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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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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 9 March 2021 for relevant articles.

Eligibility criteria for selecting studies Eligible meta-analyses compared the effects of usual care with and without exercise in patients with CKD. 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 3 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 patients with CKD.

PROSPERO registration number CRD42020223591.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A strength of this study is to comprehensively summarise the systematic review and meta-analysis of exercise interventions on the spectrum of chronic kidney disease.
⇒ Methodological quality of the included reviews was assessed using standardised measures.
⇒ The limitation of this overview is that language bias may exist in this review because the search strategy was limited to English.
⇒ Another limitation was that most studies were based on haemodialysis-dependent chronic kidney disease.

INTRODUCTION

Chronic kidney disease (CKD) is a long-term condition characterised 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] Patients with CKD 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 multifaceted intervention programme. 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 patients with CKD.[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

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HR=0.73, 95% CI: 0.69 to 0.78), and mortality risk tended to decrease as exercise frequency increased (HR for participants who exercised once/week=0.82, 95% CI: 0.73 to 0.91; HR for those who exercised 6–7 times/week=0.69, 95% CI: 0.63 to 0.76) and patients who exercised daily had lower mortality risk (HR=0.84, 95% CI: 0.74 to 0.96) than patients exercising once/week.[9] Based on data from 41 randomised controlled trials (RCT), Heiwe *et al* reported practical improvements in aerobic capacity, muscular function and walking capacity in patients with CKD 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 patients with CKD, the latter being a significant cause of sedentary behaviour in such population.[12] Because of this, some researchers and guidelines recommend that healthcare providers prescribe exercise for patients with CKD.[13–16] However, the results of meta-analyses of exercise in patients with CKD 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 patients with CKD, summarised 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/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 patients with CKD that compared usual care procedures with and without exercise interventions. PubMed, Embase, the Cochrane Database of Systematic Reviews and the Web of Science were searched for systematic reviews and meta-analyses from inception to 9 March 2021. The detailed search strategy is summarised in online supplemental 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 are shown in online supplemental figure S1 (4) systematic reviews with meta-analysis of intervention trials (RCTs and quasi-experimental studies). A meta-analysis that included fewer than 3 studies or fewer 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 standardised format that included: (1) study, (2) stage of CKD, (3) the number of included studies and participants, (4) exercise type, (5) exercise mode (intradialytic or interdialytic), (6) standardised mean difference (SMD) or mean difference (MD) with corresponding 95% CI for each outcome, (7) p values, (8) I^2 values and (9) 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 analysed 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, $25\%<I^2\leq50\%$ indicate mild heterogeneity, $50\%<I^2\leq75\%$ 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

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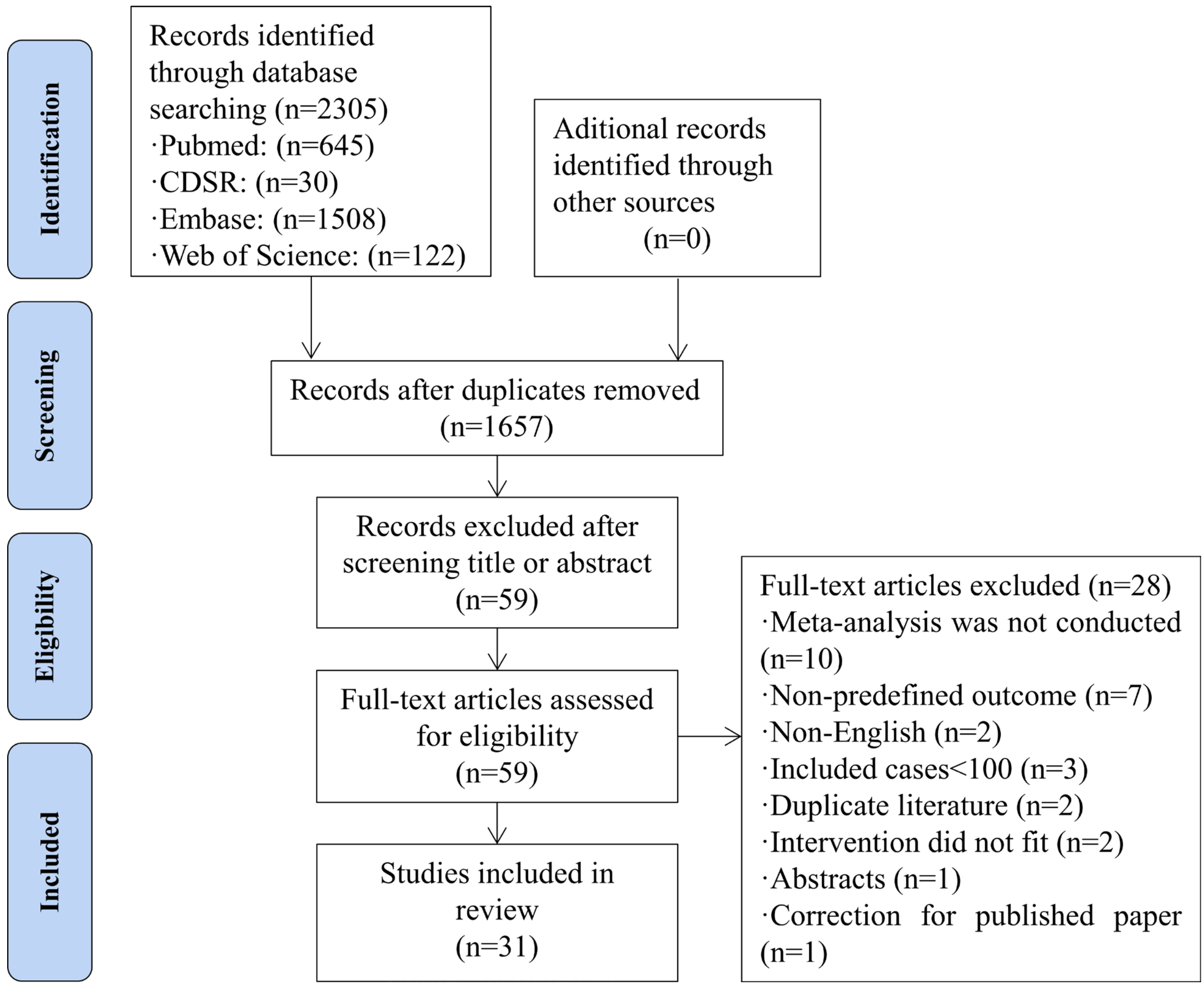

Figure 1 Flow chart of literature screening. CDSR, Cochrane Database of Systemic Review.

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 flow chart of study inclusion is illustrated in figure 1. The reasons for excluded articles are listed in online supplemental 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 online supplemental table S3. SMD data from four papers could not be obtained from the authors, and the data of their effect size were 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 (online supplemental 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 (online supplemental table S5).

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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 patients with CKD.[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 6 reported a positive statistically significant outcome.[30 33 41 43 49 52] Of the 13 meta-analyses, 9 reported a small effect size[10 27 33 34 41 43 47 48 52] and 1 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 (2 meta-analyses[34 40]) and moderate (1 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, 9 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 patients with CKD using a peak oxygen uptake (18 of 34), a 6 min 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) (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, 3 reported a low effect size,[27 39 50] 9 reported a moderate effect size[25 28 32 34 37 41 43 44 49] and 3 reported a large effect size.[24 38 47] GRADE assessment of quality indicated the overall evidence as being very low (nine meta-analyses[25 27 28 30 32 37 43 47 49]), low (eight 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 min 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, 2 reported a small effect size,[25 28] 5 reported a moderate effect size[36 37 41 43 51] and 3 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 and Jacobson[10] 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 patients with CKD with a low heterogeneity (average I^2=19.1%).[10 26 32 33 35–38 51] 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) (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, 3 reported a small effect size,[36 38 51] 5 reported a moderate effect size[10 32 33 35 36] and 2 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 eight 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 patients with CKD. 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 five 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 patients with CKD.[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 patients with CKD.[30 31 34 41 43 45 53] Each meta-analysis included a mean of 7 studies (ranging from 3 to 12

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

Study	Design	Stage of CKD	k (n)*	Exercise type	Mode	SMD or MD (95% CI)	Effect size	P value	I^2	GRADE
SBP										
Pei *et al*[40]	RCT/Quasi-RCT	Mixed	12 (514)	AE	–	MD: −2.91 (−6.68 to 0.87)	–	0.13	40.0%	⊕⊕◯◯
Wu *et al*[48]	RCT/Quasi-RCT	Predialysis	3 (204)	AE+RT	–	SMD: −0.19 (-0.46 to 0.08)	Small	0.16	50.0%	⊕◯◯◯
Chen *et al*[27]	RCT	KTRs	5 (198)	Mixed	–	SMD: 0.18 (-0.10 to 0.46)	Small	0.21	0.0%	⊕◯◯◯
Pu *et al*[41]	RCT	HD	7 (287)	Mixed	Intradialytic	SMD: −0.28 (−0.52 to 0.05)	Small	0.02	0.0%	⊕◯◯◯
Yamamoto *et al*[49]	RCT	Predialysis	10 (392)	AE	–	SMD: −0.75 (−1.24 to 0.26)	Moderate	0.003	80.3%	⊕◯◯◯
Thompson *et al*[46]	RCT	Predialysis	10 (335)	Mixed	–	MD: −4.30 (-9.00 to 0.40)	–	N.P.	50.4%	⊕◯◯◯
Zhang *et al*[52]	RCT	Predialysis	14 (463)	Mixed	–	SMD: −0.41 (−0.70 to 0.11)	Small	0.007	55.0%	⊕⊕⊕◯
Huang *et al*[34]	RCT	HD	7 (260)	Mixed	Mixed	SMD: −0.17 (-0.41 to 0.08)	Small	0.18	8.0%	⊕⊕◯◯
Heiwe *et al*[33]	RCT/Quasi-RCT	Mixed	9 (347)	Mixed	–	SMD: 0.25 (0.04 to 0.47)	Small	0.02	0.0%	⊕◯◯◯
Heiwe and Jacobson[10]	RCT	HD	10 (312)	Mixed	–	SMD: 0.04 (-0.34 to 0.41)	Small	0.8	58.0%	⊕▫◯
Sheng *et al*[43]	RCT	HD	7 (296)	Mixed	Intradialytic	SMD: −0.27 (−0.50 to 0.04)	Small	0.02	0.0%	⊕◯◯◯
Ferrari *et al*[30]	RCT	HD	10 (332)	AE	Intradialytic	MD: −10.07 (16.35 to 3.78)	–	0.002	44.0%	⊕◯◯◯
Vanden Wyngaert *et al*[47]	RCT	Predialysis	8 (269)	AE	–	SMD: 0.08 (-0.58 to 0.74)	Small	0.81	84%	⊕◯◯◯
DBP										
Pei *et al*[40]	RCT/Quasi-RCT	Mixed	12 (514)	AE	–	MD: −1.11 (−3.41 to 1.20)	–	0.35	0.0%	⊕⊕◯◯
Wu *et al*[48]	RCT/Quasi-RCT	Predialysis	4 (194)	AE+RT	–	SMD: −0.47 (-1.10 to 0.15)	Small	0.14	70.0%	⊕◯◯◯
Chen *et al*[27]	RCT	KTRs	5 (198)	Mixed	–	SMD: 0.04 (-0.45 to 0.52)	Small	0.89	59.0%	⊕◯◯◯
Pu *et al*[41]	RCT	HD	7 (287)	Mixed	Intradialytic	SMD: −0.32 (−0.55 to 0.08)	Small	0.008	42.0%	⊕◯◯◯
Thompson *et al*[46]	RCT	Predialysis	8 (303)	Mixed	–	MD: −1.18 (-4.76 to 2.40)	–	N.P.	60.5%	⊕◯◯◯
Zhang *et al*[52]	RCT	Predialysis	12 (399)	Mixed	–	SMD: −0.31 (-0.71 to 0.08)	Small	0.12	70.0%	⊕⊕◯◯
Huang *et al*[34]	RCT	HD	7 (260)	Mixed	Mixed	SMD: −0.23 (-0.69 to 0.24)	Small	0.34	68.0%	⊕◯◯◯
Heiwe *et al*[33]	RCT/Quasi-RCT	Mixed	11 (419)	Mixed	–	SMD: 0.16 (-0.04 to 0.36)	Small	0.11	40.0%	⊕◯◯◯
Heiwe and Jacobson[10]	RCT	HD	10 (212)	Mixed	Mixed	SMD: 0.17 (-0.16 to 0.49)	Small	0.3	45.0%	⊕⊕◯◯
Sheng *et al*[43]	RCT	HD	7 (296)	Mixed	Intradialytic	SMD: −0.24 (−0.47 to 0.01)	Small	0.04	52.1%	⊕◯◯◯
Ferrari *et al*[30]	RCT	HD	10 (334)	AE	Intradialytic	MD: −2.96 (-7.71 to 1.78)	–	0.22	0.0%	⊕◯◯◯
Vanden Wyngaert *et al*[47]	RCT	Predialysis	7 (237)	AE	–	SMD: −0.09 (-0.78 to 0.59)	Small	0.79	83%	⊕◯◯◯

Mixed means aerobic exercise combined with resistance training.
*Number of included studies and corresponding sample size.
AE, aerobic exercise; CKD, chronic kidney disease; DBP, diastolic blood pressure; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HD, haemodialysis; KTRs, kidney transplant recipients; MD, mean difference; N.P., no report; RCT, randomised controlled trial; RT, resistance training; SBP, systolic blood pressure; SMD, standardised mean difference.

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

Study	Design	Stage of CKD	k (n)*	Exercise type	Mode	SMD or MD (95% CI)	Effect size	P value	I^2	GRADE
$VO_{2\,peak}$										
Pei *et al*[40]	RCT/Quasi-RCT	Mixed	17 (464)	AE	–	MD: 2.08 (1.10 to 3.05)	–	<0.001	25.0%	⊕⊕◯◯
Nakamura *et al*[38]	RCT/Cross-over	Predialysis	10 (401)	Mixed	–	SMD: 0.88 (0.53 to 1.23)	Large	<0.001	56.0%	⊕⊕◯◯
Chen *et al*[27]	RCT	KTRs	6 (202)	Mixed	–	SMD: 0.33 (-0.02 to 0.69)	Small	0.06	27.0%	⊕◯◯◯
Andrade *et al*[24]	RCT	HD	5 (201)	AE+RT	Intradialytic	SMD: 1.01 (0.71 to 1.30)	Large	<0.001	0.0%	⊕⊕◯◯
Chung *et al*[28]	RCT	HD	6 (238)	Mixed	Intradialytic	SMD: 0.55 (0.18 to 0.92)	Moderate	0.003	52.9%	⊕◯◯◯
Pu *et al*[41]	RCT	HD	10 (400)	Mixed	Intradialytic	SMD: 0.57 (0.23 to 0.90)	Moderate	<0.001	59.0%	⊕⊕◯◯
Yamamoto *et al*[49]	RCT	Predialysis	10 (365)	AE	–	SMD: 0.54 (0.29 to 0.78)	Moderate	<0.001	24.6%	⊕◯◯◯
Yang *et al*[50]	RCT	Mixed	5 (179)	Mixed	–	SMD: 0.33 (0.03 to 0.63)	Small	0.003	47.0%	⊕⊕◯◯
Huang *et al*[34]	RCT	HD	10 (371)	Mixed	Mixed	SMD: 0.73 (0.52 to 0.95)	Moderate	<0.001	71.0%	⊕⊕◯◯
Matsuzawa *et al*[37]	RCT	HD	18 (582)	Mixed	Mixed	SMD: 0.62 (0.38 to 0.87)	Moderate	<0.001	49.0%	⊕⊕⊕⊕
Smart *et al*[44]	RCT	HD	8 (365)	Mixed	Mixed	SMD: 0.75 (0.39 to 1.11)	Moderate	<0.001	60.0%	⊕⊕◯◯
Bogataj *et al*[25]	RCT	HD	20 (504)	Mixed	Mixed	SMD: 0.58 (0.32 to 0.85)	Moderate	<0.001	57.4%	⊕◯◯◯
Sheng *et al*[43]	RCT	HD	7 (310)	Mixed	Intradialytic	SMD: 0.53 (0.30 to 0.76)	Moderate	<0.001	36.0%	⊕◯◯◯
Neto *et al*[32]	RCT	HD	10 (394)	Mixed	Intradialytic	SMD: 0.60 (0.15 to 1.04)	Moderate	0.008	76.0%	⊕◯◯◯
Ferrari *et al*[30]	RCT	HD	5 (201)	AE+RT	Intradialytic	MD: 5.41 (4.03 to 6.79)	–	<0.001	0.0%	⊕◯◯◯
Ferrari *et al*[30]	RCT	HD	7 (248)	AE	Intradialytic	MD: 2.07 (0.42 to 3.72)	–	<0.001	0.0%	⊕◯◯◯
Vanden Wyngaert *et al*[47]	RCT	Predialysis	11 (325)	AE	–	SMD: 0.99 (0.49 to 1.48)	Large	<0.001	74.0%	⊕◯◯◯
Oguchi *et al*[39]	RCT	KTRs	4 (182)	Mixed	–	SMD: 0.38 (-0.06 to 0.82)	Small	0.09	45.0%	⊕⊕◯◯
6MWT										
Pei *et al*[40]	RCT/Quasi-RCT	Mixed	8 (496)	AE	–	MD: 0.04 (–0.52 to 0.59)	–	0.90	86.0%	⊕◯◯◯
Nakamura *et al*[38]	RCT/Cross-over	Predialysis	5 (392)	Mixed	–	SMD: 1.04 (0.17 to 1.90)	Large	0.02	92.0%	⊕◯◯◯
Lu *et al*[36]	RCT	Dialysis	11 (300)	Mixed	Mixed	SMD: 0.52 (0.31 to 0.72)	Moderate	<0.001	39.0%	⊕⊕⊕◯
Chung *et al*[28]	RCT	HD	4 (127)	Mixed	Intradialytic	SMD: 0.44 (0.09 to 0.80)	Small	0.015	0.0%	⊕⊕◯◯
Zhang *et al*[51]	RCT	HD	8 (299)	RT	Intradialytic	SMD: 0.52 (0.28 to 0.75)	Moderate	<0.001	18.7%	⊕⊕◯◯
Pu *et al*[41]	RCT	HD	7 (219)	Mixed	Intradialytic	SMD: 0.57 (0.30 to 0.84)	Moderate	<0.001	0.0%	⊕⊕◯◯
Clarkson *et al*[29]	RCT	Dialysis	18 (744)	Mixed	–	MD: 33.64 (23.74 to 43.54)	–	<0.001	0.0%	⊕⊕⊕◯
Huang *et al*[34]	RCT	HD	7 (205)	Mixed	Mixed	SMD: 1.01 (0.26 to 1.76)	Large	0.008	83.0%	⊕◯◯◯
Matsuzawa *et al*[37]	RCT	HD	10 (326)	Mixed	Mixed	SMD: 0.58 (0.24 to 0.93)	Moderate	<0.001	53.0%	⊕⊕◯◯
Bogataj *et al*[25]	RCT	HD	19	Mixed	Mixed	SMD: 0.44 (0.21 to 0.67)	Small	<0.001	49.6%	⊕◯◯◯
Sheng *et al*[43]	RCT	HD	4 (146)	Mixed	Intradialytic	SMD: 0.58 (0.23 to 0.93)	Moderate	<0.001	89.7%	⊕◯◯◯
Neto *et al*[32]	RCT	HD	6 (158)	Mixed	Intradialytic	SMD: 0.96 (0.11 to 1.80)	Large	0.03	82.0%	⊕◯◯◯
Ferrari *et al*[30]	RCT	HD	6 (211)	RT	Intradialytic	MD: 68.5 (29.05 to 107.96)	–	<0.001	36.0%	⊕◯◯◯
Ferrari *et al*[30]	RCT	HD	6 (188)	AE	Intradialytic	MD: 64.98 (43.86 to 86.11)	–	<0.001	0.0%	⊕◯◯◯

Continued

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Table 2 Continued

Study	Design	Stage of CKD	k (n)*	Exercise type	Mode	SMD or MD (95% CI)	Effect size	P value	I^2	GRADE
Aerobic capacity										
Heiwe *et al*[33]	RCT/Quasi-RCT	Mixed	24 (847)	Mixed	–	SMD: −0.56 (−0.70 to 0.42)	Moderate	<0.001	12.0%	⊕◯◯◯
Heiwe and Jacobson[10]	RCT	HD	21 (374)	Mixed	Mixed	SMD: −0.80 (−1.02 to 0.58)	Large	<0.001	0.0%	⊕⊕◯◯

Mixed means aerobic exercise combined with resistance training.
*Number of included studies and corresponding sample size.
AE, aerobic exercise; CKD, chronic kidney disease; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HD, haemodialysis; KTRs, kidney transplant recipients; MD, mean difference; 6MWT, 6 min walk test; RCT, randomised controlled trial; RT, resistance training; SMD, standardised mean difference; $VO_{2\ peak}$, peak oxygen uptake.

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

Study	Design	Stage of CKD	k (n)*	Exercise type	Mode	SMD or MD (95% CI)	Effect size	P value	I^2	GRADE
Cheema *et al*[26]	RCT	Predialysis	7 (249)	RT	–	SMD: 1.15 (0.80 to 1.49)	Large	0.161	35.0%	⊕⊕◯◯
Nakamura *et al*[38]	RCT/Cross-over	Predialysis	4 (119)	Mixed	–	SMD: 0.35 (-0.03 to 0.73)	Small	0.07	7.0%	⊕◯◯◯
Lu *et al*[36]	RCT	Dialysis	5 (234)	Mixed	Mixed	SMD: 0.59 (0.20 to 0.98)	Moderate	0.003	52.0%	⊕⊕◯◯
Lu *et al*[36]	RCT	Dialysis	7 (224)	Mixed	Mixed	SMD: 0.47 (0.20 to 0.74)	Small	<0.001	0.0%	⊕⊕◯◯
Zhang *et al*[51]	RCT	HD	6 (300)	RT	Intradialytic	SMD: 0.35 (0.12 to 0.58)	Small	0.003	41.6%	⊕⊕◯◯
Heiwe *et al*[33]	RCT/Quasi-RCT	Mixed	9 (358)	Mixed	–	SMD: −0.52 (−0.73 to 0.31)	Moderate	<0.001	0.0%	⊕◯◯◯
Heiwe and Jacobson[10]	RCT	HD	12 (385)	Mixed	Mixed	SMD: −0.56 (−0.77 to 0.35)	Moderate	<0.001	0.0%	⊕◯◯◯
Matsuzawa *et al*[37]	RCT	HD	9 (281)	Mixed	Mixed	SMD: 0.94 (0.67 to 1.21)	Large	<0.001	10.0%	⊕◯◯◯
Neto *et al*[32]	RCT	HD	9 (250)	Mixed	Intradialytic	SMD: 0.61 (0.39 to 0.83)	Moderate	<0.001	58.9%	⊕◯◯◯
Ju *et al*[35]	RCT	Mixed	3 (115)	Mixed	–	SMD: 0.52 (0.14 to 0.89)	Moderate	0.007	0.0%	⊕◯◯◯

Mixed means aerobic exercise combined with resistance training.
*Number of included studies and corresponding sample size.
CKD, chronic kidney disease; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HD, haemodialysis; MD, mean difference; RCT, randomised controlled trial; RT, resistance training; SMD, standardised mean difference.

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

Study	Design	Stage of CKD	k (n)*	Exercise type	Mode	Outcome	SMD or MD (95% CI)	Effect size	P value	I^2	GRADE
Lu *et al*[36]	RCT	Dialysis	3 (193)	Mixed	Mixed	STS 10	MD: −4.69 (−9.01 to 0.38)	–	0.028	72.2%	⊕◯◯◯
Bogataj *et al*[25]	RCT	HD	5 (461)	Mixed	–	STS 10	SMD: −0.55 (−1.00 to 0.09)	Moderate	0.019	71.6%	⊕◯◯◯
Lu *et al*[36]	RCT	Dialysis	6 (240)	Mixed	Mixed	STS 30	SMD: 0.43 (0.17 to 0.69)	Small	0.001	2.0%	⊕⊕◯◯
Zhang *et al*[51]	RCT	HD	5 (164)	RT	Intradialytic	STS 30	SMD: 0.42 (0.11,0.74)	Small	0.008	0.0%	⊕◯◯◯
Sheng *et al*[43]	RCT	HD	3 (106)	Mixed	Intradialytic	STS 60	SMD: 0.71 (0.31,1.12)	Moderate	<0.001	0.0%	⊕◯◯◯
Pei *et al*[40]	RCT/Quasi-RCT	Mixed	5 (445)	AE	–	STS 60	MD: 2.08 (1.1,3.05)	–	0.98	82.0%	⊕◯◯◯
Nakamura *et al*[38]	RCT/Cross-over	Predialysis	3 (170)	Mixed	–	TUGT	SMD: −0.42 (−0.73 to 0.11)	Small	0.007	0.0%	⊕◯◯◯
Heiwe *et al*[33]	RCT/Quasi-RCT	Mixed	7 (191)	Mixed	–	Walking capacity	SMD: −0.48 (−0.79 to 0.17)	Small	0.003	2.0%	⊕◯◯◯
Heiwe and Jacobson[10]	RCT	HD	7 (174)	Mixed	Mixed	Walking capacity	SMD: −0.33 (-0.67,0.01)	Small	0.06	16.0%	⊕⊕⊕◯

Mixed means aerobic exercise combined with resistance training.
*Number of included studies and corresponding sample size.
AE, aerobic exercise; CKD, chronic kidney disease; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HD, haemodialysis; MD, mean difference; RCT, randomised controlled trial; RT, resistance training; SMD, standardised mean difference; 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.

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

Study	Design	Stage of CKD	k (n)*	Exercise type	Mode	SMD (95% CI)	Effect size	P value	I^2	GRADE
Chen *et al*[27]	RCT	KTRs	4 (166)	Mixed	–	SMD: 0.02 (−0.28 to 0.33)	Small	0.89	0.0%	⊕◯◯◯
Yamamoto *et al*[49]	RCT	Predialysis	10 (414)	AE	–	SMD: −0.19 (−0.38 to 0.00)	Small	0.026	0.0%	⊕⊕◯◯
Zhang *et al*[52]	RCT	Predialysis	13 (466)	Mixed	–	SMD: −0.21 (−0.39 to 0.03)	Small	0.02	0.0%	⊕⊕⊕◯
Vanden Wyngaert *et al*[47]	RCT	Predialysis	9 (294)	AE	–	SMD: −0.36 (−0.60 to 0.13)	Small	0.002	48.0%	⊕⊕◯◯

Mixed means aerobic exercise combined with resistance training.
*Number of included studies and corresponding sample size.
AE, aerobic exercise; CKD, chronic kidney disease; GRADE, Grading of Recommendations Assessment, Development and Evaluation; KTRs, kidney transplant recipients; RCT, randomised controlled trial; SMD, standardised mean difference.

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 Haemodialysis Patients Fatigue Scale. The effect of exercise on fatigue was investigated in two 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 patients with CKD.[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 five articles) investigated the effects of exercise on Kt/V in patients with CKD 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, three 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 patients with CKD.[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 patients with CKD, 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 (9 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%.

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

Study	Design	Stage of CKD	k (n)*	Exercise type	Mode	Outcomes	SMD or MD (95% CI)	Effect size	P value	I^2	GRADE
Ferreira *et al*[31]	RCT/Quasi-RCT	HD	10 (346)	AE	Intradialytic	Kt/V†	SMD: 2.21 (1.17 to 3.25)	Large	<0.001	92.0%	⊕◯◯◯
Pu *et al*[41]	RCT	HD	10 (301)	Mixed	Intradialytic	Kt/V	SMD: 0.29 (0.06 to 0.52)	Small	0.01	0.0%	⊕◯◯◯
Huang *et al*[34]	RCT	HD	8 (257)	Mixed	Mixed	Kt/V	SMD: 0.19 (-0.06 to 0.43)	Small	0.14	0.0%	⊕◯◯◯
Sheng *et al*[43]	RCT	HD	7 (233)	Mixed	Intradialytic	Kt/V	SMD: 0.27 (0.01 to 0.53)	Small	0.04	0.0%	⊕◯◯◯
Ferrari *et al*[30]	RCT	HD	12 (370)	AE	Intradialytic	Kt/V	MD: 0.08 (0.0 to 0.15)	–	0.04	56.0%	⊕◯◯◯
Ferrari *et al*[31]	RCT	HD	6 (220)	RT	Intradialytic	Kt/V	MD: 0.10 (0.0 to 0.2)	–	0.06	6.0%	⊕◯◯◯
Song *et al*[45]	RCT	HD	4 (141)	Mixed	Mixed	RLS	SMD: −1.79 (−2.21 to 1.37)	Large	<0.001	87.0%	⊕◯◯◯
Song *et al*[45]	RCT	HD	3 (139)	Mixed	Mixed	Fatigue	SMD: −0.85 (−1.20 to 0.50)	Large	<0.001	0.0%	⊕◯◯◯
Zhao *et al*[53]	RCT	Dialysis	3 (141)	Mixed	–	Fatigue	SMD: −0.97 (−1.32 to 0.62)	Large	<0.001	47.0%	⊕⊕◯◯

Mixed means aerobic exercise combined with resistance training.
*Number of included studies and corresponding sample size.
†An indicator to assess dialysis adequacy
AE, aerobic exercise; CKD, chronic kidney disease; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HD, haemodialysis; KTRs, kidney transplant recipients; MD, mean difference; RCT, randomised controlled trial; RLS, restless legs syndrome; RT, resistance training; SMD, standardised mean difference.

DISCUSSION

Summary of main results

Several meta-analyses have been published on exercise interventions in patients with CKD.[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 patients with CKD. There was low-quality 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 patients with CKD.

Interpretation of study effects

Cardiovascular disease is a frequent complication of CKD and is the leading cause of death in patients with CKD.[56] Hypertension is an important modifiable risk factor for cardiovascular diseases and progressive renal dysfunction in patients with CKD.[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 patients with CKD. However, the dose effects of exercise in the context of the cardiovascular health of patients with CKD 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 SD of all normal RR intervals and left ventricular mass index.[10] Furthermore, a recent randomised controlled trial published by Graham-Brown *et al* 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 patients with CKD, particularly those comorbid with cardiovascular disease. Future randomised 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 patients with CKD, 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

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

Study	Design	Stage of CKD	k (n)*	Exercise type	Mode	Outcomes	SMD or MD (95% CI)	Effect size	P value	I^2	GRADE
Salhab *et al*[42]	RCT	HD	5 (282)	AE	Intradialytic	PCS	SMD: 1.82 (-0.92 to 4.55)	Large	0.19	98.0%	⊕◯◯◯
Chung *et al*[28]	RCT	HD	6 (229)	Mixed	Intradialytic	PCS	SMD: 0.46 (0.20 to 0.73)	Small	<0.001	1.90%	⊕⊕◯◯
Zhang *et al*[51]	RCT	HD	7 (297)	RT	Intradialytic	PCS	SMD: 0.23 (-0.00 to 0.46)	Small	0.055	0.0%	⊕⊕◯◯
Pu *et al*[41]	RCT	HD	10 (320)	Mixed	Intradialytic	PCS	SMD: 0.57 (0.14 to 1.01)	Moderate	0.01	70.0%	⊕◯◯◯
Zhao *et al*[53]	RCT	Dialysis	5 (186)	Mixed	–	PCS	SMD: 0.31 (0.02 to 0.61)	Small	0.04	46.0%	⊕⊕◯◯
Huang *et al*[34]	RCT	HD	7 (263)	Mixed	Mixed	PCS	SMD: 0.34 (0.09 to 0.59)	Small	0.007	27.0%	⊕⊕◯◯
Matsuzawa *et al*[37]	RCT	HD	9 (264)	Mixed	Mixed	PCS	SMD: 0.53 (0.52 to 0.82)	Moderate	<0.001	19.0%	⊕◯◯◯
Sheng *et al*[43]	RCT	HD	7 (256)	Mixed	Intradialytic	PCS	SMD: 0.30 (0.05 to 0.55)	Small	0.02	39.5%	⊕◯◯◯
Neto *et al*[32]	RCT	HD	7 (187)	Mixed	Intradialytic	PCS	SMD: 0.50 (-0.19 to 1.18)	Moderate	0.16	62.0%	⊕◯◯◯
Salhab *et al*[42]	RCT	HD	5 (282)	AE	Intradialytic	MCS	SMD: 1.02 (0.31 to 1.73)	Large	0.005	75.0%	⊕◯◯◯
Chung *et al*[28]	RCT	HD	5 (193)	Mixed	Intradialytic	MCS	SMD: 0.23 (-0.05 to 0.52)	Small	0.109	0.0%	⊕⊕◯◯
Zhang *et al*[51]	RCT	HD	7 (297)	RT	Intradialytic	MCS	SMD: 0.13 (-0.10 to 0.36)	Small	0.082	46.5%	⊕⊕◯◯
Pu *et al*[41]	RCT	HD	8 (219)	Mixed	Intradialytic	MCS	SMD: 0.19 (-0.09 to 0.46)	Small	0.18	30.0%	⊕⊕◯◯
Zhao *et al*[53]	RCT	Dialysis	5 (186)	Mixed	–	MCS	SMD: 0.30 (-0.20 to 0.80)	Small	0.24	64.0%	⊕◯◯◯
Huang *et al*[34]	RCT	HD	7 (263)	Mixed	Mixed	MCS	SMD: 0.27 (0.02 to 0.51)	Small	0.03	0.0%	⊕⊕◯◯
Matsuzawa *et al*[37]	RCT	HD	8 (228)	Mixed	Mixed	MCS	SMD: 0.14 (-0.15 to 0.42)	Small	0.34	10.0%	⊕◯◯◯
Sheng *et al*[43]	RCT	HD	5 (167)	Mixed	Intradialytic	MCS	SMD: 0.14 (-0.16 to 0.43)	Small	0.37	14.8%	⊕◯◯◯
Neto *et al*[32]	RCT	HD	7 (185)	Mixed	Intradialytic	MCS	SMD: 0.39 (-0.19 to 0.98)	Small	0.19	50.0%	⊕◯◯◯
Pei *et al*[40]	RCT/Quasi-RCT	Mixed	6 (522)	AE	–	Physical function (SF-36)	MD: 8.36 (-1.24 to 17.95)	–	0.09	76.0%	⊕◯◯◯
Pei *et al*[40]	RCT/Quasi-RCT	Mixed	7 (562)	AE	–	Physical role (SF-36)	MD: 14.65 (1.47 to 27.84)	–	0.03	78.0%	⊕◯◯◯
Pei *et al*[40]	RCT/Quasi-RCT	Mixed	6 (447)	AE	–	Social function (SF-36)	MD: 8.24 (-1.09 to 17.58)	–	0.08	85.0%	⊕◯◯◯
Pei *et al*[40]	RCT/Quasi-RCT	Mixed	6 (513)	AE	–	Pain (SF-36)	MD: 5.94 (1.65 to 10.23)	–	0.007	49.0%	⊕◯◯◯
Pei *et al*[40]	RCT/Quasi-RCT	Mixed	7 (562)	AE	–	General health (SF-36)	MD: 8.90 (2.48 to 15.32)	–	0.007	71.0%	⊕◯◯◯
Pei *et al*[40]	RCT/Quasi-RCT	Mixed	6 (542)	AE	–	Mental health (SF-36)	MD: 7.30 (-0.94 to 15.54)	–	0.08	84.0%	⊕◯◯◯
Cheema *et al*[26]	RCT	Predialysis	6 (223)	RT	–	HRQOL	SMD: 0.83 (0.51 to 1.16)	Large	0.226	27.8%	⊕⊕◯◯
Oguchi *et al*[39]	RCT	KTRs	4 (179)	Mixed	–	HRQOL	SMD: 0.54 (0.02 to 1.07)	Moderate	0.04	58.0%	⊕◯◯◯

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Table 7 Continued

Study	Design	Stage of CKD	k (n)*	Exercise type	Mode	Outcomes	SMD or MD (95% CI)	Effect size	P value	I^2	GRADE
Ju *et al*[35]	RCT	Mixed	3 (387)	Mixed	–	Symptom/Problem (KDQOL)	SMD: 1.92 (-1.06 to 4.90)	Large	0.21	99.0%	⊕◯◯◯
Ju *et al*[35]	RCT	Mixed	3 (387)	Mixed	–	Effects of kidney disease (KDQOL)	SMD: −3.69 (-8.56 to 1.19)	Large	0.14	99.0%	⊕◯◯◯
Ju *et al*[35]	RCT	Mixed	3 (387)	Mixed	–	Burden of kidney disease (KDQOL)	SMD: 1.04 (-0.75 to 2.82)	Large	0.26	98.0%	⊕◯◯◯

Mixed means aerobic exercise combined with resistance training.
*Number of included studies and corresponding sample size.
AE, aerobic exercise; CKD, chronic kidney disease; COM, combine; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HD, haemodialysis; HRQOL, health-related quality of life; KDQOL, kidney disease quality of life; KTRs, kidney transplant recipients; MCS, mental component summary; MD, mean difference; PCS, physical component summary; RCT, randomised controlled trial; RT, resistance training; SF-36, Short Form Health Survey-36; SMD, standardised mean difference.

of physical performance in patients with CKD.[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 patients with CKD based on the current review. Meta-analyses by Andrade *et al* showed that combined training benefits cardiorespiratory fitness in patients with CKD.[24]

Both sarcopenia and obesity have increased mortality risk and progression to end-stage renal disease in patients with CKD.[63] Unlike patients receiving dialysis, treatment requirements for patients with predialysis CKD 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 patients with CKD. However, additional studies are needed to confirm the benefits of exercise programmes 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 patients with CKD 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 patients with CKD. 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 patients with CKD.

Several meta-analyses reported exercise-related adverse events. Based on the reported adverse events, we calculate that only three adverse events occurred per 1000 patients with CKD. The low incidence of adverse events indicated that the benefits of exercise in patients with CKD outweigh its potential risks and most reflected typical response to exercise (eg, muscle soreness). However, most meta-analyses only included intradialytic exercise for haemodialysis patients in their assessments. Exercises

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during haemodialysis 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 (eg, arrhythmias, myocardial ischaemia) 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 haemodialysis-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 patients with CKD. Evidence from most randomised 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 patients with CKD. Although exercise's effect sizes on improving health prognosis of patients with CKD 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-quality or very low-quality evidence, similar beneficial effects of exercise were reported by meta-analyses of randomised controlled trials with different grades of evidence. Remarkably, a recently published trial found that a 6-month intradialytic exercise programme 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 haemodialysis patients, limiting the results' extrapolation to other CKD stages. Second, improvement of flexibility in patients with CKD 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 have 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 patients with CKD, exercise improves muscle strength, endurance, body composition and HRQOL. At the same time, exercise decreases blood pressure and dialysis-related symptoms in patients with CKD. 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.

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