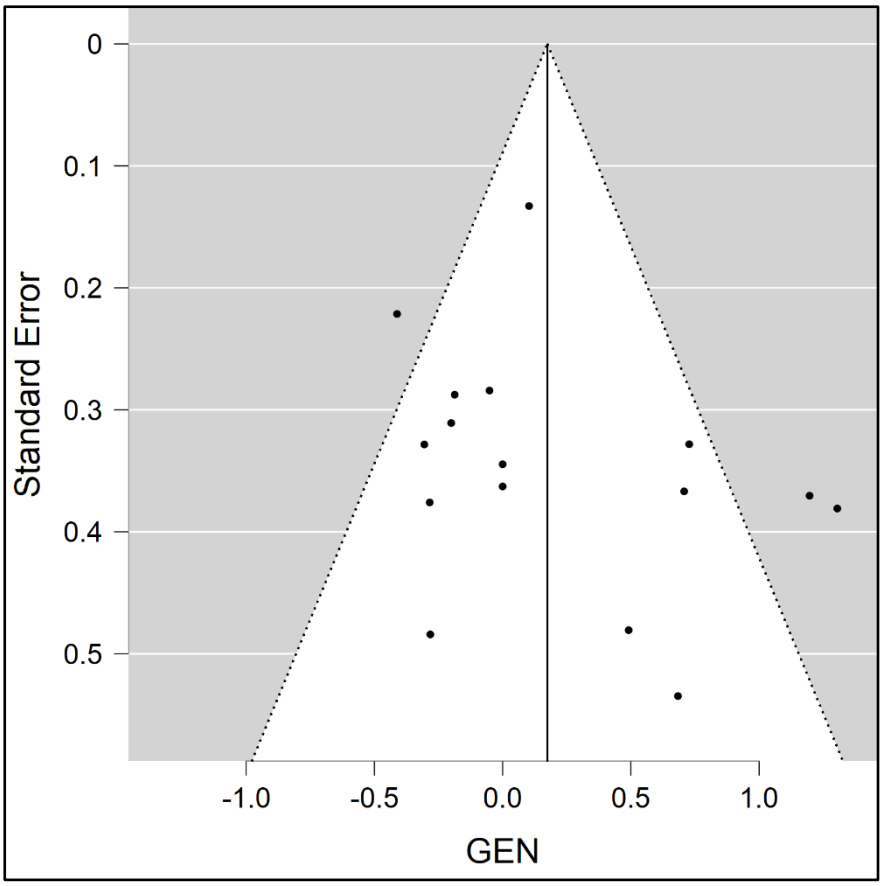


*Figure 10- funnel plot showing standardised treatment effect (x-axis) plotted against standard error (y-axis). Dotted lines represent 95% confidence intervals for the expected correlation between treatment effect and standard error under a fixed-effects analysis. While these are not applicable given the random-effects nature of the meta-analysis, they have been left in the figure to aid visual interpretation.*

## References


1. World Health Organisation: ICD-11: International Classification of Diseases (11th revision) [Internet]. icd.who.int. 2022 Available from: icd.who.int
2. World Health Organisation: Global action plan on the public health response to dementia 2017 - 2025. Geneva, Switzerland
3. World Health Organisation: Global Health Estimates 2020: Disease burden by Cause, Age, Sex, by Country and by Region, 2000-2019. Geneva, Switzerland
4. Etgen T, Chonchol M, Förstl H, Sander D: Chronic kidney disease and cognitive impairment: A systematic review and meta-analysis. *Am J Nephrol* 35: 474–482, 2012
5. Kidney Disease Improving Global Outcomes: KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl* 3: 2013
6. Levey AS, Beto J, Coronado B, Eknoyan G, Foley R, Kasiske B, Klag M, Mailloux L, Manske C, Meyer K, Parfrey P, Pfeffer M, Wenger N, Wilson P, Wright Jr J: Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease. *Am J Kidney Dis* 32: 853–906, 1998
7. Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS): National Health and Nutrition Examination Survey Questionnaire [Internet]. Available from: https://wwwn.cdc.gov/nchs/nhanes/search/datapage.aspx?Component=Questionnaire&CycleBeginYear=2015 [cited 2022 May 30]
8. Centers for Disease Control and Prevention: Chronic Kidney Disease Surveillance System - United States [Internet]. Available from: http://www.cdc.gov/ckd [cited 2022 Mar 30]
9. Ku E, Lee BJ, Wei J, Weir MR: Hypertension in CKD : Core Curriculum 2019. *Am J Kidney Dis* 74: 120–131, 2019
10. Drew DA, Weiner DE, Sarnak MJ: Cognitive Impairment in CKD: Pathophysiology, Management, and Prevention. *Am J Kidney Dis* 74: 782–790, 2019
11. Tian X, Guo X, Xia X, Yu H, Li X, Jiang A, Zhan Y: The comparison of cognitive function and risk of dementia in CKD patients under peritoneal dialysis and hemodialysis: A PRISMA-compliant systematic review and meta-analysis. *Medicine (Baltimore)* 98: e14390, 2019
12. Heiwe S, Jacobson SH: Exercise training for adults with chronic kidney disease. *Cochrane Database Syst Rev* Art. no. CD003236, 2011
13. Sofi F, Valecchi D, Bacci D, Abbate R, Gensini GF, Casini A, Macchi C: Physical

activity and risk of cognitive decline: A meta-analysis of prospective studies. *J Intern Med* 269: 107–117, 2011

14. Chu NM, Hong J, Harasemiw O, Chen X, Fowler KJ, Dasgupta I, Bohm C, Segev DL, McAdams-DeMarco MA, Global Renal Exercise Network (GREX): Chronic kidney disease , physical activity and cognitive function in older adults — results from the National Health and Nutrition Examination Survey ( 2011 – 2014 ). *Nephrol Dial Transplant* Epub ahead of print gfab338, 2021
15. Kim ED, Meoni LA, Jaar BG, Shafi T, Linda Kao WH, Estrella MM, Parekh R, Sozio SM: Association of Arterial Stiffness and Central Pressure With Cognitive Function in Incident Hemodialysis Patients: The PACE Study. 1149–1159, 2017
16. Viana JL, Kosmadakis GC, Watson EL, Bevington A, Feehally J, Bishop NC, Smith AC: Evidence for Anti-Inflammatory Effects of Exercise in CKD. *J Am Soc Nephrol* 25: 2121–2130, 2014
17. Mustata S, Groeneveld S, Davidson W, Ford G, Kiland K, Manns B: Effects of exercise training on physical impairment, arterial stiffness and health-related quality of life in patients with chronic kidney disease: a pilot study. *Int Urol Nephrol* 43: 1133–1141, 2011
18. Heiwe S, Jacobson SH: Exercise training in adults with CKD: a systematic review and meta-analysis. *Am J Kidney Dis* 64: 383–393, 2014
19. Bernier-Jean A, Beruni NA, Bondonno NP, Williams G, Teixeira-Pinto A, Craig JC, Wong G: Exercise training for adults undergoing maintenance dialysis (Review). *Cochrane Database Syst Rev* Art. No.: CD014653, 2022
20. Mustata S, Chan C, Lai V, Miller JA: Impact of an Exercise Program on Arterial Stiffness and Insulin Resistance in Hemodialysis Patients. 2713–2718, 2004
21. Goldberg AP, Geltman EM, Hagberg JM, Gavin 3rd JR, Delmez JA, Carney RM, Naumowicz A, Oldfield MH, Harter HR: Therapeutic benefits of exercise training for hemodialysis patients. *Kidney Int Suppl* 16: S303–S309, 1983
22. Molsted S, Harrison AP, Eidemak I, Andersen JL: The effects of high-load strength training with protein- or nonprotein-containing nutritional supplementation in patients undergoing dialysis. *J Ren Nutr Off J Counc Ren Nutr Natl Kidney Found* 23: 132–140, 2013
23. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H: The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 53: 695–699, 2005
24. Rosen WG, Mohs RC, Davis KL: A new rating scale for Alzheimer's disease. *Am J Psychiatry* 141: 1356–1364, 1984
25. Folstein MF, Folstein SE, McHugh PR: "Mini-mental state". A practical method for

grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12: 189–198, 1975

26. Hays RD, Kallich JD, Mapes DL, Coons SJ, Carter WB: Development of the Kidney Disease Quality of Life (KDQOLTM) Instrument. *Qual Life Res* 3: 329–338, 1994
27. Vanderlinden JA, Ross-White A, Holden R, Shamseddin MK, Day A, Boyd JG: Quantifying cognitive dysfunction across the spectrum of end-stage kidney disease: A systematic review and meta-analysis. *Nephrology* 24: 5–16, 2019
28. Walker KA, Power MC, Gottesman RF: Defining the relationship between hypertension, cognitive decline, and dementia: a review. 19: 24, 2017
29. Kueper JK, Speechley M, Montero-Odasso M: The Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog): Modifications and Responsiveness in Pre-Dementia Populations. A Narrative Review. *J Alzheimer's Dis* 63: 423–444, 2018
30. Shu Y, He Q, Xie Y, Zhang W, Zhai S, Wu T: Cognitive Gains of Aerobic Exercise in Patients With Ischemic Cerebrovascular Disorder: A Systematic Review and Meta-Analysis. *Front Cell Dev Biol* 8: 582380, 2020
31. Kaltsatou A, Grigoriou SS, Karatzaferi C, Giannaki CD, Stefanidis I, Sakkas GK: Cognitive function and exercise training for chronic renal disease patients: A literature review. *J Bodyw Mov Ther* 19: 509–515, 2015
32. Martins CTB, Ramos GSM, Guaraldo SA, Uezima CBB, Martins JPLB, Ribeiro Junior E: Comparison of cognitive function between patients on chronic hemodialysis who carry out assisted physical activity and inactive ones. *J Bras Nefrol* 33: 14–16, 2011
33. Parsons TL, Toffelmire EB, King-VanVlack CE: Exercise training during hemodialysis improves dialysis efficacy and physical performance. *Arch Phys Med Rehabil* 87: 680–687, 2006
34. Chu NM, McAdams-DeMarco MA: Exercise and cognitive function in patients with end-stage kidney disease. *Semin Dial* 32: 283–290, 2019
35. Murtaza A, Dasgupta I: Chronic Kidney Disease and Cognitive Impairment. *J Stroke Cerebrovasc Dis* 30: 105529, 2021
36. Liu H, Song Y, Zhao D, Zhan M: Effect of exercise on cognitive impairment in patients undergoing haemodialyses : A systematic review and meta - analysis of randomised controlled trials. *J Ren Care* 1–10, 2022
37. Lo CY, Li L, Lo WK, Chan ML, So E, Tang S, Yuen MC, Cheng IK, Chan TM: Benefits of exercise training in patients on continuous ambulatory peritoneal dialysis. *Am J kidney Dis Off J Natl Kidney Found* 32: 1011–1018, 1998
38. Yamamoto S, Matsuzawa R, Kamitani T, Hoshi K, Ishii D, Noguchi F, Hamazaki N, Nozaki K, Ichikawa T, Maekawa E, Matsunaga A, Yoshida K: Efficacy of Exercise Therapy Initiated in the Early Phase After Kidney Transplantation: A Pilot Study. *J*

*Ren Nutr* 2020

39. Forbes D, Forbes SC, Blake CM, Thiessen EJ, Forbes S: Exercise programs for people with dementia. *Cochrane Database Syst Rev* Art. no. CD006489, 2015
40. Cooke S, Pennington K, Jones A, Bridle C, Smith MF, Curtis F: Effects of exercise, cognitive, and dual-task interventions on cognition in type 2 diabetes mellitus: A systematic review and meta-analysis. *PLoS One* 15: e0232958, 2020
41. Wang R, Yan W, Du M, Tao L, Liu J: The effect of physical activity interventions on cognition function in patients with diabetes: A systematic review and meta-analysis. *Diabetes Metab Res Rev* 37: e3443, 2021
42. Young J, Angevaren M, Rusted J, Tabet N: Aerobic exercise to improve cognitive function in older people without known cognitive impairment (Review). Art. no. CD005381, 2015
43. Northey JM, Cherbuin N, Pumpa KL, Smee DJ, Rattray B: Exercise interventions for cognitive function in adults older than 50 : a systematic review with meta-analysis. *Br J Sport Med* 52: 154–160, 2018
44. Demurtas J, Schoene D, Torbahn G, Marengoni A, Grande G, Zou L, Petrovic M, Maggi S, Cesari M, Lamb S, Soysal P, Kemmler W, Sieber C, Mueller C, Shenkin SD, Schwingshackl L, Smith L, Veronese N: Physical Activity and Exercise in Mild Cognitive Impairment and Dementia: An Umbrella Review of Intervention and Observational Studies. *J Am Med Dir Assoc* 21: 1415–1422, 2020
45. Zheng G, Xia R, Zhou W, Tao J, Chen L: Aerobic exercise ameliorates cognitive function in older adults with mild cognitive impairment : a systematic review and meta-analysis of randomised controlled trials. *Br J Sport Med* 50: 1443–1450, 2016
46. Groot C, Hooghiemstra AM, Raijmakers PGHM, van Berckel BNM, Scheltens P, Scherder EJA, van der Flier WM, Ossenkoppele R: The effect of physical activity on cognitive function in patients with dementia: A meta-analysis of randomized control trials. *Ageing Res Rev* 25: 13–23, 2016
47. Hoffmann CM, Petrov ME, Lee RE: Aerobic physical activity to improve memory and executive function in sedentary adults without cognitive impairment: A systematic review and meta-analysis. *Prev Med Reports* 23: 101496, 2021
48. Colcombe S, Kramer AF: Fitness effects on the cognitive function of older adults: A meta-analytic study. *Psychol Sci* 14: 125–130, 2003
49. Landrigan J-F, Bell T, Crowe M, Clay OJ, Mirman D: Lifting cognition: a meta-analysis of effects of resistance exercise on cognition. *Psychol Res* 84: 1167–1183, 2020
50. Smith PJ, Blumenthal JA, Hoffman BM, Cooper H, Strauman TA, Welsh-Bohmer K, Browndyke JN, Sherwood A: Aerobic exercise and neurocognitive performance: A meta-analytic review of randomized controlled trials. *Psychosom Med* 72: 239–252,

2010
51. Chen F-T, Hopman RJ, Huang C-J, Chu C-H, Hillman CH, Hung T-M, Chang Y-K: The effect of exercise training on brain structure and function in older adults: A systematic review based on evidence from randomized control trials. *J Clin Med* 9: 914, 2020
52. WHO: Risk reduction of cognitive decline and dementia: WHO guidelines.
53. Bronas UG, Puzantian H, Hannan M: Cognitive impairment in chronic kidney disease: Vascular milieu and the potential therapeutic role of exercise. *Biomed Res Int* 2017: Art. ID 2726369, 2017
54. Madero M, Gul A, Sarnak MJ: Cognitive function in chronic kidney disease. *Semin Dial* 21: 29–37, 2008
55. Berger I, Wu S, Masson P, Kelly PJ, Duthie FA, Whiteley W, Parker D, Gillespie D, Webster AC: Cognition in chronic kidney disease: a systematic review and meta-analysis. *BMC Med* 14: 2016
56. U.S. Department of Health and Human Services: Chapter 2. Physical Activity and Health. In: *Physical Activity Guidelines for Americans.*, 2nd ed., pp 27–45, 2018
57. Afsar B, Siriopol D, Aslan G, Eren OC, Dagel T, Kilic U, Kanbay A, Burlacu A, Covic A, Kanbay M: The impact of exercise on physical function, cardiovascular outcomes and quality of life in chronic kidney disease patients: a systematic review. *Int Urol Nephrol* 50: 885–904, 2018
58. Wyngaert K V, Van Craenenbroeck AH, Van Biesen W, Dhondt A, Tanghe A, Van Ginckel A, Celie B, Calders P: The effects of aerobic exercise on eGFR, blood pressure and VO2 peak in patients with chronic kidney disease stages 3-4: A systematic review and meta-analysis. *PLoS One* 13: 1–19, 2018
59. Segura-Orti E: Exercise in haemodyalisis patients: a systematic literature review. *NEFROLOGIA* 30: 236–246, 2010
60. Segura-Orti E, Johansen KL: Exercise in end-stage renal disease. *Semin Dial* 23: 422–430, 2010
61. Baker LA, March DS, Wilkinson TJ, Billany RE, Bishop NC, Castle EM, Chilcot J, Davies MD, Brown MPMG, Greenwood SA, Junglee NA, Kanavaki AM, Lightfoot CJ, Macdonald JH, Rossetti GMK, Smith AC, Burton JO: Clinical practice guideline exercise and lifestyle in chronic kidney disease. *BMC Nephrol* 23: Art. no. 75, 2022
62. Painter PL, Krasnoff JB: End Stage Metabolic Disease: Chronic Kidney Disease and Liver Failure. In: *ACSM's Exercise Management for Persons With Chronic Diseases and Disabilities*, 3rd ed., edited by Durstine J., Moore GE, Painter PL, Roberts SO, pp 175–181, 2009
63. Stringuetta-Belik F, Shiraishi FG, Oliveira e Silva VR, Barretti P, Caramori JCT, Bôas

PJ, da Silva Franco RJ: [Greater level of physical activity associated with better cognitive function in hemodialysis in end stage renal disease]. *J Bras Nefrol* 34: 378–386, 2012

64. Fukushima RLM, Micali PN, do Carmo EG, de Souza Orlandi F, Costa JLR: Cognitive abilities and physical activity in chronic kidney disease patients undergoing hemodialysis. *Dement e Neuropsychol* 13: 329–334, 2019
65. World Health Organisation: WHO guidelines on physical activity and sedentary behaviour. Geneva, Switzerland
66. Ashby D, Borman N, Burton J, Corbett R, Davenport A, Farrington K, Flowers K, Fotheringham J, Fox A, Franklin G, Gardiner C, Gerrish M, Greenwood S, Hothi D, Khares A, Koufaki P, Levy J, Lindley E, Macdonald J, Mafrici B, Mooney A, Tattersall J, Tyerman K, Villar E, Wilkie M: Renal Association Clinical Practice Guideline Haemodialysis. Bristol, The Renal Association
67. Higgins JPT, Li T, Deeks JJ: Chapter 6: Choosing effect measures and computing estimates of effect. In: *Cochrane Handbook for Systematic Reviews of Interventions.*, edited by Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch V., 2021
68. Sterne JA., Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng H-Y, Corbett MS, Eldridge SM, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT: RoB 2: A revised tool for assessing risk of bias in randomised trials. *Br Med J* 366: l4898, 2019
69. Cohen J: Statistical Power Analysis in the Behavioral Sciences. 2nd editio. Hillsdale (NJ), Lawrence Erlbaum Associates, Inc.
70. Wan X, Wang W, Liu J, Tong T: Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 14: Art. no. 135, 2014
71. The Cochrane Collaboration: Review Manager. 2020
72. JASP Team: JASP. 2020
73. Deeks JJ, Higgins JPT, Altman DG: Chapter 10: Analysing data and undertaking meta-analyses. In: *Cochrane Handbook for Systematic Reviews of Interventions*, 6.2., edited by Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, Welch V, 2021
74. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, Nieman DC, Swain DP: Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy

adults: Guidance for prescribing exercise. *Med Sci Sports Exerc* 43: 1334–1359, 2011
75. Riebe D: Exercise Prescription. In: *ACSM's Guidelines for Exercise Testing and Prescription.*, Ninth edit., edited by Pescatello LS, Arena R, Riebe D, Thompson PD, pp 161–193, 2014
76. National Strength and Conditioning Association: Training Load Chart. 2012
77. Tonelli M, Wiebe N, Knoll G, Bello A, Browne S, Jadhav D, Klarenbach S, Gill J: Systematic review: Kidney transplantation compared with dialysis in clinically relevant outcomes. *Am J Transplant* 11: 2093–2109, 2011
78. Egger M, Smith GD, Schneider M, Minder C: Bias in meta-anlysis detected by a simple, graphical test. *BMJ* 315: 629–634, 1997
79. Kirkham JJ, Altman DG, Chan A-W, Gamble C, Dwan KM, Williamson PR: Outcome reporting bias in trials: A methodological approach for assessment and adjustment in systematic reviews. *BMJ* 362: k3802, 2018
80. Bennett PN, Fraser S, Barnard R, Haines T, Ockerby C, Street M, Wang WC, Daly R: Effects of an intradialytic resistance training programme on physical function: a prospective stepped-wedge randomized controlled trial. *Nephrol Dial Transplant* 31: 1302–1309, 2016
81. Kheirkhah D, Mirsane A, Ajorpaz NM, Rezaei M: Effects of Pilates Exercise on Quality of Life of Patients on Hemodialysis. *J Crit Care Nurs* 9: e6981, 2016
82. Suhardjono, Umami V, Tedjasukmana D, Setiati S: The effect of intradialytic exercise twice a week on the physical capacity, inflammation, and nutritional status of dialysis patients: A randomized controlled trial. *Hemodial Int* 23: 486–493, 2019
83. Rahimimoghadam Z, Rahemi Z, Sadat Z, Ajorpaz NM: Pilates exercises and quality of life of patients with chronic kidney disease. *Complement Ther Clin Pract* 34: 35–40, 2019
84. Pellizzaro CO, Thomé FS, Veronese F V: Effect of peripheral and respiratory muscle training on the functional capacity of hemodialysis patients. *Ren Fail* 35: 189–197, 2013
85. Paluchamy T, Vaidyanathan R: Effectiveness of intradialytic exercise on dialysis adequacy, physiological parameters, biochemical markers and quality of life - A pilot study. *Saudi J Kidney Dis Transplant* 29: 902–910, 2018
86. Hernández Sánchez S, Carrero JJ, Morales JS, Ruiz JR: Effects of a resistance training program in kidney transplant recipients: A randomized controlled trial. *Scand J Med Sci Sports* 31: 473–479, 2021
87. Manfredini F, Mallamaci F, D'Arrigo G, Baggetta R, Bolignano D, Torino C, Lamberti N, Bertoli S, Ciurlino D, Rocca-Rey L, Barillà A, Battaglia Y, Rapanà RM, Zuccalà A, Bonanno G, Fatuzzo P, Rapisarda F, Rastelli S, Fabrizi F, Messa P, De Paola L,

Lombardi L, Cupisti A, Fuiano G, Lucisano G, Summaria C, Felisatti M, Pozzato E, Malagoni AM, Castellino P, Aucella F, Abd ElHafeez S, Provenzano PF, Tripepi G, Catizone L, Zoccali C: Exercise in patients on dialysis: A multicenter, Randomized Clinical Trial. *J Am Soc Nephrol* 28: 1259–1268, 2017

88. Lopes LCC, Mota JF, Prestes J, Schincaglia RM, Silva DM, Queiroz NP, Freitas ATV de S, Lira FS, Peixoto M do RG: Intradialytic Resistance Training Improves Functional Capacity and Lean Mass Gain in Individuals on Hemodialysis: A Randomized Pilot Trial. *Arch Phys Med Rehabil* 100: 2151–2158, 2019
89. Tawney KW, Tawney PJ, Hladik G, Hogan SL, Falk RJ, Weaver C, Moore DT, Lee MY: The life readiness program: a physical rehabilitation program for patients on hemodialysis. *Am J Kidney Dis* 36: 581–591, 2000
90. de Lima MC, de Lima Cicotoste C, da Silva Cardoso K, Forgiarini LAJ, Monteiro MB, Dias AS: Effect of exercise performed during hemodialysis: strength versus aerobic. *Ren Fail* 35: 697–704, 2013
91. Martin-Alemañy G, Espinosa-Cuevas M de LÁ, Pérez-Navarro M, Wilund KR, Miranda-Alatriste P, Cortés-Pérez M, García-Villalobos G, Gómez-Guerrero I, Cantú-Quintanilla G, Ramírez-Mendoza M, Valdez-Ortiz R: Effect of Oral Nutritional Supplementation With and Without Exercise on Nutritional Status and Physical Function of Adult Hemodialysis Patients: A Parallel Controlled Clinical Trial (AVANTE-HEMO Study). *J Ren Nutr* 30: 126–136, 2020
92. Matsufuji S, Shoji T, Yano Y, Tsujimoto Y, Kishimoto H, Tabata T, Emoto M, Inaba M: Effect of chair stand exercise on activity of daily living: a randomized controlled trial in hemodialysis patients. *J Ren Nutr* 25: 17–24, 2015
93. Maynard LG, de Menezes DL, Lião NS, de Jesus EM, Andrade NLS, Santos JCD, da Silva Júnior WM, Bastos K de A, Barreto Filho JAS: Effects of Exercise Training Combined with Virtual Reality in Functionality and Health-Related Quality of Life of Patients on Hemodialysis. *Games Health J* 8: 339–348, 2019
94. McAdams-DeMarco MA, Konel J, Warsame F, Ying H, González Fernández M, Carlson MC, Fine DM, Appel LJ, Segev DL: Intradialytic Cognitive and Exercise Training May Preserve Cognitive Function. *Kidney Int Reports* 3: 81–88, 2018
95. Stringuetta Belik F, Oliveira E Silva VR, Braga GP, Bazan R, Perez Vogt B, Costa Teixeira Caramori J, Barretti P, de Souza Gonçalves R, Fortes Villas Bôas PJ, Hueb JC, Martin LC, da Silva Franco RJ: Influence of Intradialytic Aerobic Training in Cerebral Blood Flow and Cognitive Function in Patients with Chronic Kidney Disease: A Pilot Randomized Controlled Trial. *Nephron* 140: 9–17, 2018
96. Uchiyama K, Washida N, Morimoto K, Muraoka K, Kasai T, Yamaki K, Miyashita K, Wakino S, Itoh H: Home-based Aerobic Exercise and Resistance Training in

Peritoneal Dialysis Patients: A Randomized Controlled Trial. *Sci Rep* 9: Art. no. 2632, 2019

97. Van Craenenbroeck AH, Van Craenenbroeck EM, Van Ackeren K, Vrints CJ, Conraads VM, Verpooten GA, Kouidi E, Couttenye MM: Effect of Moderate Aerobic Exercise Training on Endothelial Function and Arterial Stiffness in CKD Stages 3-4: A Randomized Controlled Trial. *Am J Kidney Dis* 66: 285–296, 2015
98. Wu Y, He Q, Yin X, He Q, Cao S, Ying G: Effect of individualized exercise during maintenance haemodialysis on exercise capacity and health-related quality of life in patients with uraemia. *J Int Med Res* 42: 718–727, 2014
99. Martin-Alemañy G, Valdez-Ortiz R, Olvera-Soto G, Gomez-Guerrero I, Aguire-Esquivel G, Cantu-Quintanilla G, Lopez-Alvarenga JC, Miranda-Alatriste P, Espinosa-Cuevas A: The effects of resistance exercise and oral nutritional supplementation during hemodialysis on indicators of nutritional status and quality of life. *Nephrol Dial Transplant* 31: 1712–1720, 2016
100. Poorsaadet L, Soltani P, Ghassami K, Kohansal B, Ahmadlou M: The effects of aerobic exercise on cognitive performance and sleep quality haemodialysis patients. *Australas Med J* 11: 278–285, 2018
101. Baggetta R, D'Arrigo G, Torino C, ElHafeez SA, Manfredini F, Mallamaci F, Zoccali C, Tripepi G, Bolignano D, Lamberti N, Bertoli S, Ciurlino D, Rocca-Rey L, Barillà A, Battaglia Y, Rapanà RM, Zuccalà A, Bonanno G, Fatuzzo P, Rapisarda F, Rastelli S, Fabrizi F, Messa P, De Paola L, Lombardi L, Cupisti A, Fuiano G, Lucisano G, Summaria C, Felisatti M, Pozzato E, Malagoni AM, Castellino P, Aucella F, Provenzano PF, Catizone L: Effect of a home based, low intensity, physical exercise program in older adults dialysis patients: A secondary analysis of the EXCITE trial. *BMC Geriatr* 18: 1–7, 2018
102. Etgen T, Sander D, Bickel H, Förstl H: Mild cognitive impairment and dementia: the importance of modifiable risk factors. *Dtsch Arztebl Int* 108: 743–750, 2011
103. Wilund KR, Viana JL, Perez LM: A Critical Review of Exercise Training in Hemodialysis Patients: Personalized Activity Prescriptions Are Needed. *Exerc Sport Sci Rev* 48: 28–39, 2020
104. Greenwood SA, Koufaki P, Macdonald JH, Bhandari S, Burton JO, Dasgupta I, Farrington K, Ford I, Kalra PA, Kean S, Kumwenda M, Macdougall IC, Messow CM, Mitra S, Reid C, Smith AC, Taal MW, Thomson PC, Wheeler DC, White C, Yaqoob M, Mercer TH: Randomized Trial—PrEscription of intraDialytic exercise to improve quAlity of Life in Patients Receiving Hemodialysis. *Kidney Int Reports* 6: 2159–2170, 2021
105. Kurella M, Luan J, Yaffe K, Chertow GM: Validation of the Kidney Disease Quality of

Life (KDQOL) Cognitive Function subscale. *Kidney Int* 66: 2361–2367, 2004

106. Sorensen EP, Sarnak MJ, Tighiouart H, Scott T, Giang LM, Kirkpatrick B, Lou K, Weiner DE: The Kidney Disease Quality of Life Cognitive Function Subscale and Cognitive Performance in Maintenance Hemodialysis Patients. *Am J Kidney Dis* 60: 417–426, 2012
107. Sanders LMJ, Hortobágyi T, la Bastide-van Gemert S, van der Zee EA, van Heuvelen MJG: Dose-response relationship between exercise and cognitive function in older adults with and without cognitive impairment: A systematic review and meta-analysis. *PLoS One* 14: e0210036, 2019
108. Wilson S, Dhar A, Tregaskis P, Lambert G, Barton D, Walker R: Known unknowns: Examining the burden of neurocognitive impairment in the end-stage renal failure population. *Nephrology* 23: 501–506, 2018
109. Hobson P, Lewis A, Nair H, Wong S, Kumwenda M: How common are neurocognitive disorders in patients with chronic kidney disease and diabetes? Results from a cross-sectional study in a community cohort of patients in North Wales, UK. *BMJ Open* 8: 2018
110. Murray AM, Tupper DE, Knopman DS, Gilbertson DT, Pederson SL, Li S, Smith GE, Hochhalter AK, Collins A., Kane R.: Cognitive impairment in hemodialysis patients is common. *Neurology* 67: 216–223, 2006
111. Wilkinson TJ, Clarke AL, Nixon DGD, Hull KL, Song Y, Burton JO, Yates T, Smith AC: Prevalence and correlates of physical activity across kidney disease stages: An observational multicentre study. *Nephrol Dial Transplant* 36: 641–649, 2021
112. SONG Initiative: The SONG Handbook for Establishing and Implementing Core Outcomes in Clinical Trials Across the Spectrum of Chronic Kidney Disease. 1.0. Sydney, Australia
113. SONG Initiative: 2.8 Establishing the set of core outcome domains. In: *The SONG Handbook for Establishing and Implementing Core Outcomes Across the Spectrum of Chronic Kidney Disease*, p 16, 2017
114. McAdams-DeMarco MA, Chu NM, Steckel M, Kunwar S, González Fernández M, Carlson MC, Fine DM, Appel LJ, Diener-West M, Segev DL: Interventions Made to Preserve Cognitive Function Trial (IMPCT) study protocol: a multi-dialysis center 2x2 factorial randomized controlled trial of intradialytic cognitive and exercise training to preserve cognitive function. *BMC Nephrol* 21: 383, 2020
115. Chan KN, Chen Y, Lit Y, Massaband P, Kiratli J, Rabkin R, Myers JN: A randomized controlled trial of exercise to prevent muscle mass and functional loss in elderly hemodialysis patients: Rationale, study design, and baseline sample. *Contemp Clin Trials Commun* 15: 100365, 2019

116. Kastelz A, Tzvetanov IG, Fernhall B, Shetty A, Gallon L, West-Thielke P, Hachaj G, Grazman M, Benedetti E: Experimental protocol of a randomized controlled clinical trial investigating the effects of personalized exercise rehabilitation on kidney transplant recipients' outcomes. *Contemp Clin Trials* 45: 170–176, 2015
117. Klaassen G, Zelle DM, Navis GJ, Dijkema D, Bemelman FJ, Bakker SJL, Corpeleijn E: Lifestyle intervention to improve quality of life and prevent weight gain after renal transplantation: Design of the Active Care after Transplantation (ACT) randomized controlled trial. *BMC Nephrol* 18: 296, 2017
118. Morais MJD, Raimundo RD, Oliveira FS, de Abreu LC, Bezerra IMP, Silva RPM, Rodrigues AS, Valenti VE, Pérez-Riera AR: Evaluation of the effects of aerobic training during hemodialysis on autonomic heart rate modulation in patients with chronic renal disease. *Medicine (Baltimore)* 98: e15976, 2019
119. World Health Organisation: Disability-adjusted life years (DALYs) [Internet]. 2022 Available from: https://www.who.int/data/gho/indicator-metadata-registry/imr-details/158 [cited 2022 Jul 21]

## Supplementary Information

### S1. Full search strategy

This is the full search strategy employed for the Medline database, using the EBSCOhost search engine. The same search terms were used for each of the four major databases, with alterations made to truncation symbols.

1. (MH "Renal Insufficiency, Chronic+")
2. TI renal insufficiency, chronic OR AB renal insufficiency, chronic
3. TI chronic kidney disease OR AB chronic kidney disease
4. TI CKD* OR AB CKD*
5. TI chronic renal disease OR AB chronic renal disease
6. (MH "Renal Insufficiency+")
7. TI renal insufficiency OR AB renal insufficiency
8. (MH “Kidney Failure, Chronic+”)
9. TI kidney failure, chronic OR AB kidney failure, chronic
10. TI ESRF OR AB ESRF
11. TI end stage renal disease OR AB end stage renal disease
12. TI end stage kidney disease OR AB end stage kidney disease
13. TI end stage renal failure OR AB end stage renal failure
14. TI chronic renal failure OR AB chronic renal failure
15. TI chronic renal impairment OR AB chronic renal impairment
16. (MH “Renal Replacement Therapy+”)
17. TI renal replacement therap* OR AB renal replacement therap*
18. TI RRT OR AB RRT
19. TI ESKD OR AB ESKD
20. TI h?emodialysis OR AB h?emodialysis
21. TI renal transplant OR AB renal transplant
22. TI dialysis OR AB dialysis
23. TI predialysis OR AB predialysis
24. TI ESRD OR AB ESRD
25. TI kidney transplant OR AB kidney transplant
26. TI peritoneal dialysis OR AB peritoneal dialysis
27. TI pre-dialysis OR AB pre-dialysis
28. TI h?emodiafiltration OR AB h?emodiafiltration

29. TI nondialysis OR AB nondialysis
30. TI non-dialysis OR AB non-dialysis
31. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 8 OR 9 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30
32. (MH “Exercise+”)
33. TI exercise OR AB exercise
34. TI aerobic exercise OR AB aerobic exercise
35. TI exercise training OR AB exercise training
36. TI physical activity OR AB physical activity
37. TI physical exercise OR AB physical exercise
38. (MH “Exercise Therapy+”)
39. TI exercise therapy OR AB exercise therapy
40. TI non-pharmacological methods OR AB non-pharmacological methods
41. TI structured exercise OR AB structured exercise
42. TI prescribed exercise OR AB prescribed exercise
43. TI muscle training OR AB muscle training
44. (MH "Resistance Training")
45. TI resistance training OR AB resistance training
46. TI resistance exercise OR AB resistance exercise
47. TI weight-bearing exercise OR AB weight-bearing exercise
48. TI weight lifting OR AB weight lifting
49. TI muscle strengthening OR AB muscle strengthening
50. TI strength training OR AB strength training
51. (MH "High-Intensity Interval Training")
52. TI high intensity interval training OR AB high intensity interval training
53. TI HIIT OR AB HIIT
54. TI high intensity exercise OR AB high intensity exercise
55. TI moderate intensity exercise OR AB moderate intensity exercise
56. (MH “Sports+”)
57. TI sport* OR AB sport*
58. TI walking OR AB walking
59. TI running OR AB running
60. TI cycling OR AB cycling
61. TI exercise program* OR AB exercise program*
62. TI exercise intervention* OR AB exercise intervention*

63. TI non-pharmacological intervention* OR AB non-pharmacological intervention*
64. TI weight bearing exercise OR AB weight bearing exercise
65. TI weightlifting OR AB weightlifting
66. TI home based exercise OR AB home based exercise
67. TI home-based exercise OR AB home-based exercise
68. TI supervised exercise OR AB supervised exercise
69. TI low intensity exercise OR AB low intensity exercise
70. TI circuit-based exercise OR AB circuit-based exercise
71. TI swimming OR AB swimming
72. 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59 OR 60 OR 61 OR 62 OR 63 OR 64 OR 65 OR 66 OR 67 OR 68 OR 69 OR 70 OR 71
73. TI routine treatment OR AB routine treatment
74. TI routine management OR AB routine management
75. TI normal management OR AB normal management
76. TI usual care OR AB usual care
77. TI control OR AB control
78. TI stretching OR AB stretching
79. TI normal care OR AB normal care
80. TI routine care OR AB routine care
81. TI pharmacological control OR AB pharmacological control
82. TI light exercise OR AB light exercise
83. TI meditation OR AB meditation
84. TI behavio?ral intervention OR AB behavio?ral intervention
85. TI cognitive behavio?ral therapy OR AB cognitive behavio?ral therapy
86. TI CBT OR AB CBT
87. TI diet therapy OR AB diet therapy
88. TI diet change OR AB diet change
89. TI diet OR AB diet
90. TI nutrition therapy OR AB nutrition therapy
91. TI counsel?ing OR AB counsel?ing
92. TI brain training OR AB brain training
93. TI standard care OR AB standard care
94. TI low intensity exercise OR AB low intensity exercise
95. TI controls OR AB controls

96. TI normal treatment OR AB normal treatment
97. 73 OR 74 OR 75 OR 76 OR 77 OR 79 OR 80 OR 81 OR 82 OR 83 OR 84 OR 85 OR 86 OR 87 OR 88 OR 89 OR 90 OR 91 OR 92 OR 93 OR 94 OR 95 OR 96
98. TI MMSE OR AB MMSE
99. (MH “Cognition+”)
100. TI cognition OR AB cognition
101. TI cognitive impairment OR AB cognitive impairment
102. (MH “Cognitive dysfunction+”)
103. TI cognitive dysfunction OR AB cognitive dysfunction
104. TI cognitive function OR AB cognitive function
105. TI mild cognitive impairment OR AB mild cognitive impairment
106. TI cognitive decline OR AB cognitive decline
107. (MH “Memory Disorders+”)
108. TI memory disorders OR AB memory disorders
109. TI KDQOL SF OR AB KDQOL SF
110. TI TMT OR AB TMT
111. (MH “Quality of Life”)
112. TI quality of life OR AB quality of life
113. TI KDQOL CF OR AB KDQOL CF
114. TI 3MS OR AB 3MS
115. TI ADAS-cog OR AB ADAS-cog
116. TI trailmaking test OR AB trailmaking test
117. TI Alzheimer’s disease assessment scale-cognitive subscale OR AB Alzheimer’s disease assessment scale-cognitive subscale
118. TI MOCA OR AB MOCA
119. TI mini mental state examination OR AB mini mental state examination
120. TI Montreal cognitive assessment OR AB Montreal cognitive assessment
121. TI kidney disease quality of life OR AB kidney disease quality of life
122. TI modified mini mental state OR AB modified mini mental state
123. TI KDQOL-SF OR AB KDQOL-SF
124. TI QOL OR AB QOL
125. TI cognitive performance OR AB cognitive performance
126. TI short term memory OR AB short term memory
127. TI long term memory OR AB long term memory
128. TI executive function* OR AB executive function*
129. TI attention OR AB attention
130. TI cognitive speed OR AB cognitive speed

131. TI trail making test OR AB trail making test
132. TI working memory OR AB working memory
133. TI short-term memory OR AB short-term memory
134. TI long-term memory
135. TI cogstate OR AB cogstate
136. TI mini mental state exam OR AB mini mental state exam
137. 98 OR 99 OR 100 OR 101 OR 102 OR 103 OR 104 OR 105 OR 106 OR 017 OR 108 OR 109 OR 110 OR 111 OR 112 OR 113 OR 114 OR 115 OR 116 OR 117 OR 118 OR 119 OR 120 OR 121 OR 122 OR 123 OR 124 OR 125 OR 126 OR 127 OR 128 OR 129 OR 130 OR 131 OR 132 OR 133 OR 134 OR 135 OR 136
138. 31 AND 72 AND 97 AND 137

The search terms used for the OpenGrey literature search were “Exercise AND chronic kidney disease”; “Physical activity AND chronic kidney disease”; “Exercise AND dialysis”; “Physical activity AND dialysis”; “Exercise AND renal disease”; and “Physical activity AND renal disease”. No limits were used.

**S2. Conversion of length of intervention period from months to weeks.**

| **Conversion of months to weeks for purpose of subgroup analysis** | |
|---|---|
| **Length reported (months)** | **Length used for analysis (weeks)** |
| 3 | 13 |
| 4 | 17 |
| 6 | 26 |

*Table S2- Conversion of months to weeks for the purpose of subgroup analysis.*