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Exercise and Cognitive Function in Chronic Kidney Disease: A Systematic Review and Meta-Analysis of Efficacy and Harms

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Abstract:	Background: People living with chronic kidney disease (CKD) are at increased risk of cognitive impairment. Exercise may improve cognitive function. This systematic review and meta-analysis of randomized controlled trials (RCTs) was completed to determine the efficacy and harms of exercise in improving cognitive function in people living with CKD. Methods: A systematic literature review identified RCTs of people with any stage of CKD, with an intervention that exercised large-muscle groups, and with a validated outcome measure of cognitive function. First, harms were analyzed. Then a random-effects meta-analysis was completed with subsequent planned subgroup analyses to investigate heterogeneity between CKD stages and treatments, between different exercise types, durations and intensities, and between different outcome methodologies. Finally, quality of evidence was rated. Results: Nineteen trials randomized 1160 participants. Harms were reported on 94 occasions in intervention groups vs. 83 in control. The primary analysis found that exercise had a small but statistically significant effect on cognition in CKD (effect size (ES) = 0.22; 95% confidence intervals (CI95) = 0.00, 0.44; p = 0.05). However, the quality of evidence was rated as low. Subgroup analyses found that type of exercise moderated the effect on cognition (χ2 = 7.62; p = 0.02), with positive effects only observed following aerobic exercise (ES = 0.57; CI95 = 0.21, 0.93; p = 0.002). Conclusions: Across the spectrum of CKD, exercise had a small but positive and clinically meaningful effect on cognitive function and did not appear to be harmful. Aerobic exercise was particularly beneficial. However, results must be interpreted

	cautiously due to the low quality of evidence. Nevertheless, care teams may choose to recommend aerobic exercise interventions to prevent cognitive decline. Researchers should design unbiased studies to clarify what intensity and duration of exercise is required to maximize efficiency of such exercise interventions.
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Key point #1: as follow-up to "Key Points: Please state the 2-3 key points of the article. The responses included here will be included with your final published paper. The key points should be complete statements and not duplications of your keywords or index terms. At least two key points are required."	Cognitive impairment is common in chronic kidney disease (CKD). Exercise targets multiple risk factors of cognitive decline.
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Key point #3: as follow-up to "Key Points: Please state the 2-3 key points of the article. The responses included here will be included with your final published paper. The key points should be complete statements and	Further analyses revealed that aerobic exercise was particularly beneficial, and that exercise did not substantially increase harms.

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Exercise and Cognitive Function Chronic Kidney Disease: A Systematic Review and Meta-Analysis of Efficacy and Harms

Short title/running head:

Exercise and cognition in CKD

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Key Points:

- Cognitive impairment is common in chronic kidney disease (CKD). Exercise targets multiple risk factors of cognitive decline.
- Meta-analysis found that exercise had a small but positive effect on cognitive function in CKD, albeit the quality of evidence was low.
- Further analyses revealed that aerobic exercise was particularly beneficial, and that exercise did not substantially increase harms.

Abstract

Background: People living with chronic kidney disease (CKD) are at higher risk of cognitive impairment. Exercise may improve cognitive function. This systematic review and meta-analysis of randomized controlled trials (RCTs) was completed to determine the efficacy and harms of exercise in improving cognitive function in people living with CKD.

Methods: A systematic literature review identified RCTs of people with any stage of CKD, with an intervention that exercised large-muscle groups, and with a validated outcome measure of cognitive function. First, harms were analyzed. Then a random-effects meta-analysis was completed with subsequent planned subgroup analyses to investigate heterogeneity between CKD stages and treatments, between different exercise types, durations and intensities, and between different outcome methodologies. Finally, quality of evidence was rated.

Results: Nineteen trials randomized 1160 participants. Harms were reported on 94 occasions in intervention groups vs. 83 in control. The primary analysis found that exercise had a small but statistically significant effect on cognition in CKD (effect size (ES) = 0.22; 95% confidence intervals (CI_{95}) = 0.00, 0.44; P = 0.05). However, the quality of evidence was rated as low. Subgroup analyses found that type of exercise moderated the effect on cognition (χ^2 = 7.62; P = 0.02), with positive effects only observed following aerobic exercise (ES = 0.57; CI_{95} = 0.21, 0.93; P = 0.002).

Conclusions: Across the spectrum of CKD, exercise had a small but positive and clinically meaningful effect on cognitive function and did not appear to be harmful. Aerobic exercise was particularly beneficial. However, results must be interpreted cautiously due to the low quality of evidence. Nevertheless, care teams may choose to recommend aerobic exercise interventions to prevent cognitive decline. Researchers should design unbiased studies to clarify what intensity and duration of exercise is required to maximize efficiency of such exercise interventions.

Keywords:

Cognition; Cognitive impairment; Dementia; Dialysis; Physical Activity.

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Introduction

Cognitive impairment (CI) describes a range of worsening cognitive function from mild CI which does not diminish appreciably a person's ability to carry out activities of daily living (ADLs), to dementia, which does. CI burdens affect an individual, their families, and health social care systems (1).

People living with chronic kidney disease (CKD) are at higher risk of CI than those without CKD (2). Estimates of CI prevalence in CKD range from 20 – 80%, depending on degree of kidney impairment and treatment modality (3). Changes to cognitive function can occur early in the progression of CKD, and different domains of cognition are affected at different rates (4). Predictors of CI in individuals with CKD include traditional risk factors (such as cerebrovascular and cardiovascular disease, diabetes, hypertension, dyslipidemia) and non-traditional risk factors (such as increased blood concentrations of urea and its metabolites, anemia, depression, and polypharmacy) (2,3).

In the general population, the World Health Organization (WHO) strongly recommends physical exercise, as well as management (including exercise) of diabetes and hypertension to reduce risk of CI (1). Generally, physical activity seems to have beneficial effects on brain structures, but other indirect mechanisms such as positive effects of exercise on cardiovascular risk factors, and other biological mechanisms such as enhanced immune function and anti-inflammatory properties, are also possible (1). Exercise has also been proposed to improve cognition in people living with CKD, as there is evidence that it ameliorates multiple risk factors for cognitive decline, including insulin resistance (5), high blood pressure (6), arterial stiffness (7), quality of life (6,8), obesity (9), and depression (7,8).

Additionally, observational data in CKD suggests an association between activity levels and cognitive function (10), albeit not all studies concur (11). There have also been several discursive reviews of studies including people living with CKD which investigated cognition as a primary outcome (12–15), one systematic review (16), and two meta-analyses (8,17) of randomized controlled trials that only included dialysis patients. The systematic review (16) and the meta-analyses (8,17) generated contradictory findings, with the Cochrane meta-analysis concluding there was no overall effect of exercise on cognition (8). Whilst utilizing a robust methodology, the Cochrane meta-analysis included only five studies, investigated dialysis patients only, combined multiple exercise modes including very low intensity exercise (such as yoga) which may have diluted any potential effects of exercise on cognition, and did not grade the quality of evidence for the secondary outcome of cognition.

Therefore, the present meta-analysis aimed to re-examine the efficacy of exercise interventions in improving cognition in people living with CKD. We also carefully assessed harms and quality of evidence in recent trials that investigated all stages of CKD, and separately assessed the moderating effects of different exercise types and outcome methodologies. Thus, the present study provides important novel information for clinicians and researchers.

Methods

Study design and search strategy

This systematic review and meta-analysis study was registered at www.crd.york.ac.uk/prospero, number CRD42021271184.

A librarian was consulted; the full search strategy including search terms is available upon request.

Information sources

The final search of four databases (Medline, PubMed, CINAHL and Web of Science) was completed on the 1st November 2023. A search of grey literature was also completed (www.opengrey.eu) and reference lists of relevant studies were also reviewed.

Eligibility criteria

RCTs reported in English were included if they recruited adults with CKD undergoing any treatment and included any exercise intervention which exercised large muscle groups. Whilst the current guidelines recommend a minimum of 150 minutes of moderate intensity exercise per week (18), there is evidence that any level of activity is beneficial for other health-related outcomes in CKD (19). Therefore, exercise of any duration and intensity was included. Acceptable controls were usual care; attention control (including sham exercise); brain training; or diet change. Acceptable outcomes included cognition measured by any validated method.

Data collection process

The mean cognition score from the end of the intervention period, and standard deviation (SD) of this score, were collected. Where baseline data were presented as separate groups, the values were combined as previously recommended (20).

Risk of bias

Bias risk within each study was assessed using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) across five domains: the randomization 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 within trials (21).

Risk of publication bias assessment

To assess risk of publication bias, a visual assessment of a funnel plot of the included studies and Egger's regression test were used to assess asymmetry (31). The Outcome Reporting Bias in Trials (ORBIT) guidelines (32) were used to judge risk of bias arising from non-reporting of outcomes in papers which would otherwise have been included in the analysis.

Reporting of harms

Harms were defined as originally described by the primary authors and all harms were included regardless of type and severity. Because a statistical analysis of harms would likely have been underpowered, harms were only presented descriptively and no formal risk of bias when reporting harms was calculated.

Summary measures and data synthesis

The primary outcome measure was the standardized mean difference in cognitive test scores post-intervention, comparing exercise intervention to control. Results are presented as effect estimate (effect size) (ES) and 95% confidence intervals (CI_{95}), interpretated as per Cohen where 0.2 = small effect; 0.5 = moderate effect; and 0.8 = large effect (22). P-value for significance was set at $P \leq 0.05$.

Where there were multiple interventions, the exercise groups were combined into one, as recommended (20). Where data were presented as medians (range or interquartile range), sample means and SD were estimated as recommended (23). 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. Forest plots were used to visualize the effect outcomes. We predominantly used RevMan software (24), and JASP (25) for the meta-regressions and funnel plot. χ^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 as recommended (26).

To investigate heterogeneity between studies, as indicated by a statistically significant χ^2 test, a further five analyses were planned *a priori*:
i) Subgroup analysis comparing *stage and treatment of CKD*. This analysis split participants into the subgroups of stage 1 – 4, kidney transplant, and dialysis patients (4). In this and all other subgroup analyses, differences between subgroups were assessed using χ^2, and subgroups within studies adopted the moniker given by the original authors.
ii) Subgroup analysis comparing *type of exercise intervention*. This analysis grouped participants by type of exercise: aerobic (defined as structured physical activity that likely relied upon aerobic metabolism, typically activity that was sustained for more than 10 minutes and utilized large muscle groups to improve capacity of the cardiovascular system) resistance (structured physical activity that utilized dynamic or static muscle contract resisted by an external force), flexibility (structured physical activity designed to enhance joint range of motion), or combined (at least two of the above) (27–30).
iii) Meta-regression investigating *the relationship between intensity of exercise and effect size*. Exercise interventions were defined as low, moderate or high intensity (defined in Supplementary Table 1). In this and all other meta-regressions, the treatment effect within each study was adjusted by taking into account the moderator (in this example, intensity of exercise). Then, a Q-test was used to assess the relationship between the moderator and the overall treatment effect. A significant Q value suggests a moderator influences the overall treatment effect greater than would be expected by chance. Furthermore, a significant test of residual heterogeneity would suggest there was a degree of unexplained difference between the subgroups.

iv) Meta-regression exploring *the association of length of intervention period with effect size.*

v) Subgroup analysis of *objective versus subjective measures of cognition*.

Rating quality of evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to rate the quality of evidence supporting the primary and subgroup analyses (56).

Results

Study selection and characteristics

Of 922 unique studies, 124 full texts were assessed for eligibility, resulting in 19 studies included in the meta-analysis (Figure 1) (33–51). Study characteristics can be found in Supplementary Tables 2, 3 and 8. The number of participants randomized in each study ranged from 16 (34) to 296 (36); the total number of participants randomized was 1,160. There were data available for 953 participants (481 participants in intervention and 472 in control groups). (34)(36)Only six of 19 studies specifically stated that cognitive function was a primary outcome.

Participant characteristics

The weighted mean age of participants at baseline was 58 years. The proportion of women in each study ranged from 15 (51) to 60% (47). One study included kidney transplant patients (34); two studies included patients with stage 1 to 4 disease (49,50); 14 studies included hemodialysis patients (33,35, 37–47,51); one study included peritoneal dialysis (PD) patients (48) and one study (36) included both hemodialysis and PD patients (Supplementary Table 2).

One study required participants to be literate (45). Eight of the included studies excluded patients with dementia (41,43,46) or a cognitive disturbance which would affect their ability to participate (33,37,38,45,51).

Six studies explicitly included those who were sedentary or not undertaking any regular physical activity (33,34,37,38,40,42). An additional three studies found all their participants to be relatively inactive at baseline (defined by comparison to other chronically ill patients (47), or by being less fit than healthy patients by Six Minute Walking Test (39), or by stating that 55% of their participants were inactive) (45). Four studies excluded patients undertaking regular exercise or deemed to have an existing high level of fitness (35,36,42,46).

Interventions

Details of each study's exercise prescription are summarized in Supplementary Tables 2 and 8. Frequency of exercise ranged from two (34,37,38) to 28 sessions per week (50) (mode frequency = three sessions per week). Three studies or subgroups used a low intensity intervention (33,35,36); fifteen studies or subgroups used moderate intensity(34,35,37–40,42–44,46–51); one study used high intensity (45); and one study did not report exercise intensity (41). The duration of exercise sessions varied from 10 to 75 minutes.

Eleven of 15 hemodialysis studies performed intradialytic interventions (33,35,37,38,40,41,43–46,51). Eight studies or subgroups used an aerobic exercise intervention (33,36,38,41,44,45,50,51); seven used resistance exercise (33–35,37–39,43); six used combined interventions (40,42,46–49); no studies used flexibility exercise. Four studies used stretching as a control (35,39,43,51) and two studies used oral nutritional supplements in both intervention and control groups (37,38). Six interventions were home-based (36,42,47–50); two were supervised in a gym or rehab environment (34,39); and the remaining eleven were supervised at the dialysis unit (33,35,37,38,40,41,43–46,51).

Adherence

Eleven studies reported adherence, usually as a proportion of sessions completed out of those offered: mean adherence was reported between 33 – 100% (34–38,40,46,48–50). Using a different method to report adherence, Tawney *et al.* found that participants in the intervention group increased their self-reported moderate intensity activity by an hour per week (47). Six studies did not report adherence to the intervention (33,39,41,42,45,51).

Risk of bias in studies

Overall, all studies were found to be at high risk of bias (Supplementary Table 6), due to several common themes: outcome assessors and/or participants being unblinded (domain 4); missing data which could be due to the value of the missing data itself (domain 3: e.g. patients with poor cognitive function may be more likely to drop out due to assessment confusion or cognitive fatigue); and failure to report the method of allocation concealment (domain 1).

Risk of publication bias

The visual assessment of the funnel plot (see Supplementary materials Figure 1) and negative Egger's test (P = 0.52) suggested no overt asymmetry and thus no effect of publication bias.

Harms

Harms were reported on 94 occasions in intervention groups vs. 83 occasions in control. Harms were reported in the text (35,37–41,47,49,51) or participant flowcharts (33,35–38,44,48,50,51). The variable use by primary authors of passive and active harm ascertainment, of non-validated tools to measure harms, and of variable definitions of severity may have led to bias and either under or over reporting of harms. To partially overcome this possible bias, individual harms are described and reported separately for each study and each intervention in Supplementary Tables 4 and 5.

Primary analysis

In people living with CKD, exercise had a small but statistically significant and clinically meaningful effect on cognition compared to control (ES = 0.22; CI_{95} = -0.00, 0.44; *P* = 0.05: Figure 2). There was a large degree of variability within most studies (as evidenced by point estimates varying across studies, and minimal overlap between 95% confidence intervals) and the test for heterogeneity indicated a substantial degree of difference between the studies (χ^2 = 45.6, $p < 0.001$), which was unlikely to all be attributable to chance (I^2 = 61%). This inconsistency, combined with the risk of bias as described above, led to a downgrading of the quality of evidence from 'high' to 'low' (see table 1).

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

There was no meaningful nor statistical effect of exercise on cognition demonstrated in the dialysis group (ES = 0.15; CI_{95} = -0.08, 0.39; *P* = 0.21: Figure 3). Although moderate positive effect sizes of exercise on cognition were observed in people with stage 1–4 disease (ES = 0.73; CI_{95} = -0.13, 1.58; *P* = 0.09), and in people with a kidney transplant (ES = 0.49; CI_{95} = -0.51, 1.49; *P* = 0.34), these effects were also not significant. Moderation analysis revealed that CKD stage and treatment *did not* moderate the effect of exercise on cognition (χ^2 = 1.95, *P* = 0.38). Inconsistency between studies, risk of bias, and imprecision in the estimated effect led to a downgrading of the quality of evidence from 'high' to 'very low' (see table 1).

Subgroup analysis by type of exercise

Moderation analysis suggested that the type of exercise *did* moderate the effect of exercise on cognition (χ^2 = 7.62; *P*= 0.02). Aerobic exercise alone had a moderate positive effect on cognition (ES = 0.57; CI_{95} = 0.21, 0.93; *P* = 0.002: Figure 4). In contrast, neither resistance exercise (ES = 0.01; CI_{95} = -0.27, 0.29; *P* = 0.96) nor combined interventions (ES = -0.07; CI_{95} = -0.41, 0.28; *P* = 0.71) had any effect on cognition. Inconsistency between studies and risk of bias led to a downgrading of the quality of evidence from 'high' to 'low' (see table 1).

Meta-regression investigating intensity of exercise as a moderator (or covariate)

The meta-regression found no effect within the low intensity exercise subgroup (coefficient = 0.02; CI_{95} = -0.48, 0.52; *P* = 0.94, see Supplementary materials Figure 2) or within the moderate intensity exercise subgroup (coefficient = 0.16; CI_{95} = -0.40, 0.72; *P* = 0.58) on cognition but did find an effect within the high intensity exercise subgroup (coefficient = 1.29; CI_{95} = 0.15, 2.42; *P* = 0.03). However, the test of the relationship between intensity and the overall treatment effect was non-significant (*Q* = 5.1 and *P* = 0.08), indicating that the relationship between intensity and cognition could be explained by chance, and the test for residual heterogeneity indicated that there were remaining unexplained differences between the groups (*Q* = 37.4, *P* = 0.002). Inconsistency between studies, risk of bias, and imprecision in the estimated effect led to a downgrading of the quality of evidence from 'high' to 'very low' (see Table 1).

Meta-regression examining length of intervention as a moderator (or covariate)

The mode length of intervention was 12 weeks (35,37–40,48,51) (range: eight weeks (33) to six months (47)). There was no relationship between the length of the intervention in weeks and the effect on cognition (coefficient = 0.005; CI_{95} = -0.03, 0.04; *P* = 0.78, see Supplementary materials Figure 3), suggesting longer interventions were not more effective at improving cognition compared to shorter interventions. Inconsistency between studies and risk of bias led to a downgrading of the quality of evidence from 'high' to 'low' (see Table 1).

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

Six studies (39, 41-43, 45-46) used one or more objective measurements of cognition (see supplementary table 3). The remaining 13 studies used the Kidney Disease Quality of Life assessment (KDQOL) (35) or KDQOL-Short Form (KDQOL-SF) (33,34,36–38,40,44,47–51). Both contain three self-reported questions targeting cognitive function: concentration, becoming confused, and reacting slowly to stimuli. Although a moderate positive effect size was obtained for objective measures (ES = 0.38; CI_{95} = -0.16, 0.91; *P* = 0.17, see Supplementary materials Figure 4), this effect was not significant. No meaningful nor statistical effect of exercise on cognition was obtained when measured using a subjective assessment (ES = 0.15; CI_{95} = -0.08, 0.39; *P* = 0.21). Moderation analyses revealed that outcome measure *did not* moderate the relationship between exercise and cognition (χ^2 = 0.58, *P* = 0.45). Inconsistency between studies, risk of bias, and imprecision in the estimated effect led to a downgrading of the quality of evidence from 'high' to 'very low' (see Table 1).

Discussion

Based on the most comprehensive meta-analysis to date, this study found that exercise, particularly of an aerobic type, leads to a small but statistically significant and clinically meaningful improvement in cognitive function in individuals living with CKD. This positive effect was obtained without appreciably increasing the number of harms as compared to comparator treatments. However, these findings must be interpreted cautiously due to the low quality of evidence supporting the primary analysis, and the very low quality of evidence supporting the subgroup analyses.

Physical activity is known to be beneficial for people living with CKD (6) and is generally considered safe in this population (19). The present study suggests that cognitive function is an additional domain which benefits from exercise. Of two previous meta-analyses that have investigated the effect of exercise on cognition, Liu *et al.* found that exercise did improve cognition (23). In contrast, Bernier-Jean *et al.* did not (8). Differences in findings may be due to a few reasons. First, Bernier-Jean *et al.*'s analysis included only five studies. Second, Bernier-Jean *et al.* combined the results of multiple exercise modes rather than separately assessing the effects of very low intensity exercise (such as yoga) versus high intensity exercise modes in their primary analysis. Third, Bernier-Jean *et al.* only used subjective KDQOL-SF data, rather than objective measures which are more sensitive to change (61). Fourth, Bernier-Jean *et al.* included hemodialysis and PD patients only (12). It is noteworthy that the positive effect of exercise found in the present study is also consistent with the World Health Organization's recommendation that physical activity should be recommended to otherwise healthy adults with normal cognition and with mild cognitive impairment to reduce the risk of cognitive decline (1).

Within the present study, pre-planned subgroup analyses revealed that type of exercise moderated its effect on cognition. Specifically, aerobic exercise was identified as the most efficacious, more so than progressive resistance training and combined exercise programs. Although the quality of evidence was very low, this finding is consistent with previous studies in dialysis patients only (8) and with findings in people without CKD (1). Presumably, aerobic exercise enhances the physiological benefits of physical activity that reduce risk of cognitive decline, such as improved regulation of hippocampal function, neurogenesis, synaptic plasticity, and cerebral blood flow, and a reduction in cardiovascular risk and proinflammatory activity (10).

As well as the type of exercise, when prescribing exercise interventions care teams and researchers must decide on the intensity and duration of exercise. The present study found that higher intensity exercise had a higher effect size than low intensity exercise, consistent with findings in the general population suggesting the highest levels of physical exercise seem to be most protective (1). However, in the present meta-analysis the relationship between intensity and cognition was not statistically significant ($P = 0.08$). Nor was any evidence found for a relationship between the length of the intervention and its effect on cognition ($P = 0.78$). This is somewhat surprising but may be due to many of the reviewed papers including older participants, which would be consistent with the lack of relationship found in elderly adults without CKD (52), or it may be due to the lack of studies within the literature that have utilized different intensity and length interventions. Alternatively, study heterogeneity, such as differences in baseline fitness of participants, may prevent an exercise dose effect being demonstrated (52). Further research of higher quality is needed to properly examine the dose-response relation of exercise intensity and duration. For now, following guidelines (19) to gradually progress exercise duration and then intensity to recommended amounts seems prudent.

As CKD is generally a progressive disease, care teams and researchers must also decide at what stage of CKD to implement exercise intervention. The present meta-analysis found larger effect sizes of exercise in early than late CKD stages, but because there was no statistically significant moderating effect of CKD stage and treatment type (P = 0.38), further research is required to determine whether CKD stage and treatment type moderates the relationship between exercise and cognition. However, CI begins in the earlier stages of CKD and is associated with poor health literacy as CKD progresses (4). Early blood pressure control may preserve cognitive function (3). Exercise may improve blood pressure control in stages 1 to 4 CKD patients, but has little effect in HD and transplant patients (53). Poor compliance to exercise interventions is also common in later stage CKD patients, due to intercurrent medical events and fatigue (54). Taken together, exercise seems particularly pertinent for patients in the earlier stages of CKD. Another important consideration for care teams and researchers is which outcome measures are best to audit and investigate exercise interventions. We found the effect size was greater, but not significantly so (P = 0.45), for objective measures of cognition in comparison to subjective, self-reported measures. Relatedly, WHO Guidelines in the general population define objective measures as ‘critical’, and subjective measures as ‘important’ (1). For now, evaluating exercise interventions using more than one outcome measure of cognitive function seems sensible.

When evaluating the balance of benefits of exercise with potential harm, 10 of 19 studies did not exclude patients with illiteracy or dementia, yet the reporting of harms was not substantially increased with exercise intervention (94 occasions) in comparison to control (83 occasions). This suggests the observed beneficial effects of exercise are safely applicable to typical CKD patients, many of whom harbor undiagnosed CI (3).

The present findings must be interpreted in relation to the high risk of bias present within primary studies, albeit using a conservative approach to the risk of bias assessment. Bias in reporting of harms within primary studies may also have led to under or over reporting of harms. The conservative assessment of risk of bias (primarily due to lack of blinding), combined with inconsistency of results (primarily due to different estimates of the effect between studies), and for some subgroup analyses, imprecision of results (primarily due to smaller sample sizes of some subgroups), led to a downgrading of the quality of evidence from 'very high' to 'low' (primary analysis) or 'very low' (for some subgroup analyses). As per the Grading of Recommendations, Assessment, Development and Evaluation system guidance (56), it is for clinicians, patients and healthcare providers to interpret these findings together and act accordingly. But the present authors note that risk of bias due to lack of blinding will always be present in lifestyle intervention studies, and the risk of harms from exercise was apparently very low. The positive findings are also consistent with World Health Organization guidelines (1), which are supported by 'moderate' evidence quality. Taken together with the multiple additional benefits of enhancing physical activity, and the relatively low cost of exercise implementation now that digital health interventions have become viable, exercise remains an intervention that should be seriously considered to support cognitive function in patients living with CKD.

Other limitations of the primary studies include unclear methods of diagnosing dementia and CI, and inconsistent approaches on whether to include or exclude such patients. This makes determining whether exercise will be most effective in those with or without dementia and CI difficult to determine. Exclusion of those with known dementia and CI will also have removed a large proportion of CKD patients who may have benefited from exercise intervention, as it has been shown in otherwise healthy populations that the impact of exercise on cognition is potentially greater in those with CI (30) compared to normal cognition (28). Another limitation of this review was the use of broad inclusion criteria, which inevitably resulted in heterogenous participants and interventions. The pre-planned subgroup analyses were completed to mitigate this heterogeneity but their smaller sample sizes reduced power. This limitation was deemed acceptable due to enhancing applicability of the findings to the general CKD population. Finally, only six of the 19 studies specifically stated that cognition was a primary outcome, and thus many studies were not powered to detect differences in cognitive function between groups. By design, a meta-analysis will overcome lack of power, but such an analysis cannot remove risk of type I (false positive) errors in the selected studies.

In conclusion, although the quality of evidence was low, care teams may choose to recommend aerobic exercise interventions to reduce cognitive decline in people living with CKD without appreciably increasing risk of harm. Future research should endeavor to reduce bias, utilize multiple outcome assessments of cognitive function, and report exercise adherence in detail, to clarify what intensity and duration of exercise is required to maximize efficiency of such exercise interventions.

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Table of contents for supplementary materials

References

1. WHO: Risk reduction of cognitive decline and dementia: WHO guidelines. [Internet]. Available from: https://www.who.int/publications/i/item/9789241550543. Accessed 29.05.24.

2. Etgen T, Chonchol M, Förstl H, Sander D: Chronic kidney disease and cognitive impairment: A systematic review and meta-analysis. *Am J Nephrol.* 2012;35(5):474–482. doi: 10.1159/000338135.

3. Drew DA, Weiner DE, Sarnak MJ: Cognitive Impairment in CKD: Pathophysiology, Management, and Prevention. *Am J Kidney Dis.* 2019;74(6):782–790. doi: 10.1053/j.ajkd.2019.05.017.

4. 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.* 2016;14(1):206. doi: 10.1186/s12916-016-0745-9.

5. Segura-Orti E, Johansen KL: Exercise in end-stage renal disease. *Semin Dial.* 2010;23(4):422–430. doi: 10.1111/j.1525-139X.2010.00766.x

6. Heiwe S, Jacobson SH: Exercise training for adults with chronic kidney disease. *Cochrane Database Syst Rev.* 2011;2011(10):CD003236. doi: 10.1002/14651858.CD003236.pub2.

7. 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.* 2018;50(5):885–904. doi: 10.1002/14651858.CD014653. doi: 10.1007/s11255-018-1790-4.

8. 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.* 2022;1(1):CD014653. doi: 10.1371/journal.pone.0203662.

9. 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.* 2018;13(9):1–19. doi: 10.1371/journal.pone.0203662.

10. 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.* 2022;37(11):2180–2189. doi: 10.1093/ndt/gfab338.

11. 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. *Dementia Neuropsychol.* 2019; 13(3):329–334. doi: 10.1590/1980-57642018dn13-030010.

12. 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(3):2015;509–515. doi: 10.1016/j.jbmt.2015.04.006.

13. Chu NM, McAdams-DeMarco MA: Exercise and cognitive function in patients with end-stage kidney disease. *Semin Dial.* 32(4):2019;283–290. doi: 10.1111/sdi.12804.

14. Murtaza A, Dasgupta I: Chronic Kidney Disease and Cognitive Impairment. *J Stroke Cerebrovasc Dis.* 2021;30(9):105529. doi: 10.1016/j.jstrokecerebrovasdis.2020.105529.

15. Pépin M, Klimkowicz-Mrowiec A, Godefroy O, Delgado P, Carriazo S, Ferreira AC, Golenia A, Malyszko J, Grodzicki T, Giannakou K, Paolisso G, Barbieri M, Garneata L, Mocanu CA, Liabeuf S, Spasovski G, Zoccali C, Bruchfeld A, Farinha A, Arici M, Capasso G, Wiecek A, Massy ZA, the CONNECT (Cognitive Decline in European Cooperative Target) Action: Cognitive disorders in patients with chronic kidney disease: Approaches to prevention and treatment. *Eur J Neurol.* 2023;30(9):2899–2911. doi.org/10.1111/ene.15928.

16. Bogataj Š, Mesarič KK, Pajek M, Petrušič T, Pajek J: Physical exercise and cognitive training interventions to improve cognition in hemodialysis patients: A systematic review. *Front Public Health*. 2022;10:1032076. doi: 10.3389/fpubh.2022.1032076.

17. 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.* 2022;48(4):217. doi: 10.1111/jorc.12446.

18. World Health Organization: WHO guidelines on physical activity and sedentary behaviour [Internet]. Geneva, Switzerland Available from: https://www.who.int/publications/i/item/9789240015128. Accessed 06.06.24.

19. 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.* 2022;23(1):75. doi: 10.1186/s12882-021-02618-1.

20. Higgins JPT, Li T, Deeks JJ: Chapter 6: Choosing effect measures and computing estimates of effect. [Internet]. In: Cochrane Handbook for Systematic Reviews of Interventions., 6.4., edited by Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, 2023 Available from: www.training.cochrane.org/handbook. Accessed 06.06.24.

21. Sterne JAC, 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.* 2019;366:l4898. doi: 10.1136/bmj.l4898.

22. Cohen J: Statistical Power Analysis in the Behavioral Sciences. 2nd edition. Hillsdale (NJ), Lawrence Erlbaum Associates, Inc; 1988.

23. 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.* 2014;14:135. doi: 10.1186/1471-2288-14-135.

24. The Cochrane Collaboration: Review Manager [Software]. 2020.

25. JASP Team: JASP [Internet]. 2020 Available from: https://jasp-stats.org/. Accessed 06.06.24

26. Deeks J, Higgins J, Altman D (editors): Chapter 10: Analysing data and undertaking meta-analyses. [Internet]. In: Cochrane Handbook for Systematic Reviews of Interventions, 6.4., edited by Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, Welch V, 2023 Available from: www.training.cochrane.org/handbook. Accessed 06.06.24.

27. Forbes D, Forbes SC, Blake CM, Thiessen EJ, Forbes S: Exercise programs for people with dementia. *Cochrane Database Syst Rev.* 2015;2015(4):CD006489. doi: 10.1002/14651858.CD006489.pub4.

28. Young J, Angevaren M, Rusted J, Tabet N: Aerobic exercise to improve cognitive function in older people without known cognitive impairment (Review). *Cochrane Database Syst Rev.* 2015;2015(4):CD005381. doi: 10.1002/14651858.CD005381.pub4.

29. 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.* 202;84(5):1167–1183. doi: 10.1007/s00426-019-01145-x.

30. 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.* 2020;21(10):1415–1422. doi: 10.1016/j.jamda.2020.08.031.

31. Egger M, Smith GD, Schneider M, Minder C: Bias in meta-analysis detected by a simple, graphical test. *Br Med J.* 1997;315(7109):629–634. doi: 10.1136/bmj.315.7109.629.

32. 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. *Br Med J.* 2018;362:k3802. doi: 10.1136/bmj.k3802.

33. 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.* 2013;35(5):697–704. doi: 10.3109/0886022X.2013.780977.

34. Hernández Sánchez S, Carrero JJ, Morales JS, Ruiz JR, Hernandez Sanchez 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.* 2021;31(2):473–479. doi: 10.1111/sms.13853.

35. 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.* 2019;100(11):2151–2158. doi: 10.1016/j.apmr.2019.06.006.

36. 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.* 2017;28(4): 1259–1268. doi: 10.1681/ASN.2016030378.

37. 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.* 2016;31(10): 1712–1720. doi: 10.1093/ndt/gfw297.

38. 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.* 2020;30(2):126–136. doi: 10.1053/j.jrn.2019.06.010.

39. 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.* 2015;25(1):17–24. doi: 10.1053/j.jrn.2014.06.010.

40. 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.* 2019;8(5):339–348. doi: 10.1089/g4h.2018.0066.

41. 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 Rep.* 2018;3(1):81–88. doi: 10.1016/j.ekir.2017.08.006.

42. Myers J, Chan K, Chen Y, Lit Y, Patti A, Massaband P, Kiratli BJ, Tamura M, Chertow GM, Rabkin R: Effect of a Home-Based Exercise Program on Indices of Physical Function and Quality of Life in Elderly Maintenance Hemodialysis Patients. *Kidney Blood Press Res.* 2021;46(2):196–206. doi: 10.1159/000514269.

43. Nakamura-Taira N, Horikawa N, Oka F, Igarashi Y, Kobayashi S, Kato S, Enomoto T, Kimura H, Watanabe Y, Kumada T, Matsuyama K, Matsuoka N, Yoshimasu H: Quasi-cluster randomized trial of a six-month low-intensity group-based resistance exercise for hemodialysis patients on depression and cognitive function: a 12-month follow-up. *Health Psychol Behav Med.* 2021;9(1): 741–760. doi: 10.1080/21642850.2021.1966302.

44. Pereira ABN, Santana LL, Rocha LDB, Cunha KDC, Rocha LSDO, Santos MCDS, Normando VMF, Torres DDC, Rocha RSB: Physical Exercise Affects Quality of Life and Cardiac Autonomic Modulation in Patients With Chronic Kidney Failure Submitted to Hemodialysis: A Randomized Clinical Trial. *Percept Mot Skills.* 2022;129(3):696–713. doi: 10.1177/00315125221085811.

45. Poorsaadet L, Soltani P, Ghassami K, Kohansal B, Ahmadlou M: The effects of aerobic exercise on cognitive performance and sleep quality haemodialysis patients. *AMJ.* 2018;11(5):278–285. doi: 10.21767/AMJ.2017.3279.

46. Stringuetta Belik F, Oliveira E Silva VR, Braga GP, Bazan R, Perez Vogt B, Costa Teixeira Caramori J, Barretti P, de Souza Goncalves 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.* 2018;140(1):9–17. doi: 10.1159/000490005.

47. 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.* 2000;36(3):581–591. doi: 10.1053/ajkd.2000.16197.

48. 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.* 2019;9(1):2632. doi: 10.1038/s41598-019-39074-9.

49. Uchiyama K, Adachi K, Muraoka K, Nakayama T, Oshida T, Yasuda M, Hishikawa A, Minakuchi H, Miyashita K, Tokuyama H, Wakino S, Itoh H: Home-based aerobic exercise and resistance training for severe chronic kidney disease: a randomized controlled trial. *J Cachexia Sarcopenia Muscle.* 2021;12(6):1789–1802. doi: 10.1002/jcsm.12775.

50. 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*. 2015;66(2):285–296. doi: 10.1053/j.ajkd.2015.03.015.

51. 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.* 2014;42(3):718–727. doi: 10.1177/0300060513509037.

52. 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.* 2019;14(1):e0210036. doi: 10.1371/journal.pone.0210036.

53. Heiwe S, Jacobson SH: Exercise training in adults with CKD: a systematic review and meta-analysis. *Am J Kidney Dis.* 2014;64(3):383–393. doi: 10.1053/j.ajkd.2014.03.020.

54. Wilund KR, Viana JL, Perez LM: A Critical Review of Exercise Training in Hemodialysis Patients: Personalized Activity Prescriptions Are Needed. *Exerc Sport Sci Rev.* 2020;48(1):28–39. doi: 10.1249/JES.0000000000000209.

55. Maruish ME, Kosinski M, Bjorner JB, Gandek B, Turner-Bowker DM, Ware JE. User's Manual for the SF-36v2 Health Survey. 3rd edition. Lincoln (RI), Quality Metric Inc; 2011.

56. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, DeBeer H, Jaeschke R, Rind D, Meerpohl J, Dahm P, Schunemann HJ. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64(4):383-394. doi: 10.1016/j.jclinepi.2010.04.026.

Figure legends

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram illustrating literature search and study selection.

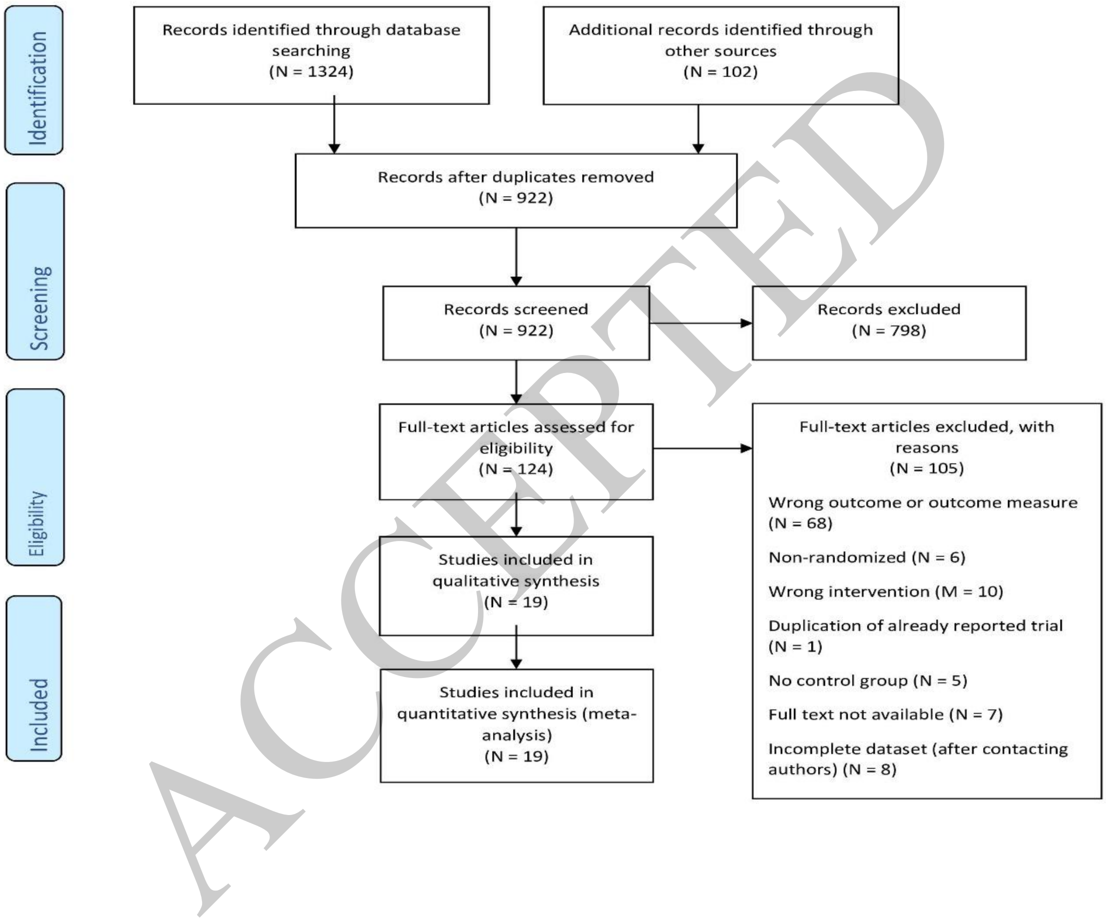


Figure 2. Meta-analysis of studies examining the effect of exercise on cognitive function.

IV = Inverse Variance; 95% CI, 95% confidence interval.

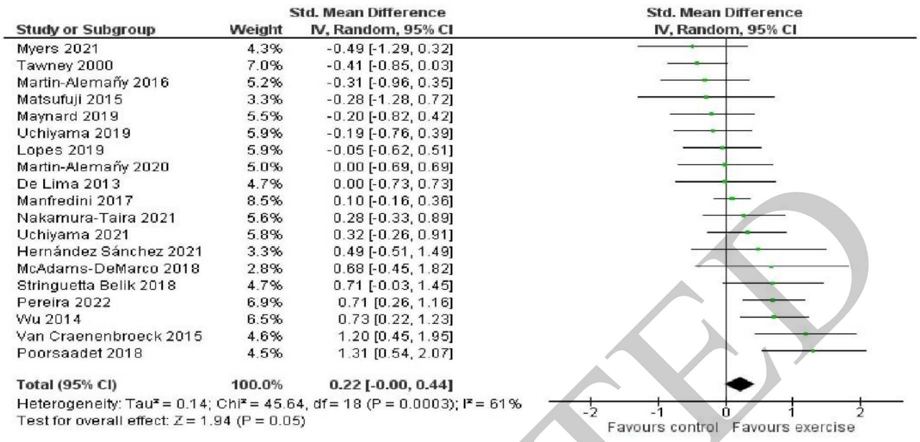


Figure 3. Subgroup analysis by chronic kidney disease stage and treatment (kidney transplant *vs* dialysis *vs* stage 1 – 4)

IV = Inverse Variance; 95% CI, 95% confidence interval.

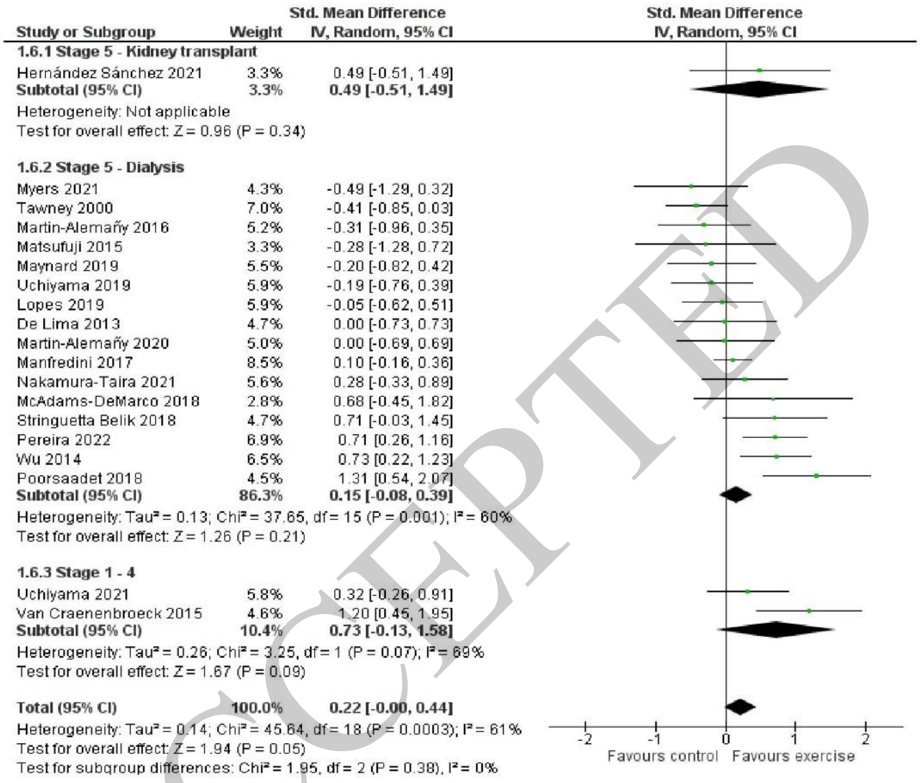
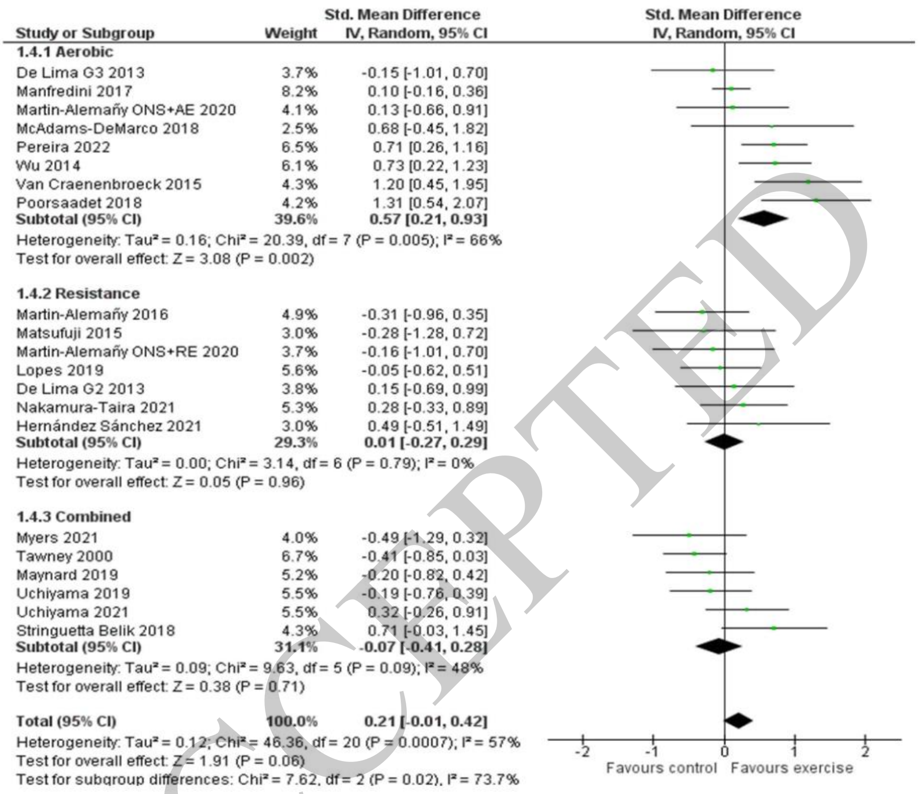


Figure 4. Subgroup analysis by type of exercise

IV = Inverse Variance; 95% CI, 95% confidence interval.



Tables

Outcomes	Number of participants randomised (studies)	Comparison	Treatment effect size (95% CI)[a] *Equivalent absolute increase in cognition (arbitrary units as utilised in KDQOL-SF)[b]*	Quality of the evidence (GRADE)[c]	Comments
Exercise on cognitive function	1160 (19)	Exercise vs. control	0.22 (0.00 to 0.44) *4.0 (0.0 to 7.9)*	⊕⊕◯◯ Low[d]	A conservative approach to risk of bias assessment downgraded quality of evidence. Lifestyle interventions are impossible to double blind, but future studies could utilise single-blinding of outcome assessors to improve the quality of evidence.
Stage and treatment of CKD	1050 (16)	5, dialysis	0.15 (-0.08 to 0.39) *2.7 (-1.4 to 7.0)*	⊕◯◯◯ Very low[e]	Future studies could include more transplant and pre-dialysis patients to reduce imprecision and improve the quality of evidence.
	16 (1)	5, transplant	0.73 (-0.13 to 1.58) *13.1 (-2.3 to 28.4)*		
	94 (2)	3 to 4, medical	0.49 (-0.51 to 1.49) *8.8 (-9.2 to 26.8)*		
	610 (8)	Aerobic	0.57 (0.21 to 0.93)	⊕⊕◯◯	

			10.3 (3.8 to 16.7)	Low[d]	
Type of exercise intervention	249 (7)	Resistance	0.01 (-0.27 to 0.29) *0.2 (-4.9 to 5.2)*		Future studies could better design, implement and describe exercise interventions to reduce inconsistency and improve the quality of evidence.
	301 (6)	Combined	-0.07 (-0.41 to 0.28) *-1.3 (-7.4 to 5.0)*		
Intensity of exercise	409 (3)	Low	0.02 (-0.48 to 0.52) *0.4 (-8.6 to 9.4)*	⊕◯◯◯ Very low[e]	Future studies could include more high intensity interventions to reduce imprecision and improve the quality of evidence.
	713(15)	Moderate	0.16 (-0.40 to 0.72) *2.9 (-7.2 to 13.0)*		
	38 (1)	High	1.29 (0.15 to 2.42) *23.2 (2.7 to 43.6)*		
Length of intervention	1160 (19)	Number of weeks	0.005 (-0.03 to 0.04) *0.1 (-0.5 to 0.7)*	⊕⊕◯◯ Low[d]	Future studies could utilize interventions of different length to add hetergeity interventions
Objective vs. subjective measures of cognition	194 (6)	Objective	0.38 (-0.16 to 0.91) *6.8 (-2.9 to 16.4)*	⊕◯◯◯ Very low[e]	Future studies could include more objective outcome measures to reduce imprecision and improve the quality of evidence.
	966 (13)	Subjective	0.17 (-0.08 to 0.41) *3.1 (-1.4 to 7.4)*		

Table 1. Summary of findings: effect of exercise on cognitive function in people living with Chronic Kidney Disease.

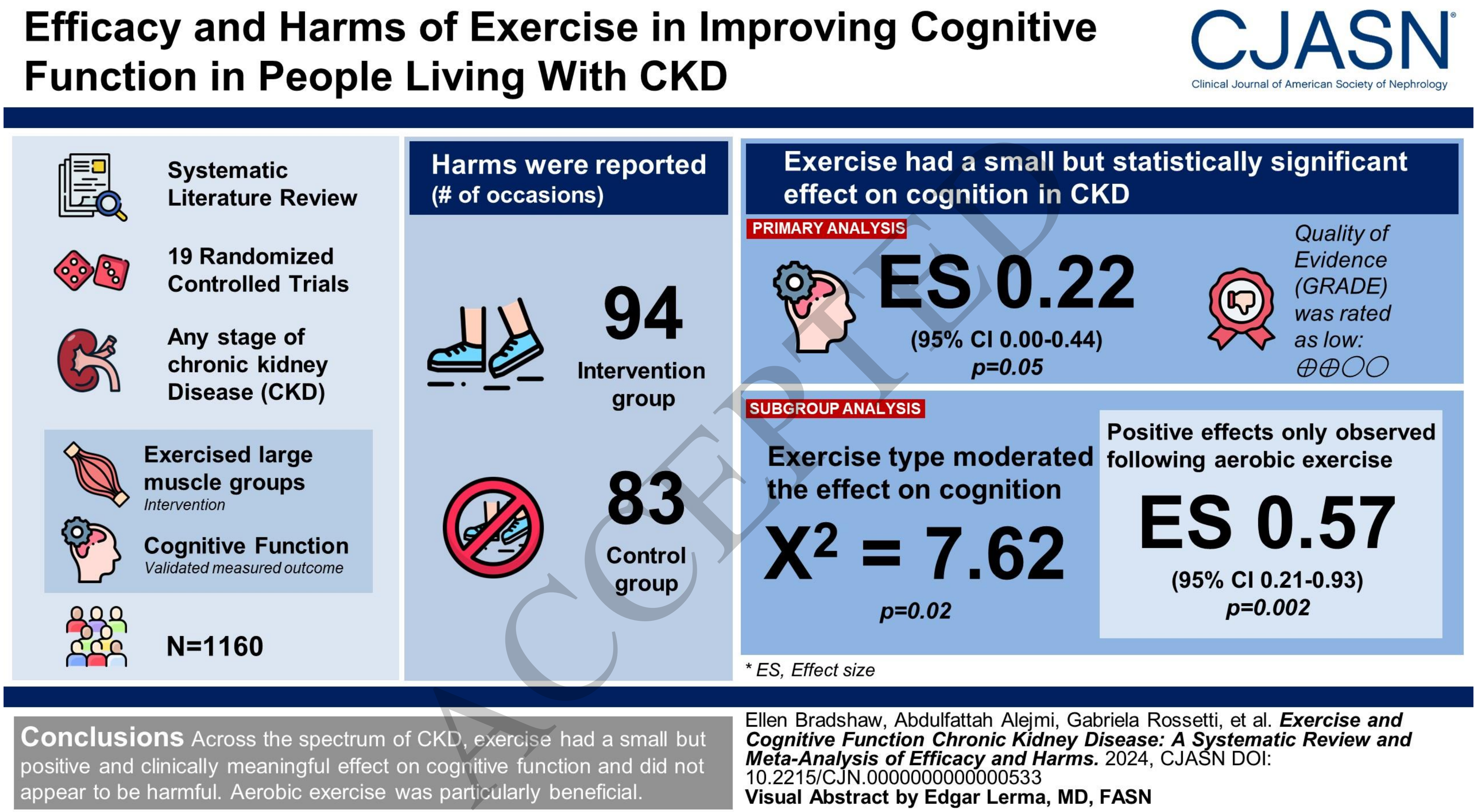
[a] As a rule of thumb, effects sizes of 0.2 represent a small difference, 0.5 a moderate, and 0.8 a large difference.

[b] A reasonable minimum important difference for the equivalent absolute increase in cognition (arbitrary units as utilised in KDQOL-SF) is 4 units, based on distribution and anchor-based approaches to determine meaningfulness of differences in SF-36 scores (55).

[c] A record of judgements made by the review authors is provided in the Grade Evidence Profile (supplementary table 7).

[d] Evidence limited by risk of bias (primarily due to lack of blinding) and inconsistency between studies.

[e] Evidence limited by risk of bias (primarily due to lack of blinding), inconsistency between studies, and imprecision (the Optimal Information Size was not met).


Efficacy and Harms of Exercise in Improving Cognitive Function in People Living With CKD
CJASN
Clinical Journal of American Society of Nephrology
Systematic Literature Review
19 Randomized Controlled Trials
Any stage of chronic kidney Disease (CKD)
Exercised large muscle groups
Intervention
Cognitive Function
Validated measured outcome
N=1160
Harms were reported (# of occasions)
94
Intervention group
83
Control group
Exercise had a small but statistically significant effect on cognition in CKD
PRIMARY ANALYSIS
ES 0.22
(95% CI 0.00-0.44)
p=0.05
Quality of Evidence (GRADE) was rated as low: ⊕⊕◯◯
SUBGROUP ANALYSIS
Exercise type moderated the effect on cognition
X² = 7.62
p=0.02
Positive effects only observed following aerobic exercise
ES 0.57
(95% CI 0.21-0.93)
p=0.002
* ES, Effect size
Conclusions Across the spectrum of CKD, exercise had a small but positive and clinically meaningful effect on cognitive function and did not appear to be harmful. Aerobic exercise was particularly beneficial.
Ellen Bradshaw, Abdulfattah Alejmi, Gabriela Rossetti, et al. Exercise and Cognitive Function Chronic Kidney Disease: A Systematic Review and Meta-Analysis of Efficacy and Harms. 2024, CJASN DOI: 10.2215/CJN.0000000000000533
Visual Abstract by Edgar Lerma, MD, FASN

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A. Alejmi has nothing to disclose.

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Name: Abdulfattah Alejmi
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Name: Ellen Jean Bradshaw
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G. d'Avossa has nothing to disclose.

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Name: Gabriella M K Rossetti
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