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Therapeutic effects of exercise interventions for patients with chronic kidney disease: an umbrella review of systematic reviews and meta-analyses

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Running Head: Exercise for chronic kidney disease

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ABSTRACT

Objective To conduct an overview of meta-analyses evaluating the impact of exercise interventions for improving health outcome in patients with chronic kidney disease (CKD).

Design An umbrella review of systematic review and meta-analyses of intervention trials was performed.

Data sources PubMed, the Web of Science, Embase, and the Cochrane Database of Systematic Reviews were searched for relevant articles.

Eligibility criteria for selecting studies Eligible meta-analyses compared the effects of usual care with and without exercise in CKD patients. Health outcomes included those related to cardiovascular risk factors, physical fitness, dialysis-related symptoms, and health-related quality of life. Systematic reviews and meta-analyses that included fewer than three RCTs or fewer than 100 participants were excluded from the analysis.

Results A total of 31 eligible systematic reviews and meta-analyses were included that assessed 120 outcomes. For physical fitness, there was a moderate effect size for cardiorespiratory fitness, muscle strength, and body composition, and a small effect size for muscle endurance. The effect sizes for cardiovascular risk factors, dialysis-related symptoms, and health-related quality of life outcomes were small. Most outcomes were scored as low or very low quality according to the Grading of Recommendations Assessment, Development and Evaluation framework.

Conclusion Exercise appears to be a safe way to affect concomitant cardiovascular risk factors, such as blood pressure, improve physical fitness and health-related quality of life, and reduce dialysis-related symptoms in CKD patients.

Ethics approval statemtent Ethics approval are not required as no private information from individuals is collected.

Dissemination The results will be published in a peer-reviewed journal or disseminated in relevant conferences.

Key words: Exercise, Chronic Kidney Disease, Systematic Review, Meta-Analyses

PROSPERO registration number CRD42020223591.

Strengths and limitations of this study

1) This overview provide a comprehensive summary of the therapeutic effects of exercise interventions for patients with chronic kidney disease.

2) Another strength of this overview allows us to identify the evidence base effect size are high or low.

3) The limitation of this overview is that language bias may exist in this review because the search strategy was limited to English.

INTRODUCTION

Chronic kidney disease (CKD) is a long-term condition characterized by the gradual loss of renal function over time.[1] In the past 30 years, the mortality attributed to CKD increased by 41.5%, a percentage rate that exceeds several cancers and cardiovascular diseases.[2] With the increasing incidence of hypertension, diabetes, and obesity, this number will continue to rise.[3 4] CKD patients experience a high symptom burden with progressively impaired physical performance, leading to decreased kidney function, lower health-related quality of life (HRQOL),increased risk of cardiovascular events, and increased all-cause mortality.[5 6]

Renal rehabilitation is a multifaced intervention program. Rehabilitation consists of exercise interventions, diet control, fluid management, and psychological support to alleviate physical/mental deficiencies caused by kidney disease and renal replacement therapy, in order to improve disease prognosis and to prolong life expectancy.[7] Since exercise is the core of renal rehabilitation, there is an increasing number of systematic reviews and meta-analyses investigating the influence of exercise on health outcomes in CKD patients.[8] Although some researchers and guidelines recommend that healthcare providers prescribe exercise for CKD patients,[9-12] the results of meta-analyses of exercise in CKD patients are inconsistent.

This umbrella review aims to assess the therapeutic effects of exercise regarding cardiovascular risk factors, physical fitness, dialysis-related symptoms, and HRQOL in CKD patients that are summarized in systematic reviews and meta-analyses.

METHODS AND ANALYSIS

This umbrella review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13] The review was prospectively registered (PROSPERO: CRD42020223591) and the protocol for this review was published.[14]

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Literature Search

A comprehensive search strategy was performed to identify systematic reviews and meta-analyses of CKD patients that compared usual care procedures with and without exercise interventions. PubMed, Embase, the Cochrane Database of Systematic Reviews (CDSR), and the Web of Science were searched for systematic reviews and meta-analyses from inception to March 9th, 2021. The detailed search strategy is summarized in Supplementary Table S1. The references of existing systematic reviews were also screened. Any reviews considered potentially relevant by authors were retrieved for further consideration.

Eligibility Criteria

Eligible systematic reviews and meta-analyses included those 1) where patients were diagnosed with CKD at various stages of treatment; 2) that compared exercise interventions with sham/no exercise or usual/standard care; 3) that reported outcomes on at least one of the following: cardiovascular risk factors, physical fitness, dialysis-related symptoms, and HRQOL. The methods to assess each outcome was shown in Supplement Figure S1; and 4) that were systematic reviews with meta-analysis of intervention trials (such as randomized controlled trials and quasi-experimental studies). Meta-analysis that included less than three studies or less than 100 participants were excluded. For duplicate literature, the article with most comprehensive data was selected. The language was restricted to English. Letters to the editor, trial protocols, and conference abstracts were excluded.

Study selection

Two independent authors screened all titles and abstracts compiled from the search results. Each paper was examined for appropriate eligibility criteria and a third author resolved disagreements.

Data extraction

Requisite data were extracted independently by two independent authors into a standardized format that included: 1) author, 2) publication year, 3) stage of CKD, 4) the number of included studies and participants, 5) exercise type, 6) exercise mode (intradialytic or interdialytic), 7) standardized mean difference (SMD) or mean difference (MD) with corresponding 95% confidence intervals (CI) for each outcome, 8) *P*-values, 9) I^2 values, and 10) exercise-related adverse events.

Risk of bias assessment

AMSTAR-2 (A Measurement Tool to Assess Systematic Reviews-2) was used to assess the risk of bias among the included systematic reviews.[15] This checklist contains 16 items, and each item was answered with a "yes" (1 point), "partial yes" (0.5 points), or "no" (0 points). A percentage score was calculated for each study based on the total score as the numerator and the maximum 16 points as the denominator. A meta-analysis scoring ≥80% was classified as high quality, those scoring 40-79% as medium quality, and those scoring <40% as low quality.[16] Risk of bias assessment was performed independently by two authors, and disagreement were resolved through discussions.

Data analysis

For each outcome, the summary effect size from each meta-analysis was analyzed qualitatively based on the SMD and its 95% CI. If they were not presented as SMD in the original meta-analysis, Review Manager V.5.3 was used to convert SMD outcomes. If data could not be

converted into SMD, we contacted the authors of the meta-analysis for the data. Effects were considered small (SMD < 0.50), moderate (SMD from 0.50 to 0.79), and large (SMD ≥ 0.80).[17] I^2 values were interpreted as follows: ≤25% indicate low heterogeneity, 25%<I^2≤50% indicate mild heterogeneity, 50%<I^2≤75% indicate moderate heterogeneity, and >75% indicate high heterogeneity.[18]

The level of evidence for each meta-analysis was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[19] The quality of evidence was assessed using five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Beginning with an initial score of 4 points, the score for each of these five domains was reduced accordingly: "not reported (-1)", "serious (-1)", "very serious (-2)", or "neutral (0)". Studies were rated as high (4 points), moderate (3 points), low (2 points), or very low (≤ 1 point) using the GRADE system. The GRADE assessment was conducted independently by two authors. Any differences were resolved by discussion or adjudication by a third author. The incidence of adverse events was based on the number of reported divided by the patients in the exercise group.

RESULTS

Characteristics of the meta-analyses

The search identified 2305 potential articles, of which 648 were duplicates. After reading the title and abstract, 1598 papers were excluded and 28 were excluded after full-text review resulting in 31 final studies. [20-50] A flow diagram of the study selection illustrates the selection process (Supplement Figure S2). The detail of reasons for excluded articles were listed in Supplementary Table S2.

The 31 included systematic reviews and meta-analyses were published from September, 2011 through March, 2021. The number of included studies assessed in the articles ranged from 3 to 24 with a mean of 8 studies. The sample sizes in the studies ranged from 106 to 874 participants with a mean of 304. The characteristics of the included meta-analyses were shown in Supplement Table S3. SMD data from four papers could not be obtained from the authors and the data of their effect size was presented as MD.[25 26 37 43]

The assessment of the methodological quality of the included meta-analyses was determined and the AMSTAR-2 scores ranged from 34.4% to 100.0% with a mean score of 68.0%. Seven (22.6%) systematic reviews were rated of high quality while 23 (74.2%) were rated of medium quality, and just one (0.3%) was rated as low quality (Supplement Table S4).

Of the GRADE evidence quality of the 120 outcomes, 1.7% (2 / 120) reported evidence of high quality, 17.5% (21 / 120) reported evidence of moderate quality, 20.0% (24 / 120) reported evidence of low quality, and 60.8% (73 / 120) reported evidence of very low quality (Supplement

Table S5).

Cardiovascular risk factor

There were 25 meta-analyses (reported in 13 articles) investigating the effect of exercise on cardiovascular risk factors (systolic and diastolic blood pressure) in CKD patients. [23 26 29-31 37 38 40 43-46 49] Of which, the number of studies ranged from 3 to 12 with a mean of 314 participants (range from 198 to 514) were included in each meta-analysis (Table 1).

The effect of exercise on systolic blood pressure was investigated in 13 meta-analyses with a mild heterogeneity (average $I^2 = 36.1\%$),[23 26 29-31 37 38 40 43-46 49] and 6 reported a positive statistically significant outcome. [26 29 38 40 46 49] Of the 13 meta-analyses, 9 reported a small effect size, [23 29-31 38 40 44 45 49] and one reported moderate.[46] GRADE assessment of quality indicated the overall evidence as being very low (10 meta-analyses[23 26 29 30 38 40 43-46]), low (2 meta-analyses[31 37]), and moderate (1 meta-analysis[49]). See Table 1.

The effect of exercise on diastolic blood pressure was investigated in 12 meta-analyses with a mild heterogeneity (average I^2=49.1%),[23 26 29-31 37 38 40 43-45 49] and 2 reported a positive statistically significant outcome.[38 40] Of the 12 meta-analyses, 9 reported a small effect size, [23 29-31 38 40 44 45 49] and all were graded as low or very low quality of evidence (Table 1).

Cardiorespiratory fitness

There were 34 meta-analyses (reported in 21 articles) that investigated the effects of exercise on cardiorespiratory fitness in CKD patients using a peak oxygen uptake (18 of 34), 6-minute walk test (14 of 34), or aerobic capacity (2 of 34). The meta-analyses included a mean of 9 studies (ranging from 5 to 20) and a mean of 330 participants (ranging from 179 to 504). See Table 2.

The effect of exercise on peak oxygen consumption was investigated in 18 meta-analyses (reported in 17 articles) with a mild heterogeneity (average I^2=42.2%),[20 21 23 24 26 28 31 34-38 40 41 44 46 47] and 16 reported positive statistically significant outcomes. [20 21 24 26 28 31 34 35 37 38 40 41 44 46 47] Of the 18 meta-analyses, 3 reported a low effect size,[23 36 47] 9 reported a moderate effect size[21 24 28 31 34 38 40 41 46] and 3 reported a large effect size.[20 35 44] GRADE assessment of quality indicated the overall evidence as being very low (9 meta-analyses[21 23 24 26 28 34 40 44 46]), low (8 meta-analyses[20 31 35-38 41 47]), and high (1 meta-analysis[34]). A meta-analysis that included kidney transplant recipients found no statistically significant difference in the SMD of the exercise group (0.38; 95% CI, -0.06 to 0.82; P=0.09).[36] See Table 2.

The effect of exercise on 6-minute walk test was investigated in 14 meta-analyses (reported in 13 articles) with a mild heterogeneity (average I^2=44.9%),[21 24-26 28 31 33-35 37 38 40 48] and 13 reported positive statistically significant outcomes.[21 24-26 28 31 33-35 38 40 48] Of the 14 meta-analyses, 2 reported a small effect size,[21 24] 5 reported a moderate effect size,[33 34 38 40 48] and 3 reported a large effect size.[28 31 35] GRADE assessment of quality indicated the overall evidence as being very low

(8 meta-analyses[21 26 28 31 35 37 40]), low (4 meta-analyses[24 34 38 48]), and moderate (2 meta-analyses[25 33]). In addition, the meta-analysis by Heiwe et al (2014) showed that regular exercise had significant beneficial effects on aerobic capacity. [29 30] See Table 2.

Muscle strength

Ten meta-analyses (reported in 9 articles) investigated the effects of exercise on muscle strength in CKD patients with a low heterogeneity (average $I^2 = 19.1\%$).[22 28-30 32-35 48] The meta-analyses included a mean of 7 studies (ranging from 3 to 12) and a mean of 252 participants (ranging from 115 to 385). See Table 3.

Muscle strength was measured using handgrip strength, lower limb muscle strength, et al. For patients in 8 of 10 meta-analyses, exercise resulted in statistically significant improvements in muscle strength. [28-30 32-34 48] Of the 10 meta-analyses, 3 reported a small effect size,[33 35 48] 5 reported a moderate effect size,[28-30 32 33] and 2 reported a large effect size,[22 34] GRADE assessment of quality indicated the overall evidence as being very low (6 meta-analyses[28-30 32 34 35]) and low (4 meta-analyses[22 33 48]). See Table 3.

Muscle endurance

Nine meta-analyses (reported in 8 articles) investigated the effects of exercise on muscle endurance with a mild heterogeneity (average $I^2 = 29.4\%$).[21 29 30 33 35 37 40 48] A mean of 5 studies (ranging from 3 to 7) and a mean of 238 participants (ranging from 106 to 461) were included in meta-analyses (Table 4).

Muscle endurance was measured using a sit-to-stand test, timed up and go test, and walking capacity exercise. Pooled effect estimates from all 9 meta-analyses suggested a beneficial effect of exercise on muscle endurance in CKD patients. Power to detect a statistically significant effect was reported by 7 of the 9 meta-analyses. [21 29 33 35 40 48] Two meta-analyses reported a moderate effect size and 5 reported a small effect size. GRADE assessment of quality indicated the overall evidence as being very low (7 meta-analyses[21 29 33 35 37 40 48]), low (1 meta-analyses[33]) and moderate (1 meta-analyses[30]). See Table 4.

Body composition

Four meta-analyses consisting of a mean of 9 studies (ranging from 4 to 13) and a mean of 335 participants (ranging from 166 to 466) included body mass index as an outcome.[23 44 46 49] There was a low heterogeneity (average $I^2 = 12.0\%$) among the study outcomes (Table 5).

Of the 4 meta-analyses, 3 showed a positive statistically significant impact on body mass index using exercise interventions in CKD patients.[44 46 49] Small effect size was reported in all meta-analyses. GRADE assessment of quality indicated the overall evidence as being very low (1 meta-analyses), low (2 meta-analyses[44 46]) and moderate (1 meta-analyses[49]). See Table 5.

Dialysis-related symptoms

Nine meta-analyses (reported in 7 articles) investigated the effect of exercise on dialysis-related symptoms in CKD patients.[26 27 31 38 40 42 50] Each meta-analysis included a mean of 7 studies (ranging from 3 to 12 studies) and a mean of 239 participants (ranging from 139 to 370). See Table 6.

Dialysis adequacy was measured using the value of Kt/V. Six meta-analyses (reported in 5 articles) investigated the effects of exercise on Kt/V in CKD patients with a mild heterogeneity (average $I^2 = 25.7\%$).[26 27 31 38 40] Comprehensive effect estimates from all the 6 meta-analyses with Kt/V outcomes showed that exercise had a beneficial effect. Of the 6 meta-analyses, 3 reported a small effect size[31 38 40] and 1 reported a large effect size.[27] According to GRADE criteria, all meta-analyses were rated as very low quality of evidence (Table 6).

Fatigue was measured using the Rhoten Fatigue Scale, Visual Analogue Scale, and Hemodialysis Patients Fatigue Scale. The effect of exercise on fatigue was investigated in 2 meta-analyses with a low heterogeneity (average I^2=23.5%).[42 50] The 2 meta-analyses revealed a statistically significant effect of exercise on fatigue. Although the meta-analyses reported large effect size, the quality of evidence was low[42] or very low[50] according to GRADE criteria (Table 6).

Just one meta-analysis investigated the effects of exercise on restless legs syndrome in CKD patients.[42] Result showed that pooled effect estimated for restless legs syndrome with statistically significant but considerable average heterogeneity ($I^2 = 87.0\%$). According to GRADE criteria, the overall of evidence for this outcome was rated as very low (Table 6).

Health-related quality of life

Twenty-nine meta-analyses (reported in 13 articles) investigated the effect of exercise on HRQOL in CKD patients.[22 24 28 31 32 34 36-40 48 50] Among them, nine the meta-analyses each assessed physical and mental subscale of the Short-Form Health Survey-36.[24 28 31 34 38-40 48 50] A mean of 6 studies (ranging from 3 to 10) and a mean of 311 participants (ranging from 167 to 562) were included in each meta-analysis. The included meta-analyses had moderate heterogeneity (average $I^2 = 51.0\%$). See Table 7.

Of the 29 meta-analyses, a comprehensive effect estimate of the 28 meta-analyses shows that exercise is beneficial to the HRQOL of CKD patients, but only 12 of 29 meta-analyses reported a statistically significant outcome.[24 31 34 36 38-40 50] There were 13 of 29 meta-analyses reporting a small effect size, [24 28 31 34 38 40 48 50] 4 were moderate,[28 34 36 38] and 6 were large.[22 32 39] According to GRADE criteria, the overall of evidence for HRQOL was rated as very low (20 meta-analyses[28 32 34 36-40 50]) or low (9 meta-analyses[22 24 31 38 48 50]). See Table 7.

Adverse events

Six meta-analyses reported exercise-related adverse events.[22 24 35 38 40 41] Of the adverse effects, the most commonly reported were hypotension and cramping. Overall, the incidence of adverse events was approximately 0.3%.

DISCUSSION

Several meta-analyses have been published in the area of exercise interventions in CKD patients.[51] The findings of these meta-analyses should be assessed to determine if evidence is consistent among the studies. This umbrella review included 31 eligible articles involving 120 separate meta-analyses investigating the effect of exercise on the health outcomes in CKD patients. There was low- or very low-quality evidence for moderate beneficial effects of exercise on cardiorespiratory fitness, muscle strength, and body composition. In addition, there was very low-quality evidence for small beneficial effects of exercise on muscle endurance, cardiovascular risk factors, dialysis-related symptoms, and HRQOL. There were few adverse events related to exercise, indicating that exercise is safe for CKD patients.

Cardiovascular disease is a frequent complication of CKD and is the leading cause of death in CKD patients.[52] Hypertension is an important modifiable risk factor for cardiovascular diseases and progressive renal dysfunction in CKD patients.[53] The present overview showed that exercise has a small to moderate effect on blood pressure (SMD: -0.75 to 0.04 for systolic blood pressure, and SMD: -0.47 to 0.04 for diastolic blood pressure), it is an appealing strategy for blood pressure control in CKD patients. However, the dose effects of exercise in the context of the cardiovascular health of CKD patients should be considered. A recent cohort study found that 7.5-15 metabolic equivalent-hours per week (MET-h/week) was associated with the lowest risk of cardiovascular events.[54] Regrettable, the benefit of exercise on cardiovascular risk factors cannot be determined because there are an insufficient number of conclusive studies that assess exercise effects on overall cardiovascular health. A recent randomized controlled trial published by Graham-Brown indicated that intradialytic exercise can reduce left ventricular mass and is safe, deliverable, and well-tolerated.[55] Although the GRADE evidence generated was low, exercise should be recommended for CKD patients, particularly those comorbid with cardiovascular disease.

Physical fitness is necessary for participation in activities of daily living. Exercise provided the best results in improving cardiorespiratory fitness and muscle strength in CKD patients, with more than a half of the meta-analyses reporting moderate or large effect sizes, regardless of the quality of evidence. Cardiorespiratory fitness is considered an important independent predictor of mortality and muscle strength is an important indicator of physical performance in CKD patients.[56] It is well known that aerobic exercise is the "gold standard" for cardiorespiratory rehabilitation[57] and resistance training for muscle strength improvement.[58] However, a combination of aerobic and resistance exercises may have a more profound effect in CKD patients based on the current review. Meta-analyses conducted by Andrade et al. showed that combined

training has an exert benefits in cardiorespiratory fitness in CKD patients.[20]

Both sarcopenia and obesity have been shown to increase mortality risk and increase progression to end-stage renal disease in CKD patients.[59] Unlike patients receiving dialysis, treatment requirements for predialysis CKD patient are based upon the principle of maintaining a "healthy weight" and the prevention or attenuation of obesity.[10] In this overview, the effectiveness of exercise for body mass index was supported by 4 analyses with small effect sizes and a moderate quality of evidence. Based on the results, exercise may contribute to lower body mass index in CKD patients. However, additional studies are needed to confirm the benefits of exercise programs for reducing sarcopenia and weight.

CKD population experience multiple symptoms that affect patient's prognosis and HRQOL.[60] Patients who received dialysis treatment commonly reported restless legs syndrome, fatigue, and dialysis inadequate due to both the deterioration of kidney function and dialysis-related side effects.[61 62] These symptoms affect sleep, daily activities, and impose a considerable amount of psychological distress and economic burden.[63] An increasing number of researchers have investigated the role of exercise as an important non-pharmacological strategy for preventing and/or treating symptoms. [64 65] The results of a small number of meta-analyses suggested that the beneficial effect of exercise on dialysis adequacy (SMD: 0.19 to 2.21), and improving restless legs syndrome (SMD: -1.79) and fatigue symptoms (SMD: -0.97 to -0.85). Nevertheless, the efficacy of exercise in CKD patients for preventing dialysis-related symptoms awaits new clinical evidence.

With similar results obtained in another overview that included chronic disease,[66] results from this overview demonstrated small beneficial effects of exercise on HRQOL, irrespective of the evidence level in CKD patients. Improved HRQOL is important because most of the population reported ongoing poor health and well-being due to diet restriction, weakness, and dialysis treatment.[67] The consistent health benefits of exercise in this overview demonstrated that exercise could be a strategy to improve the poor long-term prognosis in CKD patients.

Several meta-analyses reported exercise-related adverse events. Based on the number of adverse events reported, we calculate that only 3 adverse events occurred per 1000 CKD patients. The low incidence of adverse events indicated that the benefits of exercise in CKD patients outweigh its potential risks. However, most meta-analyses only included intradialytic exercise for hemodialysis patients in their assessments. Exercises during hemodialysis are usually performed under the supervision of a healthcare worker to ensure safety.[68] Due to the potential lack of supervision in an in-home exercise regime, a stepwise exercise is recommended for CKD patients.

Taken together, there is good reason to recommend exercise for improving prognosis in CKD patients. Evidence from most randomized controlled trials increased confidence in the findings of this umbrella review. Because most of the meta-analyses assessed in this study did not detail the

exercises instituted, it is difficult to make recommendations about the type of exercise that would be the most beneficial for CKD patients. Although the effect sizes of exercise on improving the health prognosis of CKD patients were generally moderate, these effects may bring some clinical benefit to patients experiencing impaired function or symptom distress. Despite numerous meta-analyses provided only low or very low-quality evidence, similar beneficial effects of exercise were reported by meta-analyses of randomized controlled trials with different grades of evidence. Remarkably, a recently published trial found that a 6-month program of intradialytic exercise is effective in reducing healthcare costs.[69] Overall, exercise should be integrated into the care of CKD.

There are several limitations to this overview: 1) the majority of meta-analyses included in this review involves hemodialysis patients. This limits the extrapolation of the results to other stages of CKD; 2) improvement of flexibility in CKD patients was not investigated. Flexibility is an important component of physical fitness that is believed to have an impact on muscular injury.[70] The evidence for the efficacy of exercise on flexibility improvement is insufficient for a systematic review or meta-analysis; 3) language bias may exist in this review because the search strategy was limited to English. It is unknown if meta-analyses published in other languages would influence the outcomes of our findings; 4) the results may be had been influenced by overlap in the original studies; 5) the accuracy of the MD data cannot be guaranteed; and 6) sub-group analyses of different types of exercise were not performed as described in the published protocol because of most the included meta-analyses did not detail the exercises.

CONCLUSION

Exercise appears to be effective in improving muscle strength and endurance, body composition, and HRQOL in CKD patients. At the same time, exercise appears to decrease blood pressure and dialysis-related symptoms in CKD patients. Accordingly, exercise should be integrated into renal care for a patient with any stage of CKD.

Contributors

FZ, LYH, HCZ concepted and designed the review. YB and XZ searched databases, extrated the data, and statistical analysis. WQZ and WQW revised the mauscript. HCZ provided technical support. All authors had read and approved the final manuscript and agreed on its submission.

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Table 1 Summary of the effect of exercise on cardiovascular risk factor in CKD patients

Author (year)	Design	Stage of CKD	k (n)	Exercise type	Mode	SMD or MD (95% CI)	Effect size	*P*	I^2	GRADE
SBP										
Pei (2019)	RCT/quasi-RCT	Mixed	12(514)	AE	-	MD:−2.91 (−6.68, 0.87)	-	0.13	40.0%	⊕⊕◯◯
Wu (2020)	RCT/quasi-RCT	Predialysis	3 (204)	AE+RT	-	SMD:-0.19(-0.46,0.08)	Small	0.16	50.0%	⊕◯◯◯
Chen (2019)	RCT	KTRs	5(198)	Mixed	-	SMD:0.18(-0.10,0.46)	Small	0.21	0.0%	⊕◯◯◯
Pu (2019)	RCT	HD	7(287)	Mixed	Intradialytic	SMD:-0.28(-0.52,-0.05)	Small	0.02	0.0%	⊕◯◯◯
Yamamoto (2021)	RCT	Predialysis	10(392)	AE	-	SMD:-0.75(-1.24,-0.26)	Moderate	0.003	80.3%	⊕◯◯◯
Thompson (2019)	RCT	Predialysis	10(335)	Mixed	-	MD:-4.30(-9.00,0.40)	-	N.P.	50.4%	⊕◯◯◯
Zhang (2019)	RCT	Predialysis	14(463)	Mixed	-	SMD:-0.41(-0.70,-0.11)	Small	0.007	55.0%	⊕⊕⊕◯
Huang (2019)	RCT	HD	7(260)	Mixed	Mixed	SMD:-0.17(-0.41,0.08)	Small	0.18	8.0%	⊕⊕◯◯
Heiwe (2011)	RCT/quasi-RCT	Mixed	9(347)	Mixed	-	SMD:0.25(0.04,0.47)	Small	0.02	0.0%	⊕◯◯◯
Heiwe (2014)	RCT	HD	10(312)	Mixed	-	SMD:0.04(-0.34,0.41)	Small	0.8	58.0%	⊕◯◯◯
Sheng (2014)	RCT	HD	7(296)	Mixed	Intradialytic	SMD:-0.27(-0.50,-0.04)	Small	0.02	0.0%	⊕◯◯◯
Ferrari (2019)	RCT	HD	10(332)	AE	Intradialytic	MD:-10.07(16.35,-3.78)	-	0.002	44.0%	⊕◯◯◯
Wyngaert (2018)	RCT	Predialysis	8(269)	AE	-	SMD:0.08(-0.58,0.74)	Small	0.81	84%	⊕◯◯◯
DBP										
Pei (2019)	RCT/quasi-RCT	Mixed	12(514)	AE	-	MD:−1.11 (−3.41, 1.20)	-	0.35	0.0%	⊕⊕◯◯
Wu (2020)	RCT/quasi-RCT	Predialysis	4 (194)	AE+RT	-	SMD:-0.47(-1.10,0.15)	Small	0.14	70.0%	⊕◯◯◯
Chen (2019)	RCT	KTRs	5(198)	Mixed	-	SMD:0.04(-0.45,0.52)	Small	0.89	59.0%	⊕◯◯◯
Pu (2019)	RCT	HD	7(287)	Mixed	Intradialytic	SMD:-0.32(-0.55,-0.08)	Small	0.008	42.0%	⊕◯◯◯

Thompson (2019)	RCT	Predialysis	8(303)	Mixed	-	MD:-1.18(-4.76,2.40)	-	N.P.	60.5%	⊕◯◯◯
Zhang (2019)	RCT	Predialysis	12(399)	Mixed	-	SMD:-0.31(-0.71,0.08)	Small	0.12	70.0%	⊕⊕◯◯
Huang (2019)	RCT	HD	7(260)	Mixed	Mixed	SMD:-0.23(-0.69,0.24)	Small	0.34	68.0%	⊕◯◯◯
Heiwe (2011)	RCT/quasi-RCT	Mixed	11(419)	Mixed	-	SMD:0.16(-0.04,0.36)	Small	0.11	40.0%	⊕◯◯◯
Heiwe (2014)	RCT	HD	10(212)	Mixed	Mixed	SMD:0.17(-0.16,0.49)	Small	0.3	45.0%	⊕⊕◯◯
Sheng (2014)	RCT	HD	7(296)	Mixed	Intradialytic	SMD:-0.24(-0.47,-0.01)	Small	0.04	52.1%	⊕◯◯◯
Ferrari (2019)	RCT	HD	10(334)	AE	Intradialytic	MD:-2.96(-7.71,1.78)	-	0.22	0.0%	⊕◯◯◯
Wyngaert (2018)	RCT	Predialysis	7(237)	AE	-	SMD-0.09(-0.78,0.59)	Small	0.79	83%	⊕◯◯◯

Abbreviation: RCT = randomized controlled trial; AE = aerobic exercise; RT = resistance training; DBP = diastolic blood pressure; SBP = systolic blood pressure; SMD = standardized mean difference; MD = mean difference; HD = hemodialysis; KTRs = kidney transplant recipients; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; N.P. = no report.

Table 2 Summary of the effect of exercise on cardiopulmonary fitness in CKD patients

Author (year)	Design	Stage of CKD	k (n)	Exercise type	Mode	SMD or MD (95% CI)	Effect size	*P*	I^2	GRADE
VO_{2peak}										
Pei (2019)	RCT/quasi-RCT	Mixed	17(464)	AE	-	MD:2.08(1.10,3.05)	-	<0.001	25.0%	⊕⊕◯◯
Nakamura (2020)	RCT/cross-over	Predialysis	10(401)	Mixed	-	SMD:0.88(0.53,1.23)	Large	<0.001	56.0%	⊕⊕◯◯
Chen (2019)	RCT	KTRs	6(202)	Mixed	-	SMD:0.33(-0.02,0.69)	Small	0.06	27.0%	⊕◯◯◯
Andrade (2019)	RCT	HD	5(201)	AE+RT	Intradialytic	SMD:1.01(0.71,1.30)	Large	<0.001	0.0%	⊕⊕◯◯
Chung (2016)	RCT	HD	6(238)	Mixed	Intradialytic	SMD:0.55(0.18,0.92)	Moderate	0.003	52.9%	⊕◯◯◯
Pu (2019)	RCT	HD	10(400)	Mixed	Intradialytic	SMD:0.57(0.23,0.90)	Moderate	<0.001	59.0%	⊕⊕◯◯
Yamamoto (2021)	RCT	Predialysis	10(365)	AE	-	SMD:0.54(0.29,0.78)	Moderate	<0.001	24.6%	⊕◯◯◯
Yang (2017)	RCT	Mixed	5(179)	Mixed	-	SMD:0.33(0.03,0.63)	Small	0.003	47.0%	⊕⊕◯◯
Huang (2019)	RCT	HD	10(371)	Mixed	Mixed	SMD:0.73(0.52,0.95)	Moderate	<0.001	71.0%	⊕⊕◯◯
Matsuzawa (2017)	RCT	HD	18(582)	Mixed	Mixed	SMD:0.62(0.38,0.87)	Moderate	<0.001	49.0%	⊕⊕⊕⊕
Smart (2011)	RCT	HD	8(365)	Mixed	Mixed	SMD:0.75(0.39,1.11)	Moderate	<0.001	60.0%	⊕⊕◯◯
Bogataj (2020)	RCT	HD	20(504)	Mixed	Mixed	SMD:0.58(0.32,0.85)	Moderate	<0.001	57.4%	⊕◯◯◯
Sheng (2014)	RCT	HD	7(310)	Mixed	Intradialytic	SMD:0.53(0.30,0.76)	Moderate	<0.001	36.0%	⊕◯◯◯
Neto (2018)	RCT	HD	10(394)	Mixed	Intradialytic	SMD:0.60(0.15,1.04)	Moderate	0.008	76.0%	⊕◯◯◯
Ferrari (2019)	RCT	HD	5(201)	AE+RT	Intradialytic	MD:5.41(4.03,6.79)	-	<0.001	0.0%	⊕◯◯◯
Ferrari (2019)	RCT	HD	7(248)	AE	Intradialytic	MD:2.07(0.42,3.72)	-	<0.001	0.0%	⊕◯◯◯
Wyngaert (2018)	RCT	Predialysis	11(325)	AE	-	SMD:0.99(0.49,1.48)	Large	<0.001	74.0%	⊕◯◯◯
Oguchi (2018)	RCT	KTRs	4(182)	Mixed	-	SMD:0.38(-0.06,0.82)	Small	0.09	45.0%	⊕⊕◯◯

6MWT										
Pei (2019)	RCT/quasi-RCT	Mixed	8 (496)	AE	-	MD:0.04 (−0.52, 0.59)	-	0.90	86.0%	⊕◯◯◯
Nakamura (2020)	RCT/cross-over	Predialysis	5(392)	Mixed	-	SMD:1.04(0.17,1.90)	Large	0.02	92.0%	⊕◯◯◯
Lu (2019)	RCT	Dialysis	11(300)	Mixed	Mixed	SMD:0.52(0.31,0.72)	Moderate	<0.001	39.0%	⊕⊕⊕◯
Chung (2016)	RCT	HD	4(127)	Mixed	Intradialytic	SMD:0.44(0.09,0.80)	Small	0.015	0.0%	⊕⊕◯◯
Zhang (2021)	RCT	HD	8(299)	RT	Intradialytic	SMD:0.52(0.28,0.75)	Moderate	<0.001	18.7%	⊕⊕◯◯
Pu (2019)	RCT	HD	7(219)	Mixed	Intradialytic	SMD:0.57(0.30,0.84)	Moderate	<0.001	0.0%	⊕⊕◯◯
Clarkson (2019)	RCT	Dialysis	18(744)	Mixed	-	MD:33.64(23.74,43.54)	-	<0.001	0.0%	⊕⊕⊕◯
Huang (2019)	RCT	HD	7(205)	Mixed	Mixed	SMD:1.01(0.26,1.76)	Large	0.008	83.0%	⊕◯◯◯
Matsuzawa (2017)	RCT	HD	10(326)	Mixed	Mixed	SMD:0.58(0.24,0.93)	Moderate	<0.001	53.0%	⊕⊕◯◯
Bogataj (2020)	RCT	HD	19	Mixed	Mixed	SMD:0.44(0.21,0.67)	Small	<0.001	49.6%	⊕◯◯◯
Sheng (2014)	RCT	HD	4(146)	Mixed	Intradialytic	SMD:0.58(0.23,0.93)	Moderate	<0.001	89.7%	⊕◯◯◯
Neto (2018)	RCT	HD	6(158)	Mixed	Intradialytic	SMD:0.96(0.11,1.80)	Large	0.03	82.0%	⊕◯◯◯
Ferrari (2019)	RCT	HD	6(211)	RT	Intradialytic	MD:68.5(29.05,107.96)	-	<0.001	36.0%	⊕◯◯◯
Ferrari (2019)	RCT	HD	6(188)	AE	Intradialytic	MD:64.98(43.86,86.11)	-	<0.001	0.0%	⊕◯◯◯
Aerobic capacity										
Heiwe (2011)	RCT/quasi-RCT	Mixed	24(847)	Mixed	-	SMD:-0.56(-0.70,-0.42)	Moderate	<0.001	12.0%	⊕◯◯◯
Heiwe (2014)	RCT	HD	21(374)	Mixed	Mixed	SMD:-0.80(-1.02,-0.58)	Large	<0.001	0.0%	⊕⊕◯◯

Abbreviation: RCT = randomized controlled trial; AE = aerobic exercise; RT = resistance training; VO_{2peak} = peak oxygen uptake; 6MWT = 6 minutes walk test; SMD = standardized mean difference; MD = mean difference; HD = hemodialysis; KTRs = kidney transplant recipients; GRADE = Grading of Recommendations Assessment, Development, and Evaluation.

Table 3 Summary of the effect of exercise on muscle strength in CKD patients

Author(year)	Design	Stage of CKD	k (n)	Exercise type	Mode	SMD or MD (95% CI)	Effect size	*P*	I^2	GRADE
Cheema (2014)	RCT	Predialysis	7(249)	RT	-	SMD:1.15(0.80,1.49)	Large	0.161	35.0%	⊕⊕◯◯
Nakamura (2020)	RCT/cross-over	Predialysis	4(119)	Mixed	-	SMD:0.35(-0.03,0.73)	Small	0.07	7.0%	⊕◯◯◯
Lu (2019)	RCT	Dialysis	5(234)	Mixed	Mixed	SMD:0.59(0.20,0.98)	Moderate	0.003	52.0%	⊕⊕◯◯
Lu (2019)	RCT	Dialysis	7(224)	Mixed	Mixed	SMD:0.47(0.20,0.74)	Small	<0.001	0.0%	⊕⊕◯◯
Zhang (2021)	RCT	HD	6(300)	RT	Intradialytic	SMD:0.35(0.12,0.58)	Small	0.003	41.6%	⊕⊕◯◯
Heiwe (2011)	RCT/quasi-RCT	Mixed	9(358)	Mixed	-	SMD:-0.52(-0.73,-0.31)	Moderate	<0.001	0.0%	⊕◯◯◯
Heiwe (2014)	RCT	HD	12(385)	Mixed	Mixed	SMD:-0.56(-0.77,-0.35)	Moderate	<0.001	0.0%	⊕◯◯◯
Matsuzawa (2017)	RCT	HD	9(281)	Mixed	Mixed	SMD:0.94(0.67,1.21)	Large	<0.001	10.0%	⊕◯◯◯
Neto (2018)	RCT	HD	9(250)	Mixed	Intradialytic	SMD:0.61(0.39,0.83)	Moderate	<0.001	58.9%	⊕◯◯◯
Ju (2020)	RCT	Mixed	3(115)	Mixed	-	SMD:0.52(0.14,0.89)	Moderate	0.007	0.0%	⊕◯◯◯

Abbreviation: RCT = randomized controlled trial; RT = resistance training; SMD = standardized mean difference; MD = mean difference; HD = hemodialysis; GRADE = Grading of Recommendations Assessment, Development, and Evaluation.

Table 4 Summary of the effect of exercise on muscle endurance in CKD patients

Author (year)	Design	Stage of CKD	k (n)	Exercise type	Mode	Outcome	SMD or MD (95% CI)	Effect size	*P*	I^2	GRADE
Lu (2019)	RCT	Dialysis	3(193)	Mixed	Mixed	STS 10	MD:-4.69(-9.01,-0.38)	-	0.028	72.2%	⊕◯◯◯
Bogataj (2020)	RCT	HD	5(461)	Mixed	-	STS 10	SMD:-0.55(-1.00,-0.09)	Moderate	0.019	71.6%	⊕◯◯◯
Lu (2019)	RCT	Dialysis	6(240)	Mixed	Mixed	STS 30	SMD:0.43(0.17,0.69)	Small	0.001	2.0%	⊕⊕◯◯
Zhang (2021)	RCT	HD	5(164)	RT	Intradialytic	STS 30	SMD:0.42(0.11,0.74)	Small	0.008	0.0%	⊕◯◯◯
Sheng (2014)	RCT	HD	3(106)	Mixed	Intradialytic	STS 60	SMD:0.71(0.31,1.12)	Moderate	<0.001	0.0%	⊕◯◯◯
Pei (2019)	RCT/quasi-RCT	Mixed	5(445)	AE	-	STS 60	MD:2.08(1.1,3.05)	-	0.98	82.0%	⊕◯◯◯
Nakamura (2020)	RCT/cross-over	Predialysis	3(170)	Mixed	-	TUGT	SMD:-0.42(-0.73,-0.11)	Small	0.007	0.0%	⊕◯◯◯
Heiwe (2011)	RCT/quasi-RCT	Mixed	7(191)	Mixed	-	Walking capacity	SMD:-0.48(-0.79,-0.17)	Small	0.003	2.0%	⊕◯◯◯
Heiwe (2014)	RCT	HD	7(174)	Mixed	Mixed	Walking capacity	SMD:-0.33(-0.67,0.01)	Small	0.06	16.0%	⊕⊕⊕◯

Abbreviation: RCT = randomized controlled trial; AE = aerobic exercise; RT = resistance training; STS 10 = sit to stand 10 test; STS 30 = sit to stand 30 test; STS 60 = sit to stand 60 test; TUGT = timed up and go test; SMD = standardized mean difference; MD = mean difference; HD = hemodialysis; GRADE = Grading of Recommendations Assessment, Development, and Evaluation.

Table 5 Summary of the effect of exercise on body composition in CKD patients

Author (year)	Design	Stage of CKD	k (n)	Exercise type	Mode	SMD (95% CI)	Effect size	*P*	I^2	GRADE
Chen (2019)	RCT	KTRs	4(166)	Mixed	-	SMD:0.02(-0.28,0.33)	Small	0.89	0.0%	⊕◯◯◯
Yamamoto (2021)	RCT	Predialysis	10(414)	AE	-	SMD:-0.19(-0.38,-0.00)	Small	0.026	0.0%	⊕⊕◯◯
Zhang (2019)	RCT	Predialysis	13(466)	Mixed	-	SMD:-0.21(-0.39,-0.03)	Small	0.02	0.0%	⊕⊕⊕◯
Wyngaert (2018)	RCT	Predialysis	9(294)	AE	-	SMD:-0.36(-0.60,-0.13)	Small	0.002	48.0%	⊕⊕◯◯

Abbreviation: RCT = randomized controlled trial; AE = aerobic exercise; SMD = standardized mean difference; KTRs = kidney transplant recipients;;GRADE = Grading of Recommendations Assessment, Development, and Evaluation.

Table 6 Summary of the effect of exercise on dialysis-related symptoms in CKD patients

Author (year)	Design	Stage of CKD	k (n)	Exercise type	Mode	Outcomes	SMD or MD (95% CI)	Effect size	*P*	I^2	GRADE
Ferreira (2019)	RCT/quasi-RCT	HD	10(346)	AE	Intradialytic	Kt/V	SMD:2.21(1.17,3.25)	Large	<0.001	92.0%	⊕◯◯◯
Pu (2019)	RCT	HD	10(301)	Mixed	Intradialytic	Kt/V	SMD:0.29(0.06,0.52)	Small	0.01	0.0%	⊕◯◯◯
Huang (2019)	RCT	HD	8(257)	Mixed	Mixed	Kt/V	SMD:0.19(-0.06,0.43)	Small	0.14	0.0%	⊕◯◯◯
Sheng (2014)	RCT	HD	7(233)	Mixed	Intradialytic	Kt/V	SMD:0.27(0.01,0.53)	Small	0.04	0.0%	⊕◯◯◯
Ferrari (2019)	RCT	HD	12(370)	AE	Intradialytic	Kt/V	MD:0.08(0.0,0.15)	-	0.04	56.0%	⊕◯◯◯
Ferrari (2019)	RCT	HD	6(220)	RT	Intradialytic	Kt/V	MD:0.10(0.0,0.2)	-	0.06	6.0%	⊕◯◯◯
Song (2018)	RCT	HD	4(141)	Mixed	Mixed	RLS	SMD:-1.79(-2.21,-1.37)	Large	<0.001	87.0%	⊕◯◯◯
Song (2018)	RCT	HD	3(139)	Mixed	Mixed	Fatigue	SMD:-0.85(-1.20,-0.50)	Large	<0.001	0.0%	⊕◯◯◯
Zhao (2019)	RCT	Dialysis	3(141)	Mixed	-	Fatigue	SMD:-0.97(-1.32,-0.62)	Large	<0.001	47.0%	⊕⊕◯◯

Abbreviation: RCT = randomized controlled trial; AE = aerobic exercise; RT = resistance training; SMD = standardized mean difference; MD = mean difference; HD = hemodialysis; KTRs = kidney transplant recipients; RLS = Restless Legs Syndrome; GRADE = Grading of Recommendations Assessment, Development, and Evaluation.

Table 7 Summary of the effect of exercise on health-related quality of lifes in CKD patients

Author (year)	Design	Stage of CKD	k (n)	Exercise type	Mode	Outcomes	SMD or MD (95% CI)	Effect size	*P*	I^2	GRADE
Salhab (2019)	RCT	HD	5(282)	AE	Intradialytic	PCS	SMD:1.82(-0.92,4.55)	Large	0.19	98.0%	⊕◯◯◯
Chung (2016)	RCT	HD	6(229)	Mixed	Intradialytic	PCS	SMD:0.46(0.20,0.73)	Small	<0.001	1.90%	⊕⊕◯◯
Zhang (2021)	RCT	HD	7(297)	RT	Intradialytic	PCS	SMD:0.23(-0.00,0.46)	Small	0.055	0.0%	⊕⊕◯◯
Pu (2019)	RCT	HD	10(320)	Mixed	Intradialytic	PCS	SMD:0.57(0.14,1.01)	Moderate	0.01	70.0%	⊕◯◯◯
Zhao (2019)	RCT	Dialysis	5(186)	Mixed	-	PCS	SMD:0.31(0.02,0.61)	Small	0.04	46.0%	⊕⊕◯◯
Huang (2019)	RCT	HD	7(263)	Mixed	Mixed	PCS	SMD:0.34(0.09,0.59)	Small	0.007	27.0%	⊕⊕◯◯
Matsuzawa (2017)	RCT	HD	9(264)	Mixed	Mixed	PCS	SMD:0.53(0.52,0.82)	Moderate	<0.001	19.0%	⊕◯◯◯
Sheng (2014)	RCT	HD	7(256)	Mixed	Intradialytic	PCS	SMD:0.30(0.05,0.55)	Small	0.02	39.5%	⊕◯◯◯
Neto (2018)	RCT	HD	7(187)	Mixed	Intradialytic	PCS	SMD:0.50(-0.19,1.18)	Moderate	0.16	62.0%	⊕◯◯◯
Salhab (2019)	RCT	HD	5(282)	AE	Intradialytic	MCS	SMD:1.02(0.31,1.73)	Large	0.005	75.0%	⊕◯◯◯
Chung (2016)	RCT	HD	5(193)	Mixed	Intradialytic	MCS	SMD:0.23(-0.05,0.52)	Small	0.109	0.0%	⊕⊕◯◯
Zhang (2021)	RCT	HD	7(297)	RT	Intradialytic	MCS	SMD:0.13(-0.10,0.36)	Small	0.082	46.5%	⊕⊕◯◯
Pu (2019)	RCT	HD	8(219)	Mixed	Intradialytic	MCS	SMD:0.19(-0.09,0.46)	Small	0.18	30.0%	⊕⊕◯◯
Zhao (2019)	RCT	Dialysis	5(186)	Mixed	-	MCS	SMD:0.30(-0.20,0.80)	Small	0.24	64.0%	⊕◯◯◯
Huang (2019)	RCT	HD	7(263)	Mixed	Mixed	MCS	SMD:0.27(0.02,0.51)	Small	0.03	0.0%	⊕⊕◯◯
Matsuzawa (2017)	RCT	HD	8(228)	Mixed	Mixed	MCS	SMD:0.14(-0.15,0.42)	Small	0.34	10.0%	⊕◯◯◯
Sheng (2014)	RCT	HD	5(167)	Mixed	Intradialytic	MCS	SMD:0.14(-0.16,0.43)	Small	0.37	14.8%	⊕◯◯◯

Neto (2018)	RCT	HD	7(185)	Mixed	Intradialytic	MCS	SMD:0.39(-0.19,0.98)	Small	0.19	50.0%	⊕◯◯◯
Pei (2019)	RCT/quasi-RCT	Mixed	6(522)	AE	-	Physical function (SF-36)	MD:8.36(-1.24,17.95)	-	0.09	76.0%	⊕◯◯◯
Pei (2019)	RCT/quasi-RCT	Mixed	7(562)	AE	-	Physical role (SF-36)	MD:14.65(1.47,27.84)	-	0.03	78.0%	⊕◯◯◯
Pei (2019)	RCT/quasi-RCT	Mixed	6(447)	AE	-	Social function (SF-36)	MD:8.24(-1.09,17.58)	-	0.08	85.0%	⊕◯◯◯
Pei (2019)	RCT/quasi-RCT	Mixed	6(513)	AE	-	Pain (SF-36)	MD:5.94(1.65,10.23)	-	0.007	49.0%	⊕◯◯◯
Pei (2019)	RCT/quasi-RCT	Mixed	7(562)	AE	-	General health (SF-36)	MD:8.90(2.48,15.32)	-	0.007	71.0%	⊕◯◯◯
Pei (2019)	RCT/quasi-RCT	Mixed	6(542)	AE	-	Mental health (SF-36)	MD:7.30(-0.94,15.54)	-	0.08	84.0%	⊕◯◯◯
Cheema (2014)	RCT	Predialysis	6 (223)	RT	-	HRQOL	SMD:0.83(0.51,1.16)	Large	0.226	27.8%	⊕⊕◯◯
Oguchi (2018)	RCT	KTRs	4(179)	Mixed	-	HRQOL	SMD:0.54(0.02,1.07)	Moderate	0.04	58.0%	⊕◯◯◯
Ju (2020)	RCT	Mixed	3 (387)	Mixed	-	Symptom/problem (KDQOL)	SMD:1.92(-1.06,4.90)	Large	0.21	99.0%	⊕◯◯◯
Ju (2020)	RCT	Mixed	3 (387)	Mixed	-	Effects of kidney disease (KDQOL)	SMD:-3.69(-8.56,1.19)	Large	0.14	99.0%	⊕◯◯◯
Ju (2020)	RCT	Mixed	3 (387)	Mixed	-	Burden of kidney disease (KDQOL)	SMD:1.04 (-0.75,2.82)	Large	0.26	98.0%	⊕◯◯◯

Abbreviation: RCT = randomized controlled trial; AE = aerobic exercise; RT = resistance training; COM = combine; HRQOL = health-related quality of life; PCS = physical component summary; MCS = mental component summary; SMD = standardized mean difference; MD = mean difference; HD = hemodialysis; KTRs = kidney transplant recipients; SF-36 = Short-Form Health Survey-36; KDQOL = kidney disease quality of life; GRADE = Grading of Recommendations Assessment,

Development, and Evaluation.

Supplementary Table S1 The detailed search strategy

Databases	#	Search strategy
Pubmed	1	"renal insufficiency, chronic"[MeSH Terms]
	2	"chronic renal insufficiency"[Title/Abstract] or "chronic kidney insufficiency"[Title/Abstract] or "chronic kidney disease"[Title/Abstract] or "chronic renal disease"[Title/Abstract]
	3	"CKD"[Title/Abstract] or "CKF"[Title/Abstract] or "CRD"[Title/Abstract] or "CRF"[Title/Abstract]
	4	"end-stage kidney"[Title/Abstract] or "end-stage renal"[Title/Abstract] or "endstage kidney"[Title/Abstract] or "endstage renal"[Title/Abstract]
	5	"ESRD"[Title/Abstract] or "ESRF"[Title/Abstract] or "ESKD"[Title/Abstract] or "ESKF"[Title/Abstract]
	6	"Renal Replacement Therapy"[MeSH Terms]
	7	"dialysis"[Title/Abstract]
	8	"hemodialysis"[Title/Abstract] or "haemodialysis"[Title/Abstract] or "hemodiafiltration"[Title/Abstract] or "haemodiafiltration"[Title/Abstract] or "HD"[Title/Abstract]
	9	"PD"[Title/Abstract]
	10	"renal transplantation"[Title/Abstract] or "kidney grafting"[Title/Abstract] or "kidney transplantation"[Title/Abstract]
	11	"KTRs"[Title/Abstract]
	12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
	13	"Exercise"[MeSH Terms]
	14	"Exercise Movement Techniques"[MeSH Terms]
	15	"Exercise Therapy"[MeSH Terms]
	16	"Sports"[MeSH Terms]
	17	"train"[Title/Abstract] or "physical activity"[Title/Abstract] or "exercise"[Title/Abstract]
	18	#13 or #14 or #15 or #16 or #17
	19	"Systematic Review"[Publication Type] or "Systematic Reviews as Topic"[MeSH Terms]
	20	"meta analysis"[Publication Type] or "Meta-Analysis as Topic"[MeSH Terms]

	21	"Systematic Review"[Title/Abstract] or "system review"[Title/Abstract] or "data pooling"[Title/Abstract] or "meta"[Title/Abstract]
	22	#19 or #20 or #21
	23	#12 and #18 and #22
CDSR	1	MeSH descriptor: [Kidney Diseases] explode all trees
	2	("chronic kidney disease") or ("chronic renal disease") or ("chronic kidney failure") or ("chronic renal failure"):ti,ab,kw
	3	(CKF or CKD or CRF or CRD):ti,ab,kw
	4	("end-stage kidney") or ("end-stage renal") or ("endstage kidney") or ("endstage renal"):ti,ab,kw
	5	ESRD or ESRF or ESKD or ESKF:ti,ab,kw
	6	MeSH descriptor: [Renal Replacement Therapy] explode all trees
	7	dialysis:ti,ab,kw
	8	(hemodialysis or haemodialysis or hemodiafiltration or haemodiafiltration or HD):ti,ab,kw
	9	PD:ti,ab,kw
	10	("renal transplantation") or ("kidney grafting") or ("kidney transplantation"):ti,ab,kw
	11	KTRs:ti,ab,kw
	12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
	13	MeSH descriptor: [Exercise] explode all trees
	14	MeSH descriptor: [Exercise Movement Techniques] explode all trees
	15	MeSH descriptor: [Exercise Therapy] explode all trees
	16	MeSH descriptor: [Sports] explode all trees
	17	(train or ("physical activity") or exercise):ti,ab,kw
	18	#13 or #14 or #15 or #16 or #17
	19	MeSH descriptor: [Meta-Analysis as Topic] explode all trees
	20	MeSH descriptor: [Systematic Reviews as Topic] explode all trees
	21	("systematic review") or ("system review") or ("data pooling") or (meta):ti,ab,kw
	22	#19 or #20 or #21

	23	#12 and #18 and #22
Embase	1	'kidney disease'/exp
	2	('chronic kidney disease' or 'chronic renal disease' or 'chronic kidney failure' or 'chronic renal failure'):ti,ab,kw
	3	(CKF or CKD or CRFor CRD):ti,ab,kw
	4	('end-stage kidney' or 'end-stage renal' or 'endstage kidney' or 'endstage renal'):ti,ab,kw
	5	(ESRD or ESRF or ESKD or ESKF):ti,ab,kw
	6	'renal replacement therapy'/exp
	7	'dialysis':ti,ab,kw
	8	(hemodialysis or haemodialysis or hemofiltration or haemofiltration or hemodiafiltration or haemodiafiltration or HD):ti,ab,kw
	9	PD:ti,ab,kw
	10	('renal transplantation' or 'kidney grafting' or 'kidney transplantation'):ti,ab,kw
	11	KTRs:ti,ab,kw
	12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
	13	'exercise'/exp
	14	'physical activity'/exp
	15	'sport'/exp
	16	(train or 'physical activity' or exercise):ti,ab,kw
	17	#13 or #14 or #15 or #16
	18	'systematic review (topic)'/exp or 'systematic review'/exp
	19	'meta analysis (topic)'/exp or 'meta analysis'/exp
	20	('systematic review' or 'system review' or 'data pooling' or meta):ti,ab,kw
	21	#18 or #19 or #20
	22	#12 and #17 and #21
Web of Science	1	TS: ("chronic kidney disease" or "chronic renal disease" or "chronic kidney failure" or "chronic renal failure" or CKD or CRD or CKF or CRF)

	2	TS: ("end-stage kidney" or "end-stage renal" or "endstage kidney" or "endstage renal" or ESKD or ESKF or ESRD or ESRF)
	3	TS: ("renal replacement therapy" or dialysis or hemodialysis or haemodialysis or hemofiltration or haemofiltration or hemodiafiltration or haemodiafiltration or HD or PD)
	4	TS: ("renal transplantation" or "kidney grafting" or "kidney transplantation" or KTRs)
	5	#1 or #2 or #3 or #4
	6	TS: (train or exercise or "physical activity")
	7	TS: ("systematic review" or "system review" or "data pooling" or meta)
	8	#1 and #2 and #3 and #4 and #5

Supplementary Table S2 The characteristic of excluded studies

Studies	Reasons for exclusion
Nantakool et al (2020)	Non predefine outcome
Sawant et al (2014)	Non predefine outcome
Smart et al (2014)	Duplicate literature
Barcellos et al (2015)	Meta-analysis was not conducted
Yang et al (2020)	Non predefine outcome
Young et al (2018)	Included cases<100
Phan et al (2015)	Duplicate literature
Molsted et al (2019)	Included cases<100
Segura et al (2010)	Non-English
Ferreira et al (2020)	Non predefine outcome
Koufaki et al (2013)	Meta-analysis was not conducted
Smart et al (2012)	Abstracts
Howden et al (2012)	Meta-analysis was not conducted
Calella et al (2019)	Meta-analysis was not conducted
Singh et al (2005)	Meta-analysis was not conducted
Cardoso et al (2020)	Non predefine outcome
Villanego et al (2020)	Non-English
Medeiros et al (2017)	Intervention did not fit
Macdonald et al (2009)	Meta-analysis was not conducted
Wen et al (2019)	Non predefine outcome
Yang et al (2015)	Non predefine outcome
Thangarasa et al (2018)	Included cases<100
Chan et al (2016)	Meta-analysis was not conducted

Johansen et al (2010)	Intervention did not fit
Thompson et al (2020)	Correction for published paper
Bakaloudi et al (2020)	Meta-analysis was not conducted
Kirkman et al (2019)	Meta-analysis was not conducted
Afsar et al (2018)	Meta-analysis was not conducted

Supplementary Table S3 The basic characteristics of the included meta-analyses

Author (year)	Design	Stage of CKD	k (n)	Exercise type	Mode	Outcomes	SMD or MD(95% CI)	Effect size	*P*	I^2	GRADE
Pei (2019)	RCT/quasi-RCT	Mixed	17(464)	AE	-	VO_{2peak}	MD:2.08 (1.1,3.05)	-	<0.001	25.0%	Low
			5 (445)			STS 60	MD:2.08 (1.1,3.05)	-	0.98	82.0%	Very low
			8 (496)			6MWT	MD:0.04 (−0.52, 0.59)	-	0.9	86.0%	Very low
			12(514)			SBP	MD:−2.91 (−6.68, 0.87)	-	0.13	40.0%	Low
			12(514)			DBP	MD:−1.11 (−3.41, 1.20)	-	0.35	0.0%	Low
			6(522)			Physical function (SF-36)	MD:8.36(-1.24,17.95)	-	0.09	76.0%	Very low
			7(562)			Physical role (SF-36)	MD:14.65(1.47,27.84)	-	0.03	78.0%	Very low
			6(447)			Social function (SF-36)	MD:8.24(-1.09,17.58)	-	0.08	85.0%	Very low
			6(513)			Pain (SF-36)	MD:5.94(1.65,10.23)	-	0.007	49.0%	Very low
			7(562)			General health (SF-36)	MD:8.90(2.48,15.32)	-	0.007	71.0%	Very low
			6(542)			Mental health (SF-36)	MD:7.30(-0.94,15.54)	-	0.08	84.0%	Very low
Ferreira (2019)	RCT/quasi-RCT	HD	10(346)	AE	Intradialytic	Kt/V	SMD:2.21(1.17,3.25)	Large	<0.001	92.0%	Very low
Cheema (2014)	RCT	Predialysis	7(249)	RT	-	Muscle Strength	SMD:1.15（0.80-1.49）	Large	0.161	35.0%	Low
			6(223)			HRQoL	SMD:0.83(0.51-1.16)	Large	0.226	27.8%	Low
Wu (2020)	RCT/quasi-RCT	Predialysis	3(204)	AE+RT	-	SBP	SMD:-0.19(-0.46,0.08)	Small	0.16	50.0%	Very low
			4(194)			DBP	SMD:-0.47(-1.10,0.15)	Small	0.14	70.0%	Very low

Nakamura (2020)	RCT/cross-over	Predialysis	10(401)	Mixed	-	VO_{2peak}	SMD:0.88(0.53,1.23)	Large	<0.001	56.0%	Low
			4(119)			Muscle Strength	SMD:0.35(-0.03,0.73)	Small	0.07	7.0%	Very low
			5(392)			6MWT	SMD:1.04(0.17,1.90)	Large	0.02	92.0%	Very low
			3(170)			TUGT	SMD:-0.42(-0.73,-0.11)	Small	0.007	0.0%	Very low
Lu (2019)	RCT	Dialysis	11(300)	Mixed	Mixed	6MWT	MD:67.6(49.93,85.26)	-	<0.001	30.6%	Moderate
			3(193)			STS 10	MD:-4.69(-9.01,-0.38)	-	0.028	72.2%	Very low
			5(234)			HGS	MD:5.35(3.34,7.37)	-	<0.001	0.3%	Low
			7(224)			Muscle strength	MD:3.67(1.37,5.97)	-	0.020	38.6%	Low
			6(240)			STS 30	MD:2.43(0.91,3.96)	-	0.002	21.2%	Low
Chen (2019)	RCT	KTRs	5(198)	Mixed	-	SBP	SMD:0.18(-0.10,0.46)	Small	0.21	0.0%	Very low
			5(198)			DBP	SMD:0.04(-0.45,0.52)	Small	0.89	59.0%	Very low
			4(166)			BMI	SMD:0.02(-0.28,0.33)	Small	0.89	0.0%	Very low
			6(202)			VO_{2peak}	SMD:0.33(-0.02,0.69)	Small	0.06	27.0%	Very low
Song (2018)	RCT	HD	4(141)	Mixed	Mixed	RLS	SMD:-1.79(-2.21,-1.37)	Large	<0.001	87.0%	Very low
			3(139)			Fatigue	SMD:-0.85(-1.20,-0.50)	Large	<0.001	0.0%	Very low
Salhab (2019)	RCT	HD	5(282)	AE	Intradialytic	PCS	SMD:1.82(-0.92,4.55)	Large	0.19	98.0%	Very low
			5(282)			MCS	SMD:1.02(0.31,1.73)	Large	0.005	75.0%	Very low
Andrade (2019)	RCT	HD	5(201)	AE+RT	Intradialytic	VO_{2peak}	SMD:1.01(0.71,1.30)	Large	<0.001	0.0%	Low
Chung (2016)	RCT	HD	4(127)	Mixed	Intradialytic	6MWT	SMD:0.44(0.09,0.80)	Small	0.015	0.0%	Low
			6(238)			VO_{2peak}	SMD:0.55(0.18,0.92)	Moderate	0.003	52.9%	Very low
			6(229)			PCS	SMD:0.46(0.20,0.73)	Small	<0.001	1.90%	Low
			5(193)			MCS	SMD:0.23(-0.05,0.52)	Small	0.109	0.0%	Low
Zhang (2021)	RCT	HD	8(299)	RT	Intradialytic	6MWT	SMD:0.52(0.28,0.75)	Moderate	<0.001	18.7%	Very low
			5(164)			STS 30	SMD:0.42(0.11,0.74)	Small	0.008	0.0%	Very low

			6(300)			HGS	SMD:0.35(0.12,0.58)	Small	0.003	41.6%	Very low
			7(297)			PCS	SMD:0.23(-0.00,0.46)	Small	0.055	0.0%	Very low
			7(297)			MCS	SMD:0.13(-0.10,0.36)	Small	0.082	46.5%	Very low
Pu (2019)	RCT	HD	10(301)	Mixed	Intradialytic	Kt/V	SMD:0.29(0.06,0.52)	Small	0.01	0.0%	Very low
			10(400)			VO_{2peak}	SMD:0.57(0.23,0.90)	Moderate	<0.001	59.0%	Low
			7(219)			6MWT	SMD:0.57(0.30,0.84)	Moderate	<0.001	0.0%	Low
			10(320)			PCS	SMD:0.57(0.14,1.01)	Moderate	0.01	70.0%	Very low
			8(219)			MCS	SMD:0.19(-0.09,0.46)	Small	0.18	30.0%	Low
			7(287)			SBP	SMD:-0.28(-0.52,-0.05)	Small	0.02	0.0%	Very low
			7(287)			DBP	SMD:-0.32(-0.55,-0.08)	Small	0.008	42.0%	Very low
Yamamoto (2021)	RCT	Predialysis	10(392)	AE	-	SBP	SMD:-0.75(-1.24,-0.26)	Moderate	0.003	80.3%	Very low
			10(365)			VO_{2peak}	SMD:0.54(0.29,0.78)	Moderate	<0.001	24.6%	Very low
			10(414)			BMI	SMD:-0.19(-0.38,-0.00)	Small	0.026	0.0%	Low
Thompson (2019)	RCT	Predialysis	10(335)	Mixed	-	SBP	MD:-4.3(-9.0,0.4)	-	N.P.	50.4%	Very low
			8(303)			DBP	MD:-1.18(-4.76,2.40)	-	N.P.	60.5%	Very low
Yang (2017)	RCT	Mixed	4(150)	Mixed	-	VO_{2peak}	SMD:0.33(0.03,0.63)	Small	0.003	47.0%	Low
Clarkson (2019)	RCT	Dialysis	18(744)	Mixed	-	6MWT	MD:33.64(23.74,43.54)	-	<0.001	0.0%	Moderate
Zhao (2019)	RCT	Dialysis	3(141)	Mixed	-	Fatigue	SMD:-0.97(-1.32,-0.62)	Large	<0.001	47.0%	Low
			5(186)			PCS	SMD:0.31(0.02,0.61)	Small	0.04	46.0%	Low
			5(186)			MCS	SMD:0.30(-0.20,0.80)	Small	0.24	64.0%	Very low
Zhang (2019)	RCT	Predialysis	14(463)	Mixed	-	SBP	SMD:-0.41(-0.70,-0.11)	Small	0.007	55.0%	Moderate
			12(399)			DBP	SMD:-0.31(-0.71,0.08)	Small	0.12	70.0%	Low
			13(466)			BMI	SMD:-0.21(-0.39,-0.03)	Small	0.02	0.0%	Moderate

Huang (2019)	RCT	HD	8(257)	Mixed	-	Kt/V	SMD:0.19(-0.06,0.43)	Small	0.14	0.0%	Very low
			7(260)			SBP	SMD:-0.17(-0.41,0.08)	Small	0.18	8.0%	Low
			7(260)			DBP	SMD:-0.23(-0.69,0.24)	Small	0.34	68.0%	Very low
			7(205)			6MWT	SMD:1.01(0.26,1.76)	Large	0.008	83.0%	Very low
			7(263)			PCS	SMD:0.34(0.09,0.59)	Small	0.007	27.0%	Low
			7(263)			MCS	SMD:0.27(0.02,0.51)	Small	0.03	0.0%	Low
			10(371)			VO_{2peak}	SMD:0.73(0.52,0.95)	Moderate	<0.001	71.0%	Low
Heiwe (2011)	RCT/quasi-RCT	Mixed	24(847)	Mixed	-	Aerobic capacity	SMD:-0.56(-0.70,-0.42)	Moderate	<0.001	12.0%	Moderate
			9(358)			Muscle strength	SMD:-0.52(-0.73,-0.31)	Moderate	<0.001	0.0%	Low
			7(191)			Walking capacity	SMD:-0.48(-0.79,-0.17)	Small	0.003	2.0%	Low
			9(347)			SBP	SMD:0.25(0.04,0.47)	Small	0.02	0.0%	Low
			11(419)			DBP	SMD:0.16(-0.04,0.36)	Small	0.11	40.0%	High
Heiwe (2014)	RCT	HD	21(374)	Mixed	-	Aerobic capacity	SMD:-0.80(-1.02,-0.58)	Large	<0.001	0.0%	Low
			10(212)			DBP	SMD:0.17(-0.16,0.49)	Small	0.3	45.0%	Low
			10(312)			SBP	SMD:0.04(-0..4,0.41)	Small	0.8	58.0%	Very low
			10(385)			Muscle strength	SMD:-0.56(-0.77,-0.35)	Moderate	<0.001	0.0%	Very low
			7(174)			Walking capacity	SMD:-0.33(-0.67,0.01)	Small	0.06	16.0%	Low
Matsuzawa (2017)	RCT	HD	18(582)	Mixed	-	VO_{2peak}	SMD:0.62(0.38,0.87)	Moderate	<0.001	49.0%	High
			10(326)			6MWT	SMD:0.58(0.24,0.93)	Moderate	<0.001	53.0%	Low
			9(281)			Muscle strength	SMD:0.94(0.67,1.21)	Large	<0.001	10.0%	Very low
			9(264)			PCS	SMD:0.53(0.52,0.82)	Moderate	<0.001	19.0%	Very low
			8(228)			MCS	SMD:0.14(-0.15,0.42)	Small	0.34	10.0%	Very low
Smart (2011)	RCT	HD	8(365)	Mixed	-	VO_{2peak}	SMD:0.75(0.39,1.11)	Moderate	<0.001	60.0%	Low
Bogataj	RCT	HD	19(571)	Mixed	-	6MWT	SMD:0.44(0.21,0.67)	Small	<0.001	49.6%	Very low

(2020)			20(504)			VO_{2peak}	SMD:0.58(0.32,0.85)	Moderate	<0.001	57.4%	Very low
			5(461)			STS 10	SMD:-0.55(-1.00,-0.09)	Moderate	0.019	71.6%	Very low
Sheng (2014)	RCT	HD	7(233)	Mixed	Intradialytic	Kt/V	SMD:0.27(0.01,0.53)	Small	0.040	0.0%	Very low
			7(310)			VO_{2peak}	SMD:0.53(0.30,0.76)	Moderate	<0.001	36.0%	Very low
			7(256)			PCS	SMD:0.30(0.05,0.55)	Small	0.02	39.5%	Very low
			5(167)			MCS	SMD:0.14(-0.16,0.43)	Small	0.37	14.8%	Very low
			4(146)			6MWT	SMD:0.58(0.23,0.93)	Moderate	<0.001	89.7%	Very low
			7(296)			DBP	SMD:-0.24(-0.47,-0.01)	Small	0.04	52.1%	Very low
			7(296)			SBP	SMD:-0.27(-0.50,-0.04)	Small	0.02	0.0%	Very low
			3(106)			STS 60	SMD:0.71(0.31,1.12)	Moderate	<0.001	0.0%	Very low
Neto (2018)	RCT	HD	10(394)	Mixed	Intradialytic	VO_{2peak}	SMD:0.60(0.15,1.04)	Moderate	0.008	76.0%	Very low
			7(187)			PCS	SMD:0.50(-0.19,1.18)	Moderate	0.16	62.0%	Very low
			7(185)			MCS	SMD:0.39(-0.19,0.98)	Small	0.19	50.0%	Very low
			6(158)			6MWT	SMD:0.96(0.11,1.80)	Large	0.03	82.0%	Very low
			9(250)			Muscle strength	SMD:0.61(0.39,0.83)	Moderate	<0.001	58.9%	Very low
Ferrari (2019)	RCT	HD	12(370)	AE	Intradialytic	Kt/V	MD:0.08(0,0.15)	-	0.04	56.0%	Low
			6(220)	RT		Kt/V	MD:0.1(0,0.2)	-	0.06	6.0%	Very low
			5(201)	COM		VO_{2peak}	MD:5.41(4.03,6.79)	-	<0.001	0.0%	Low
			7(248)	AE		VO_{2peak}	MD:2.07(0.42,3.72)	-	<0.001	0.0%	Very low
			6(211)	RT		6MWT	MD:68.5(29.05,107.96)	-	<0.001	36.0%	Low
			6(188)	AE		6MWT	MD:64.98(43.86,86.11)	-	<0.001	0.0%	Low
			10(332)	AE		SBP	MD:-10.07(16.35,-3.78)	-	0.002	44.0%	Low
			10(334)	AE		DBP	MD:-2.96(-7.71,1.78)	-	0.22	0.0%	Low
Wyngaert (2018)	RCT	Predialysis	8(269)	AE	-	SBP	SMD:0.08(-0.58,0.74)	Small	0.81	84%	Very low
			7(237)			DBP	SMD:-0.09(-0.78,0.59)	Small	0.79	83%	Very low

			11(325)			VO_{2peak}	SMD:0.99(0.49,1.48)	Large	<0.001	74.0%	Very low
			9(294)			BMI	SMD:-0.36(-0.60,-0.13)	Small	0.002	48.0%	Low
Oguch (2018)	RCT	KTRs	4(182)	Mixed	-	VO_{2peak}	SMD:0.38(-0.06,0.82)	Small	0.09	45.0%	Low
			4(179)			HRQoL	SMD:0.54(0.02,1.07)	Moderate	0.04	58.0%	Very low
Ju (2020)	RCT		3 (115)	Mixed	-	HGS	SMD:0.52(0.14,0.89)	Moderate	0.007	0.0%	Very low
			3 (387)			Symptom/problem (KDQoL)	SMD:1.92(-1.06,4.90)	Large	0.21	99.0%	Very low
			3 (387)			Effects of kidney disease (KDQoL)	SMD:-3.69(-8.56,1.19)	Large	0.14	99.0%	Very low
			3 (387)			Burden of kidney disease (KDQoL)	SMD:1.04 (-0.75,2.82)	Large	0.26	98.0%	Very low

Abbreviation: RCT = randomized controlled trial; AE = aerobic exercise; RT = resistance training; COM = combine; VO_{2peak} = peak oxygen uptake; HRQoL = health-related quality of life; DBP = diastolic blood pressure; SBP = systolic blood pressure; PCS = physical component summary; MCS = mental component summary; 6MWT = 6 minutes walk test; STS 10 = sit to stand 10 test; STS 30 = sit to stand 30 test; STS 60 = sit to stand 60 test; TUGT = timed up and go test; RLS = Restless Legs Syndrome; BMI = body mass index; SMD = standardized mean difference; MD = mean difference; HD = hemodialysis; KTRs = kidney transplant recipients; SF-36 = short form-36; KDQoL = kidney disease quality of life; GRADE = Grading of Recommendations Assessment, Development, and Evaluation.

Supplementary Table S4 Results of the assessment of the methodological quality of the included meta-analyses using AMSTAR-2

Author	AMSTAR-2 Items																Score
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Pei(2019)	√	×	√	○	√	√	×	√	√	×	√	×	×	×	√	×	53.1%
Ferreira(2019)	√	√	√	○	√	√	×	○	√	×	√	×	×	×	×	×	50.0%
Cheema(2014)	√	×	√	√	√	√	√	√	√	×	√	√	√	√	√	√	87.5%
Wu(2020)	√	√	√	○	√	√	×	√	√	×	√	√	√	√	√	√	84.4%
Nakamura(2020)	√	√	√	○	√	√	×	√	√	×	√	√	√	√	√	√	84.4%
Lu(2019)	√	×	√	○	√	×	×	○	○	×	√	×	×	×	√	√	46.9%
Chen(2019)	√	×	√	○	×	√	×	√	○	×	√	×	×	×	×	√	43.8%
Song(2018)	√	×	√	○	√	√	×	√	√	×	√	×	√	√	√	√	71.9%
Salhab(2021)	√	√	√	○	√	√	×	√	×	×	√	×	×	√	×	×	53.1%
Andrade(2019)	√	√	√	○	√	√	×	√	√	×	√	×	×	√	×	√	65.6%
Chung(2016)	√	×	√	○	√	√	√	√	√	×	√	√	√	√	√	×	78.1%
Zhang(2019)	√	×	√	○	√	√	×	√	√	×	√	×	√	√	√	×	65.6%
Pu(2019)	√	×	√	○	√	√	×	√	√	×	√	√	√	√	×	√	71.9%
Yamamoto(2021)	√	×	√	×	√	√	×	○	√	×	√	√	√	√	√	√	71.9%
Thompson(2019)	√	×	√	○	√	√	×	√	√	√	√	√	√	√	√	√	84.4%
Yang(2017)	√	×	√	○	√	√	×	○	√	×	√	√	√	√	√	√	75.0%
Clarkson(2019)	√	×	√	○	√	√	×	√	√	×	√	√	√	√	√	√	78.1%
Zhao(2019)	√	×	√	○	√	√	×	√	√	×	√	×	√	×	×	√	59.4%
Zhang(2019)	√	×	√	○	√	√	×	○	√	×	√	√	×	×	√	√	62.5%
Huang(2019)	√	√	√	○	√	√	×	√	√	×	√	√	×	×	√	√	71.9%
Heiwe(2011)	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	100.0%
Heiwe(2014)	√	√	√	○	√	√	√	√	√	×	√	×	√	√	×	√	78.1%

Matsuzawa(2017)	√	√	√	○	√	√	×	√	√	×	√	×	×	√	√	√	71.9%
Smart(2011)	√	×	√	○	√	×	×	○	○	×	√	×	×	√	×	×	40.6%
Bogataj(2020)	√	×	√	○	√	×	×	√	√	×	√	√	×	√	×	√	59.4%
Sheng(2014)	√	×	√	○	√	√	√	√	√	×	√	×	×	√	√	×	65.6%
Neto(2018)	√	×	√	○	√	√	×	√	√	×	√	×	×	×	×	√	53.1%
Ferrari(2019)	√	√	√	○	√	√	√	√	√	×	√	√	√	√	√	√	90.6%
Wyngaert(2018)	√	√	√	○	√	√	×	√	√	×	√	√	√	√	√	√	84.4%
Oguchi(2018)	√	√	√	○	√	√	×	√	√	×	√	√	√	×	√	×	71.9%
Ju(2020)	√	×	√	○	×	×	×	√	√	×	√	×	×	×	×	×	34.4%

√ mean yes; ○ mean partial yes; ×mean no.

1. Did the research questions and inclusion criteria for the review include the components of PICO? 2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? 3. Did the review authors explain their selection of the study designs for inclusion in the review? 4. Did the review authors use a comprehensive literature search strategy? 5. Did the review authors perform study selection in duplicate? 6. Did the review authors perform data extraction in duplicate? 7. Did the review authors provide a list of excluded studies and justify the exclusions? 8. Did the review authors describe the included studies in adequate detail? 9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? 10. Did the review authors report on the sources of funding for the studies included in the review? 11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? 12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? 13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review? 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? 15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? 16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

Supplementary Table S5: Results of the assessment of the quality of evidence for each outcome of the included meta-analyses using GRADE

Author	Outcome	GRADE items					Quality of the evidence
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	
Pei (2019)	VO_{2peak}	Very serious (-2)	Neutral	Neutral	Neutral	Neutral	Moderate
	STS 60	Serious (-1)	Very serious (-2)	Neutral	Neutral	Serious (-1)	Very low
	6MWT	Serious (-1)	Very serious (-2)	Neutral	Neutral	Serious (-1)	Very low
	SBP	Serious (-1)	Neutral	Neutral	Neutral	Not reported (-1)	Moderate
	DBP	Serious (-1)	Neutral	Neutral	Neutral	Not reported (-1)	Moderate
	Physical function (SF-36)	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Serious (-1)	Very low
	Physical role (SF-36)	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Serious (-1)	Very low
	Social function (SF-36)	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Serious (-1)	Very low
	Pain (SF-36)	Serious (-1)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	General health (SF-36)	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Serious (-1)	Very low
	Mental health (SF-36)	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Serious (-1)	Very low
Ferreira (2019)	Kt/V	Very serious (-2)	Very serious (-2)	Neutral	Serious (-1)	Not reported (-1)	Very low
Cheema (2014)	Muscle Strength	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
	HRQoL	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
Wu (2020)	SBP	Very serious (-2)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	DBP	Very serious (-2)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low

Nakamura (2020)	VO_{2peak}	Neutral	Serious (-1)	Neutral	Neutral	Serious (-1)	Moderate
	Muscle Strength	Very serious (-2)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	6MWT	Neutral	Very serious (-2)	Neutral	Serious (-1)	Serious (-1)	Very low
	TUGT	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
Lu (2019)	6MWT	Neutral	Neutral	Neutral	Serious (-1)	Neutral	Moderate
	STS 10	Neutral	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	HGS	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
	Muscle strength	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
	STS 30	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
Chen (2019)	SBP	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	DBP	Serious (-1)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	BMI	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	VO_{2peak}	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
Song (2018)	RLS	Serious (-1)	Serious (-1)	Neutral	Very serious (-2)	Serious (-1)	Very low
	Fatigue	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
Salhab (2019)	PCS	Not reported (-1)	Serious (-1)	Neutral	Very serious (-2)	Serious (-1)	Very low
	MCS	Not reported (-1)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
Andrade (2019)	VO_{2peak}	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
Chung (2019)	6MWT	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
	VO_{2peak}	Neutral	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	PCS	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
	MCS	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
Zhang (2021)	6MWT	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	STS 30	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low

	HGS	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	PCS	Very serious (-2)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	MCS	Very serious (-2)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
Pu (2019)	Kt/V	Serious (-1)	Neutral	Neutral	Serious (-1)	Not reported (-1)	Very low
	VO_{2peak}	Neutral	Serious (-1)	Neutral	Neutral	Not reported (-1)	Moderate
	6MWT	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
	PCS	Neutral	Serious (-1)	Neutral	Serious (-1)	Not reported (-1)	Very low
	MCS	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
	SBP	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	DBP	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
Yamamoto (2021)	SBP	Very serious (-2)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	VO_{2peak}	Very serious (-2)	Neutral	Neutral	Serious (-1)	Neutral	Very low
	BMI	Very serious (-2)	Neutral	Neutral	Neutral	Neutral	Low
Thompson (2019)	SBP	Very serious (-2)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	DBP	Very serious (-2)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
Yang (2017)	VO_{2peak}	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
Clarkson (2019)	6MWT	Neutral	Neutral	Neutral	Neutral	Serious (-1)	Moderate
Zhao (2019)	Fatigue	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	PCS	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	MCS	Neutral	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
Zhang (2019)	SBP	Neutral	Serious (-1)	Neutral	Neutral	Neutral	Moderate
	DBP	Neutral	Serious (-1)	Neutral	Serious (-1)	Neutral	Low
	BMI	Serious (-1)	Neutral	Neutral	Neutral	Neutral	Moderate

Huang (2019)	Kt/V	Very serious (-2)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	SBP	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	DBP	Neutral	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	6MWT	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Serious (-1)	Very low
	PCS	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	MCS	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	VO_{2peak}	Serious (-1)	Neutral	Neutral	Serious (-1)	Neutral	Low
Heiwe (2011)	Aerobic capacity	Neutral	Neutral	Neutral	Neutral	Serious (-1)	Moderate
	Muscle strength	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	Walking capacity	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	SBP	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	DBP	Neutral	Neutral	Neutral	Neutral	Neutral	High
Heiwe (2014)	Aerobic capacity	Neutral	Neutral	Neutral	Serious (-1)	Not reported (-1)	Low
	DBP	Neutral	Neutral	Neutral	Serious (-1)	Not reported (-1)	Low
	SBP	Neutral	Serious (-1)	Neutral	Serious (-1)	Not reported (-1)	Very low
	Muscle strength	Serious (-1)	Neutral	Neutral	Serious (-1)	Not reported (-1)	Very low
	Walking capacity	Neutral	Neutral	Neutral	Serious (-1)	Not reported (-1)	Low
Matsuzawa (2017)	VO_{2peak}	Neutral	Neutral	Neutral	Neutral	Neutral	High
	6MWT	Serious (-1)	Serious (-1)	Neutral	Serious (-1)	Neutral	Very low
	Muscle strength	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	PCS	Very serious (-2)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	MCS	Very serious (-2)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
Smart (2011)	VO_{2peak}	Neutral	Serious (-1)	Neutral	Neutral	Serious (-1)	Low
Bogataj	6MWT	Serious (-1)	Serious (-1)	Neutral	Not reported (-1)	Not reported (-1)	Very low

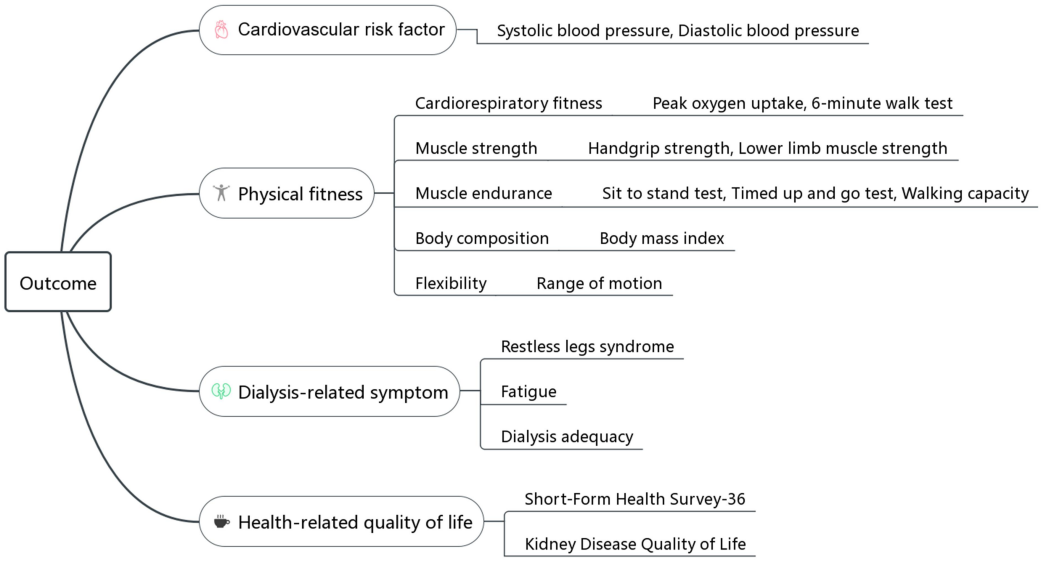
(2020)	VO_{2peak}	Very serious (-2)	Serious (-1)	Neutral	Not reported (-1)	Not reported (-1)	Very low
	STS 10	Neutral	Serious (-1)	Neutral	Not reported (-1)	Serious (-1)	Very low
Sheng (2014)	Kt/V	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	VO_{2peak}	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	PCS	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	MCS	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	6MWT	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Serious (-1)	Very low
	DBP	Serious (-1)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	SBP	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	STS60	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
Neto (2018)	VO_{2peak}	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Not reported (-1)	Very low
	PCS	Serious (-1)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	MCS	Serious (-1)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	6MWT	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Serious (-1)	Very low
	Muscle strength	Neutral	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
Ferrari (2019)	Kt/V (AE)	Neutral	Serious (-1)	Neutral	Serious (-1)	Neutral	Low
	Kt/V (RT)	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	VO_{2peak} (COM)	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	VO_{2peak} (AE)	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	6MWT (RT)	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	6MWT(AE)	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	SBP	Serious (-1)	Neutral	Neutral	Serious (-1)	Neutral	Low
	DBP	Serious (-1)	Neutral	Neutral	Serious (-1)	Neutral	Low
Wyngaert (2018)	SBP	Serious (-1)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	DBP	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Serious (-1)	Very low

	VO_{2peak}	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Neutral	Very low
	BMI	Serious (-1)	Neutral	Neutral	Serious (-1)	Neutral	Low
Oguchi (2018)	VO_{2peak}	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	HRQoL	Serious (-1)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
Ju (2020)	HGS	Very serious (-2)	Neutral	Neutral	Serious (-1)	Neutral	Very low
	Symptom/problem (KDQoL)	Very serious (-2)	Very serious (-2)	Neutral	Serious (-1)	Not reported (-1)	Very low
	effects of kidney disease (KDQoL)	Very serious (-2)	Very serious (-2)	Neutral	Serious (-1)	Not reported (-1)	Very low
	burden of kidney disease (KDQoL)	Very serious (-2)	Very serious (-2)	Neutral	Serious (-1)	Not reported (-1)	Very low

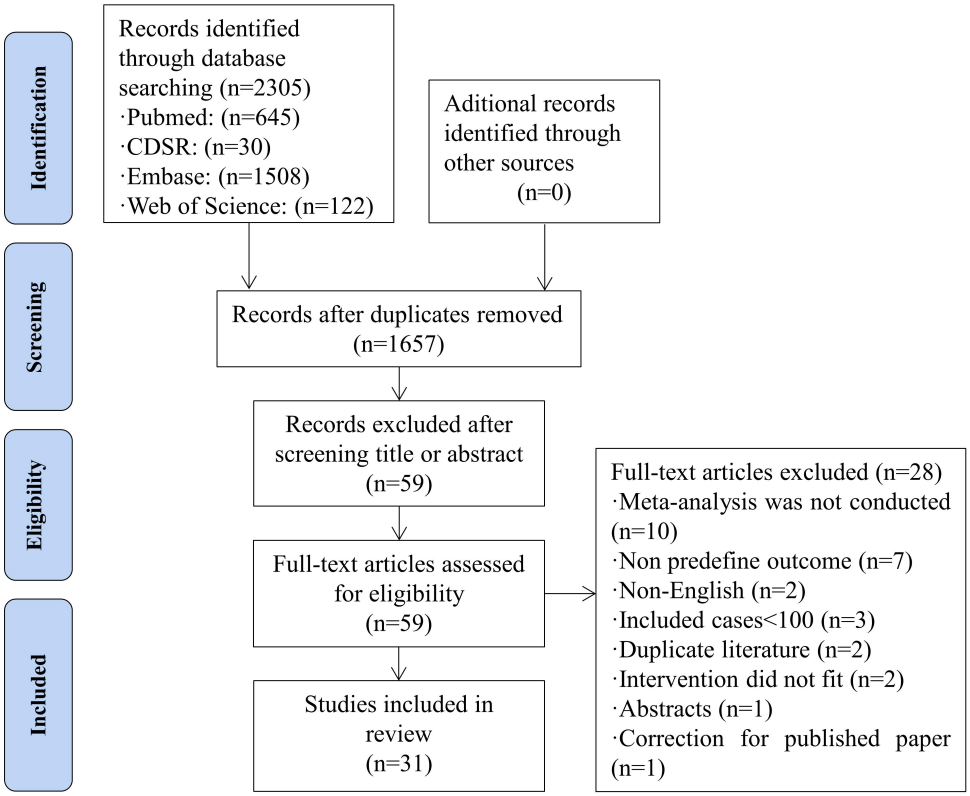
Abbreviation: AE = aerobic exercise; RT = resistance training; COM = combine; VO_{2peak} = peak oxygen uptake; HRQoL = health-related quality of life; DBP = diastolic blood pressure; SBP = systolic blood pressure; PCS = physical component summary; MCS = mental component summary; 6MWT = 6 minutes walk test; STS 10 = sit to stand 10 test; STS 30 = sit to stand 30 test; STS 60 = sit to stand 60 test; TUGT = timed up and go test; BMI = body mass index; SMD = standardized mean difference; HD = hemodialysis; KTRs = kidney transplant recipients; SF-36 = short form-36; KDQoL = kidney disease quality of life;

Very serious mean the included studies existed two or more high risk of bias in terms of randomization, blinding, allocation concealment, completeness of result data, or selective reporting, or $75\% \leq I^2 \leq 100\%$.

Serious mean the included studies existed two or more high risk of bias in terms of randomization, blinding, allocation concealment, completeness of result data, or selective reporting, or $50\% \leq I^2 < 75\%$, or the included study sample size< 400, asymmetric funnel plot or less than 9 studies included.



Supplemental Figures S1



Supplemental Figures S2

CDSR = Cochrane Database of Systemic Review

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 4-5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 4-5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 5-6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 4-5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	None
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Not applicable
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	None
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	None
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	None
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 6

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 6
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 6
Study characteristics	17	Cite each included study and present its characteristics.	Page 6
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 6
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 18-32
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Not applicable
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Not applicable
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not applicable
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	None
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 6
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 6
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 10
	23b	Discuss any limitations of the evidence included in the review.	Page 12
	23c	Discuss any limitations of the review processes used.	Page 12
	23d	Discuss implications of the results for practice, policy, and future research.	None
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	None
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 1
Competing interests	26	Declare any competing interests of review authors.	Page 1
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 1

PRISMA 2020 Checklist

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

BMJ Open

Therapeutic effects of exercise interventions for patients with chronic kidney disease: an umbrella review of systematic reviews and meta-analyses

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Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Rehabilitation medicine, Evidence based practice
Keywords:	Nephrology < INTERNAL MEDICINE, Rehabilitation medicine < INTERNAL MEDICINE, Chronic renal failure < NEPHROLOGY

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Therapeutic effects of exercise interventions for patients with chronic kidney disease: an umbrella review of systematic reviews and meta-analyses

Title page

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Key words: Exercise, chronic kidney disease, systematic review, meta-analyses

Running Head: Exercise for chronic kidney disease

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ABSTRACT

Objective To conduct an overview of meta-analyses evaluating the impact of exercise interventions for improving health outcomes in patients with chronic kidney disease (CKD).

Design An umbrella review of systematic review and meta-analyses of intervention trials was performed.

Data sources PubMed, Web of Science, Embase, and the Cochrane Database of Systematic Reviews were searched from inception to March 9th, 2021 for relevant articles.

Eligibility criteria for selecting studies Eligible meta-analyses compared the effects of usual care with and without exercise in CKD patients. Health outcomes included those related to cardiovascular risk factors, physical fitness, dialysis-related symptoms, dialysis adequacy, and health-related quality of life. Systematic reviews and meta-analyses that included fewer than three RCTs or fewer than 100 participants were excluded from the analysis.

Results A total of 31 eligible systematic reviews and meta-analyses were included that assessed 120 outcomes. For physical fitness, there was a moderate effect size for cardiorespiratory fitness, muscle strength, and body composition and a small effect size for muscle endurance. The effect sizes for cardiovascular risk factors, dialysis-related symptoms, and health-related quality of life outcomes were small. According to the Grading of Recommendations Assessment, Development, and Evaluation framework, most outcomes were scored as low or very low quality.

Conclusion Exercise appears to be a safe way to affect concomitant cardiovascular risk factors, such as blood pressure, improve physical fitness and health-related quality of life, and reduce dialysis-related symptoms in CKD patients.

Keywords: Exercise, Chronic Kidney Disease, Systematic Review, Meta-Analyses

PROSPERO registration number CRD42020223591.

Strengths and limitations of this study

1) This overview provides a comprehensive summary of the therapeutic effects of exercise interventions for patients with chronic kidney disease.

2) Methodological quality of the included reviews was assessed using standardized measures.

3) The limitation of this overview is that language bias may exist in this review because the search strategy was limited to English.

4) Most studies are based on hemodialysis-dependent chronic kidney disease.

INTRODUCTION

Chronic kidney disease (CKD) is a long-term condition characterized by the gradual loss of renal function over time.[1] In the past 30 years, the mortality attributed to CKD increased by 41.5%, a percentage rate that exceeds several cancers and cardiovascular diseases.[2] With the increasing incidence of hypertension, diabetes, and obesity, this number will continue to rise.[3, 4] CKD patients experience a high symptom burden with progressively impaired physical performance, leading to decreased kidney function, lower health-related quality of life (HRQOL), increased risk of cardiovascular events, and increased all-cause mortality.[5, 6]

With an increasing number of patients with CKD living longer, the effectiveness and accessibility of their health services have never been more critical. Renal rehabilitation is a multifaced intervention program. Rehabilitation consists of exercise interventions, diet control, fluid management, and psychological support to alleviate physical/mental deficiencies caused by kidney disease and renal replacement therapy to improve disease prognosis and prolong life expectancy.[7] Since exercise is the core of renal rehabilitation, there is an increasing number of systematic reviews and meta-analyses investigating the influence of exercise on health outcomes in CKD patients.[8]

Data from large cohort studies show that mortality risk was lower for regular (equal to or more than once/week) versus non-regular (less than once/week) exercisers [adjusted hazard ratio (HR)=0.73, 95% confidence interval (CI): 0.69–0.78], and mortality risk tended to decrease as exercise frequency increased ($HR_{\text{for participants who exercised once/week}}$ = 0.82, 95% CI: 0.73–0.91; $HR_{\text{for those who exercised 6–7 times/week}}$ = 0.69, 95% CI: 0.63–0.76) and patients who exercised daily had lower mortality risk (HR = 0.84, 95% CI: 0.74–0.96) than patients exercising once/week.[9] Based on data from 41 randomized controlled trials (RCT), Heiwe et al. reported effective improvements in aerobic capacity, muscular function, and walking capacity in CKD patients after exercise, [10] indicators that are the core of frailty. [11] In other words, exercise is an essential non-pharmacological strategy to improve frailty symptoms in CKD patients, the latter being a significant cause of sedentary behavior in such population. [12] Because of this, some researchers and guidelines recommend that healthcare providers prescribe exercise for CKD patients.[13-16] However, the results of meta-analyses of exercise in CKD patients are inconsistent.

This umbrella review aims to assess the therapeutic effects of exercise regarding cardiovascular risk factors, physical fitness, dialysis-related symptoms, dialysis adequacy, and HRQOL in CKD patients summarized in systematic reviews and meta-analyses.

METHODS AND ANALYSIS

This umbrella review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[17] The review was prospectively registered (PROSPERO: CRD42020223591), and the protocol for this review was published.[18]

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Literature Search

A comprehensive search strategy was performed to identify systematic reviews and meta-analyses of CKD patients that compared usual care procedures with and without exercise interventions. PubMed, Embase, the Cochrane Database of Systematic Reviews (CDSR), and the Web of Science were searched for systematic reviews and meta-analyses from inception to March 9th, 2021. The detailed search strategy is summarized in **Supplementary Table S1**. The references of existing systematic reviews were also screened. Any reviews considered potentially relevant by authors were retrieved for further consideration.

Eligibility Criteria

Eligible systematic reviews and meta-analyses included those 1) where patients were diagnosed with CKD at various stages of treatment; 2) that compared exercise interventions with sham/no exercise or usual/standard care; 3) that reported outcomes on at least one of the following: cardiovascular risk factors (blood pressure), physical fitness, dialysis-related symptoms, dialysis adequacy, and HRQOL. The methods to assess each outcome were shown in **Supplement Figure S1**; 4) systematic reviews with meta-analysis of intervention trials (RCTs and quasi-experimental studies). A meta-analysis that included less than three studies or less than 100 participants was excluded. For duplicate literature, the article with the most comprehensive data was selected. The language was restricted to English. Letters to the editor, trial protocols, and conference abstracts were excluded.

Study selection

Two independent authors screened all titles and abstracts compiled from the search results. Each paper was examined for appropriate eligibility criteria, and a third author resolved disagreements.

Data extraction

Requisite data were extracted independently by two independent authors into a standardized format that included: 1) author, 2) publication year, 3) stage of CKD, 4) the number of included studies and participants, 5) exercise type, 6) exercise mode (intradialytic or interdialytic), 7) standardized mean difference (SMD) or mean difference (MD) with corresponding 95% CI for each outcome, 8) *P*-values, 9) I^2 values, and 10) exercise-related adverse events.

Risk of bias assessment

A Measurement Tool to Assess Systematic Reviews-2 (AMSTAR-2) was used to assess the risk of bias among the included systematic reviews.[19] This checklist contains 16 items, and each item was answered with a "yes" (1 point), "partial yes" (0.5 points), or "no" (0 points). A percentage score was calculated for each study based on the total score as the numerator and the maximum 16 points as the denominator. A meta-analysis scoring ≥80% was classified as high quality, those scoring 40-79% as medium quality, and those scoring <40% as low quality.[20] Two authors performed the risk of bias assessment independently, and discussions resolved the disagreement.

Data analysis

The summary effect size from each meta-analysis was analyzed qualitatively based on the SMD and its 95% CI for each outcome. If they were not presented as SMD in the original meta-analysis, Review Manager V.5.3 was used to convert SMD outcomes. If data could not be converted into SMD, we contacted the authors of the meta-analysis for the data. Effects were considered small (SMD < 0.50), moderate (SMD from 0.50 to 0.79), and large (SMD ≥ 0.80).[21] I^2 values were interpreted as follows: ≤25% indicate low heterogeneity, 25%<I^2≤50% indicate mild heterogeneity, 50%<I^2≤75% indicate moderate heterogeneity and >75% indicate high heterogeneity.[22]

The level of evidence for each meta-analysis was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.[23] The quality of evidence was assessed using five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Beginning with an initial score of 4 points, the score for each of these five domains was reduced accordingly: "not reported (-1)", "serious (-1)", "very serious (-2)", or "neutral (0)". Studies were rated as high (4 points), moderate (3 points), low (2 points), or very low (≤1 point) using the GRADE system. The GRADE assessment was conducted independently by two authors. Any differences were resolved by discussion or adjudication by a third author. The incidence of adverse events was based on the number of reported divided by the patients in the exercise group.

RESULTS

Characteristics of the meta-analyses

The search identified 2305 potential articles, of which 648 were duplicates. After reading the title and abstract, 1598 papers were excluded, and 28 were excluded after full-text review resulting in 31 final studies. [10, 24-53] The PRISMA flowchart of study inclusion is illustrated in **Figure 1**. The reasons for excluded articles are listed in **Supplementary Table S2**.

The 31 included systematic reviews and meta-analyses were published from September 2011 through March 2021. The number of included studies assessed in the articles ranged from 3 to 24, with a mean of 8 studies. The study sample sizes ranged from 106 to 874 participants, with a mean of 304. The characteristics of the included meta-analyses are shown in **Supplement Table S3**. SMD data from four papers could not be obtained from the authors, and the data of their effect size was presented as MD.[29, 30, 40, 46]

The methodological quality assessment of the included meta-analyses was determined, and the AMSTAR-2 scores ranged from 34.4% to 100.0%, with a mean score of 68.0%. Seven (22.6%) systematic reviews were rated of high quality, while 23 (74.2%) were rated of medium quality, and just one (0.3%) was rated as low quality (**Supplement Table S4**).

Of the GRADE evidence quality of the 120 outcomes, 1.7% (2 / 120) reported evidence of high quality, 17.5% (21 / 120) reported evidence of moderate quality, 20.0% (24 / 120) reported evidence of low quality, and 60.8% (73 / 120) reported evidence of very low quality (**Supplement Table S5**).

Blood pressure

There were 25 meta-analyses (reported in 13 articles) investigating the effect of exercise on cardiovascular risk factors (systolic and diastolic blood pressure) in CKD patients. [10, 27, 30, 33, 34, 40, 41, 43, 46-49, 52] Of which, the number of studies ranged from 3 to 12 with a mean of 314 participants (range from 198 to 514) were included in each meta-analysis (**Table 1**).

The effect of exercise on systolic blood pressure was investigated in 13 meta-analyses with a mild heterogeneity (average $I^2 = 36.1\%$),[10, 27, 30, 33, 34, 40, 41, 43, 46-49, 52] and six reported a positive statistically significant outcome. [30, 33, 41, 43, 49, 52] Of the 13 meta-analyses, nine reported a small effect size, [10, 27, 33, 34, 41, 43, 47, 48, 52] and one reported moderate.[49] GRADE assessment of quality indicated the overall evidence as being very low (10 meta-analyses[10, 27, 30, 33, 41, 43, 46-49]), low (two meta-analyses[34, 40]), and moderate (one meta-analysis[52]).

The effect of exercise on diastolic blood pressure was investigated in 12 meta-analyses with a mild heterogeneity (average I^2=49.1%),[10, 27, 30, 33, 34, 40, 41, 43, 46-48, 52] and 2 reported a positive statistically significant outcome.[41, 43] Of the 12 meta-analyses, nine reported small effect sizes [10, 27, 33, 34, 41, 43, 47, 48, 52], and all were graded as low or very low quality of evidence.

Cardiorespiratory fitness

There were 34 meta-analyses (reported in 21 articles) that investigated the effects of exercise on cardiorespiratory fitness in CKD patients using a peak oxygen uptake (18 of 34), 6-minute walk test (14 of 34), or aerobic capacity (2 of 34). The meta-analyses included a mean of nine studies (ranging from 5 to 20) and a mean of 330 participants (ranging from 179 to 504) (**Table 2**).

The effect of exercise on peak oxygen consumption was investigated in 18 meta-analyses (reported in 17 articles) with a mild heterogeneity (average I^2=42.2%),[24, 25, 27, 28, 30, 32, 34, 37, 38, 40, 41, 43, 44, 49, 50, 54] and 16 reported positive statistically significant outcomes. [24, 25, 28, 30, 32, 34, 37, 38, 40, 41, 43, 44, 47, 49, 50] Of the 18 meta-analyses, three reported a low effect size,[27, 39, 50] nine reported a moderate effect size[25, 28, 32, 34, 37, 41, 43, 44, 49] and three reported a large effect size.[24, 38, 47] GRADE assessment of quality indicated the overall evidence as being

very low (9 meta-analyses[25, 27, 28, 30, 32, 37, 43, 47, 49]), low (8 meta-analyses[24, 34, 38-41, 44, 50]), and high (one meta-analysis[37]). A meta-analysis that included kidney transplant recipients found no statistically significant difference in the SMD of the exercise group (0.38; 95% CI, -0.06 to 0.82; *P*=0.09).[39]

The effect of exercise on 6-minute walk test was investigated in 14 meta-analyses (reported in 13 articles) with a mild heterogeneity (average I^2=44.9%),[25, 28-30, 32, 34, 36-38, 40, 41, 43, 51] and 13 reported positive statistically significant outcomes.[25, 28-30, 32, 34, 36-38, 41, 43, 51] Of the 14 meta-analyses, two reported a small effect size,[25, 28] five reported a moderate effect size,[36, 37, 41, 43, 51] and three reported a large effect size.[32, 34, 38] GRADE assessment of quality indicated the overall evidence as being very low (eight meta-analyses[25, 30, 32, 34, 38, 40, 43]), low (four meta-analyses[28, 37, 41, 51]), and moderate (two meta-analyses[29, 36]). In addition, the meta-analysis by Heiwe et al. (2014) showed that regular exercise had significant beneficial effects on aerobic capacity. [10, 33]

Muscle strength

Ten meta-analyses (reported in nine articles) investigated the effects of exercise on muscle strength in CKD patients with a low heterogeneity (average I^2 = 19.1%).[10, 26, 32, 33, 35-38, 51] The meta-analyses included a mean of seven studies (ranging from 3 to 12) and a mean of 252 participants (ranging from 115 to 385) (**Table 3**).

Muscle strength was measured using handgrip strength and lower limb muscle strength. For patients in 8 of 10 meta-analyses, exercise resulted in statistically significant improvements in muscle strength. [10, 32, 33, 35-37, 51] Of the 10 meta-analyses, three reported a small effect size,[36, 38, 51] five reported a moderate effect size,[10, 32, 33, 35, 36] and two reported a large effect size,[26, 37] GRADE assessment of quality indicated the overall evidence as being very low (six meta-analyses[10, 32, 33, 35, 37, 38]) and low (four meta-analyses[26, 36, 51]).

Muscle endurance

Nine meta-analyses (reported in 8 articles) investigated the effects of exercise on muscle endurance with a mild heterogeneity (average I^2 = 29.4%).[10, 25, 33, 36, 38, 40, 43, 51] A mean of five studies (ranging from 3 to 7) and a mean of 238 participants (ranging from 106 to 461) were included in meta-analyses (**Table 4**).

Muscle endurance was measured using a sit-to-stand test, timed up and go test, and walking capacity exercise. Pooled effect estimates from all nine meta-analyses suggested a beneficial effect of exercise on muscle endurance in CKD patients. Seven of the nine meta-analyses reported power to detect a statistically significant effect. [25, 33, 36, 38, 43, 51] Two meta-analyses reported moderate effect size, and 5 reported small effect size. GRADE assessment of quality indicated the overall evidence as being very low (seven meta-analyses[25, 33, 36, 38, 40, 43, 51]), low (one meta-analyses[36]) and moderate (one meta-analyses[10]).

Body composition

Four meta-analyses consisting of a mean of 9 studies (ranging from 4 to 13) and a mean of 335 participants (ranging from 166 to 466) included body mass index as an outcome.[27, 47, 49, 52] There was a low heterogeneity (average $I^2 = 12.0\%$) among the study outcomes (**Table 5**).

Of the four meta-analyses, three showed a positive statistically significant impact on body mass index using exercise interventions in CKD patients.[47, 49, 52] Small effect size was reported in all meta-analyses. GRADE assessment of quality indicated the overall evidence as being very low (one meta-analysis), low (two meta-analyses[47, 49]), and moderate (one meta-analysis [52]).

Dialysis-related symptoms

Nine meta-analyses (reported in seven articles) investigated the effect of exercise on dialysis-related symptoms in CKD patients.[30, 31, 34, 41, 43, 45, 53] Each meta-analysis included a mean of seven studies (ranging from 3 to 12 studies) and a mean of 239 participants (ranging from 139 to 370). (**Table 6**).

Fatigue was measured using the Rhoten Fatigue Scale, Visual Analogue Scale, and Hemodialysis Patients Fatigue Scale. The effect of exercise on fatigue was investigated in 2 meta-analyses with a low heterogeneity (average I^2=23.5%).[45, 53] The two meta-analyses revealed a statistically significant effect of exercise on fatigue. Although the meta-analyses reported a large effect size, the quality of evidence was low[45] or very low[53] according to GRADE criteria.

Just one meta-analysis investigated the effects of exercise on restless legs syndrome in CKD patients.[45] The results showed that pooled effect estimated for restless legs syndrome with statistically significant but considerable average heterogeneity ($I^2 = 87.0\%$). According to GRADE criteria, the overall evidence for this outcome was rated as very low.

Dialysis adequacy

Dialysis adequacy was measured using the value of Kt/V. Six meta-analyses (reported in 5 articles) investigated the effects of exercise on Kt/V in CKD patients with a mild heterogeneity (average $I^2 = 25.7\%$).[30, 31, 34, 41, 43] Comprehensive effect estimates from all the six meta-analyses with Kt/V outcomes showed that exercise had a beneficial effect. Of the six meta-analyses, 3 reported a small effect size[34, 41, 43], and one reported large effect size.[31] According to GRADE criteria, all meta-analyses were rated as very low quality of evidence (**Table 6**).

Health-related quality of life

Twenty-nine meta-analyses (reported in 13 articles) investigated the effect of exercise on HRQOL in CKD patients.[26, 28, 32, 34, 35, 37, 39-43, 51, 53] Among them, nine the meta-analyses each assessed physical and mental subscale of the Short-Form Health Survey-36.[28, 32, 34, 37, 41-43, 51, 53] A mean of six studies (ranging from 3 to 10) and a mean of 311 participants (ranging from

167 to 562) were included in each meta-analysis. The included meta-analyses had moderate heterogeneity (average $I^2 = 51.0\%$) (**Table 7**).

Of the 29 meta-analyses, a comprehensive effect estimate of the 28 meta-analyses shows that exercise is beneficial to the HRQOL of CKD patients, but only 12 of 29 meta-analyses reported a statistically significant outcome.[28, 34, 37, 39, 41-43, 53] There were 13 of 29 meta-analyses reporting a small effect size, [28, 32, 34, 37, 41, 43, 51, 53] 4 were moderate,[32, 37, 39, 41] and 6 were large.[26, 35, 42] According to GRADE criteria, the overall of evidence for HRQOL was rated as very low (20 meta-analyses[32, 35, 37, 39-43, 53]) or low (nine meta-analyses[26, 28, 34, 41, 51, 53]).

Adverse events

Six meta-analyses reported exercise-related adverse events.[26, 28, 38, 41, 43, 44] Of the adverse effects, the most commonly reported were hypotension and cramping. Overall, the incidence of adverse events was approximately 0.3%.

DISCUSSION

Summary of main results

Several meta-analyses have been published in exercise interventions in CKD patients.[55] The findings of these meta-analyses should be assessed to determine if the evidence is consistent among the studies. This umbrella review included 31 eligible articles involving 120 separate meta-analyses investigating the effect of exercise on the health outcomes in CKD patients. There was low- or very low-quality evidence for moderate beneficial effects of exercise on cardiorespiratory fitness, muscle strength, and body composition. In addition, there was very low-quality evidence for minor beneficial effects of exercise on muscle endurance, cardiovascular risk factors, dialysis-related symptoms, and HRQOL. There were few adverse events related to exercise, indicating that exercise is safe for CKD patients.

Interpretation of study effects

Cardiovascular disease is a frequent complication of CKD and is the leading cause of death in CKD patients.[56] Hypertension is an important modifiable risk factor for cardiovascular diseases and progressive renal dysfunction in CKD patients.[57] The present overview showed that exercise has a small to moderate effect on blood pressure (SMD: -0.75 to 0.04 for systolic blood pressure, and SMD: -0.47 to 0.04 for diastolic blood pressure), it is an appealing strategy for blood pressure control in CKD patients. However, the dose effects of exercise in the context of the cardiovascular health of CKD patients should be considered. A recent cohort study found that 7.5-15 metabolic equivalent hours per week (MET-h/week) was associated with the lowest risk of cardiovascular events.[58] Regrettably, the benefit of exercise on cardiovascular risk factors cannot be determined

because there are an insufficient number of conclusive studies that assess exercise effects on overall cardiovascular health. In a systematic review by Heiwe et al., a meta-analysis including two trials found that exercise improved cardiovascular function in patients with CKD, as reflected in the standard deviation of all normal RR intervals and left ventricular mass index.[10] Furthermore, a recent randomized controlled trial published by Graham-Brown indicated that intradialytic exercise could reduce left ventricular mass and is safe, deliverable, and well-tolerated.[59] Although the GRADE evidence generated was low, exercise should be recommended for CKD patients, particularly those comorbid with cardiovascular disease. Future randomized controlled exercise trials need to focus more on the role of exercise in cardiovascular events in patients with CKD.

Physical fitness is necessary for participation in activities of daily living. The exercise provided the best results in improving cardiorespiratory fitness and muscle strength in CKD patients, with more than a half of the meta-analyses reporting moderate or large effect sizes, regardless of the quality of evidence. Cardiorespiratory fitness is considered an important independent predictor of mortality, and muscle strength is an important indicator of physical performance in CKD patients.[60] It is well known that aerobic exercise is the "gold standard" for cardiorespiratory rehabilitation[61] and resistance training for muscle strength improvement.[62] However, a combination of aerobic and resistance exercises may have a more profound effect in CKD patients based on the current review. Meta-analyses conducted by Andrade et al. showed that combined training benefits cardiorespiratory fitness in CKD patients.[24]

Both sarcopenia and obesity have been shown to increase mortality risk and increase progression to end-stage renal disease in CKD patients.[63] Unlike patients receiving dialysis, treatment requirements for predialysis CKD patients are based upon the principle of maintaining a "healthy weight" and preventing or attenuating obesity.[14] In this overview, the effectiveness of exercise for body mass index was supported by four analyses with small effect sizes and moderate quality of evidence. Based on the results, exercise may contribute to lower body mass index in CKD patients. However, additional studies are needed to confirm the benefits of exercise programs for reducing sarcopenia and weight.

CKD population experience multiple symptoms that affect patient's prognosis and HRQOL.[64] Patients who received dialysis treatment commonly reported restless legs syndrome, fatigue, and inadequate dialysis due to kidney function deterioration and dialysis-related side effects.[65, 66] These symptoms affect sleep, daily activities and impose a considerable amount of psychological distress and economic burden.[67] An increasing number of researchers have investigated the role of exercise as an important non-pharmacological strategy for preventing and/or treating symptoms.[68, 69] The results of a small number of meta-analyses suggested the beneficial effect of exercise on dialysis adequacy (SMD: 0.19 to 2.21) and improving restless legs syndrome (SMD: -1.79) and fatigue symptoms (SMD: -0.97 to -0.85). Nevertheless, the efficacy of exercise in CKD patients for preventing dialysis-related symptoms awaits new clinical evidence.

With similar results obtained in another overview that included chronic disease,[70] results from this overview demonstrated minor beneficial effects of exercise on HRQOL, irrespective of the evidence level in CKD patients. Improved HRQOL is important because most of the population reported ongoing poor health and well-being due to diet restriction, weakness, and dialysis treatment.[71] The consistent health benefits of exercise in this overview demonstrated that exercise could be a strategy to improve the poor long-term prognosis in CKD patients.

Several meta-analyses reported exercise-related adverse events. Based on the number of adverse events reported, we calculate that only three adverse events occurred per 1000 CKD patients. The low incidence of adverse events indicated that the benefits of exercise in CKD patients outweigh its potential risks and most reflected typical response to exercise (e.g., muscle soreness). However, most meta-analyses only included intradialytic exercise for hemodialysis patients in their assessments. Exercises during hemodialysis are usually performed under the supervision of a healthcare worker to ensure safety.[72] It has been reported that all patients with CKD are at risk for cardiovascular events (e.g., arrhythmias, myocardial ischemia) during exercise. Therefore, medical screening should be performed before exercise to determine which patients may be at increased risk for cardiovascular accidents. [73] In addition, special attention should be paid to dry weight and blood pressure in patients with hemodialysis-dependent CKD to avoid excessive volume loading or dehydration, which may increase the risk associated with exercise. [60]

Implications for clinical

Taken together, there is good reason to recommend exercise for improving prognosis in CKD patients. Evidence from most randomized controlled trials increased confidence in the findings of this umbrella review. Because most of the meta-analyses assessed in this study did not detail the exercises instituted, it is difficult to make recommendations about the type of exercise that would be the most beneficial for CKD patients. Although the effect sizes of exercise on improving the health prognosis of CKD patients were generally moderate, these effects may bring some clinical benefit to patients experiencing impaired function or symptom distress. Despite numerous meta-analyses providing only low or very low-quality evidence, similar beneficial effects of exercise were reported by meta-analyses of randomized controlled trials with different grades of evidence. Remarkably, a recently published trial found that a 6-month program of intradialytic exercise effectively reduces healthcare costs.[74] Overall, exercise should be integrated into the care of CKD, but the overall benefit of the exercise to CKD is still debatable.

Limitations

There are several limitations to this overview: 1) Most meta-analyses included in this review involve hemodialysis patients, limiting the extrapolation of the results to other stages of CKD; 2) improvement of flexibility in CKD patients was not investigated. Flexibility is an important component of physical fitness that impacts muscular injury.[75] The evidence for the efficacy of

exercise on flexibility improvement is insufficient for a systematic review or meta-analysis; 3) language bias may exist in this review because the search strategy was limited to English. It is unknown if meta-analyses published in other languages would influence the outcomes of our findings; 4) the results may be had been influenced by an overlap in the original studies; 5) the accuracy of the MD data cannot be guaranteed; 6) sub-group analyses of different types of exercise were not performed as described in the published protocol because of most the included meta-analyses did not detail the exercises, and 7) both body composition and cardiovascular risk factors are common terms. However, the inclusion of studies was limited, so this review focused only on body mass index and blood pressure, and more evidence is still needed for the effects of other assessment metrics.

CONCLUSION

In CKD patients, exercise appears to improve muscle strength and endurance, body composition, and HRQOL. At the same time, exercise decreases blood pressure and dialysis-related symptoms in CKD patients. However, the quality of the evidence was considered low or very low for all outcomes indicating that we have low certainty evidence to support the findings above, more rigorous study is still needed in the future. Nevertheless, given the health benefits of physical activity, exercise should be integrated into renal care for a patient with any stage of CKD.

Contributors

FZ and LYH conceived and designed the review. YB and XZ searched databases, extracted the data, and statistical analysis. WQZ revised the manuscript. WQW and HCZ provided technical support. All authors had read and approved the final manuscript and agreed on its submission.

Ethics approval statement

Ethics approval is not required as no private information from individuals is collected.

Dissemination

The results will be published in a peer-reviewed journal or disseminated in relevant conferences.

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Table 1 Summary of the effect of exercise on cardiovascular risk factor in CKD patients

Author (year)	Design	Stage of CKD	k (n)*	Exercise type	Mode	SMD or MD (95% CI)	Effect size	*P*	I^2	GRADE
SBP										
Pei (2019)	RCT/quasi-RCT	Mixed	12(514)	AE	-	MD:−2.91 (−6.68, 0.87)	-	0.13	40.0%	⊕⊕◯◯
Wu (2020)	RCT/quasi-RCT	Predialysis	3 (204)	AE+RT	-	SMD:-0.19(-0.46,0.08)	Small	0.16	50.0%	⊕◯◯◯
Chen (2019)	RCT	KTRs	5(198)	Mixed	-	SMD:0.18(-0.10,0.46)	Small	0.21	0.0%	⊕◯◯◯
Pu (2019)	RCT	HD	7(287)	Mixed	Intradialytic	SMD:-0.28(-0.52,-0.05)	Small	0.02	0.0%	⊕◯◯◯
Yamamoto (2021)	RCT	Predialysis	10(392)	AE	-	SMD:-0.75(-1.24,-0.26)	Moderate	0.003	80.3%	⊕◯◯◯
Thompson (2019)	RCT	Predialysis	10(335)	Mixed	-	MD:-4.30(-9.00,0.40)	-	N.P.	50.4%	⊕◯◯◯
Zhang (2019)	RCT	Predialysis	14(463)	Mixed	-	SMD:-0.41(-0.70,-0.11)	Small	0.007	55.0%	⊕⊕⊕◯
Huang (2019)	RCT	HD	7(260)	Mixed	Mixed	SMD:-0.17(-0.41,0.08)	Small	0.18	8.0%	⊕⊕◯◯
Heiwe (2011)	RCT/quasi-RCT	Mixed	9(347)	Mixed	-	SMD:0.25(0.04,0.47)	Small	0.02	0.0%	⊕◯◯◯
Heiwe (2014)	RCT	HD	10(312)	Mixed	-	SMD:0.04(-0.34,0.41)	Small	0.8	58.0%	⊕◯◯◯
Sheng (2014)	RCT	HD	7(296)	Mixed	Intradialytic	SMD:-0.27(-0.50,-0.04)	Small	0.02	0.0%	⊕◯◯◯
Ferrari (2019)	RCT	HD	10(332)	AE	Intradialytic	MD:-10.07(16.35,-3.78)	-	0.002	44.0%	⊕◯◯◯
Wyngaert (2018)	RCT	Predialysis	8(269)	AE	-	SMD:0.08(-0.58,0.74)	Small	0.81	84%	⊕◯◯◯
DBP										
Pei (2019)	RCT/quasi-RCT	Mixed	12(514)	AE	-	MD:−1.11 (−3.41, 1.20)	-	0.35	0.0%	⊕⊕◯◯
Wu (2020)	RCT/quasi-RCT	Predialysis	4 (194)	AE+RT	-	SMD:-0.47(-1.10,0.15)	Small	0.14	70.0%	⊕◯◯◯
Chen (2019)	RCT	KTRs	5(198)	Mixed	-	SMD:0.04(-0.45,0.52)	Small	0.89	59.0%	⊕◯◯◯
Pu (2019)	RCT	HD	7(287)	Mixed	Intradialytic	SMD:-0.32(-0.55,-0.08)	Small	0.008	42.0%	⊕◯◯◯
Thompson (2019)	RCT	Predialysis	8(303)	Mixed	-	MD:-1.18(-4.76,2.40)	-	N.P.	60.5%	⊕◯◯◯

Zhang (2019)	RCT	Predialysis	12(399)	Mixed	-	SMD:-0.31(-0.71,0.08)	Small	0.12	70.0%	⊕⊕◯◯
Huang (2019)	RCT	HD	7(260)	Mixed	Mixed	SMD:-0.23(-0.69,0.24)	Small	0.34	68.0%	⊕◯◯◯
Heiwe (2011)	RCT/quasi-RCT	Mixed	11(419)	Mixed	-	SMD:0.16(-0.04,0.36)	Small	0.11	40.0%	⊕◯◯◯
Heiwe (2014)	RCT	HD	10(212)	Mixed	Mixed	SMD:0.17(-0.16,0.49)	Small	0.3	45.0%	⊕⊕◯◯
Sheng (2014)	RCT	HD	7(296)	Mixed	Intradialytic	SMD:-0.24(-0.47,-0.01)	Small	0.04	52.1%	⊕◯◯◯
Ferrari (2019)	RCT	HD	10(334)	AE	Intradialytic	MD:-2.96(-7.71,1.78)	-	0.22	0.0%	⊕◯◯◯
Wyngaert (2018)	RCT	Predialysis	7(237)	AE	-	SMD-0.09(-0.78,0.59)	Small	0.79	83%	⊕◯◯◯

Abbreviation: RCT = randomized controlled trial; AE = aerobic exercise; RT = resistance training; DBP = diastolic blood pressure; SBP = systolic blood pressure; SMD = standardized mean difference; MD = mean difference; HD = hemodialysis; KTRs = kidney transplant recipients; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; N.P. = no report.

*Number of included studies and corresponding sample size.

Mixed means aerobic exercise combined with resistance training.

Table 2 Summary of the effect of exercise on cardiopulmonary fitness in CKD patients

Author (year)	Design	Stage of CKD	k (n)*	Exercise type	Mode	SMD or MD (95% CI)	Effect size	*P*	I^2	GRADE
VO_{2peak}										
Pei (2019)	RCT/quasi-RCT	Mixed	17(464)	AE	-	MD:2.08(1.10,3.05)	-	<0.001	25.0 %	⊕⊕◯◯
Nakamura (2020)	RCT/cross-over	Predialysis	10(401)	Mixed	-	SMD:0.88(0.53,1.23)	Large	<0.001	56.0 %	⊕⊕◯◯
Chen (2019)	RCT	KTRs	6(202)	Mixed	-	SMD:0.33(-0.02,0.69)	Small	0.06	27.0 %	⊕◯◯◯
Andrade (2019)	RCT	HD	5(201)	AE+RT	Intradialytic	SMD:1.01(0.71,1.30)	Large	<0.001	0.0%	⊕⊕◯◯
Chung (2016)	RCT	HD	6(238)	Mixed	Intradialytic	SMD:0.55(0.18,0.92)	Moderate	0.003	52.9 %	⊕◯◯◯
Pu (2019)	RCT	HD	10(400)	Mixed	Intradialytic	SMD:0.57(0.23,0.90)	Moderate	<0.001	59.0 %	⊕⊕◯◯
Yamamoto (2021)	RCT	Predialysis	10(365)	AE	-	SMD:0.54(0.29,0.78)	Moderate	<0.001	24.6 %	⊕◯◯◯
Yang (2017)	RCT	Mixed	5(179)	Mixed	-	SMD:0.33(0.03,0.63)	Small	0.003	47.0 %	⊕⊕◯◯
Huang (2019)	RCT	HD	10(371)	Mixed	Mixed	SMD:0.73(0.52,0.95)	Moderate	<0.001	71.0 %	⊕⊕◯◯
Matsuzawa (2017)	RCT	HD	18(582)	Mixed	Mixed	SMD:0.62(0.38,0.87)	Moderate	<0.001	49.0 %	⊕⊕⊕⊕

Smart (2011)	RCT	HD	8(365)	Mixed	Mixed	SMD:0.75(0.39,1.11)	Moderate	<0.001	60.0 %	⊕⊕◯◯
Bogataj (2020)	RCT	HD	20(504)	Mixed	Mixed	SMD:0.58(0.32,0.85)	Moderate	<0.001	57.4 %	⊕◯◯◯
Sheng (2014)	RCT	HD	7(310)	Mixed	Intradialytic	SMD:0.53(0.30,0.76)	Moderate	<0.001	36.0 %	⊕◯◯◯
Neto (2018)	RCT	HD	10(394)	Mixed	Intradialytic	SMD:0.60(0.15,1.04)	Moderate	0.008	76.0 %	⊕◯◯◯
Ferrari (2019)	RCT	HD	5(201)	AE+RT	Intradialytic	MD:5.41(4.03,6.79)	-	<0.001	0.0%	⊕◯◯◯
Ferrari (2019)	RCT	HD	7(248)	AE	Intradialytic	MD:2.07(0.42,3.72)	-	<0.001	0.0%	⊕◯◯◯
Wyngaert (2018)	RCT	Predialysis	11(325)	AE	-	SMD:0.99(0.49,1.48)	Large	<0.001	74.0 %	⊕◯◯◯
Oguchi (2018)	RCT	KTRs	4(182)	Mixed	-	SMD:0.38(-0.06,0.82)	Small	0.09	45.0 %	⊕⊕◯◯
6MWT										
Pei (2019)	RCT/quasi-RCT	Mixed	8 (496)	AE	-	MD:0.04 (−0.52, 0.59)	-	0.90	86.0 %	⊕◯◯◯
Nakamura (2020)	RCT/cross-over	Predialysis	5(392)	Mixed	-	SMD:1.04(0.17,1.90)	Large	0.02	92.0 %	⊕◯◯◯
Lu (2019)	RCT	Dialysis	11(300)	Mixed	Mixed	SMD:0.52(0.31,0.72)	Moderate	<0.001	39.0 %	⊕⊕⊕◯
Chung (2016)	RCT	HD	4(127)	Mixed	Intradialytic	SMD:0.44(0.09,0.80)	Small	0.015	0.0%	⊕⊕◯◯

Zhang (2021)	RCT	HD	8(299)	RT	Intradialytic	SMD:0.52(0.28,0.75)	Moderate	<0.001	18.7%	⊕⊕◯◯
Pu (2019)	RCT	HD	7(219)	Mixed	Intradialytic	SMD:0.57(0.30,0.84)	Moderate	<0.001	0.0%	⊕⊕◯◯
Clarkson (2019)	RCT	Dialysis	18(744)	Mixed	-	MD:33.64(23.74,43.54)	-	<0.001	0.0%	⊕⊕⊕◯
Huang (2019)	RCT	HD	7(205)	Mixed	Mixed	SMD:1.01(0.26,1.76)	Large	0.008	83.0%	⊕◯◯◯
Matsuzawa (2017)	RCT	HD	10(326)	Mixed	Mixed	SMD:0.58(0.24,0.93)	Moderate	<0.001	53.0%	⊕⊕◯◯
Bogataj (2020)	RCT	HD	19	Mixed	Mixed	SMD:0.44(0.21,0.67)	Small	<0.001	49.6%	⊕◯◯◯
Sheng (2014)	RCT	HD	4(146)	Mixed	Intradialytic	SMD:0.58(0.23,0.93)	Moderate	<0.001	89.7%	⊕◯◯◯
Neto (2018)	RCT	HD	6(158)	Mixed	Intradialytic	SMD:0.96(0.11,1.80)	Large	0.03	82.0%	⊕◯◯◯
Ferrari (2019)	RCT	HD	6(211)	RT	Intradialytic	MD:68.5(29.05,107.96)	-	<0.001	36.0%	⊕◯◯◯
Ferrari (2019)	RCT	HD	6(188)	AE	Intradialytic	MD:64.98(43.86,86.11)	-	<0.001	0.0%	⊕◯◯◯
Aerobic capacity										
Heiwe (2011)	RCT/quasi-RCT	Mixed	24(847)	Mixed	-	SMD:-0.56(-0.70,-0.42)	Moderate	<0.001	12.0%	⊕◯◯◯
Heiwe (2014)	RCT	HD	21(374)	Mixed	Mixed	SMD:-0.80(-1.02,-0.58)	Large	<0.001	0.0%	⊕⊕◯◯

Abbreviation: RCT = randomized controlled trial; AE = aerobic exercise; RT = resistance training; VO_{2peak} = peak oxygen uptake; 6MWT = 6 minutes walk test; SMD = standardized mean difference; MD = mean difference; HD = hemodialysis; KTRs = kidney transplant recipients; GRADE = Grading of Recommendations Assessment, Development, and Evaluation.

*Number of included studies and corresponding sample size.
Mixed means aerobic exercise combined with resistance training.

Table 3 Summary of the effect of exercise on muscle strength in CKD patients

Author(year)	Design	Stage of CKD	k (n)*	Exercise type	Mode	SMD or MD(95% CI)	Effect size	*P*	I^2	GRADE
Cheema (2014)	RCT	Predialysis	7(249)	RT	-	SMD:1.15(0.80,1.49)	Large	0.161	35.0%	⊕⊕◯◯
Nakamura (2020)	RCT/cross-over	Predialysis	4(119)	Mixed	-	SMD:0.35(-0.03,0.73)	Small	0.07	7.0%	⊕◯◯◯
Lu (2019)	RCT	Dialysis	5(234)	Mixed	Mixed	SMD:0.59(0.20,0.98)	Moderate	0.003	52.0%	⊕⊕◯◯
Lu (2019)	RCT	Dialysis	7(224)	Mixed	Mixed	SMD:0.47(0.20,0.74)	Small	<0.001	0.0%	⊕⊕◯◯
Zhang (2021)	RCT	HD	6(300)	RT	Intradialytic	SMD:0.35(0.12,0.58)	Small	0.003	41.6%	⊕⊕◯◯
Heiwe (2011)	RCT/quasi-RCT	Mixed	9(358)	Mixed	-	SMD:-0.52(-0.73,-0.31)	Moderate	<0.001	0.0%	⊕◯◯◯
Heiwe (2014)	RCT	HD	12(385)	Mixed	Mixed	SMD:-0.56(-0.77,-0.35)	Moderate	<0.001	0.0%	⊕◯◯◯
Matsuzawa (2017)	RCT	HD	9(281)	Mixed	Mixed	SMD:0.94(0.67,1.21)	Large	<0.001	10.0%	⊕◯◯◯
Neto (2018)	RCT	HD	9(250)	Mixed	Intradialytic	SMD:0.61(0.39,0.83)	Moderate	<0.001	58.9%	⊕◯◯◯
Ju (2020)	RCT	Mixed	3(115)	Mixed	-	SMD:0.52(0.14,0.89)	Moderate	0.007	0.0%	⊕◯◯◯

Abbreviation: RCT = randomized controlled trial; RT = resistance training; SMD = standardized mean difference; MD = mean difference; HD = hemodialysis; GRADE = Grading of Recommendations Assessment, Development, and Evaluation.

*Number of included studies and corresponding sample size.

Mixed means aerobic exercise combined with resistance training.

Table 4 Summary of the effect of exercise on muscle endurance in CKD patients

Author (year)	Design	Stage of CKD	k (n)*	Exercise type	Mode	Outcome	SMD or MD (95% CI)	Effect size	*P*	I^2	GRADE
Lu (2019)	RCT	Dialysis	3(193)	Mixed	Mixed	STS 10	MD:-4.69(-9.01,-0.38)	-	0.028	72.2%	⊕◯◯◯
Bogataj (2020)	RCT	HD	5(461)	Mixed	-	STS 10	SMD:-0.55(-1.00,-0.09)	Moderate	0.019	71.6%	⊕◯◯◯
Lu (2019)	RCT	Dialysis	6(240)	Mixed	Mixed	STS 30	SMD:0.43(0.17,0.69)	Small	0.001	2.0%	⊕⊕◯◯
Zhang (2021)	RCT	HD	5(164)	RT	Intradialytic	STS 30	SMD:0.42(0.11,0.74)	Small	0.008	0.0%	⊕◯◯◯
Sheng (2014)	RCT	HD	3(106)	Mixed	Intradialytic	STS 60	SMD:0.71(0.31,1.12)	Moderate	<0.001	0.0%	⊕◯◯◯
Pei (2019)	RCT/quasi-RCT	Mixed	5(445)	AE	-	STS 60	MD:2.08(1.1,3.05)	-	0.98	82.0%	⊕◯◯◯
Nakamura (2020)	RCT/cross-over	Predialysis	3(170)	Mixed	-	TUGT	SMD:-0.42(-0.73,-0.11)	Small	0.007	0.0%	⊕◯◯◯
Heiwe (2011)	RCT/quasi-RCT	Mixed	7(191)	Mixed	-	Walking capacity	SMD:-0.48(-0.79,-0.17)	Small	0.003	2.0%	⊕◯◯◯
Heiwe (2014)	RCT	HD	7(174)	Mixed	Mixed	Walking capacity	SMD:-0.33(-0.67,0.01)	Small	0.06	16.0%	⊕⊕⊕◯

Abbreviation: RCT = randomized controlled trial; AE = aerobic exercise; RT = resistance training; STS 10 = sit to stand 10 test; STS 30 = sit to stand 30 test; STS 60 = sit to stand 60 test; TUGT = timed up and go test; SMD = standardized mean difference; MD = mean difference; HD = hemodialysis; GRADE = Grading of Recommendations Assessment, Development, and Evaluation.

*Number of included studies and corresponding sample size.

Mixed means aerobic exercise combined with resistance training.

Table 5 Summary of the effect of exercise on body composition in CKD patients

Author (year)	Design	Stage of CKD	k (n)*	Exercise type	Mode	SMD (95% CI)	Effect size	*P*	I^2	GRADE
Chen (2019)	RCT	KTRs	4(166)	Mixed	-	SMD:0.02(-0.28,0.33)	Small	0.89	0.0%	⊕◯◯◯
Yamamoto (2021)	RCT	Predialysis	10(414)	AE	-	SMD:-0.19(-0.38,-0.00)	Small	0.026	0.0%	⊕⊕◯◯
Zhang (2019)	RCT	Predialysis	13(466)	Mixed	-	SMD:-0.21(-0.39,-0.03)	Small	0.02	0.0%	⊕⊕⊕◯
Wyngaert (2018)	RCT	Predialysis	9(294)	AE	-	SMD:-0.36(-0.60,-0.13)	Small	0.002	48.0%	⊕⊕◯◯

Abbreviation: RCT = randomized controlled trial; AE = aerobic exercise; SMD = standardized mean difference; KTRs = kidney transplant recipients;;GRADE = Grading of Recommendations Assessment, Development, and Evaluation.

*Number of included studies and corresponding sample size.

Mixed means aerobic exercise combined with resistance training.

Table 6 Summary of the effect of exercise on dialysis-related symptoms in CKD patients

Author (year)	Design	Stage of CKD	k (n)*	Exercise type	Mode	Outcomes	SMD or MD(95% CI)	Effect size	*P*	I^2	GRADE
Ferreira (2019)	RCT/quasi-RCT	HD	10(346)	AE	Intradialytic	Kt/V	SMD:2.21(1.17,3.25)	Large	<0.001	92.0%	⊕◯◯◯
Pu (2019)	RCT	HD	10(301)	Mixed	Intradialytic	Kt/V	SMD:0.29(0.06,0.52)	Small	0.01	0.0%	⊕◯◯◯
Huang (2019)	RCT	HD	8(257)	Mixed	Mixed	Kt/V	SMD:0.19(-0.06,0.43)	Small	0.14	0.0%	⊕◯◯◯
Sheng (2014)	RCT	HD	7(233)	Mixed	Intradialytic	Kt/V	SMD:0.27(0.01,0.53)	Small	0.04	0.0%	⊕◯◯◯
Ferrari (2019)	RCT	HD	12(370)	AE	Intradialytic	Kt/V	MD:0.08(0.0,0.15)	-	0.04	56.0%	⊕◯◯◯
Ferrari (2019)	RCT	HD	6(220)	RT	Intradialytic	Kt/V	MD:0.10(0.0,0.2)	-	0.06	6.0%	⊕◯◯◯
Song (2018)	RCT	HD	4(141)	Mixed	Mixed	RLS	SMD:-1.79(-2.21,-1.37)	Large	<0.001	87.0%	⊕◯◯◯
Song (2018)	RCT	HD	3(139)	Mixed	Mixed	Fatigue	SMD:-0.85(-1.20,-0.50)	Large	<0.001	0.0%	⊕◯◯◯
Zhao (2019)	RCT	Dialysis	3(141)	Mixed	-	Fatigue	SMD:-0.97(-1.32,-0.62)	Large	<0.001	47.0%	⊕⊕◯◯

Abbreviation: RCT = randomized controlled trial; AE = aerobic exercise; RT = resistance training; SMD = standardized mean difference; MD = mean difference; HD = hemodialysis; KTRs = kidney transplant recipients; RLS = Restless Legs Syndrome; GRADE = Grading of Recommendations Assessment, Development, and Evaluation.

*Number of included studies and corresponding sample size.

Mixed means aerobic exercise combined with resistance training.

Table 7 Summary of the effect of exercise on health-related quality of lifes in CKD patients

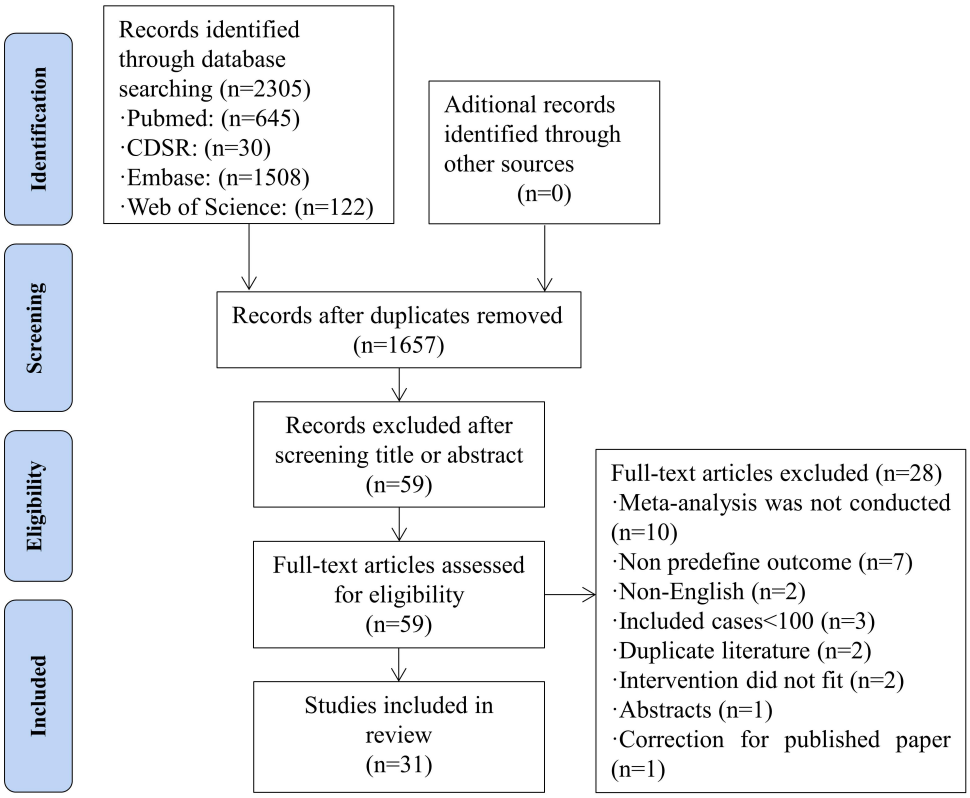
Author (year)	Design	Stage of CKD	k (n)*	Exercise type	Mode	Outcomes	SMD or MD (95% CI)	Effect size	*P*	I^2	GRADE
Salhab (2019)	RCT	HD	5(282)	AE	Intradialytic	PCS	SMD:1.82(-0.92,4.55)	Large	0.19	98.0%	⊕◯◯◯
Chung (2016)	RCT	HD	6(229)	Mixed	Intradialytic	PCS	SMD:0.46(0.20,0.73)	Small	<0.001	1.90%	⊕⊕◯◯
Zhang (2021)	RCT	HD	7(297)	RT	Intradialytic	PCS	SMD:0.23(-0.00,0.46)	Small	0.055	0.0%	⊕⊕◯◯
Pu (2019)	RCT	HD	10(320)	Mixed	Intradialytic	PCS	SMD:0.57(0.14,1.01)	Moderate	0.01	70.0%	⊕◯◯◯
Zhao (2019)	RCT	Dialysis	5(186)	Mixed	-	PCS	SMD:0.31(0.02,0.61)	Small	0.04	46.0%	⊕⊕◯◯
Huang (2019)	RCT	HD	7(263)	Mixed	Mixed	PCS	SMD:0.34(0.09,0.59)	Small	0.007	27.0%	⊕⊕◯◯
Matsuzawa (2017)	RCT	HD	9(264)	Mixed	Mixed	PCS	SMD:0.53(0.52,0.82)	Moderate	<0.001	19.0%	⊕◯◯◯
Sheng (2014)	RCT	HD	7(256)	Mixed	Intradialytic	PCS	SMD:0.30(0.05,0.55)	Small	0.02	39.5%	⊕◯◯◯
Neto (2018)	RCT	HD	7(187)	Mixed	Intradialytic	PCS	SMD:0.50(-0.19,1.18)	Moderate	0.16	62.0%	⊕◯◯◯
Salhab (2019)	RCT	HD	5(282)	AE	Intradialytic	MCS	SMD:1.02(0.31,1.73)	Large	0.005	75.0%	⊕◯◯◯
Chung (2016)	RCT	HD	5(193)	Mixed	Intradialytic	MCS	SMD:0.23(-0.05,0.52)	Small	0.109	0.0%	⊕⊕◯◯
Zhang (2021)	RCT	HD	7(297)	RT	Intradialytic	MCS	SMD:0.13(-0.10,0.36)	Small	0.082	46.5%	⊕⊕◯◯
Pu (2019)	RCT	HD	8(219)	Mixed	Intradialytic	MCS	SMD:0.19(-0.09,0.46)	Small	0.18	30.0%	⊕⊕◯◯
Zhao (2019)	RCT	Dialysis	5(186)	Mixed	-	MCS	SMD:0.30(-0.20,0.80)	Small	0.24	64.0%	⊕◯◯◯
Huang (2019)	RCT	HD	7(263)	Mixed	Mixed	MCS	SMD:0.27(0.02,0.51)	Small	0.03	0.0%	⊕⊕◯◯
Matsuzawa (2017)	RCT	HD	8(228)	Mixed	Mixed	MCS	SMD:0.14(-0.15,0.42)	Small	0.34	10.0%	⊕◯◯◯
Sheng (2014)	RCT	HD	5(167)	Mixed	Intradialytic	MCS	SMD:0.14(-0.16,0.43)	Small	0.37	14.8%	⊕◯◯◯
Neto (2018)	RCT	HD	7(185)	Mixed	Intradialytic	MCS	SMD:0.39(-0.19,0.98)	Small	0.19	50.0%	⊕◯◯◯

Pei (2019)	RCT/quasi-RCT	Mixed	6(522)	AE	-	Physical function (SF-36)	MD:8.36(-1.24,17.95)	-	0.09	76.0%	⊕◯◯◯
Pei (2019)	RCT/quasi-RCT	Mixed	7(562)	AE	-	Physical role (SF-36)	MD:14.65(1.47,27.84)	-	0.03	78.0%	⊕◯◯◯
Pei (2019)	RCT/quasi-RCT	Mixed	6(447)	AE	-	Social function (SF-36)	MD:8.24(-1.09,17.58)	-	0.08	85.0%	⊕◯◯◯
Pei (2019)	RCT/quasi-RCT	Mixed	6(513)	AE	-	Pain (SF-36)	MD:5.94(1.65,10.23)	-	0.007	49.0%	⊕◯◯◯
Pei (2019)	RCT/quasi-RCT	Mixed	7(562)	AE	-	General health (SF-36)	MD:8.90(2.48,15.32)	-	0.007	71.0%	⊕◯◯◯
Pei (2019)	RCT/quasi-RCT	Mixed	6(542)	AE	-	Mental health (SF-36)	MD:7.30(-0.94,15.54)	-	0.08	84.0%	⊕◯◯◯
Cheema (2014)	RCT	Predialysis	6 (223)	RT	-	HRQOL	SMD:0.83(0.51,1.16)	Large	0.226	27.8%	⊕⊕◯◯
Oguchi (2018)	RCT	KTRs	4(179)	Mixed	-	HRQOL	SMD:0.54(0.02,1.07)	Moderate	0.04	58.0%	⊕◯◯◯
Ju (2020)	RCT	Mixed	3 (387)	Mixed	-	Symptom/problem (KDQOL)	SMD:1.92(-1.06,4.90)	Large	0.21	99.0%	⊕◯◯◯
Ju (2020)	RCT	Mixed	3 (387)	Mixed	-	Effects of kidney disease (KDQOL)	SMD:-3.69(-8.56,1.19)	Large	0.14	99.0%	⊕◯◯◯
Ju (2020)	RCT	Mixed	3 (387)	Mixed	-	Burden of kidney disease (KDQOL)	SMD:1.04 (-0.75,2.82)	Large	0.26	98.0%	⊕◯◯◯

Abbreviation: RCT = randomized controlled trial; AE = aerobic exercise; RT = resistance training; COM = combine; HRQOL = health-related quality of life; PCS = physical component summary; MCS = mental component summary; SMD = standardized mean difference; MD = mean difference; HD = hemodialysis; KTRs = kidney transplant recipients; SF-36 = Short-Form Health Survey-36; KDQOL = kidney disease quality of life; GRADE = Grading of Recommendations Assessment, Development, and Evaluation.

*Number of included studies and corresponding sample size.

Mixed means aerobic exercise combined with resistance training.



Figures 1 Flowchart of literature screening.

CDSR = Cochrane Database of Systemic Review

Supplementary Table S1 The detailed search strategy

Databases	#	Search strategy
Pubmed	1	"renal insufficiency, chronic"[MeSH Terms]
	2	"chronic renal insufficiency"[Title/Abstract] or "chronic kidney insufficiency"[Title/Abstract] or "chronic kidney disease"[Title/Abstract] or "chronic renal disease"[Title/Abstract]
	3	"CKD"[Title/Abstract] or "CKF"[Title/Abstract] or "CRD"[Title/Abstract] or "CRF"[Title/Abstract]
	4	"end-stage kidney"[Title/Abstract] or "end-stage renal"[Title/Abstract] or "endstage kidney"[Title/Abstract] or "endstage renal"[Title/Abstract]
	5	"ESRD"[Title/Abstract] or "ESRF"[Title/Abstract] or "ESKD"[Title/Abstract] or "ESKF"[Title/Abstract]
	6	"Renal Replacement Therapy"[MeSH Terms]
	7	"dialysis"[Title/Abstract]
	8	"hemodialysis"[Title/Abstract] or "haemodialysis"[Title/Abstract] or "hemodiafiltration"[Title/Abstract] or "haemodiafiltration"[Title/Abstract] or "HD"[Title/Abstract]
	9	"PD"[Title/Abstract]
	10	"renal transplantation"[Title/Abstract] or "kidney grafting"[Title/Abstract] or "kidney transplantation"[Title/Abstract]
	11	"KTRs"[Title/Abstract]
	12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
	13	"Exercise"[MeSH Terms]
	14	"Exercise Movement Techniques"[MeSH Terms]
	15	"Exercise Therapy"[MeSH Terms]
	16	"Sports"[MeSH Terms]
	17	"train"[Title/Abstract] or "physical activity"[Title/Abstract] or "exercise"[Title/Abstract]
	18	#13 or #14 or #15 or #16 or #17
	19	"Systematic Review"[Publication Type] or "Systematic Reviews as Topic"[MeSH Terms]
	20	"meta analysis"[Publication Type] or "Meta-Analysis as Topic"[MeSH Terms]

	21	"Systematic Review"[Title/Abstract] or "system review"[Title/Abstract] or "data pooling"[Title/Abstract] or "meta"[Title/Abstract]
	22	#19 or #20 or #21
	23	#12 and #18 and #22
CDSR	1	MeSH descriptor: [Kidney Diseases] explode all trees
	2	("chronic kidney disease") or ("chronic renal disease") or ("chronic kidney failure") or ("chronic renal failure"):ti,ab,kw
	3	(CKF or CKD or CRF or CRD):ti,ab,kw
	4	("end-stage kidney") or ("end-stage renal") or ("endstage kidney") or ("endstage renal"):ti,ab,kw
	5	ESRD or ESRF or ESKD or ESKF:ti,ab,kw
	6	MeSH descriptor: [Renal Replacement Therapy] explode all trees
	7	dialysis:ti,ab,kw
	8	(hemodialysis or haemodialysis or hemodiafiltration or haemodiafiltration or HD):ti,ab,kw
	9	PD:ti,ab,kw
	10	("renal transplantation") or ("kidney grafting") or ("kidney transplantation"):ti,ab,kw
	11	KTRs:ti,ab,kw
	12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
	13	MeSH descriptor: [Exercise] explode all trees
	14	MeSH descriptor: [Exercise Movement Techniques] explode all trees
	15	MeSH descriptor: [Exercise Therapy] explode all trees
	16	MeSH descriptor: [Sports] explode all trees
	17	(train or ("physical activity") or exercise):ti,ab,kw
	18	#13 or #14 or #15 or #16 or #17
	19	MeSH descriptor: [Meta-Analysis as Topic] explode all trees
	20	MeSH descriptor: [Systematic Reviews as Topic] explode all trees
	21	("systematic review") or ("system review") or ("data pooling") or (meta):ti,ab,kw
	22	#19 or #20 or #21

	23	#12 and #18 and #22
Embase	1	'kidney disease'/exp
	2	('chronic kidney disease' or 'chronic renal disease' or 'chronic kidney failure' or 'chronic renal failure'):ti,ab,kw
	3	(CKF or CKD or CRFor CRD):ti,ab,kw
	4	('end-stage kidney' or 'end-stage renal' or 'endstage kidney' or 'endstage renal'):ti,ab,kw
	5	(ESRD or ESRF or ESKD or ESKF):ti,ab,kw
	6	'renal replacement therapy'/exp
	7	'dialysis':ti,ab,kw
	8	(hemodialysis or haemodialysis or hemofiltration or haemofiltration or hemodiafiltration or haemodiafiltration or HD):ti,ab,kw
	9	PD:ti,ab,kw
	10	('renal transplantation' or 'kidney grafting' or 'kidney transplantation'):ti,ab,kw
	11	KTRs:ti,ab,kw
	12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
	13	'exercise'/exp
	14	'physical activity'/exp
	15	'sport'/exp
	16	(train or 'physical activity' or exercise):ti,ab,kw
	17	#13 or #14 or #15 or #16
	18	'systematic review (topic)'/exp or 'systematic review'/exp
	19	'meta analysis (topic)'/exp or 'meta analysis'/exp
	20	('systematic review' or 'system review' or 'data pooling' or meta):ti,ab,kw
	21	#18 or #19 or #20
	22	#12 and #17 and #21
Web of Science	1	TS: ("chronic kidney disease" or "chronic renal disease" or "chronic kidney failure" or "chronic renal failure" or CKD or CRD or CKF or CRF)

	2	TS: ("end-stage kidney" or "end-stage renal" or "endstage kidney" or "endstage renal" or ESKD or ESKF or ESRD or ESRF)
	3	TS: ("renal replacement therapy" or dialysis or hemodialysis or haemodialysis or hemofiltration or haemofiltration or hemodiafiltration or haemodiafiltration or HD or PD)
	4	TS: ("renal transplantation" or "kidney grafting" or "kidney transplantation" or KTRs)
	5	#1 or #2 or #3 or #4
	6	TS: (train or exercise or "physical activity")
	7	TS: ("systematic review" or "system review" or "data pooling" or meta)
	8	#1 and #2 and #3 and #4 and #5

Supplementary Table S2 The characteristic of excluded studies

Studies	Reasons for exclusion
Nantakool et al (2020)	Non predefine outcome
Sawant et al (2014)	Non predefine outcome
Smart et al (2014)	Duplicate literature
Barcellos et al (2015)	Meta-analysis was not conducted
Yang et al (2020)	Non predefine outcome
Young et al (2018)	Included cases<100
Phan et al (2015)	Duplicate literature
Molsted et al (2019)	Included cases<100
Segura et al (2010)	Non-English
Ferreira et al (2020)	Non predefine outcome
Koufaki et al (2013)	Meta-analysis was not conducted
Smart et al (2012)	Abstracts
Howden et al (2012)	Meta-analysis was not conducted
Calella et al (2019)	Meta-analysis was not conducted
Singh et al (2005)	Meta-analysis was not conducted
Cardoso et al (2020)	Non predefine outcome
Villanego et al (2020)	Non-English
Medeiros et al (2017)	Intervention did not fit
Macdonald et al (2009)	Meta-analysis was not conducted
Wen et al (2019)	Non predefine outcome
Yang et al (2015)	Non predefine outcome
Thangarasa et al (2018)	Included cases<100
Chan et al (2016)	Meta-analysis was not conducted

Johansen et al (2010)	Intervention did not fit
Thompson et al (2020)	Correction for published paper
Bakaloudi et al (2020)	Meta-analysis was not conducted
Kirkman et al (2019)	Meta-analysis was not conducted
Afsar et al (2018)	Meta-analysis was not conducted

Supplementary Table S3 The basic characteristics of the included meta-analyses

Author (year)	Design	Stage of CKD	k (n)*	Exercise type	Mode	Outcomes	SMD or MD(95% CI)	Effect size	*P*	I^2	GRADE
Pei (2019)	RCT/quasi-RCT	Mixed	17(464)	AE	-	VO_{2peak}	MD:2.08 (1.1,3.05)	-	<0.001	25.0%	Low
			5 (445)			STS 60	MD:2.08 (1.1,3.05)	-	0.98	82.0%	Very low
			8 (496)			6MWT	MD:0.04 (−0.52, 0.59)	-	0.9	86.0%	Very low
			12(514)			SBP	MD:−2.91 (−6.68, 0.87)	-	0.13	40.0%	Low
			12(514)			DBP	MD:−1.11 (−3.41, 1.20)	-	0.35	0.0%	Low
			6(522)			Physical function (SF-36)	MD:8.36(-1.24,17.95)	-	0.09	76.0%	Very low
			7(562)			Physical role (SF-36)	MD:14.65(1.47,27.84)	-	0.03	78.0%	Very low
			6(447)			Social function (SF-36)	MD:8.24(-1.09,17.58)	-	0.08	85.0%	Very low
			6(513)			Pain (SF-36)	MD:5.94(1.65,10.23)	-	0.007	49.0%	Very low
			7(562)			General health (SF-36)	MD:8.90(2.48,15.32)	-	0.007	71.0%	Very low
			6(542)			Mental health (SF-36)	MD:7.30(-0.94,15.54)	-	0.08	84.0%	Very low
Ferreira (2019)	RCT/quasi-RCT	HD	10(346)	AE	Intradialytic	Kt/V	SMD:2.21(1.17,3.25)	Large	<0.001	92.0%	Very low
Cheema (2014)	RCT	Predialysis	7(249)	RT	-	Muscle Strength	SMD:1.15（0.80-1.49）	Large	0.161	35.0%	Low
			6(223)			HRQoL	SMD:0.83(0.51-1.16)	Large	0.226	27.8%	Low
Wu (2020)	RCT/quasi-RCT	Predialysis	3(204)	AE+RT	-	SBP	SMD:-0.19(-0.46,0.08)	Small	0.16	50.0%	Very low
			4(194)			DBP	SMD:-0.47(-1.10,0.15)	Small	0.14	70.0%	Very low

Nakamura (2020)	RCT/cross-over	Predialysis	10(401)	Mixed	-	VO_{2peak}	SMD:0.88(0.53,1.23)	Large	<0.001	56.0%	Low
			4(119)			Muscle Strength	SMD:0.35(-0.03,0.73)	Small	0.07	7.0%	Very low
			5(392)			6MWT	SMD:1.04(0.17,1.90)	Large	0.02	92.0%	Very low
			3(170)			TUGT	SMD:-0.42(-0.73,-0.11)	Small	0.007	0.0%	Very low
Lu (2019)	RCT	Dialysis	11(300)	Mixed	Mixed	6MWT	MD:67.6(49.93,85.26)	-	<0.001	30.6%	Moderate
			3(193)			STS 10	MD:-4.69(-9.01,-0.38)	-	0.028	72.2%	Very low
			5(234)			HGS	MD:5.35(3.34,7.37)	-	<0.001	0.3%	Low
			7(224)			Muscle strength	MD:3.67(1.37,5.97)	-	0.020	38.6%	Low
			6(240)			STS 30	MD:2.43(0.91,3.96)	-	0.002	21.2%	Low
Chen (2019)	RCT	KTRs	5(198)	Mixed	-	SBP	SMD:0.18(-0.10,0.46)	Small	0.21	0.0%	Very low
			5(198)			DBP	SMD:0.04(-0.45,0.52)	Small	0.89	59.0%	Very low
			4(166)			BMI	SMD:0.02(-0.28,0.33)	Small	0.89	0.0%	Very low
			6(202)			VO_{2peak}	SMD:0.33(-0.02,0.69)	Small	0.06	27.0%	Very low
Song (2018)	RCT	HD	4(141)	Mixed	Mixed	RLS	SMD:-1.79(-2.21,-1.37)	Large	<0.001	87.0%	Very low
			3(139)			Fatigue	SMD:-0.85(-1.20,-0.50)	Large	<0.001	0.0%	Very low
Salhab (2019)	RCT	HD	5(282)	AE	Intradialytic	PCS	SMD:1.82(-0.92,4.55)	Large	0.19	98.0%	Very low
			5(282)			MCS	SMD:1.02(0.31,1.73)	Large	0.005	75.0%	Very low
Andrade (2019)	RCT	HD	5(201)	AE+RT	Intradialytic	VO_{2peak}	SMD:1.01(0.71,1.30)	Large	<0.001	0.0%	Low
Chung (2016)	RCT	HD	4(127)	Mixed	Intradialytic	6MWT	SMD:0.44(0.09,0.80)	Small	0.015	0.0%	Low
			6(238)			VO_{2peak}	SMD:0.55(0.18,0.92)	Moderate	0.003	52.9%	Very low
			6(229)			PCS	SMD:0.46(0.20,0.73)	Small	<0.001	1.90%	Low
			5(193)			MCS	SMD:0.23(-0.05,0.52)	Small	0.109	0.0%	Low
Zhang (2021)	RCT	HD	8(299)	RT	Intradialytic	6MWT	SMD:0.52(0.28,0.75)	Moderate	<0.001	18.7%	Very low
			5(164)			STS 30	SMD:0.42(0.11,0.74)	Small	0.008	0.0%	Very low

			6(300)			HGS	SMD:0.35(0.12,0.58)	Small	0.003	41.6%	Very low
			7(297)			PCS	SMD:0.23(-0.00,0.46)	Small	0.055	0.0%	Very low
			7(297)			MCS	SMD:0.13(-0.10,0.36)	Small	0.082	46.5%	Very low
Pu (2019)	RCT	HD	10(301)	Mixed	Intradialytic	Kt/V	SMD:0.29(0.06,0.52)	Small	0.01	0.0%	Very low
			10(400)			VO_{2peak}	SMD:0.57(0.23,0.90)	Moderate	<0.001	59.0%	Low
			7(219)			6MWT	SMD:0.57(0.30,0.84)	Moderate	<0.001	0.0%	Low
			10(320)			PCS	SMD:0.57(0.14,1.01)	Moderate	0.01	70.0%	Very low
			8(219)			MCS	SMD:0.19(-0.09,0.46)	Small	0.18	30.0%	Low
			7(287)			SBP	SMD:-0.28(-0.52,-0.05)	Small	0.02	0.0%	Very low
			7(287)			DBP	SMD:-0.32(-0.55,-0.08)	Small	0.008	42.0%	Very low
Yamamoto (2021)	RCT	Predialysis	10(392)	AE	-	SBP	SMD:-0.75(-1.24,-0.26)	Moderate	0.003	80.3%	Very low
			10(365)			VO_{2peak}	SMD:0.54(0.29,0.78)	Moderate	<0.001	24.6%	Very low
			10(414)			BMI	SMD:-0.19(-0.38,-0.00)	Small	0.026	0.0%	Low
Thompson (2019)	RCT	Predialysis	10(335)	Mixed	-	SBP	MD:-4.3(-9.0,0.4)	-	N.P.	50.4%	Very low
			8(303)			DBP	MD:-1.18(-4.76,2.40)	-	N.P.	60.5%	Very low
Yang (2017)	RCT	Mixed	4(150)	Mixed	-	VO_{2peak}	SMD:0.33(0.03,0.63)	Small	0.003	47.0%	Low
Clarkson (2019)	RCT	Dialysis	18(744)	Mixed	-	6MWT	MD:33.64(23.74,43.54)	-	<0.001	0.0%	Moderate
Zhao (2019)	RCT	Dialysis	3(141)	Mixed	-	Fatigue	SMD:-0.97(-1.32,-0.62)	Large	<0.001	47.0%	Low
			5(186)			PCS	SMD:0.31(0.02,0.61)	Small	0.04	46.0%	Low
			5(186)			MCS	SMD:0.30(-0.20,0.80)	Small	0.24	64.0%	Very low
Zhang (2019)	RCT	Predialysis	14(463)	Mixed	-	SBP	SMD:-0.41(-0.70,-0.11)	Small	0.007	55.0%	Moderate
			12(399)			DBP	SMD:-0.31(-0.71,0.08)	Small	0.12	70.0%	Low
			13(466)			BMI	SMD:-0.21(-0.39,-0.03)	Small	0.02	0.0%	Moderate

Huang (2019)	RCT	HD	8(257)	Mixed	-	Kt/V	SMD:0.19(-0.06,0.43)	Small	0.14	0.0%	Very low
			7(260)			SBP	SMD:-0.17(-0.41,0.08)	Small	0.18	8.0%	Low
			7(260)			DBP	SMD:-0.23(-0.69,0.24)	Small	0.34	68.0%	Very low
			7(205)			6MWT	SMD:1.01(0.26,1.76)	Large	0.008	83.0%	Very low
			7(263)			PCS	SMD:0.34(0.09,0.59)	Small	0.007	27.0%	Low
			7(263)			MCS	SMD:0.27(0.02,0.51)	Small	0.03	0.0%	Low
			10(371)			VO_{2peak}	SMD:0.73(0.52,0.95)	Moderate	<0.001	71.0%	Low
Heiwe (2011)	RCT/quasi-RCT	Mixed	24(847)	Mixed	-	Aerobic capacity	SMD:-0.56(-0.70,-0.42)	Moderate	<0.001	12.0%	Moderate
			9(358)			Muscle strength	SMD:-0.52(-0.73,-0.31)	Moderate	<0.001	0.0%	Low
			7(191)			Walking capacity	SMD:-0.48(-0.79,-0.17)	Small	0.003	2.0%	Low
			9(347)			SBP	SMD:0.25(0.04,0.47)	Small	0.02	0.0%	Low
			11(419)			DBP	SMD:0.16(-0.04,0.36)	Small	0.11	40.0%	High
Heiwe (2014)	RCT	HD	21(374)	Mixed	-	Aerobic capacity	SMD:-0.80(-1.02,-0.58)	Large	<0.001	0.0%	Low
			10(212)			DBP	SMD:0.17(-0.16,0.49)	Small	0.3	45.0%	Low
			10(312)			SBP	SMD:0.04(-0..4,0.41)	Small	0.8	58.0%	Very low
			10(385)			Muscle strength	SMD:-0.56(-0.77,-0.35)	Moderate	<0.001	0.0%	Very low
			7(174)			Walking capacity	SMD:-0.33(-0.67,0.01)	Small	0.06	16.0%	Low
Matsuzawa (2017)	RCT	HD	18(582)	Mixed	-	VO_{2peak}	SMD:0.62(0.38,0.87)	Moderate	<0.001	49.0%	High
			10(326)			6MWT	SMD:0.58(0.24,0.93)	Moderate	<0.001	53.0%	Low
			9(281)			Muscle strength	SMD:0.94(0.67,1.21)	Large	<0.001	10.0%	Very low
			9(264)			PCS	SMD:0.53(0.52,0.82)	Moderate	<0.001	19.0%	Very low
			8(228)			MCS	SMD:0.14(-0.15,0.42)	Small	0.34	10.0%	Very low
Smart (2011)	RCT	HD	8(365)	Mixed	-	VO_{2peak}	SMD:0.75(0.39,1.11)	Moderate	<0.001	60.0%	Low
Bogataj	RCT	HD	19(571)	Mixed	-	6MWT	SMD:0.44(0.21,0.67)	Small	<0.001	49.6%	Very low

(2020)			20(504)			VO_{2peak}	SMD:0.58(0.32,0.85)	Moderate	<0.001	57.4%	Very low
			5(461)			STS 10	SMD:-0.55(-1.00,-0.09)	Moderate	0.019	71.6%	Very low
Sheng (2014)	RCT	HD	7(233)	Mixed	Intradialytic	Kt/V	SMD:0.27(0.01,0.53)	Small	0.040	0.0%	Very low
			7(310)			VO_{2peak}	SMD:0.53(0.30,0.76)	Moderate	<0.001	36.0%	Very low
			7(256)			PCS	SMD:0.30(0.05,0.55)	Small	0.02	39.5%	Very low
			5(167)			MCS	SMD:0.14(-0.16,0.43)	Small	0.37	14.8%	Very low
			4(146)			6MWT	SMD:0.58(0.23,0.93)	Moderate	<0.001	89.7%	Very low
			7(296)			DBP	SMD:-0.24(-0.47,-0.01)	Small	0.04	52.1%	Very low
			7(296)			SBP	SMD:-0.27(-0.50,-0.04)	Small	0.02	0.0%	Very low
			3(106)			STS 60	SMD:0.71(0.31,1.12)	Moderate	<0.001	0.0%	Very low
Neto (2018)	RCT	HD	10(394)	Mixed	Intradialytic	VO_{2peak}	SMD:0.60(0.15,1.04)	Moderate	0.008	76.0%	Very low
			7(187)			PCS	SMD:0.50(-0.19,1.18)	Moderate	0.16	62.0%	Very low
			7(185)			MCS	SMD:0.39(-0.19,0.98)	Small	0.19	50.0%	Very low
			6(158)			6MWT	SMD:0.96(0.11,1.80)	Large	0.03	82.0%	Very low
			9(250)			Muscle strength	SMD:0.61(0.39,0.83)	Moderate	<0.001	58.9%	Very low
Ferrari (2019)	RCT	HD	12(370)	AE	Intradialytic	Kt/V	MD:0.08(0,0.15)	-	0.04	56.0%	Low
			6(220)	RT		Kt/V	MD:0.1(0,0.2)	-	0.06	6.0%	Very low
			5(201)	COM		VO_{2peak}	MD:5.41(4.03,6.79)	-	<0.001	0.0%	Low
			7(248)	AE		VO_{2peak}	MD:2.07(0.42,3.72)	-	<0.001	0.0%	Very low
			6(211)	RT		6MWT	MD:68.5(29.05,107.96)	-	<0.001	36.0%	Low
			6(188)	AE		6MWT	MD:64.98(43.86,86.11)	-	<0.001	0.0%	Low
			10(332)	AE		SBP	MD:-10.07(16.35,-3.78)	-	0.002	44.0%	Low
			10(334)	AE		DBP	MD:-2.96(-7.71,1.78)	-	0.22	0.0%	Low
Wyngaert (2018)	RCT	Predialysis	8(269)	AE	-	SBP	SMD:0.08(-0.58,0.74)	Small	0.81	84%	Very low
			7(237)			DBP	SMD:-0.09(-0.78,0.59)	Small	0.79	83%	Very low

			11(325)			VO_{2peak}	SMD:0.99(0.49,1.48)	Large	<0.001	74.0%	Very low
			9(294)			BMI	SMD:-0.36(-0.60,-0.13)	Small	0.002	48.0%	Low
Oguch (2018)	RCT	KTRs	4(182)	Mixed	-	VO_{2peak}	SMD:0.38(-0.06,0.82)	Small	0.09	45.0%	Low
			4(179)			HRQoL	SMD:0.54(0.02,1.07)	Moderate	0.04	58.0%	Very low
Ju (2020)	RCT		3 (115)	Mixed	-	HGS	SMD:0.52(0.14,0.89)	Moderate	0.007	0.0%	Very low
			3 (387)			Symptom/problem (KDQoL)	SMD:1.92(-1.06,4.90)	Large	0.21	99.0%	Very low
			3 (387)			Effects of kidney disease (KDQoL)	SMD:-3.69(-8.56,1.19)	Large	0.14	99.0%	Very low
			3 (387)			Burden of kidney disease (KDQoL)	SMD:1.04 (-0.75,2.82)	Large	0.26	98.0%	Very low

Abbreviation: RCT = randomized controlled trial; AE = aerobic exercise; RT = resistance training; COM = combine; VO_{2peak} = peak oxygen uptake; HRQoL = health-related quality of life; DBP = diastolic blood pressure; SBP = systolic blood pressure; PCS = physical component summary; MCS = mental component summary; 6MWT = 6 minutes walk test; STS 10 = sit to stand 10 test; STS 30 = sit to stand 30 test; STS 60 = sit to stand 60 test; TUGT = timed up and go test; RLS = Restless Legs Syndrome; BMI = body mass index; SMD = standardized mean difference; MD = mean difference; HD = hemodialysis; KTRs = kidney transplant recipients; SF-36 = short form-36; KDQoL = kidney disease quality of life; GRADE = Grading of Recommendations Assessment, Development, and Evaluation.

*Number of included studies and corresponding sample size.

Mixed means aerobic exercise combined with resistance training.

Supplementary Table S4 Results of the assessment of the methodological quality of the included meta-analyses using AMSTAR-2

Author	AMSTAR-2 Items																Score
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Pei(2019)	√	×	√	○	√	√	×	√	√	×	√	×	×	×	√	×	53.1%
Ferreira(2019)	√	√	√	○	√	√	×	○	√	×	√	×	×	×	×	×	50.0%
Cheema(2014)	√	×	√	√	√	√	√	√	√	×	√	√	√	√	√	√	87.5%
Wu(2020)	√	√	√	○	√	√	×	√	√	×	√	√	√	√	√	√	84.4%
Nakamura(2020)	√	√	√	○	√	√	×	√	√	×	√	√	√	√	√	√	84.4%
Lu(2019)	√	×	√	○	√	×	×	○	○	×	√	×	×	×	√	√	46.9%
Chen(2019)	√	×	√	○	×	√	×	√	○	×	√	×	×	×	×	√	43.8%
Song(2018)	√	×	√	○	√	√	×	√	√	×	√	×	√	√	√	√	71.9%
Salhab(2021)	√	√	√	○	√	√	×	√	×	×	√	×	×	√	×	×	53.1%
Andrade(2019)	√	√	√	○	√	√	×	√	√	×	√	×	×	√	×	√	65.6%
Chung(2016)	√	×	√	○	√	√	√	√	√	×	√	√	√	√	√	×	78.1%
Zhang(2019)	√	×	√	○	√	√	×	√	√	×	√	×	√	√	√	×	65.6%
Pu(2019)	√	×	√	○	√	√	×	√	√	×	√	√	√	√	×	√	71.9%
Yamamoto(2021)	√	×	√	×	√	√	×	○	√	×	√	√	√	√	√	√	71.9%
Thompson(2019)	√	×	√	○	√	√	×	√	√	√	√	√	√	√	√	√	84.4%
Yang(2017)	√	×	√	○	√	√	×	○	√	×	√	√	√	√	√	√	75.0%
Clarkson(2019)	√	×	√	○	√	√	×	√	√	×	√	√	√	√	√	√	78.1%
Zhao(2019)	√	×	√	○	√	√	×	√	√	×	√	×	√	×	×	√	59.4%
Zhang(2019)	√	×	√	○	√	√	×	○	√	×	√	√	×	×	√	√	62.5%
Huang(2019)	√	√	√	○	√	√	×	√	√	×	√	√	×	×	√	√	71.9%
Heiwe(2011)	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	100.0%
Heiwe(2014)	√	√	√	○	√	√	√	√	√	×	√	×	√	√	×	√	78.1%

Matsuzawa(2017)	√	√	√	○	√	√	×	√	√	×	√	×	×	√	√	√	71.9%
Smart(2011)	√	×	√	○	√	×	×	○	○	×	√	×	×	√	×	×	40.6%
Bogataj(2020)	√	×	√	○	√	×	×	√	√	×	√	√	×	√	×	√	59.4%
Sheng(2014)	√	×	√	○	√	√	√	√	√	×	√	×	×	√	√	×	65.6%
Neto(2018)	√	×	√	○	√	√	×	√	√	×	√	×	×	×	×	√	53.1%
Ferrari(2019)	√	√	√	○	√	√	√	√	√	×	√	√	√	√	√	√	90.6%
Wyngaert(2018)	√	√	√	○	√	√	×	√	√	×	√	√	√	√	√	√	84.4%
Oguchi(2018)	√	√	√	○	√	√	×	√	√	×	√	√	√	×	√	×	71.9%
Ju(2020)	√	×	√	○	×	×	×	√	√	×	√	×	×	×	×	×	34.4%

√ mean yes; ○ mean partial yes; ×mean no.

1. Did the research questions and inclusion criteria for the review include the components of PICO? 2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? 3. Did the review authors explain their selection of the study designs for inclusion in the review? 4. Did the review authors use a comprehensive literature search strategy? 5. Did the review authors perform study selection in duplicate? 6. Did the review authors perform data extraction in duplicate? 7. Did the review authors provide a list of excluded studies and justify the exclusions? 8. Did the review authors describe the included studies in adequate detail? 9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? 10. Did the review authors report on the sources of funding for the studies included in the review? 11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? 12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? 13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review? 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? 15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? 16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

Supplementary Table S5: Results of the assessment of the quality of evidence for each outcome of the included meta-analyses using GRADE

Author	Outcome	GRADE items					Quality of the evidence
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	
Pei (2019)	VO_{2peak}	Very serious (-2)	Neutral	Neutral	Neutral	Neutral	Moderate
	STS 60	Serious (-1)	Very serious (-2)	Neutral	Neutral	Serious (-1)	Very low
	6MWT	Serious (-1)	Very serious (-2)	Neutral	Neutral	Serious (-1)	Very low
	SBP	Serious (-1)	Neutral	Neutral	Neutral	Not reported (-1)	Moderate
	DBP	Serious (-1)	Neutral	Neutral	Neutral	Not reported (-1)	Moderate
	Physical function (SF-36)	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Serious (-1)	Very low
	Physical role (SF-36)	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Serious (-1)	Very low
	Social function (SF-36)	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Serious (-1)	Very low
	Pain (SF-36)	Serious (-1)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	General health (SF-36)	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Serious (-1)	Very low
	Mental health (SF-36)	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Serious (-1)	Very low
Ferreira (2019)	Kt/V	Very serious (-2)	Very serious (-2)	Neutral	Serious (-1)	Not reported (-1)	Very low
Cheema (2014)	Muscle Strength	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
	HRQoL	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
Wu (2020)	SBP	Very serious (-2)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	DBP	Very serious (-2)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low

Nakamura (2020)	VO_{2peak}	Neutral	Serious (-1)	Neutral	Neutral	Serious (-1)	Moderate
	Muscle Strength	Very serious (-2)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	6MWT	Neutral	Very serious (-2)	Neutral	Serious (-1)	Serious (-1)	Very low
	TUGT	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
Lu (2019)	6MWT	Neutral	Neutral	Neutral	Serious (-1)	Neutral	Moderate
	STS 10	Neutral	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	HGS	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
	Muscle strength	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
	STS 30	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
Chen (2019)	SBP	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	DBP	Serious (-1)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	BMI	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	VO_{2peak}	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
Song (2018)	RLS	Serious (-1)	Serious (-1)	Neutral	Very serious (-2)	Serious (-1)	Very low
	Fatigue	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
Salhab (2019)	PCS	Not reported (-1)	Serious (-1)	Neutral	Very serious (-2)	Serious (-1)	Very low
	MCS	Not reported (-1)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
Andrade (2019)	VO_{2peak}	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
Chung (2019)	6MWT	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
	VO_{2peak}	Neutral	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	PCS	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
	MCS	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
Zhang (2021)	6MWT	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	STS 30	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low

	HGS	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	PCS	Very serious (-2)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	MCS	Very serious (-2)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
Pu (2019)	Kt/V	Serious (-1)	Neutral	Neutral	Serious (-1)	Not reported (-1)	Very low
	VO_{2peak}	Neutral	Serious (-1)	Neutral	Neutral	Not reported (-1)	Moderate
	6MWT	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
	PCS	Neutral	Serious (-1)	Neutral	Serious (-1)	Not reported (-1)	Very low
	MCS	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
	SBP	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	DBP	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
Yamamoto (2021)	SBP	Very serious (-2)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	VO_{2peak}	Very serious (-2)	Neutral	Neutral	Serious (-1)	Neutral	Very low
	BMI	Very serious (-2)	Neutral	Neutral	Neutral	Neutral	Low
Thompson (2019)	SBP	Very serious (-2)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	DBP	Very serious (-2)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
Yang (2017)	VO_{2peak}	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
Clarkson (2019)	6MWT	Neutral	Neutral	Neutral	Neutral	Serious (-1)	Moderate
Zhao (2019)	Fatigue	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	PCS	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	MCS	Neutral	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
Zhang (2019)	SBP	Neutral	Serious (-1)	Neutral	Neutral	Neutral	Moderate
	DBP	Neutral	Serious (-1)	Neutral	Serious (-1)	Neutral	Low
	BMI	Serious (-1)	Neutral	Neutral	Neutral	Neutral	Moderate

Huang (2019)	Kt/V	Very serious (-2)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	SBP	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	DBP	Neutral	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	6MWT	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Serious (-1)	Very low
	PCS	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	MCS	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	VO_{2peak}	Serious (-1)	Neutral	Neutral	Serious (-1)	Neutral	Low
Heiwe (2011)	Aerobic capacity	Neutral	Neutral	Neutral	Neutral	Serious (-1)	Moderate
	Muscle strength	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	Walking capacity	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	SBP	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	DBP	Neutral	Neutral	Neutral	Neutral	Neutral	High
Heiwe (2014)	Aerobic capacity	Neutral	Neutral	Neutral	Serious (-1)	Not reported (-1)	Low
	DBP	Neutral	Neutral	Neutral	Serious (-1)	Not reported (-1)	Low
	SBP	Neutral	Serious (-1)	Neutral	Serious (-1)	Not reported (-1)	Very low
	Muscle strength	Serious (-1)	Neutral	Neutral	Serious (-1)	Not reported (-1)	Very low
	Walking capacity	Neutral	Neutral	Neutral	Serious (-1)	Not reported (-1)	Low
Matsuzawa (2017)	VO_{2peak}	Neutral	Neutral	Neutral	Neutral	Neutral	High
	6MWT	Serious (-1)	Serious (-1)	Neutral	Serious (-1)	Neutral	Very low
	Muscle strength	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	PCS	Very serious (-2)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	MCS	Very serious (-2)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
Smart (2011)	VO_{2peak}	Neutral	Serious (-1)	Neutral	Neutral	Serious (-1)	Low
Bogataj	6MWT	Serious (-1)	Serious (-1)	Neutral	Not reported (-1)	Not reported (-1)	Very low

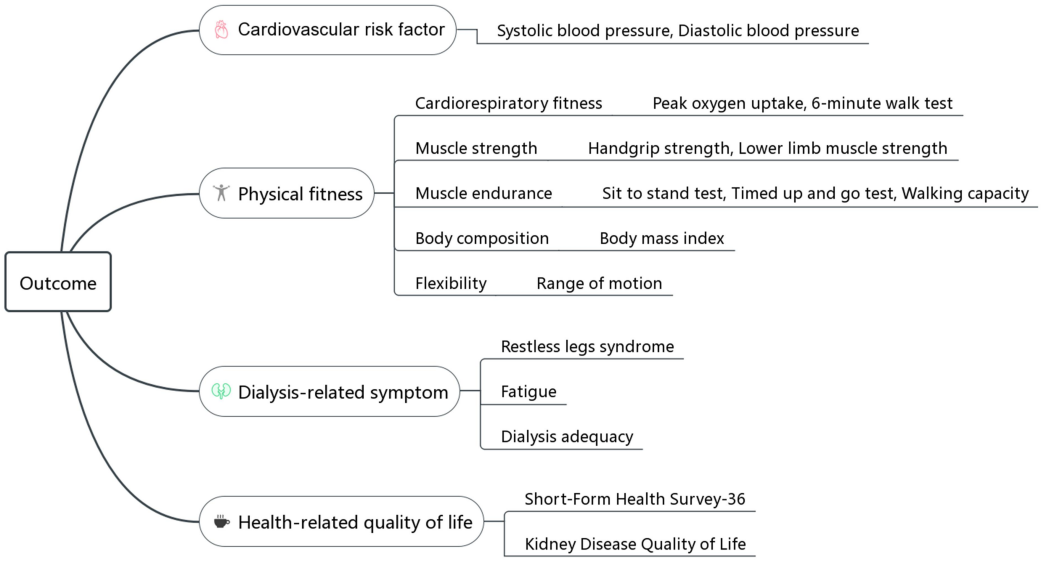
(2020)	VO_{2peak}	Very serious (-2)	Serious (-1)	Neutral	Not reported (-1)	Not reported (-1)	Very low
	STS 10	Neutral	Serious (-1)	Neutral	Not reported (-1)	Serious (-1)	Very low
Sheng (2014)	Kt/V	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	VO_{2peak}	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	PCS	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	MCS	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	6MWT	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Serious (-1)	Very low
	DBP	Serious (-1)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	SBP	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	STS60	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
Neto (2018)	VO_{2peak}	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Not reported (-1)	Very low
	PCS	Serious (-1)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	MCS	Serious (-1)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	6MWT	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Serious (-1)	Very low
	Muscle strength	Neutral	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
Ferrari (2019)	Kt/V (AE)	Neutral	Serious (-1)	Neutral	Serious (-1)	Neutral	Low
	Kt/V (RT)	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	VO_{2peak} (COM)	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	VO_{2peak} (AE)	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	6MWT (RT)	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	6MWT(AE)	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	SBP	Serious (-1)	Neutral	Neutral	Serious (-1)	Neutral	Low
	DBP	Serious (-1)	Neutral	Neutral	Serious (-1)	Neutral	Low
Wyngaert (2018)	SBP	Serious (-1)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	DBP	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Serious (-1)	Very low

	VO_{2peak}	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Neutral	Very low
	BMI	Serious (-1)	Neutral	Neutral	Serious (-1)	Neutral	Low
Oguchi (2018)	VO_{2peak}	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	HRQoL	Serious (-1)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
Ju (2020)	HGS	Very serious (-2)	Neutral	Neutral	Serious (-1)	Neutral	Very low
	Symptom/problem (KDQoL)	Very serious (-2)	Very serious (-2)	Neutral	Serious (-1)	Not reported (-1)	Very low
	effects of kidney disease (KDQoL)	Very serious (-2)	Very serious (-2)	Neutral	Serious (-1)	Not reported (-1)	Very low
	burden of kidney disease (KDQoL)	Very serious (-2)	Very serious (-2)	Neutral	Serious (-1)	Not reported (-1)	Very low

Abbreviation: AE = aerobic exercise; RT = resistance training; COM = combine; VO_{2peak} = peak oxygen uptake; HRQoL = health-related quality of life; DBP = diastolic blood pressure; SBP = systolic blood pressure; PCS = physical component summary; MCS = mental component summary; 6MWT = 6 minutes walk test; STS 10 = sit to stand 10 test; STS 30 = sit to stand 30 test; STS 60 = sit to stand 60 test; TUGT = timed up and go test; BMI = body mass index; SMD = standardized mean difference; HD = hemodialysis; KTRs = kidney transplant recipients; SF-36 = short form-36; KDQoL = kidney disease quality of life;

Very serious mean the included studies existed two or more high risk of bias in terms of randomization, blinding, allocation concealment, completeness of result data, or selective reporting, or $75\% \leq I^2 \leq 100\%$.

Serious mean the included studies existed two or more high risk of bias in terms of randomization, blinding, allocation concealment, completeness of result data, or selective reporting, or $50\% \leq I^2 < 75\%$, or the included study sample size< 400, asymmetric funnel plot or less than 9 studies included.



Supplemental Figures S1

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 4-5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 4-5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 5-6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 4-5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	None
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Not applicable
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	None
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	None
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	None
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 6

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 6
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 6
Study characteristics	17	Cite each included study and present its characteristics.	Page 6
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 6
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 18-32
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Not applicable
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Not applicable
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not applicable
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	None
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 6
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 6
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 10
	23b	Discuss any limitations of the evidence included in the review.	Page 12
	23c	Discuss any limitations of the review processes used.	Page 12
	23d	Discuss implications of the results for practice, policy, and future research.	None
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	None
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 1
Competing interests	26	Declare any competing interests of review authors.	Page 1
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 1

PRISMA 2020 Checklist

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

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Therapeutic effects of exercise interventions for patients with chronic kidney disease: an umbrella review of systematic reviews and meta-analyses

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Therapeutic effects of exercise interventions for patients with chronic kidney disease: an umbrella review of systematic reviews and meta-analyses

Title page

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Key words: Exercise, chronic kidney disease, systematic review, meta-analyses

Running Head: Exercise for chronic kidney disease

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ABSTRACT

Objective To conduct an overview of meta-analyses evaluating the impact of exercise interventions on improving health outcomes in patients with chronic kidney disease (CKD).

Design An umbrella review of systematic review and meta-analyses of intervention trials was performed.

Data sources PubMed, Web of Science, Embase, and the Cochrane Database of Systematic Reviews were searched from inception to March 9th, 2021, for relevant articles.

Eligibility criteria for selecting studies Eligible meta-analyses compared the effects of usual care with and without exercise in CKD patients. Health outcomes included those related to cardiovascular risk factors, physical fitness, dialysis-related symptoms, dialysis adequacy, and health-related quality of life. Systematic reviews and meta-analyses that included fewer than three RCTs or fewer than 100 participants were excluded from the analysis.

Results A total of 31 eligible systematic reviews and meta-analyses were included that assessed 120 outcomes. For physical fitness, there was a moderate effect size for cardiorespiratory fitness, muscle strength, and body composition and small effect size for muscle endurance. The effect sizes for cardiovascular risk factors, dialysis-related symptoms, and health-related quality of life outcomes were small. According to the Grading of Recommendations Assessment, Development, and Evaluation framework, most outcomes were low or very low quality.

Conclusion Exercise appears to be a safe way to affect concomitant cardiovascular risk factors, such as blood pressure, improve physical fitness and health-related quality of life, and reduce dialysis-related symptoms in CKD patients.

Keywords: Exercise, Chronic Kidney Disease, Systematic Review, Meta-Analyses

PROSPERO registration number CRD42020223591.

Strengths and limitations of this study

1) A strength of this study is to comprehensively summarize the systematic review and meta-analysis of exercise interventions on the spectrum of chronic kidney disease.

2) Methodological quality of the included reviews was assessed using standardized measures.

3) The limitation of this overview is that language bias may exist in this review because the search strategy was limited to English.

4) Another limitation was that most studies were based on hemodialysis-dependent chronic kidney disease.

INTRODUCTION

Chronic kidney disease (CKD) is a long-term condition characterized by the gradual loss of renal function over time.[1] In the past 30 years, the mortality attributed to CKD increased by 41.5%, a percentage rate that exceeds several cancers and cardiovascular diseases.[2] With the increasing incidence of hypertension, diabetes, and obesity, this number will continue to rise.[3, 4] CKD patients experience a high symptom burden with progressively impaired physical performance, leading to decreased kidney function, lower health-related quality of life (HRQOL), increased risk of cardiovascular events, and increased all-cause mortality.[5, 6]

With an increasing number of patients with CKD living longer, the effectiveness and accessibility of their health services have never been more critical. Renal rehabilitation is a multifaced intervention program. Rehabilitation consists of exercise interventions, diet control, fluid management, and psychological support to alleviate physical/mental deficiencies caused by kidney disease and renal replacement therapy to improve disease prognosis and prolong life expectancy.[7] Since exercise is the core of renal rehabilitation, there is an increasing number of systematic reviews and meta-analyses investigating the influence of exercise on health outcomes in CKD patients.[8]

Data from large cohort studies show that mortality risk was lower for regular (equal to or more than once/week) versus non-regular (less than once/week) exercisers [adjusted hazard ratio (HR)=0.73, 95% confidence interval (CI): 0.69–0.78], and mortality risk tended to decrease as exercise frequency increased ($HR_{\text{for participants who exercised once/week}}$ = 0.82, 95% CI: 0.73–0.91; $HR_{\text{for those who exercised 6–7 times/week}}$ = 0.69, 95% CI: 0.63–0.76) and patients who exercised daily had lower mortality risk (HR = 0.84, 95% CI: 0.74–0.96) than patients exercising once/week.[9] Based on data from 41 randomized controlled trials (RCT), Heiwe et al. reported practical improvements in aerobic capacity, muscular function, and walking capacity in CKD patients after exercise, [10] indicators that are the core of frailty. [11] In other words, exercise is an essential non-pharmacological strategy to improve frailty symptoms in CKD patients, the latter being a significant cause of sedentary behavior in such population. [12] Because of this, some researchers and guidelines recommend that healthcare providers prescribe exercise for CKD patients.[13-16] However, the results of meta-analyses of exercise in CKD patients are inconsistent.

This umbrella review aims to assess the therapeutic effects of exercise on cardiovascular risk factors, physical fitness, dialysis-related symptoms, dialysis adequacy, and HRQOL in CKD patients, summarized in systematic reviews and meta-analyses.

METHODS AND ANALYSIS

This umbrella review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[17] The review was prospectively registered (PROSPERO: CRD42020223591), and the protocol for this review was published.[18]

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Literature Search

A comprehensive search strategy was performed to identify systematic reviews and meta-analyses of CKD patients that compared usual care procedures with and without exercise interventions. PubMed, Embase, the Cochrane Database of Systematic Reviews (CDSR), and the Web of Science were searched for systematic reviews and meta-analyses from inception to March 9th, 2021. The detailed search strategy is summarized in **Supplementary Table S1**. The references of existing systematic reviews were also screened. Any reviews considered potentially relevant by authors were retrieved for further consideration.

Eligibility Criteria

Eligible systematic reviews and meta-analyses included those 1) where patients were diagnosed with CKD at various stages of treatment; 2) that compared exercise interventions with sham/no exercise or usual/standard care; 3) that reported outcomes on at least one of the following: cardiovascular risk factors (blood pressure), physical fitness, dialysis-related symptoms, dialysis adequacy, and HRQOL. The methods to assess each outcome were shown in **Supplement Figure S1**; 4) systematic reviews with meta-analysis of intervention trials (RCTs and quasi-experimental studies). A meta-analysis that included less than three studies or less than 100 participants was excluded. For duplicate literature, the article with the most comprehensive data was selected. The language was restricted to English. Letters to the editor, trial protocols, and conference abstracts were excluded.

Study selection

Two independent authors screened all titles and abstracts compiled from the search results. Each paper was examined for appropriate eligibility criteria, and a third author resolved disagreements.

Data extraction

Requisite data were extracted independently by two independent authors into a standardized format that included: 1) author, 2) publication year, 3) stage of CKD, 4) the number of included studies and participants, 5) exercise type, 6) exercise mode (intradialytic or interdialytic), 7) standardized mean difference (SMD) or mean difference (MD) with corresponding 95% CI for each outcome, 8) *P*-values, 9) I^2 values, and 10) exercise-related adverse events.

Risk of bias assessment

A Measurement Tool to Assess Systematic Reviews-2 (AMSTAR-2) was used to assess the risk of bias among the included systematic reviews.[19] This checklist contains 16 items, and each item was answered with a "yes" (1 point), "partial yes" (0.5 points), or "no" (0 points). The percentage score for each study was calculated using the total score as the numerator and the highest score of 16 points as the denominator. A meta-analysis scoring ≥80% was classified as high quality, 40-79% as medium quality, and those scoring <40% as low quality.[20] Two authors performed the risk of bias assessment independently, and discussions resolved the disagreement.

Data analysis

The summary effect size from each meta-analysis was analyzed qualitatively based on the SMD and its 95% CI for each outcome. If they were not presented as SMD in the original meta-analysis, Review Manager V.5.3 was used to convert SMD outcomes. If data could not be converted into SMD, we contacted the authors of the meta-analysis for the data. Effects were considered small (SMD < 0.50), moderate (SMD from 0.50 to 0.79), and large (SMD ≥0.80).[21] I^2 values were interpreted as follows: ≤25% indicate low heterogeneity, 25%<I^2≤50% indicate mild heterogeneity, 50%<I^2≤75% indicate moderate heterogeneity, and >75% indicate high heterogeneity.[22]

The level of evidence for each meta-analysis was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.[23] The quality of evidence was assessed using five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Beginning with an initial score of 4 points, the score for each of these five domains was reduced accordingly: "not reported (-1)", "serious (-1)", "very serious (-2)", or "neutral (0)". Studies were rated as high (4 points), moderate (3 points), low (2 points), or very low (≤ 1 point) using the GRADE system. The GRADE assessment was conducted independently by two authors. Any differences were resolved by discussion or adjudication by a third author. The incidence of adverse events was based on the number of reported divided by the patients in the exercise group.

RESULTS

Characteristics of the meta-analyses

The search identified 2305 potential articles, of which 648 were duplicates. After reading the title and abstract, 1598 papers were excluded, and 28 were excluded after full-text review resulting in 31 final studies. [10, 24-53] The PRISMA flowchart of study inclusion is illustrated in **Figure 1**. The reasons for excluded articles are listed in **Supplementary Table S2**.

Figure 1 Flowchart of literature screening.
Legend: CDSR = Cochrane Database of Systemic Review

The 31 included systematic reviews and meta-analyses were published from September 2011 through March 2021. The number of included studies assessed in the articles ranged from 3 to 24, with a mean of 8 studies. The study sample sizes ranged from 106 to 874 participants, with a mean of 304. The characteristics of the included meta-analyses are shown in **Supplement Table S3**. SMD data from four papers could not be obtained from the authors, and the data of their effect size was presented as MD.[29, 30, 40, 46]

Scores based on AMSTAR-2 ranged from 34.4% to 100.0%, with an average score of 68.0%. Seven (22.6%) systematic reviews were rated high quality, while 23 (74.2%) were rated medium quality, and just one (0.3%) was rated low quality (**Supplement Table S4**).

Of the GRADE evidence quality of the 120 outcomes, 1.7% (2 / 120) reported evidence of high quality, 17.5% (21 / 120) reported evidence of moderate quality, 20.0% (24 / 120) reported evidence of low quality, and 60.8% (73 / 120) reported evidence of very low quality (**Supplement Table S5**).

Blood pressure

There were 25 meta-analyses (reported in 13 articles) investigating the effect of exercise on cardiovascular risk factors (systolic and diastolic blood pressure) in CKD patients. [10, 27, 30, 33, 34, 40, 41, 43, 46-49, 52] Of which, the number of studies ranged from 3 to 12 with a mean of 314 participants (range from 198 to 514) were included in each meta-analysis (**Table 1**).

The effect of exercise on systolic blood pressure was investigated in 13 meta-analyses with a mild heterogeneity (average $I^2 = 36.1\%$),[10, 27, 30, 33, 34, 40, 41, 43, 46-49, 52] and six reported a positive statistically significant outcome. [30, 33, 41, 43, 49, 52] Of the 13 meta-analyses, nine reported a small effect size, [10, 27, 33, 34, 41, 43, 47, 48, 52] and one reported moderate.[49] GRADE assessment of quality indicated the

overall evidence as being very low (10 meta-analyses[10, 27, 30, 33, 41, 43, 46-49]), low (two meta-analyses[34, 40]), and moderate (one meta-analysis[52]).

The effect of exercise on diastolic blood pressure was investigated in 12 meta-analyses with a mild heterogeneity (average I^2=49.1%),[10, 27, 30, 33, 34, 40, 41, 43, 46-48, 52] and 2 reported a positive statistically significant outcome.[41, 43] Of the 12 meta-analyses, nine reported small effect sizes [10, 27, 33, 34, 41, 43, 47, 48, 52], and all were graded as low or very low quality of evidence.

Cardiorespiratory fitness

There were 34 meta-analyses (reported in 21 articles) that investigated the effects of exercise on cardiorespiratory fitness in CKD patients using a peak oxygen uptake (18 of 34), a 6-minute walk test (14 of 34), or aerobic capacity (2 of 34). The meta-analyses included a mean of nine studies (ranging from 5 to 20) and a mean of 330 participants (ranging from 179 to 504) (**Table 2**).

The effect of exercise on peak oxygen consumption was investigated in 18 meta-analyses (reported in 17 articles) with a mild heterogeneity (average I^2=42.2%),[24, 25, 27, 28, 30, 32, 34, 37, 38, 40, 41, 43, 44, 49, 50, 54] and 16 reported positive statistically significant outcomes. [24, 25, 28, 30, 32, 34, 37, 38, 40, 41, 43, 44, 47, 49, 50] Of the 18 meta-analyses, three reported a low effect size,[27, 39, 50] nine reported a moderate effect size[25, 28, 32, 34, 37, 41, 43, 44, 49] and three reported a large effect size.[24, 38, 47] GRADE assessment of quality indicated the overall evidence as being very low (9 meta-analyses[25, 27, 28, 30, 32, 37, 43, 47, 49]), low (8 meta-analyses[24, 34, 38-41, 44, 50]), and high (one meta-analysis[37]). A meta-analysis that included kidney transplant recipients found no statistically significant difference in the SMD of the exercise group (0.38; 95% CI, -0.06 to 0.82; P=0.09).[39]

The effect of exercise on the 6-minute walk test was investigated in 14 meta-analyses (reported in 13 articles) with a mild heterogeneity (average I^2=44.9%),[25, 28-30, 32, 34, 36-38, 40, 41, 43, 51] and 13 reported positive statistically significant outcomes.[25, 28-30, 32, 34, 36-38, 41, 43, 51] Of the 14 meta-analyses, two reported a small effect size,[25, 28] five reported a moderate effect size,[36, 37, 41, 43, 51] and three reported a large effect size.[32, 34, 38] GRADE assessment of quality indicated the overall evidence as being very low (eight meta-analyses[25, 30, 32, 34, 38, 40, 43]), low (four meta-analyses[28, 37, 41, 51]), and moderate (two meta-analyses[29, 36]). In addition, the meta-analysis by Heiwe et al. (2014) showed that regular exercise had significant beneficial effects on aerobic capacity. [10, 33]

Muscle strength

Ten meta-analyses (reported in nine articles) investigated the effects of exercise on muscle strength in CKD patients with a low heterogeneity (average $I^2 = 19.1\%$).[10, 26, 32, 33, 35-38, 51] The meta-analyses included a mean of seven studies (ranging from 3 to 12) and a mean of 252 participants (ranging from 115 to 385) (**Table 3**).

Muscle strength was measured using handgrip strength and lower limb muscle strength. For patients in 8 of 10 meta-analyses, exercise resulted in statistically significant improvements in muscle strength. [10, 32, 33, 35-37, 51] Of the 10 meta-analyses, three reported a small effect size,[36, 38, 51] five reported a moderate effect size,[10, 32, 33, 35, 36] and two reported a large effect size,[26, 37] GRADE assessment of quality indicated the overall evidence as being very low (six meta-analyses[10, 32, 33, 35, 37, 38]) and low (four meta-analyses[26, 36, 51]).

Muscle endurance

Nine meta-analyses (reported in 8 articles) investigated the effects of exercise on muscle endurance with a mild heterogeneity (average $I^2 = 29.4\%$).[10, 25, 33, 36, 38, 40, 43, 51] An average of 238 participants (ranging from 106 to 461) from 5 studies (ranging from 3 to 7) were included in the meta-analysis (**Table 4**).

Muscle endurance was measured using a sit-to-stand test, timed up and go test, and walking capacity exercise. Pooled effect estimates from all nine meta-analyses suggested a beneficial effect of exercise on muscle endurance in CKD patients. Seven of the nine meta-analyses reported power to detect a statistically significant effect. [25, 33, 36, 38, 43, 51] Two meta-analyses reported moderate effect size, and 5 reported small effect size. GRADE assessment of quality indicated the overall evidence as being very low (seven meta-analyses[25, 33, 36, 38, 40, 43, 51]), low (one meta-analyses[36]) and moderate (one meta-analyses[10]).

Body composition

Four meta-analyses consisting of 9 studies (ranging from 4 to 13) and a mean of 335 participants (ranging from 166 to 466) included body mass index as an outcome.[27, 47, 49, 52] There was a low heterogeneity (average $I^2 = 12.0\%$) among the study outcomes (**Table 5**).

Three of the four meta-analyses showed a positive statistically significant impact on body mass index using exercise interventions in CKD patients.[47, 49, 52] Small effect size was reported in all meta-analyses. GRADE assessment of quality indicated the overall evidence as being very low (one meta-analysis), low (two meta-analyses[47, 49]), and moderate (one meta-analysis [52]).

Dialysis-related symptoms

Nine meta-analyses (reported in seven articles) investigated the effect of exercise on dialysis-related symptoms in CKD patients.[30, 31, 34, 41, 43, 45, 53] Each meta-analysis included a mean of seven studies (ranging from 3 to 12 studies) and a mean of 239 participants (ranging from 139 to 370). (**Table 6**).

Fatigue was measured using the Rhoten Fatigue Scale, Visual Analogue Scale, and Hemodialysis Patients Fatigue Scale. The effect of exercise on fatigue was investigated in 2 meta-analyses with a low heterogeneity (average I^2=23.5%).[45, 53] The two meta-analyses revealed a statistically significant effect of exercise on fatigue. Although the meta-analyses reported large effect size, the quality of evidence was low[45] or very low[53] according to GRADE criteria.

Just one meta-analysis investigated the effects of exercise on restless legs syndrome in CKD patients.[45] The results showed that pooled effect estimated for restless legs syndrome with statistically significant but considerable average heterogeneity (I^2 = 87.0%). According to GRADE criteria, the overall evidence for this outcome was very low.

Dialysis adequacy

Dialysis adequacy was measured using the value of Kt/V. Six meta-analyses (reported in 5 articles) investigated the effects of exercise on Kt/V in CKD patients with a mild heterogeneity (average I^2 = 25.7%).[30, 31, 34, 41, 43] Comprehensive effect estimates from all the six meta-analyses with Kt/V outcomes showed that exercise had a beneficial effect. In three of the six meta-analyses, 3 reported a small effect size[34, 41, 43], and one reported large effect size.[31] According to GRADE criteria, all meta-analyses were rated as very low-quality evidence (**Table 6**).

Health-related quality of life

Twenty-nine meta-analyses (reported in 13 articles) investigated the effect of exercise on HRQOL in CKD patients.[26, 28, 32, 34, 35, 37, 39-43, 51, 53] Among them, nine meta-analyses assessed the physical and mental subscale of the Short-Form Health Survey-36.[28, 32, 34, 37, 41-43, 51, 53] Each meta-analysis included an average of 6 studies (ranging from 3 to 10) and 311 participants (ranging from 167 to 562). The included meta-analyses had moderate heterogeneity (average I^2 = 51.0%) (**Table 7**).

Of the 29 meta-analyses, a comprehensive effect estimate of the 28 meta-analyses shows that exercise is beneficial to the HRQOL of CKD patients, but only 12 of 29 meta-analyses reported a statistically significant outcome.[28, 34, 37, 39, 41-43, 53] There were 13 of 29 meta-analyses reporting a small effect size, [28, 32, 34, 37, 41, 43, 51, 53] 4 were moderate,[32, 37, 39, 41] and 6 were large.[26, 35, 42] According to

GRADE criteria, the overall of evidence for HRQOL was rated as very low (20 meta-analyses[32, 35, 37, 39-43, 53]) or low (nine meta-analyses[26, 28, 34, 41, 51, 53]).

Adverse events

Six meta-analyses reported exercise-related adverse events.[26, 28, 38, 41, 43, 44] Of the adverse effects, the most commonly reported were hypotension and cramping. Overall, the incidence of adverse events was approximately 0.3%.

DISCUSSION

Summary of main results

Several meta-analyses have been published on exercise interventions in CKD patients.[55] The findings of these meta-analyses should be assessed to determine if the evidence is consistent among the studies. This umbrella review included 31 eligible articles involving 120 separate meta-analyses investigating the effect of exercise on the health outcomes in CKD patients. There was low- or very low-quality evidence for moderate beneficial effects of exercise on cardiorespiratory fitness, muscle strength, and body composition. In addition, there was very low-quality evidence for minor beneficial effects of exercise on muscle endurance, cardiovascular risk factors, dialysis-related symptoms, and HRQOL. Few adverse events related to exercise indicate that exercise is safe for CKD patients.

Interpretation of study effects

Cardiovascular disease is a frequent complication of CKD and is the leading cause of death in CKD patients.[56] Hypertension is an important modifiable risk factor for cardiovascular diseases and progressive renal dysfunction in CKD patients.[57] The present overview showed that exercise has a small to moderate effect on blood pressure (SMD: -0.75 to 0.04 for systolic blood pressure and SMD: -0.47 to 0.04 for diastolic blood pressure); it is an appealing strategy for blood pressure control in CKD patients. However, the dose effects of exercise in the context of the cardiovascular health of CKD patients should be considered. A recent cohort study found that 7.5-15 metabolic equivalent hours per week (MET-h/week) was associated with the lowest risk of cardiovascular events.[58] Regrettably, the benefit of exercise on cardiovascular risk factors cannot be determined because there are an insufficient number of conclusive studies that assess exercise effects on overall cardiovascular health. In a systematic review by Heiwe et al., a meta-analysis including two trials found that exercise improved cardiovascular function in patients with CKD, as reflected in the standard deviation of all normal RR intervals and left ventricular mass index.[10] Furthermore,

a recent randomized controlled trial published by Graham-Brown indicated that intradialytic exercise could reduce left ventricular mass and is safe, deliverable, and well-tolerated.[59] Although the GRADE evidence was low, exercise should be recommended for CKD patients, particularly those comorbid with cardiovascular disease. Future randomized controlled exercise trials need to focus more on the role of exercise in cardiovascular events in patients with CKD.

Physical fitness is necessary for participation in activities of daily living. The exercise provided the best results in improving cardiorespiratory fitness and muscle strength in CKD patients, with more than half of the meta-analyses reporting moderate or large effect sizes, regardless of the quality of evidence. Cardiorespiratory fitness is considered a significant independent predictor of mortality, and muscle strength is an essential indicator of physical performance in CKD patients.[60] It is well known that aerobic exercise is the "gold standard" for cardiorespiratory rehabilitation[61] and resistance training for muscle strength improvement.[62] However, a combination of aerobic and resistance exercises may have a more profound effect on CKD patients based on the current review. Meta-analyses by Andrade et al. showed that combined training benefits cardiorespiratory fitness in CKD patients.[24]

Both sarcopenia and obesity have increased mortality risk and progression to end-stage renal disease in CKD patients.[63] Unlike patients receiving dialysis, treatment requirements for predialysis CKD patients are based on maintaining a “healthy weight” and preventing or attenuating obesity.[14] In this overview, the effectiveness of exercise for body mass index was supported by four analyses with small effect sizes and moderate quality of evidence. Based on the results, exercise may contribute to lower body mass index in CKD patients. However, additional studies are needed to confirm the benefits of exercise programs for reducing sarcopenia and weight.

CKD population experience multiple symptoms that affect the patient’s prognosis and HRQOL.[64] Patients who received dialysis treatment commonly reported restless legs syndrome, fatigue, and inadequate dialysis due to kidney function deterioration and dialysis-related side effects.[65, 66] These symptoms affect sleep and daily activities and impose considerable psychological distress and economic burden.[67] An increasing number of researchers have investigated the role of exercise as an important non-pharmacological strategy for preventing and/or treating symptoms. [68, 69] The results of a small number of meta-analyses suggested the beneficial effect of exercise on dialysis adequacy (SMD: 0.19 to 2.21) and improving restless legs syndrome (SMD: -1.79) and fatigue symptoms (SMD: -0.97 to -0.85). Nevertheless, the efficacy of exercise in CKD patients for preventing dialysis-related symptoms awaits new clinical evidence.

With similar results obtained in another overview that included chronic disease,[70] results from this overview demonstrated minor beneficial effects of exercise on HRQOL, irrespective of the evidence level in CKD patients. Improved HRQOL is vital because most of the population reported poor health and well-being due to diet restriction, weakness, and dialysis treatment.[71] The consistent health benefits of exercise in this overview demonstrated that exercise could be a strategy to improve the poor long-term prognosis in CKD patients.

Several meta-analyses reported exercise-related adverse events. Based on the reported adverse events, we calculate that only three adverse events occurred per 1000 CKD patients. The low incidence of adverse events indicated that the benefits of exercise in CKD patients outweigh its potential risks and most reflected typical response to exercise (e.g., muscle soreness). However, most meta-analyses only included intradialytic exercise for hemodialysis patients in their assessments. Exercises during hemodialysis are usually performed under the supervision of a healthcare worker to ensure safety.[72] It has been reported that all patients with CKD are at risk for cardiovascular events (e.g., arrhythmias, myocardial ischemia) during exercise. Therefore, medical screening should be performed before exercise to determine which patients may be at increased risk for cardiovascular accidents. [73] In addition, special attention should be paid to dry weight and blood pressure in patients with hemodialysis-dependent CKD to avoid excessive volume loading or dehydration, which may increase the risk associated with exercise. [60]

Implications for clinical

Taken together, there is good reason to recommend exercise for improving prognosis in CKD patients. Evidence from most randomized controlled trials increased confidence in the findings of this umbrella review. Because most of the meta-analyses assessed in this study did not detail the exercises instituted, it is difficult to make recommendations about the type of exercise that would be the most beneficial for CKD patients. Although exercise's effect sizes on improving CKD patients' health prognosis were generally moderate, these effects may bring some clinical benefit to patients experiencing impaired function or symptom distress. Despite numerous meta-analyses providing only low or very low-quality evidence, similar beneficial effects of exercise were reported by meta-analyses of randomized controlled trials with different grades of evidence. Remarkably, a recently published trial found that a 6-month intradialytic exercise program effectively reduces healthcare costs.[74] Overall, exercise should be integrated into the care of CKD, but the overall benefit of exercise to CKD is still debatable.

Limitations

This overview has several limitations. First, most meta-analyses included in this review involve hemodialysis patients, limiting the results' extrapolation to other CKD stages. Second, improvement of flexibility in CKD patients was not investigated. Flexibility is an important component of physical fitness that impacts muscular injury.[75] The evidence for the efficacy of exercise on flexibility improvement is insufficient for a systematic review or meta-analysis. Third, since the search strategy was limited to English, this review may have language bias. It is unknown whether meta-analyses published in other languages would affect the results of our study. Fourth, the results may be had been influenced by an overlap in the original studies. Fifth, the accuracy of the MD data cannot be guaranteed. Sixth, subgroup analyses of different types of exercise were not performed as described in the published protocol because most of the included meta-analyses did not detail the exercises. Seventh, both body composition and cardiovascular risk factors are common terms. However, the inclusion of studies was limited, so this review focused only on body mass index and blood pressure, and more evidence is still needed for the effects of other assessment metrics.

CONCLUSION

In CKD patients, exercise improves muscle strength, endurance, body composition, and HRQOL. At the same time, exercise decreases blood pressure and dialysis-related symptoms in CKD patients. However, the quality of the evidence was considered low or very low for all outcomes indicating that we have low certainty evidence to support the findings above. More rigorous study is still needed in the future. Nevertheless, given the health benefits of physical activity, exercise should be integrated into renal care for a patient with any stage of CKD.

Contributors

FZ and LYH conceived and designed the review. YB and XZ searched databases, extracted the data, and conducted the statistical analysis. WQZ revised the manuscript. WQW and HCZ provided technical support. All authors had read and approved the final manuscript and agreed on its submission.

Ethics approval statement

Ethics approval is not required as no private information from individuals is collected.

Dissemination

The results will be published in a peer-reviewed journal or disseminated in relevant

conferences.

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Table 1 Summary of the effect of exercise on cardiovascular risk factor in CKD patients

Author (year)	Design	Stage of CKD	k (n)*	Exercise type	Mode	SMD or MD (95% CI)	Effect size	*P*	I^2	GRADE
SBP										
Pei (2019)	RCT/quasi-RCT	Mixed	12(514)	AE	-	MD:−2.91 (−6.68, 0.87)	-	0.13	40.0%	⊕⊕◯◯
Wu (2020)	RCT/quasi-RCT	Predialysis	3 (204)	AE+RT	-	SMD:-0.19(-0.46,0.08)	Small	0.16	50.0%	⊕◯◯◯
Chen (2019)	RCT	KTRs	5(198)	Mixed	-	SMD:0.18(-0.10,0.46)	Small	0.21	0.0%	⊕◯◯◯
Pu (2019)	RCT	HD	7(287)	Mixed	Intradialytic	SMD:-0.28(-0.52,-0.05)	Small	0.02	0.0%	⊕◯◯◯
Yamamoto (2021)	RCT	Predialysis	10(392)	AE	-	SMD:-0.75(-1.24,-0.26)	Moderate	0.003	80.3%	⊕◯◯◯
Thompson (2019)	RCT	Predialysis	10(335)	Mixed	-	MD:-4.30(-9.00,0.40)	-	N.P.	50.4%	⊕◯◯◯
Zhang (2019)	RCT	Predialysis	14(463)	Mixed	-	SMD:-0.41(-0.70,-0.11)	Small	0.007	55.0%	⊕⊕⊕◯
Huang (2019)	RCT	HD	7(260)	Mixed	Mixed	SMD:-0.17(-0.41,0.08)	Small	0.18	8.0%	⊕⊕◯◯
Heiwe (2011)	RCT/quasi-RCT	Mixed	9(347)	Mixed	-	SMD:0.25(0.04,0.47)	Small	0.02	0.0%	⊕◯◯◯
Heiwe (2014)	RCT	HD	10(312)	Mixed	-	SMD:0.04(-0.34,0.41)	Small	0.8	58.0%	⊕◯◯◯
Sheng (2014)	RCT	HD	7(296)	Mixed	Intradialytic	SMD:-0.27(-0.50,-0.04)	Small	0.02	0.0%	⊕◯◯◯
Ferrari (2019)	RCT	HD	10(332)	AE	Intradialytic	MD:-10.07(16.35,-3.78)	-	0.002	44.0%	⊕◯◯◯
Wyngaert (2018)	RCT	Predialysis	8(269)	AE	-	SMD:0.08(-0.58,0.74)	Small	0.81	84%	⊕◯◯◯
DBP										
Pei (2019)	RCT/quasi-RCT	Mixed	12(514)	AE	-	MD:−1.11 (−3.41, 1.20)	-	0.35	0.0%	⊕⊕◯◯
Wu (2020)	RCT/quasi-RCT	Predialysis	4 (194)	AE+RT	-	SMD:-0.47(-1.10,0.15)	Small	0.14	70.0%	⊕◯◯◯
Chen (2019)	RCT	KTRs	5(198)	Mixed	-	SMD:0.04(-0.45,0.52)	Small	0.89	59.0%	⊕◯◯◯
Pu (2019)	RCT	HD	7(287)	Mixed	Intradialytic	SMD:-0.32(-0.55,-0.08)	Small	0.008	42.0%	⊕◯◯◯
Thompson (2019)	RCT	Predialysis	8(303)	Mixed	-	MD:-1.18(-4.76,2.40)	-	N.P.	60.5%	⊕◯◯◯

Zhang (2019)	RCT	Predialysis	12(399)	Mixed	-	SMD:-0.31(-0.71,0.08)	Small	0.12	70.0%	⊕⊕◯◯
Huang (2019)	RCT	HD	7(260)	Mixed	Mixed	SMD:-0.23(-0.69,0.24)	Small	0.34	68.0%	⊕◯◯◯
Heiwe (2011)	RCT/quasi-RCT	Mixed	11(419)	Mixed	-	SMD:0.16(-0.04,0.36)	Small	0.11	40.0%	⊕◯◯◯
Heiwe (2014)	RCT	HD	10(212)	Mixed	Mixed	SMD:0.17(-0.16,0.49)	Small	0.3	45.0%	⊕⊕◯◯
Sheng (2014)	RCT	HD	7(296)	Mixed	Intradialytic	SMD:-0.24(-0.47,-0.01)	Small	0.04	52.1%	⊕◯◯◯
Ferrari (2019)	RCT	HD	10(334)	AE	Intradialytic	MD:-2.96(-7.71,1.78)	-	0.22	0.0%	⊕◯◯◯
Wyngaert (2018)	RCT	Predialysis	7(237)	AE	-	SMD-0.09(-0.78,0.59)	Small	0.79	83%	⊕◯◯◯

Abbreviation: RCT = randomized controlled trial; AE = aerobic exercise; RT = resistance training; DBP = diastolic blood pressure; SBP = systolic blood pressure; SMD = standardized mean difference; MD = mean difference; HD = hemodialysis; KTRs = kidney transplant recipients; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; N.P. = no report.

*Number of included studies and corresponding sample size.

Mixed means aerobic exercise combined with resistance training.

Table 2 Summary of the effect of exercise on cardiopulmonary fitness in CKD patients

Author (year)	Design	Stage of CKD	k (n)*	Exercise type	Mode	SMD or MD (95% CI)	Effect size	*P*	I^2	GRADE
VO_{2peak}										
Pei (2019)	RCT/quasi-RCT	Mixed	17(464)	AE	-	MD:2.08(1.10,3.05)	-	<0.001	25.0%	⊕⊕◯◯
Nakamura (2020)	RCT/cross-over	Predialysis	10(401)	Mixed	-	SMD:0.88(0.53,1.23)	Large	<0.001	56.0%	⊕⊕◯◯
Chen (2019)	RCT	KTRs	6(202)	Mixed	-	SMD:0.33(-0.02,0.69)	Small	0.06	27.0%	⊕◯◯◯
Andrade (2019)	RCT	HD	5(201)	AE+RT	Intradialytic	SMD:1.01(0.71,1.30)	Large	<0.001	0.0%	⊕⊕◯◯
Chung (2016)	RCT	HD	6(238)	Mixed	Intradialytic	SMD:0.55(0.18,0.92)	Moderate	0.003	52.9%	⊕◯◯◯
Pu (2019)	RCT	HD	10(400)	Mixed	Intradialytic	SMD:0.57(0.23,0.90)	Moderate	<0.001	59.0%	⊕⊕◯◯
Yamamoto (2021)	RCT	Predialysis	10(365)	AE	-	SMD:0.54(0.29,0.78)	Moderate	<0.001	24.6%	⊕◯◯◯
Yang (2017)	RCT	Mixed	5(179)	Mixed	-	SMD:0.33(0.03,0.63)	Small	0.003	47.0%	⊕⊕◯◯
Huang (2019)	RCT	HD	10(371)	Mixed	Mixed	SMD:0.73(0.52,0.95)	Moderate	<0.001	71.0%	⊕⊕◯◯
Matsuzawa (2017)	RCT	HD	18(582)	Mixed	Mixed	SMD:0.62(0.38,0.87)	Moderate	<0.001	49.0%	⊕⊕⊕⊕
Smart (2011)	RCT	HD	8(365)	Mixed	Mixed	SMD:0.75(0.39,1.11)	Moderate	<0.001	60.0%	⊕⊕◯◯
Bogataj (2020)	RCT	HD	20(504)	Mixed	Mixed	SMD:0.58(0.32,0.85)	Moderate	<0.001	57.4%	⊕◯◯◯
Sheng (2014)	RCT	HD	7(310)	Mixed	Intradialytic	SMD:0.53(0.30,0.76)	Moderate	<0.001	36.0%	⊕◯◯◯
Neto (2018)	RCT	HD	10(394)	Mixed	Intradialytic	SMD:0.60(0.15,1.04)	Moderate	0.008	76.0%	⊕◯◯◯
Ferrari (2019)	RCT	HD	5(201)	AE+RT	Intradialytic	MD:5.41(4.03,6.79)	-	<0.001	0.0%	⊕◯◯◯
Ferrari (2019)	RCT	HD	7(248)	AE	Intradialytic	MD:2.07(0.42,3.72)	-	<0.001	0.0%	⊕◯◯◯
Wyngaert (2018)	RCT	Predialysis	11(325)	AE	-	SMD:0.99(0.49,1.48)	Large	<0.001	74.0%	⊕◯◯◯
Oguchi (2018)	RCT	KTRs	4(182)	Mixed	-	SMD:0.38(-0.06,0.82)	Small	0.09	45.0%	⊕⊕◯◯
6MWT										

Pei (2019)	RCT/quasi-RCT	Mixed	8 (496)	AE	-	MD:0.04 (−0.52, 0.59)	-	0.90	86.0%	⊕◯◯◯
Nakamura (2020)	RCT/cross-over	Predialysis	5(392)	Mixed	-	SMD:1.04(0.17,1.90)	Large	0.02	92.0%	⊕◯◯◯
Lu (2019)	RCT	Dialysis	11(300)	Mixed	Mixed	SMD:0.52(0.31,0.72)	Moderate	<0.001	39.0%	⊕⊕⊕◯
Chung (2016)	RCT	HD	4(127)	Mixed	Intradialytic	SMD:0.44(0.09,0.80)	Small	0.015	0.0%	⊕⊕◯◯
Zhang (2021)	RCT	HD	8(299)	RT	Intradialytic	SMD:0.52(0.28,0.75)	Moderate	<0.001	18.7%	⊕⊕◯◯
Pu (2019)	RCT	HD	7(219)	Mixed	Intradialytic	SMD:0.57(0.30,0.84)	Moderate	<0.001	0.0%	⊕⊕◯◯
Clarkson (2019)	RCT	Dialysis	18(744)	Mixed	-	MD:33.64(23.74,43.54)	-	<0.001	0.0%	⊕⊕⊕◯
Huang (2019)	RCT	HD	7(205)	Mixed	Mixed	SMD:1.01(0.26,1.76)	Large	0.008	83.0%	⊕◯◯◯
Matsuzawa (2017)	RCT	HD	10(326)	Mixed	Mixed	SMD:0.58(0.24,0.93)	Moderate	<0.001	53.0%	⊕⊕◯◯
Bogataj (2020)	RCT	HD	19	Mixed	Mixed	SMD:0.44(0.21,0.67)	Small	<0.001	49.6%	⊕◯◯◯
Sheng (2014)	RCT	HD	4(146)	Mixed	Intradialytic	SMD:0.58(0.23,0.93)	Moderate	<0.001	89.7%	⊕◯◯◯
Neto (2018)	RCT	HD	6(158)	Mixed	Intradialytic	SMD:0.96(0.11,1.80)	Large	0.03	82.0%	⊕◯◯◯
Ferrari (2019)	RCT	HD	6(211)	RT	Intradialytic	MD:68.5(29.05,107.96)	-	<0.001	36.0%	⊕◯◯◯
Ferrari (2019)	RCT	HD	6(188)	AE	Intradialytic	MD:64.98(43.86,86.11)	-	<0.001	0.0%	⊕◯◯◯
Aerobic capacity										
Heiwe (2011)	RCT/quasi-RCT	Mixed	24(847)	Mixed	-	SMD:-0.56(-0.70,-0.42)	Moderate	<0.001	12.0%	⊕◯◯◯
Heiwe (2014)	RCT	HD	21(374)	Mixed	Mixed	SMD:-0.80(-1.02,-0.58)	Large	<0.001	0.0%	⊕⊕◯◯

Abbreviation: RCT = randomized controlled trial; AE = aerobic exercise; RT = resistance training; VO_{2peak} = peak oxygen uptake; 6MWT = 6 minutes walk test; SMD = standardized mean difference; MD = mean difference; HD = hemodialysis; KTRs = kidney transplant recipients; GRADE = Grading of Recommendations Assessment, Development, and Evaluation.

*Number of included studies and corresponding sample size.

Mixed means aerobic exercise combined with resistance training.

Table 3 Summary of the effect of exercise on muscle strength in CKD patients

Author(year)	Design	Stage of CKD	k (n)*	Exercise type	Mode	SMD or MD(95% CI)	Effect size	*P*	I^2	GRADE
Cheema (2014)	RCT	Predialysis	7(249)	RT	-	SMD:1.15(0.80,1.49)	Large	0.161	35.0%	⊕⊕◯◯
Nakamura (2020)	RCT/cross-over	Predialysis	4(119)	Mixed	-	SMD:0.35(-0.03,0.73)	Small	0.07	7.0%	⊕◯◯◯
Lu (2019)	RCT	Dialysis	5(234)	Mixed	Mixed	SMD:0.59(0.20,0.98)	Moderate	0.003	52.0%	⊕⊕◯◯
Lu (2019)	RCT	Dialysis	7(224)	Mixed	Mixed	SMD:0.47(0.20,0.74)	Small	<0.001	0.0%	⊕⊕◯◯
Zhang (2021)	RCT	HD	6(300)	RT	Intradialytic	SMD:0.35(0.12,0.58)	Small	0.003	41.6%	⊕⊕◯◯
Heiwe (2011)	RCT/quasi-RCT	Mixed	9(358)	Mixed	-	SMD:-0.52(-0.73,-0.31)	Moderate	<0.001	0.0%	⊕◯◯◯
Heiwe (2014)	RCT	HD	12(385)	Mixed	Mixed	SMD:-0.56(-0.77,-0.35)	Moderate	<0.001	0.0%	⊕◯◯◯
Matsuzawa (2017)	RCT	HD	9(281)	Mixed	Mixed	SMD:0.94(0.67,1.21)	Large	<0.001	10.0%	⊕◯◯◯
Neto (2018)	RCT	HD	9(250)	Mixed	Intradialytic	SMD:0.61(0.39,0.83)	Moderate	<0.001	58.9%	⊕◯◯◯
Ju (2020)	RCT	Mixed	3(115)	Mixed	-	SMD:0.52(0.14,0.89)	Moderate	0.007	0.0%	⊕◯◯◯

Abbreviation: RCT = randomized controlled trial; RT = resistance training; SMD = standardized mean difference; MD = mean difference; HD = hemodialysis; GRADE = Grading of Recommendations Assessment, Development, and Evaluation.

*Number of included studies and corresponding sample size.

Mixed means aerobic exercise combined with resistance training.

Table 4 Summary of the effect of exercise on muscle endurance in CKD patients

Author (year)	Design	Stage of CKD	k (n)*	Exercise type	Mode	Outcome	SMD or MD (95% CI)	Effect size	*P*	I^2	GRADE
Lu (2019)	RCT	Dialysis	3(193)	Mixed	Mixed	STS 10	MD:-4.69(-9.01,-0.38)	-	0.028	72.2%	⊕◯◯◯
Bogataj (2020)	RCT	HD	5(461)	Mixed	-	STS 10	SMD:-0.55(-1.00,-0.09)	Moderate	0.019	71.6%	⊕◯◯◯
Lu (2019)	RCT	Dialysis	6(240)	Mixed	Mixed	STS 30	SMD:0.43(0.17,0.69)	Small	0.001	2.0%	⊕⊕◯◯
Zhang (2021)	RCT	HD	5(164)	RT	Intradialytic	STS 30	SMD:0.42(0.11,0.74)	Small	0.008	0.0%	⊕◯◯◯
Sheng (2014)	RCT	HD	3(106)	Mixed	Intradialytic	STS 60	SMD:0.71(0.31,1.12)	Moderate	<0.001	0.0%	⊕◯◯◯
Pei (2019)	RCT/quasi-RCT	Mixed	5(445)	AE	-	STS 60	MD:2.08(1.1,3.05)	-	0.98	82.0%	⊕◯◯◯
Nakamura (2020)	RCT/cross-over	Predialysis	3(170)	Mixed	-	TUGT	SMD:-0.42(-0.73,-0.11)	Small	0.007	0.0%	⊕◯◯◯
Heiwe (2011)	RCT/quasi-RCT	Mixed	7(191)	Mixed	-	Walking capacity	SMD:-0.48(-0.79,-0.17)	Small	0.003	2.0%	⊕◯◯◯
Heiwe (2014)	RCT	HD	7(174)	Mixed	Mixed	Walking capacity	SMD:-0.33(-0.67,0.01)	Small	0.06	16.0%	⊕⊕⊕◯

Abbreviation: RCT = randomized controlled trial; AE = aerobic exercise; RT = resistance training; STS 10 = sit to stand 10 test; STS 30 = sit to stand 30 test; STS 60 = sit to stand 60 test; TUGT = timed up and go test; SMD = standardized mean difference; MD = mean difference; HD = hemodialysis; GRADE = Grading of Recommendations Assessment, Development, and Evaluation.

*Number of included studies and corresponding sample size.

Mixed means aerobic exercise combined with resistance training.

Table 5 Summary of the effect of exercise on body composition in CKD patients

Author (year)	Design	Stage of CKD	k (n)*	Exercise type	Mode	SMD (95% CI)	Effect size	*P*	I^2	GRADE
Chen (2019)	RCT	KTRs	4(166)	Mixed	-	SMD:0.02(-0.28,0.33)	Small	0.89	0.0%	⊕◯◯◯
Yamamoto (2021)	RCT	Predialysis	10(414)	AE	-	SMD:-0.19(-0.38,-0.00)	Small	0.026	0.0%	⊕⊕◯◯
Zhang (2019)	RCT	Predialysis	13(466)	Mixed	-	SMD:-0.21(-0.39,-0.03)	Small	0.02	0.0%	⊕⊕⊕◯
Wyngaert (2018)	RCT	Predialysis	9(294)	AE	-	SMD:-0.36(-0.60,-0.13)	Small	0.002	48.0%	⊕⊕◯◯

Abbreviation: RCT = randomized controlled trial; AE = aerobic exercise; SMD = standardized mean difference; KTRs = kidney transplant recipients;;GRADE = Grading of Recommendations Assessment, Development, and Evaluation.

*Number of included studies and corresponding sample size.

Mixed means aerobic exercise combined with resistance training.

Table 6 Summary of the effect of exercise on dialysis-related symptoms in CKD patients

Author (year)	Design	Stage of CKD	k (n)*	Exercise type	Mode	Outcomes	SMD or MD(95% CI)	Effect size	*P*	I^2	GRADE
Ferreira (2019)	RCT/quasi-RCT	HD	10(346)	AE	Intradialytic	Kt/V	SMD:2.21(1.17,3.25)	Large	<0.001	92.0%	⊕◯◯◯
Pu (2019)	RCT	HD	10(301)	Mixed	Intradialytic	Kt/V	SMD:0.29(0.06,0.52)	Small	0.01	0.0%	⊕◯◯◯
Huang (2019)	RCT	HD	8(257)	Mixed	Mixed	Kt/V	SMD:0.19(-0.06,0.43)	Small	0.14	0.0%	⊕◯◯◯
Sheng (2014)	RCT	HD	7(233)	Mixed	Intradialytic	Kt/V	SMD:0.27(0.01,0.53)	Small	0.04	0.0%	⊕◯◯◯
Ferrari (2019)	RCT	HD	12(370)	AE	Intradialytic	Kt/V	MD:0.08(0.0,0.15)	-	0.04	56.0%	⊕◯◯◯
Ferrari (2019)	RCT	HD	6(220)	RT	Intradialytic	Kt/V	MD:0.10(0.0,0.2)	-	0.06	6.0%	⊕◯◯◯
Song (2018)	RCT	HD	4(141)	Mixed	Mixed	RLS	SMD:-1.79(-2.21,-1.37)	Large	<0.001	87.0%	⊕◯◯◯
Song (2018)	RCT	HD	3(139)	Mixed	Mixed	Fatigue	SMD:-0.85(-1.20,-0.50)	Large	<0.001	0.0%	⊕◯◯◯
Zhao (2019)	RCT	Dialysis	3(141)	Mixed	-	Fatigue	SMD:-0.97(-1.32,-0.62)	Large	<0.001	47.0%	⊕⊕◯◯

Abbreviation: RCT = randomized controlled trial; AE = aerobic exercise; RT = resistance training; SMD = standardized mean difference; MD = mean difference; HD = hemodialysis; KTRs = kidney transplant recipients; RLS = Restless Legs Syndrome; GRADE = Grading of Recommendations Assessment, Development, and Evaluation.

*Number of included studies and corresponding sample size.

Mixed means aerobic exercise combined with resistance training.

Table 7 Summary of the effect of exercise on health-related quality of lifes in CKD patients

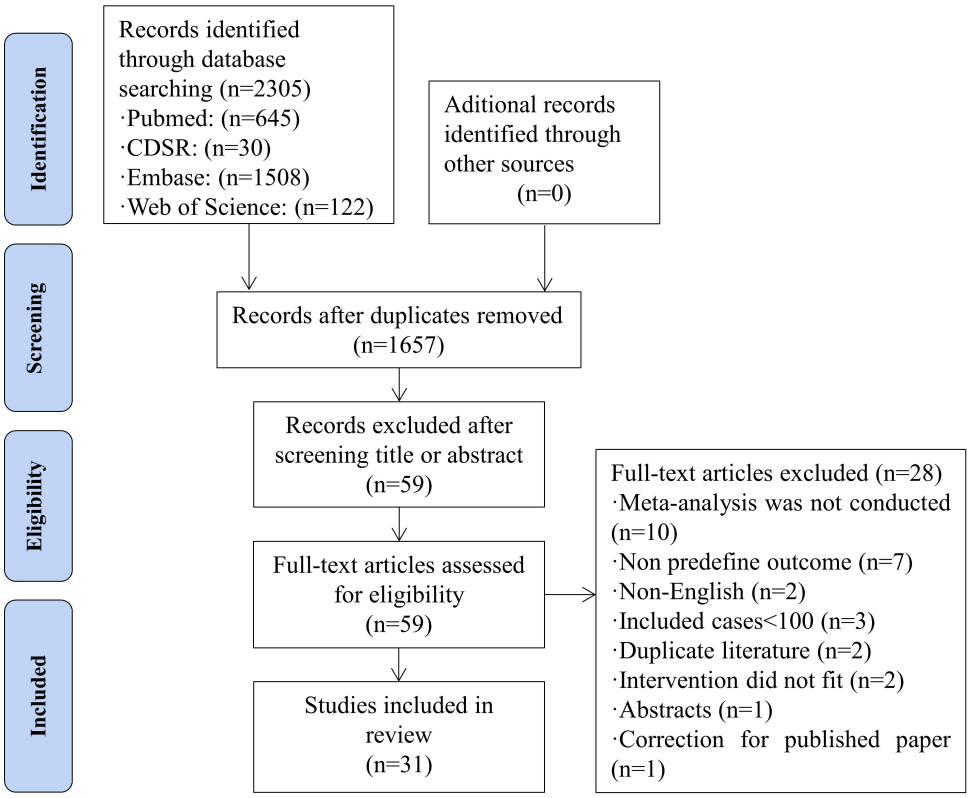
Author (year)	Design	Stage of CKD	k (n)*	Exercise type	Mode	Outcomes	SMD or MD (95% CI)	Effect size	*P*	I^2	GRADE
Salhab (2019)	RCT	HD	5(282)	AE	Intradialytic	PCS	SMD:1.82(-0.92,4.55)	Large	0.19	98.0%	⊕◯◯◯
Chung (2016)	RCT	HD	6(229)	Mixed	Intradialytic	PCS	SMD:0.46(0.20,0.73)	Small	<0.001	1.90%	⊕⊕◯◯
Zhang (2021)	RCT	HD	7(297)	RT	Intradialytic	PCS	SMD:0.23(-0.00,0.46)	Small	0.055	0.0%	⊕⊕◯◯
Pu (2019)	RCT	HD	10(320)	Mixed	Intradialytic	PCS	SMD:0.57(0.14,1.01)	Moderate	0.01	70.0%	⊕◯◯◯
Zhao (2019)	RCT	Dialysis	5(186)	Mixed	-	PCS	SMD:0.31(0.02,0.61)	Small	0.04	46.0%	⊕⊕◯◯
Huang (2019)	RCT	HD	7(263)	Mixed	Mixed	PCS	SMD:0.34(0.09,0.59)	Small	0.007	27.0%	⊕⊕◯◯
Matsuzawa (2017)	RCT	HD	9(264)	Mixed	Mixed	PCS	SMD:0.53(0.52,0.82)	Moderate	<0.001	19.0%	⊕◯◯◯
Sheng (2014)	RCT	HD	7(256)	Mixed	Intradialytic	PCS	SMD:0.30(0.05,0.55)	Small	0.02	39.5%	⊕◯◯◯
Neto (2018)	RCT	HD	7(187)	Mixed	Intradialytic	PCS	SMD:0.50(-0.19,1.18)	Moderate	0.16	62.0%	⊕◯◯◯
Salhab (2019)	RCT	HD	5(282)	AE	Intradialytic	MCS	SMD:1.02(0.31,1.73)	Large	0.005	75.0%	⊕◯◯◯
Chung (2016)	RCT	HD	5(193)	Mixed	Intradialytic	MCS	SMD:0.23(-0.05,0.52)	Small	0.109	0.0%	⊕⊕◯◯
Zhang (2021)	RCT	HD	7(297)	RT	Intradialytic	MCS	SMD:0.13(-0.10,0.36)	Small	0.082	46.5%	⊕⊕◯◯
Pu (2019)	RCT	HD	8(219)	Mixed	Intradialytic	MCS	SMD:0.19(-0.09,0.46)	Small	0.18	30.0%	⊕⊕◯◯
Zhao (2019)	RCT	Dialysis	5(186)	Mixed	-	MCS	SMD:0.30(-0.20,0.80)	Small	0.24	64.0%	⊕◯◯◯
Huang (2019)	RCT	HD	7(263)	Mixed	Mixed	MCS	SMD:0.27(0.02,0.51)	Small	0.03	0.0%	⊕⊕◯◯
Matsuzawa (2017)	RCT	HD	8(228)	Mixed	Mixed	MCS	SMD:0.14(-0.15,0.42)	Small	0.34	10.0%	⊕◯◯◯
Sheng (2014)	RCT	HD	5(167)	Mixed	Intradialytic	MCS	SMD:0.14(-0.16,0.43)	Small	0.37	14.8%	⊕◯◯◯
Neto (2018)	RCT	HD	7(185)	Mixed	Intradialytic	MCS	SMD:0.39(-0.19,0.98)	Small	0.19	50.0%	⊕◯◯◯
Pei (2019)	RCT/quasi-RCT	Mixed	6(522)	AE	-	Physical function (SF-36)	MD:8.36(-1.24,17.95)	-	0.09	76.0%	⊕◯◯◯

Pei (2019)	RCT/quasi-RCT	Mixed	7(562)	AE	-	Physical role (SF-36)	MD:14.65(1.47,27.84)	-	0.03	78.0%	⊕◯◯◯
Pei (2019)	RCT/quasi-RCT	Mixed	6(447)	AE	-	Social function (SF-36)	MD:8.24(-1.09,17.58)	-	0.08	85.0%	⊕◯◯◯
Pei (2019)	RCT/quasi-RCT	Mixed	6(513)	AE	-	Pain (SF-36)	MD:5.94(1.65,10.23)	-	0.007	49.0%	⊕◯◯◯
Pei (2019)	RCT/quasi-RCT	Mixed	7(562)	AE	-	General health (SF-36)	MD:8.90(2.48,15.32)	-	0.007	71.0%	⊕◯◯◯
Pei (2019)	RCT/quasi-RCT	Mixed	6(542)	AE	-	Mental health (SF-36)	MD:7.30(-0.94,15.54)	-	0.08	84.0%	⊕◯◯◯
Cheema (2014)	RCT	Predialysis	6 (223)	RT	-	HRQOL	SMD:0.83(0.51,1.16)	Large	0.226	27.8%	⊕⊕◯◯
Oguchi (2018)	RCT	KTRs	4(179)	Mixed	-	HRQOL	SMD:0.54(0.02,1.07)	Moderate	0.04	58.0%	⊕◯◯◯
Ju (2020)	RCT	Mixed	3 (387)	Mixed	-	Symptom/problem (KDQOL)	SMD:1.92(-1.06,4.90)	Large	0.21	99.0%	⊕◯◯◯
Ju (2020)	RCT	Mixed	3 (387)	Mixed	-	Effects of kidney disease (KDQOL)	SMD:-3.69(-8.56,1.19)	Large	0.14	99.0%	⊕◯◯◯
Ju (2020)	RCT	Mixed	3 (387)	Mixed	-	Burden of kidney disease (KDQOL)	SMD:1.04 (-0.75,2.82)	Large	0.26	98.0%	⊕◯◯◯

Abbreviation: RCT = randomized controlled trial; AE = aerobic exercise; RT = resistance training; COM = combine; HRQOL = health-related quality of life; PCS = physical component summary; MCS = mental component summary; SMD = standardized mean difference; MD = mean difference; HD = hemodialysis; KTRs = kidney transplant recipients; SF-36 = Short-Form Health Survey-36; KDQOL = kidney disease quality of life; GRADE = Grading of Recommendations Assessment, Development, and Evaluation.

*Number of included studies and corresponding sample size.

Mixed means aerobic exercise combined with resistance training.



Figures 1 Flowchart of literature screening.

CDSR = Cochrane Database of Systemic Review

Supplementary Table S1 The detailed search strategy

Databases	#	Search strategy
Pubmed	1	"renal insufficiency, chronic"[MeSH Terms]
	2	"chronic renal insufficiency"[Title/Abstract] or "chronic kidney insufficiency"[Title/Abstract] or "chronic kidney disease"[Title/Abstract] or "chronic renal disease"[Title/Abstract]
	3	"CKD"[Title/Abstract] or "CKF"[Title/Abstract] or "CRD"[Title/Abstract] or "CRF"[Title/Abstract]
	4	"end-stage kidney"[Title/Abstract] or "end-stage renal"[Title/Abstract] or "endstage kidney"[Title/Abstract] or "endstage renal"[Title/Abstract]
	5	"ESRD"[Title/Abstract] or "ESRF"[Title/Abstract] or "ESKD"[Title/Abstract] or "ESKF"[Title/Abstract]
	6	"Renal Replacement Therapy"[MeSH Terms]
	7	"dialysis"[Title/Abstract]
	8	"hemodialysis"[Title/Abstract] or "haemodialysis"[Title/Abstract] or "hemodiafiltration"[Title/Abstract] or "haemodiafiltration"[Title/Abstract] or "HD"[Title/Abstract]
	9	"PD"[Title/Abstract]
	10	"renal transplantation"[Title/Abstract] or "kidney grafting"[Title/Abstract] or "kidney transplantation"[Title/Abstract]
	11	"KTRs"[Title/Abstract]
	12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
	13	"Exercise"[MeSH Terms]
	14	"Exercise Movement Techniques"[MeSH Terms]
	15	"Exercise Therapy"[MeSH Terms]
	16	"Sports"[MeSH Terms]
	17	"train"[Title/Abstract] or "physical activity"[Title/Abstract] or "exercise"[Title/Abstract]
	18	#13 or #14 or #15 or #16 or #17
	19	"Systematic Review"[Publication Type] or "Systematic Reviews as Topic"[MeSH Terms]
	20	"meta analysis"[Publication Type] or "Meta-Analysis as Topic"[MeSH Terms]

	21	"Systematic Review"[Title/Abstract] or "system review"[Title/Abstract] or "data pooling"[Title/Abstract] or "meta"[Title/Abstract]
	22	#19 or #20 or #21
	23	#12 and #18 and #22
CDSR	1	MeSH descriptor: [Kidney Diseases] explode all trees
	2	("chronic kidney disease") or ("chronic renal disease") or ("chronic kidney failure") or ("chronic renal failure"):ti,ab,kw
	3	(CKF or CKD or CRF or CRD):ti,ab,kw
	4	("end-stage kidney") or ("end-stage renal") or ("endstage kidney") or ("endstage renal"):ti,ab,kw
	5	ESRD or ESRF or ESKD or ESKF:ti,ab,kw
	6	MeSH descriptor: [Renal Replacement Therapy] explode all trees
	7	dialysis:ti,ab,kw
	8	(hemodialysis or haemodialysis or hemodiafiltration or haemodiafiltration or HD):ti,ab,kw
	9	PD:ti,ab,kw
	10	("renal transplantation") or ("kidney grafting") or ("kidney transplantation"):ti,ab,kw
	11	KTRs:ti,ab,kw
	12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
	13	MeSH descriptor: [Exercise] explode all trees
	14	MeSH descriptor: [Exercise Movement Techniques] explode all trees
	15	MeSH descriptor: [Exercise Therapy] explode all trees
	16	MeSH descriptor: [Sports] explode all trees
	17	(train or ("physical activity") or exercise):ti,ab,kw
	18	#13 or #14 or #15 or #16 or #17
	19	MeSH descriptor: [Meta-Analysis as Topic] explode all trees
	20	MeSH descriptor: [Systematic Reviews as Topic] explode all trees
	21	("systematic review") or ("system review") or ("data pooling") or (meta):ti,ab,kw
	22	#19 or #20 or #21

	23	#12 and #18 and #22
Embase	1	'kidney disease'/exp
	2	('chronic kidney disease' or 'chronic renal disease' or 'chronic kidney failure' or 'chronic renal failure'):ti,ab,kw
	3	(CKF or CKD or CRFor CRD):ti,ab,kw
	4	('end-stage kidney' or 'end-stage renal' or 'endstage kidney' or 'endstage renal'):ti,ab,kw
	5	(ESRD or ESRF or ESKD or ESKF):ti,ab,kw
	6	'renal replacement therapy'/exp
	7	'dialysis':ti,ab,kw
	8	(hemodialysis or haemodialysis or hemofiltration or haemofiltration or hemodiafiltration or haemodiafiltration or HD):ti,ab,kw
	9	PD:ti,ab,kw
	10	('renal transplantation' or 'kidney grafting' or 'kidney transplantation'):ti,ab,kw
	11	KTRs:ti,ab,kw
	12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
	13	'exercise'/exp
	14	'physical activity'/exp
	15	'sport'/exp
	16	(train or 'physical activity' or exercise):ti,ab,kw
	17	#13 or #14 or #15 or #16
	18	'systematic review (topic)'/exp or 'systematic review'/exp
	19	'meta analysis (topic)'/exp or 'meta analysis'/exp
	20	('systematic review' or 'system review' or 'data pooling' or meta):ti,ab,kw
	21	#18 or #19 or #20
	22	#12 and #17 and #21
Web of Science	1	TS: ("chronic kidney disease" or "chronic renal disease" or "chronic kidney failure" or "chronic renal failure" or CKD or CRD or CKF or CRF)

	2	TS: ("end-stage kidney" or "end-stage renal" or "endstage kidney" or "endstage renal" or ESKD or ESKF or ESRD or ESRF)
	3	TS: ("renal replacement therapy" or dialysis or hemodialysis or haemodialysis or hemofiltration or haemofiltration or hemodiafiltration or haemodiafiltration or HD or PD)
	4	TS: ("renal transplantation" or "kidney grafting" or "kidney transplantation" or KTRs)
	5	#1 or #2 or #3 or #4
	6	TS: (train or exercise or "physical activity")
	7	TS: ("systematic review" or "system review" or "data pooling" or meta)
	8	#1 and #2 and #3 and #4 and #5

Supplementary Table S2 The characteristic of excluded studies

Studies	Reasons for exclusion
Nantakool et al (2020)	Non predefine outcome
Sawant et al (2014)	Non predefine outcome
Smart et al (2014)	Duplicate literature
Barcellos et al (2015)	Meta-analysis was not conducted
Yang et al (2020)	Non predefine outcome
Young et al (2018)	Included cases<100
Phan et al (2015)	Duplicate literature
Molsted et al (2019)	Included cases<100
Segura et al (2010)	Non-English
Ferreira et al (2020)	Non predefine outcome
Koufaki et al (2013)	Meta-analysis was not conducted
Smart et al (2012)	Abstracts
Howden et al (2012)	Meta-analysis was not conducted
Calella et al (2019)	Meta-analysis was not conducted
Singh et al (2005)	Meta-analysis was not conducted
Cardoso et al (2020)	Non predefine outcome
Villanego et al (2020)	Non-English
Medeiros et al (2017)	Intervention did not fit
Macdonald et al (2009)	Meta-analysis was not conducted
Wen et al (2019)	Non predefine outcome
Yang et al (2015)	Non predefine outcome
Thangarasa et al (2018)	Included cases<100
Chan et al (2016)	Meta-analysis was not conducted

Johansen et al (2010)	Intervention did not fit
Thompson et al (2020)	Correction for published paper
Bakaloudi et al (2020)	Meta-analysis was not conducted
Kirkman et al (2019)	Meta-analysis was not conducted
Afsar et al (2018)	Meta-analysis was not conducted

Supplementary Table S3 The basic characteristics of the included meta-analyses

Author (year)	Design	Stage of CKD	k (n)*	Exercise type	Mode	Outcomes	SMD or MD(95% CI)	Effect size	*P*	I^2	GRADE
Pei (2019)	RCT/quasi-RCT	Mixed	17(464)	AE	-	VO_{2peak}	MD:2.08 (1.1,3.05)	-	<0.001	25.0%	Low
			5 (445)			STS 60	MD:2.08 (1.1,3.05)	-	0.98	82.0%	Very low
			8 (496)			6MWT	MD:0.04 (−0.52, 0.59)	-	0.9	86.0%	Very low
			12(514)			SBP	MD:−2.91 (−6.68, 0.87)	-	0.13	40.0%	Low
			12(514)			DBP	MD:−1.11 (−3.41, 1.20)	-	0.35	0.0%	Low
			6(522)			Physical function (SF-36)	MD:8.36(-1.24,17.95)	-	0.09	76.0%	Very low
			7(562)			Physical role (SF-36)	MD:14.65(1.47,27.84)	-	0.03	78.0%	Very low
			6(447)			Social function (SF-36)	MD:8.24(-1.09,17.58)	-	0.08	85.0%	Very low
			6(513)			Pain (SF-36)	MD:5.94(1.65,10.23)	-	0.007	49.0%	Very low
			7(562)			General health (SF-36)	MD:8.90(2.48,15.32)	-	0.007	71.0%	Very low
			6(542)			Mental health (SF-36)	MD:7.30(-0.94,15.54)	-	0.08	84.0%	Very low
Ferreira (2019)	RCT/quasi-RCT	HD	10(346)	AE	Intradialytic	Kt/V	SMD:2.21(1.17,3.25)	Large	<0.001	92.0%	Very low
Cheema (2014)	RCT	Predialysis	7(249)	RT	-	Muscle Strength	SMD:1.15（0.80-1.49）	Large	0.161	35.0%	Low
			6(223)			HRQoL	SMD:0.83(0.51-1.16)	Large	0.226	27.8%	Low
Wu (2020)	RCT/quasi-RCT	Predialysis	3(204)	AE+RT	-	SBP	SMD:-0.19(-0.46,0.08)	Small	0.16	50.0%	Very low
			4(194)			DBP	SMD:-0.47(-1.10,0.15)	Small	0.14	70.0%	Very low

Nakamura (2020)	RCT/cross-over	Predialysis	10(401)	Mixed	-	VO_{2peak}	SMD:0.88(0.53,1.23)	Large	<0.001	56.0%	Low
			4(119)			Muscle Strength	SMD:0.35(-0.03,0.73)	Small	0.07	7.0%	Very low
			5(392)			6MWT	SMD:1.04(0.17,1.90)	Large	0.02	92.0%	Very low
			3(170)			TUGT	SMD:-0.42(-0.73,-0.11)	Small	0.007	0.0%	Very low
Lu (2019)	RCT	Dialysis	11(300)	Mixed	Mixed	6MWT	MD:67.6(49.93,85.26)	-	<0.001	30.6%	Moderate
			3(193)			STS 10	MD:-4.69(-9.01,-0.38)	-	0.028	72.2%	Very low
			5(234)			HGS	MD:5.35(3.34,7.37)	-	<0.001	0.3%	Low
			7(224)			Muscle strength	MD:3.67(1.37,5.97)	-	0.020	38.6%	Low
			6(240)			STS 30	MD:2.43(0.91,3.96)	-	0.002	21.2%	Low
Chen (2019)	RCT	KTRs	5(198)	Mixed	-	SBP	SMD:0.18(-0.10,0.46)	Small	0.21	0.0%	Very low
			5(198)			DBP	SMD:0.04(-0.45,0.52)	Small	0.89	59.0%	Very low
			4(166)			BMI	SMD:0.02(-0.28,0.33)	Small	0.89	0.0%	Very low
			6(202)			VO_{2peak}	SMD:0.33(-0.02,0.69)	Small	0.06	27.0%	Very low
Song (2018)	RCT	HD	4(141)	Mixed	Mixed	RLS	SMD:-1.79(-2.21,-1.37)	Large	<0.001	87.0%	Very low
			3(139)			Fatigue	SMD:-0.85(-1.20,-0.50)	Large	<0.001	0.0%	Very low
Salhab (2019)	RCT	HD	5(282)	AE	Intradialytic	PCS	SMD:1.82(-0.92,4.55)	Large	0.19	98.0%	Very low
			5(282)			MCS	SMD:1.02(0.31,1.73)	Large	0.005	75.0%	Very low
Andrade (2019)	RCT	HD	5(201)	AE+RT	Intradialytic	VO_{2peak}	SMD:1.01(0.71,1.30)	Large	<0.001	0.0%	Low
Chung (2016)	RCT	HD	4(127)	Mixed	Intradialytic	6MWT	SMD:0.44(0.09,0.80)	Small	0.015	0.0%	Low
			6(238)			VO_{2peak}	SMD:0.55(0.18,0.92)	Moderate	0.003	52.9%	Very low
			6(229)			PCS	SMD:0.46(0.20,0.73)	Small	<0.001	1.90%	Low
			5(193)			MCS	SMD:0.23(-0.05,0.52)	Small	0.109	0.0%	Low
Zhang (2021)	RCT	HD	8(299)	RT	Intradialytic	6MWT	SMD:0.52(0.28,0.75)	Moderate	<0.001	18.7%	Very low
			5(164)			STS 30	SMD:0.42(0.11,0.74)	Small	0.008	0.0%	Very low

			6(300)			HGS	SMD:0.35(0.12,0.58)	Small	0.003	41.6%	Very low
			7(297)			PCS	SMD:0.23(-0.00,0.46)	Small	0.055	0.0%	Very low
			7(297)			MCS	SMD:0.13(-0.10,0.36)	Small	0.082	46.5%	Very low
Pu (2019)	RCT	HD	10(301)	Mixed	Intradialytic	Kt/V	SMD:0.29(0.06,0.52)	Small	0.01	0.0%	Very low
			10(400)			VO_{2peak}	SMD:0.57(0.23,0.90)	Moderate	<0.001	59.0%	Low
			7(219)			6MWT	SMD:0.57(0.30,0.84)	Moderate	<0.001	0.0%	Low
			10(320)			PCS	SMD:0.57(0.14,1.01)	Moderate	0.01	70.0%	Very low
			8(219)			MCS	SMD:0.19(-0.09,0.46)	Small	0.18	30.0%	Low
			7(287)			SBP	SMD:-0.28(-0.52,-0.05)	Small	0.02	0.0%	Very low
			7(287)			DBP	SMD:-0.32(-0.55,-0.08)	Small	0.008	42.0%	Very low
Yamamoto (2021)	RCT	Predialysis	10(392)	AE	-	SBP	SMD:-0.75(-1.24,-0.26)	Moderate	0.003	80.3%	Very low
			10(365)			VO_{2peak}	SMD:0.54(0.29,0.78)	Moderate	<0.001	24.6%	Very low
			10(414)			BMI	SMD:-0.19(-0.38,-0.00)	Small	0.026	0.0%	Low
Thompson (2019)	RCT	Predialysis	10(335)	Mixed	-	SBP	MD:-4.3(-9.0,0.4)	-	N.P.	50.4%	Very low
			8(303)			DBP	MD:-1.18(-4.76,2.40)	-	N.P.	60.5%	Very low
Yang (2017)	RCT	Mixed	4(150)	Mixed	-	VO_{2peak}	SMD:0.33(0.03,0.63)	Small	0.003	47.0%	Low
Clarkson (2019)	RCT	Dialysis	18(744)	Mixed	-	6MWT	MD:33.64(23.74,43.54)	-	<0.001	0.0%	Moderate
Zhao (2019)	RCT	Dialysis	3(141)	Mixed	-	Fatigue	SMD:-0.97(-1.32,-0.62)	Large	<0.001	47.0%	Low
			5(186)			PCS	SMD:0.31(0.02,0.61)	Small	0.04	46.0%	Low
			5(186)			MCS	SMD:0.30(-0.20,0.80)	Small	0.24	64.0%	Very low
Zhang (2019)	RCT	Predialysis	14(463)	Mixed	-	SBP	SMD:-0.41(-0.70,-0.11)	Small	0.007	55.0%	Moderate
			12(399)			DBP	SMD:-0.31(-0.71,0.08)	Small	0.12	70.0%	Low
			13(466)			BMI	SMD:-0.21(-0.39,-0.03)	Small	0.02	0.0%	Moderate

Huang (2019)	RCT	HD	8(257)	Mixed	-	Kt/V	SMD:0.19(-0.06,0.43)	Small	0.14	0.0%	Very low
			7(260)			SBP	SMD:-0.17(-0.41,0.08)	Small	0.18	8.0%	Low
			7(260)			DBP	SMD:-0.23(-0.69,0.24)	Small	0.34	68.0%	Very low
			7(205)			6MWT	SMD:1.01(0.26,1.76)	Large	0.008	83.0%	Very low
			7(263)			PCS	SMD:0.34(0.09,0.59)	Small	0.007	27.0%	Low
			7(263)			MCS	SMD:0.27(0.02,0.51)	Small	0.03	0.0%	Low
			10(371)			VO_{2peak}	SMD:0.73(0.52,0.95)	Moderate	<0.001	71.0%	Low
Heiwe (2011)	RCT/quasi-RCT	Mixed	24(847)	Mixed	-	Aerobic capacity	SMD:-0.56(-0.70,-0.42)	Moderate	<0.001	12.0%	Moderate
			9(358)			Muscle strength	SMD:-0.52(-0.73,-0.31)	Moderate	<0.001	0.0%	Low
			7(191)			Walking capacity	SMD:-0.48(-0.79,-0.17)	Small	0.003	2.0%	Low
			9(347)			SBP	SMD:0.25(0.04,0.47)	Small	0.02	0.0%	Low
			11(419)			DBP	SMD:0.16(-0.04,0.36)	Small	0.11	40.0%	High
Heiwe (2014)	RCT	HD	21(374)	Mixed	-	Aerobic capacity	SMD:-0.80(-1.02,-0.58)	Large	<0.001	0.0%	Low
			10(212)			DBP	SMD:0.17(-0.16,0.49)	Small	0.3	45.0%	Low
			10(312)			SBP	SMD:0.04(-0..4,0.41)	Small	0.8	58.0%	Very low
			10(385)			Muscle strength	SMD:-0.56(-0.77,-0.35)	Moderate	<0.001	0.0%	Very low
			7(174)			Walking capacity	SMD:-0.33(-0.67,0.01)	Small	0.06	16.0%	Low
Matsuzawa (2017)	RCT	HD	18(582)	Mixed	-	VO_{2peak}	SMD:0.62(0.38,0.87)	Moderate	<0.001	49.0%	High
			10(326)			6MWT	SMD:0.58(0.24,0.93)	Moderate	<0.001	53.0%	Low
			9(281)			Muscle strength	SMD:0.94(0.67,1.21)	Large	<0.001	10.0%	Very low
			9(264)			PCS	SMD:0.53(0.52,0.82)	Moderate	<0.001	19.0%	Very low
			8(228)			MCS	SMD:0.14(-0.15,0.42)	Small	0.34	10.0%	Very low
Smart (2011)	RCT	HD	8(365)	Mixed	-	VO_{2peak}	SMD:0.75(0.39,1.11)	Moderate	<0.001	60.0%	Low
Bogataj	RCT	HD	19(571)	Mixed	-	6MWT	SMD:0.44(0.21,0.67)	Small	<0.001	49.6%	Very low

(2020)			20(504)			VO_{2peak}	SMD:0.58(0.32,0.85)	Moderate	<0.001	57.4%	Very low
			5(461)			STS 10	SMD:-0.55(-1.00,-0.09)	Moderate	0.019	71.6%	Very low
Sheng (2014)	RCT	HD	7(233)	Mixed	Intradialytic	Kt/V	SMD:0.27(0.01,0.53)	Small	0.040	0.0%	Very low
			7(310)			VO_{2peak}	SMD:0.53(0.30,0.76)	Moderate	<0.001	36.0%	Very low
			7(256)			PCS	SMD:0.30(0.05,0.55)	Small	0.02	39.5%	Very low
			5(167)			MCS	SMD:0.14(-0.16,0.43)	Small	0.37	14.8%	Very low
			4(146)			6MWT	SMD:0.58(0.23,0.93)	Moderate	<0.001	89.7%	Very low
			7(296)			DBP	SMD:-0.24(-0.47,-0.01)	Small	0.04	52.1%	Very low
			7(296)			SBP	SMD:-0.27(-0.50,-0.04)	Small	0.02	0.0%	Very low
			3(106)			STS 60	SMD:0.71(0.31,1.12)	Moderate	<0.001	0.0%	Very low
Neto (2018)	RCT	HD	10(394)	Mixed	Intradialytic	VO_{2peak}	SMD:0.60(0.15,1.04)	Moderate	0.008	76.0%	Very low
			7(187)			PCS	SMD:0.50(-0.19,1.18)	Moderate	0.16	62.0%	Very low
			7(185)			MCS	SMD:0.39(-0.19,0.98)	Small	0.19	50.0%	Very low
			6(158)			6MWT	SMD:0.96(0.11,1.80)	Large	0.03	82.0%	Very low
			9(250)			Muscle strength	SMD:0.61(0.39,0.83)	Moderate	<0.001	58.9%	Very low
Ferrari (2019)	RCT	HD	12(370)	AE	Intradialytic	Kt/V	MD:0.08(0,0.15)	-	0.04	56.0%	Low
			6(220)	RT		Kt/V	MD:0.1(0,0.2)	-	0.06	6.0%	Very low
			5(201)	COM		VO_{2peak}	MD:5.41(4.03,6.79)	-	<0.001	0.0%	Low
			7(248)	AE		VO_{2peak}	MD:2.07(0.42,3.72)	-	<0.001	0.0%	Very low
			6(211)	RT		6MWT	MD:68.5(29.05,107.96)	-	<0.001	36.0%	Low
			6(188)	AE		6MWT	MD:64.98(43.86,86.11)	-	<0.001	0.0%	Low
			10(332)	AE		SBP	MD:-10.07(16.35,-3.78)	-	0.002	44.0%	Low
			10(334)	AE		DBP	MD:-2.96(-7.71,1.78)	-	0.22	0.0%	Low
Wyngaert (2018)	RCT	Predialysis	8(269)	AE	-	SBP	SMD:0.08(-0.58,0.74)	Small	0.81	84%	Very low
			7(237)			DBP	SMD:-0.09(-0.78,0.59)	Small	0.79	83%	Very low

			11(325)			VO_{2peak}	SMD:0.99(0.49,1.48)	Large	<0.001	74.0%	Very low
			9(294)			BMI	SMD:-0.36(-0.60,-0.13)	Small	0.002	48.0%	Low
Oguch (2018)	RCT	KTRs	4(182)	Mixed	-	VO_{2peak}	SMD:0.38(-0.06,0.82)	Small	0.09	45.0%	Low
			4(179)			HRQoL	SMD:0.54(0.02,1.07)	Moderate	0.04	58.0%	Very low
Ju (2020)	RCT		3 (115)	Mixed	-	HGS	SMD:0.52(0.14,0.89)	Moderate	0.007	0.0%	Very low
			3 (387)			Symptom/problem (KDQoL)	SMD:1.92(-1.06,4.90)	Large	0.21	99.0%	Very low
			3 (387)			Effects of kidney disease (KDQoL)	SMD:-3.69(-8.56,1.19)	Large	0.14	99.0%	Very low
			3 (387)			Burden of kidney disease (KDQoL)	SMD:1.04 (-0.75,2.82)	Large	0.26	98.0%	Very low

Abbreviation: RCT = randomized controlled trial; AE = aerobic exercise; RT = resistance training; COM = combine; VO_{2peak} = peak oxygen uptake; HRQoL = health-related quality of life; DBP = diastolic blood pressure; SBP = systolic blood pressure; PCS = physical component summary; MCS = mental component summary; 6MWT = 6 minutes walk test; STS 10 = sit to stand 10 test; STS 30 = sit to stand 30 test; STS 60 = sit to stand 60 test; TUGT = timed up and go test; RLS = Restless Legs Syndrome; BMI = body mass index; SMD = standardized mean difference; MD = mean difference; HD = hemodialysis; KTRs = kidney transplant recipients; SF-36 = short form-36; KDQoL = kidney disease quality of life; GRADE = Grading of Recommendations Assessment, Development, and Evaluation.

*Number of included studies and corresponding sample size.

Mixed means aerobic exercise combined with resistance training.

Supplementary Table S4 Results of the assessment of the methodological quality of the included meta-analyses using AMSTAR-2

Author	AMSTAR-2 Items																Score
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Pei(2019)	√	×	√	○	√	√	×	√	√	×	√	×	×	×	√	×	53.1%
Ferreira(2019)	√	√	√	○	√	√	×	○	√	×	√	×	×	×	×	×	50.0%
Cheema(2014)	√	×	√	√	√	√	√	√	√	×	√	√	√	√	√	√	87.5%
Wu(2020)	√	√	√	○	√	√	×	√	√	×	√	√	√	√	√	√	84.4%
Nakamura(2020)	√	√	√	○	√	√	×	√	√	×	√	√	√	√	√	√	84.4%
Lu(2019)	√	×	√	○	√	×	×	○	○	×	√	×	×	×	√	√	46.9%
Chen(2019)	√	×	√	○	×	√	×	√	○	×	√	×	×	×	×	√	43.8%
Song(2018)	√	×	√	○	√	√	×	√	√	×	√	×	√	√	√	√	71.9%
Salhab(2021)	√	√	√	○	√	√	×	√	×	×	√	×	×	√	×	×	53.1%
Andrade(2019)	√	√	√	○	√	√	×	√	√	×	√	×	×	√	×	√	65.6%
Chung(2016)	√	×	√	○	√	√	√	√	√	×	√	√	√	√	√	×	78.1%
Zhang(2019)	√	×	√	○	√	√	×	√	√	×	√	×	√	√	√	×	65.6%
Pu(2019)	√	×	√	○	√	√	×	√	√	×	√	√	√	√	×	√	71.9%
Yamamoto(2021)	√	×	√	×	√	√	×	○	√	×	√	√	√	√	√	√	71.9%
Thompson(2019)	√	×	√	○	√	√	×	√	√	√	√	√	√	√	√	√	84.4%
Yang(2017)	√	×	√	○	√	√	×	○	√	×	√	√	√	√	√	√	75.0%
Clarkson(2019)	√	×	√	○	√	√	×	√	√	×	√	√	√	√	√	√	78.1%
Zhao(2019)	√	×	√	○	√	√	×	√	√	×	√	×	√	×	×	√	59.4%
Zhang(2019)	√	×	√	○	√	√	×	○	√	×	√	√	×	×	√	√	62.5%
Huang(2019)	√	√	√	○	√	√	×	√	√	×	√	√	×	×	√	√	71.9%
Heiwe(2011)	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	100.0%
Heiwe(2014)	√	√	√	○	√	√	√	√	√	×	√	×	√	√	×	√	78.1%

Matsuzawa(2017)	√	√	√	○	√	√	×	√	√	×	√	×	×	√	√	√	71.9%
Smart(2011)	√	×	√	○	√	×	×	○	○	×	√	×	×	√	×	×	40.6%
Bogataj(2020)	√	×	√	○	√	×	×	√	√	×	√	√	×	√	×	√	59.4%
Sheng(2014)	√	×	√	○	√	√	√	√	√	×	√	×	×	√	√	×	65.6%
Neto(2018)	√	×	√	○	√	√	×	√	√	×	√	×	×	×	×	√	53.1%
Ferrari(2019)	√	√	√	○	√	√	√	√	√	×	√	√	√	√	√	√	90.6%
Wyngaert(2018)	√	√	√	○	√	√	×	√	√	×	√	√	√	√	√	√	84.4%
Oguchi(2018)	√	√	√	○	√	√	×	√	√	×	√	√	√	×	√	×	71.9%
Ju(2020)	√	×	√	○	×	×	×	√	√	×	√	×	×	×	×	×	34.4%

√ mean yes; ○ mean partial yes; ×mean no.

1. Did the research questions and inclusion criteria for the review include the components of PICO? 2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? 3. Did the review authors explain their selection of the study designs for inclusion in the review? 4. Did the review authors use a comprehensive literature search strategy? 5. Did the review authors perform study selection in duplicate? 6. Did the review authors perform data extraction in duplicate? 7. Did the review authors provide a list of excluded studies and justify the exclusions? 8. Did the review authors describe the included studies in adequate detail? 9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? 10. Did the review authors report on the sources of funding for the studies included in the review? 11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? 12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? 13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review? 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? 15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? 16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

Supplementary Table S5: Results of the assessment of the quality of evidence for each outcome of the included meta-analyses using GRADE

Author	Outcome	GRADE items					Quality of the evidence
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	
Pei (2019)	VO_{2peak}	Very serious (-2)	Neutral	Neutral	Neutral	Neutral	Moderate
	STS 60	Serious (-1)	Very serious (-2)	Neutral	Neutral	Serious (-1)	Very low
	6MWT	Serious (-1)	Very serious (-2)	Neutral	Neutral	Serious (-1)	Very low
	SBP	Serious (-1)	Neutral	Neutral	Neutral	Not reported (-1)	Moderate
	DBP	Serious (-1)	Neutral	Neutral	Neutral	Not reported (-1)	Moderate
	Physical function (SF-36)	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Serious (-1)	Very low
	Physical role (SF-36)	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Serious (-1)	Very low
	Social function (SF-36)	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Serious (-1)	Very low
	Pain (SF-36)	Serious (-1)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	General health (SF-36)	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Serious (-1)	Very low
	Mental health (SF-36)	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Serious (-1)	Very low
Ferreira (2019)	Kt/V	Very serious (-2)	Very serious (-2)	Neutral	Serious (-1)	Not reported (-1)	Very low
Cheema (2014)	Muscle Strength	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
	HRQoL	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
Wu (2020)	SBP	Very serious (-2)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	DBP	Very serious (-2)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low

Nakamura (2020)	VO_{2peak}	Neutral	Serious (-1)	Neutral	Neutral	Serious (-1)	Moderate
	Muscle Strength	Very serious (-2)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	6MWT	Neutral	Very serious (-2)	Neutral	Serious (-1)	Serious (-1)	Very low
	TUGT	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
Lu (2019)	6MWT	Neutral	Neutral	Neutral	Serious (-1)	Neutral	Moderate
	STS 10	Neutral	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	HGS	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
	Muscle strength	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
	STS 30	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
Chen (2019)	SBP	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	DBP	Serious (-1)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	BMI	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	VO_{2peak}	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
Song (2018)	RLS	Serious (-1)	Serious (-1)	Neutral	Very serious (-2)	Serious (-1)	Very low
	Fatigue	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
Salhab (2019)	PCS	Not reported (-1)	Serious (-1)	Neutral	Very serious (-2)	Serious (-1)	Very low
	MCS	Not reported (-1)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
Andrade (2019)	VO_{2peak}	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
Chung (2019)	6MWT	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
	VO_{2peak}	Neutral	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	PCS	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
	MCS	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
Zhang (2021)	6MWT	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	STS 30	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low

	HGS	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	PCS	Very serious (-2)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	MCS	Very serious (-2)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
Pu (2019)	Kt/V	Serious (-1)	Neutral	Neutral	Serious (-1)	Not reported (-1)	Very low
	VO_{2peak}	Neutral	Serious (-1)	Neutral	Neutral	Not reported (-1)	Moderate
	6MWT	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
	PCS	Neutral	Serious (-1)	Neutral	Serious (-1)	Not reported (-1)	Very low
	MCS	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Moderate
	SBP	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	DBP	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
Yamamoto (2021)	SBP	Very serious (-2)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	VO_{2peak}	Very serious (-2)	Neutral	Neutral	Serious (-1)	Neutral	Very low
	BMI	Very serious (-2)	Neutral	Neutral	Neutral	Neutral	Low
Thompson (2019)	SBP	Very serious (-2)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	DBP	Very serious (-2)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
Yang (2017)	VO_{2peak}	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
Clarkson (2019)	6MWT	Neutral	Neutral	Neutral	Neutral	Serious (-1)	Moderate
Zhao (2019)	Fatigue	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	PCS	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	MCS	Neutral	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
Zhang (2019)	SBP	Neutral	Serious (-1)	Neutral	Neutral	Neutral	Moderate
	DBP	Neutral	Serious (-1)	Neutral	Serious (-1)	Neutral	Low
	BMI	Serious (-1)	Neutral	Neutral	Neutral	Neutral	Moderate

Huang (2019)	Kt/V	Very serious (-2)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	SBP	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	DBP	Neutral	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	6MWT	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Serious (-1)	Very low
	PCS	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	MCS	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	VO_{2peak}	Serious (-1)	Neutral	Neutral	Serious (-1)	Neutral	Low
Heiwe (2011)	Aerobic capacity	Neutral	Neutral	Neutral	Neutral	Serious (-1)	Moderate
	Muscle strength	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	Walking capacity	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	SBP	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	DBP	Neutral	Neutral	Neutral	Neutral	Neutral	High
Heiwe (2014)	Aerobic capacity	Neutral	Neutral	Neutral	Serious (-1)	Not reported (-1)	Low
	DBP	Neutral	Neutral	Neutral	Serious (-1)	Not reported (-1)	Low
	SBP	Neutral	Serious (-1)	Neutral	Serious (-1)	Not reported (-1)	Very low
	Muscle strength	Serious (-1)	Neutral	Neutral	Serious (-1)	Not reported (-1)	Very low
	Walking capacity	Neutral	Neutral	Neutral	Serious (-1)	Not reported (-1)	Low
Matsuzawa (2017)	VO_{2peak}	Neutral	Neutral	Neutral	Neutral	Neutral	High
	6MWT	Serious (-1)	Serious (-1)	Neutral	Serious (-1)	Neutral	Very low
	Muscle strength	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	PCS	Very serious (-2)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	MCS	Very serious (-2)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
Smart (2011)	VO_{2peak}	Neutral	Serious (-1)	Neutral	Neutral	Serious (-1)	Low
Bogataj	6MWT	Serious (-1)	Serious (-1)	Neutral	Not reported (-1)	Not reported (-1)	Very low

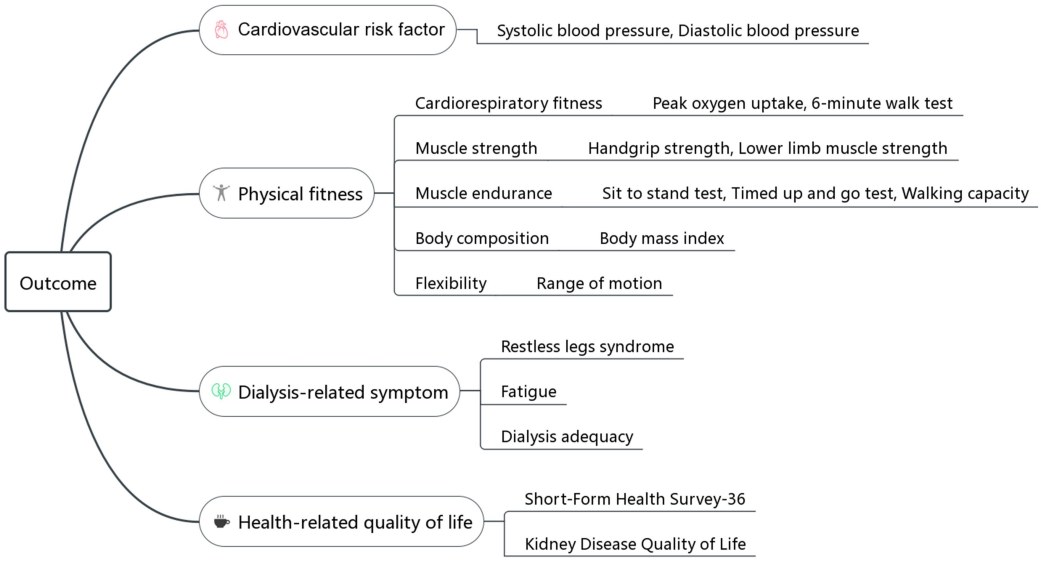
(2020)	VO_{2peak}	Very serious (-2)	Serious (-1)	Neutral	Not reported (-1)	Not reported (-1)	Very low
	STS 10	Neutral	Serious (-1)	Neutral	Not reported (-1)	Serious (-1)	Very low
Sheng (2014)	Kt/V	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	VO_{2peak}	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	PCS	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	MCS	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	6MWT	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Serious (-1)	Very low
	DBP	Serious (-1)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	SBP	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	STS60	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
Neto (2018)	VO_{2peak}	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Not reported (-1)	Very low
	PCS	Serious (-1)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	MCS	Serious (-1)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	6MWT	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Serious (-1)	Very low
	Muscle strength	Neutral	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
Ferrari (2019)	Kt/V (AE)	Neutral	Serious (-1)	Neutral	Serious (-1)	Neutral	Low
	Kt/V (RT)	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	VO_{2peak} (COM)	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	VO_{2peak} (AE)	Serious (-1)	Neutral	Neutral	Serious (-1)	Serious (-1)	Very low
	6MWT (RT)	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	6MWT(AE)	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	SBP	Serious (-1)	Neutral	Neutral	Serious (-1)	Neutral	Low
	DBP	Serious (-1)	Neutral	Neutral	Serious (-1)	Neutral	Low
Wyngaert (2018)	SBP	Serious (-1)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
	DBP	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Serious (-1)	Very low

	VO_{2peak}	Serious (-1)	Very serious (-2)	Neutral	Serious (-1)	Neutral	Very low
	BMI	Serious (-1)	Neutral	Neutral	Serious (-1)	Neutral	Low
Oguchi (2018)	VO_{2peak}	Neutral	Neutral	Neutral	Serious (-1)	Serious (-1)	Low
	HRQoL	Serious (-1)	Serious (-1)	Neutral	Serious (-1)	Serious (-1)	Very low
Ju (2020)	HGS	Very serious (-2)	Neutral	Neutral	Serious (-1)	Neutral	Very low
	Symptom/problem (KDQoL)	Very serious (-2)	Very serious (-2)	Neutral	Serious (-1)	Not reported (-1)	Very low
	effects of kidney disease (KDQoL)	Very serious (-2)	Very serious (-2)	Neutral	Serious (-1)	Not reported (-1)	Very low
	burden of kidney disease (KDQoL)	Very serious (-2)	Very serious (-2)	Neutral	Serious (-1)	Not reported (-1)	Very low

Abbreviation: AE = aerobic exercise; RT = resistance training; COM = combine; VO_{2peak} = peak oxygen uptake; HRQoL = health-related quality of life; DBP = diastolic blood pressure; SBP = systolic blood pressure; PCS = physical component summary; MCS = mental component summary; 6MWT = 6 minutes walk test; STS 10 = sit to stand 10 test; STS 30 = sit to stand 30 test; STS 60 = sit to stand 60 test; TUGT = timed up and go test; BMI = body mass index; SMD = standardized mean difference; HD = hemodialysis; KTRs = kidney transplant recipients; SF-36 = short form-36; KDQoL = kidney disease quality of life;

Very serious mean the included studies existed two or more high risk of bias in terms of randomization, blinding, allocation concealment, completeness of result data, or selective reporting, or $75\% \leq I^2 \leq 100\%$.

Serious mean the included studies existed two or more high risk of bias in terms of randomization, blinding, allocation concealment, completeness of result data, or selective reporting, or $50\% \leq I^2 < 75\%$, or the included study sample size< 400, asymmetric funnel plot or less than 9 studies included.



Supplemental Figures S1

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 4-5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 4-5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 5-6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 4-5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	None
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Not applicable
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	None
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	None
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	None
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 6

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 6
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 6
Study characteristics	17	Cite each included study and present its characteristics.	Page 6
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 6
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 18-32
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Not applicable
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Not applicable
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not applicable
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	None
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 6
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 6
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 10
	23b	Discuss any limitations of the evidence included in the review.	Page 12
	23c	Discuss any limitations of the review processes used.	Page 12
	23d	Discuss implications of the results for practice, policy, and future research.	None
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	None
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 1
Competing interests	26	Declare any competing interests of review authors.	Page 1
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 1

PRISMA 2020 Checklist

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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