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REVIEW

Physical activity and cardiorenal health—from associations to interventional studies

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ABSTRACT

Clustering of traditional and kidney-specific risk factors leads to elevated cardiovascular disease (CVD) risk across the trajectory of chronic kidney disease (CKD) and transplantation. As kidney function declines, the prevalence of CVD, cardiovascular events, and mortality increases. This review considers recent evidence for the association between physical activity (PA) and exercise and cardiorenal health, and the effectiveness of interventions for the prevention and management of cardiorenal decline across the CKD spectrum. Evidence supports a beneficial dose–response effect of PA in the prevention of incident CKD, and growing evidence in prevalent CKD patients for the attenuation of kidney function decline, and a reduction in CVD risk, morbidity, and mortality. Broadly speaking, across the trajectory of CKD, the literature supports the efficacy of exercise interventions for improving cardiorespiratory fitness and aspects of cardiorenal health. The mechanisms underlying improvements indicate differential effects on traditional and non-traditional risk factors for CKD progression and CVD. To date, there is limited transfer of these findings into clinical care, although the evaluation of available evidence has led to the development of the first detailed clinical practice guideline for exercise and lifestyle in CKD. There is a lack of large-scale multicentre randomized controlled trials, and trials exploring hard clinical outcomes and long-term effects of exercise on cardiorenal outcomes. However, research should also address the challenges of implementing programmes of exercise and PA as part of routine care in combination with addressing the shortfall in literature to improve cardiorenal outcomes in all patients with CKD.

Keywords: cardiorenal, chronic kidney disease, intervention, physical activity, transplantation

INTRODUCTION

As early as 1836, Robert Bright highlighted the intricate and interdependent relationship between the kidneys and the heart, specifically the notable cardiac structural deviations evident in patients with advanced kidney disease [1]. Fast forward to the present and significant progress has been made in elucidating the cardiorenal interrelationship; the heart and kidneys are essential for cardiovascular homeostasis and disease or dysfunction of one organ, may initiate, accentuate, or precipitate the same in the other [2]. There are also independent processes and diseases that may simultaneously affect both organs, including advanced age, hypertension, diabetes, atherosclerosis, and arteriosclerosis [2]. Whilst traditional risk factors for cardiovascular disease (CVD) are over-represented in patients with chronic kidney disease (CKD), they do not explain the high prevalence of CVD across the spectrum of CKD [3], including transplantation [4], or why CVD is a leading cause of mortality [5, 6]. It is clustering of traditional and kidney-specific risk factors that drives changes in cardiovascular structure and function that associate most closely with patient outcomes (Fig. 1) [3, 7]. Traditional risk factors such as hypertension, diabetes, and dyslipidaemia drive CVD in the early stages and later, as disease progresses, kidney-specific risk factors dominate [8]. This is reflected in the pathophysiology of CVD in CKD; as kidney function declines non-atherosclerotic cardiac events become more common and are the leading mode of death in patients receiving haemodialysis [8]. After transplantation, although kidney function is in most cases improved and fatal cardiovascular events reduced, immunosuppressive medication regimes can have hypertensive, diabetogenic, and atherogenic effects, which tip the balance back towards 'traditional' risk factors (Fig. 1) [8]. The consequences of poor 'cardiovascular-kidney-metabolic' health are clear, with the most significant clinical implications being excess cardiovascular events and cardiovascular mortality [9].

Physical activity (PA) is any voluntary bodily movement produced by the skeletal muscle that requires expending energy. This can include occupational (e.g. activities at work), domestic (e.g. cleaning), transportation, or leisure-time activities (e.g. golf, cycling, walking). Exercise (or exercise training) is a sub-set of PA that is structured with the aims of sustaining or improving health and/or physical fitness (e.g. resistance training or running). We have long known the positive effects of being physically active on the prevention of CVD, even before a landmark study that showed the protective benefits of PA against coronary heart disease in active London bus conductors compared with their more sedentary driver colleagues [10]. Physical inactivity, or having a PA level that is insufficient to meet specific recommendations, is highly prevalent across the trajectory of CKD [11–13, 14]. Fatigue and muscle weakness are commonly experienced symptoms of CKD that can lead to a spiral of inactivity [15]. A large observation

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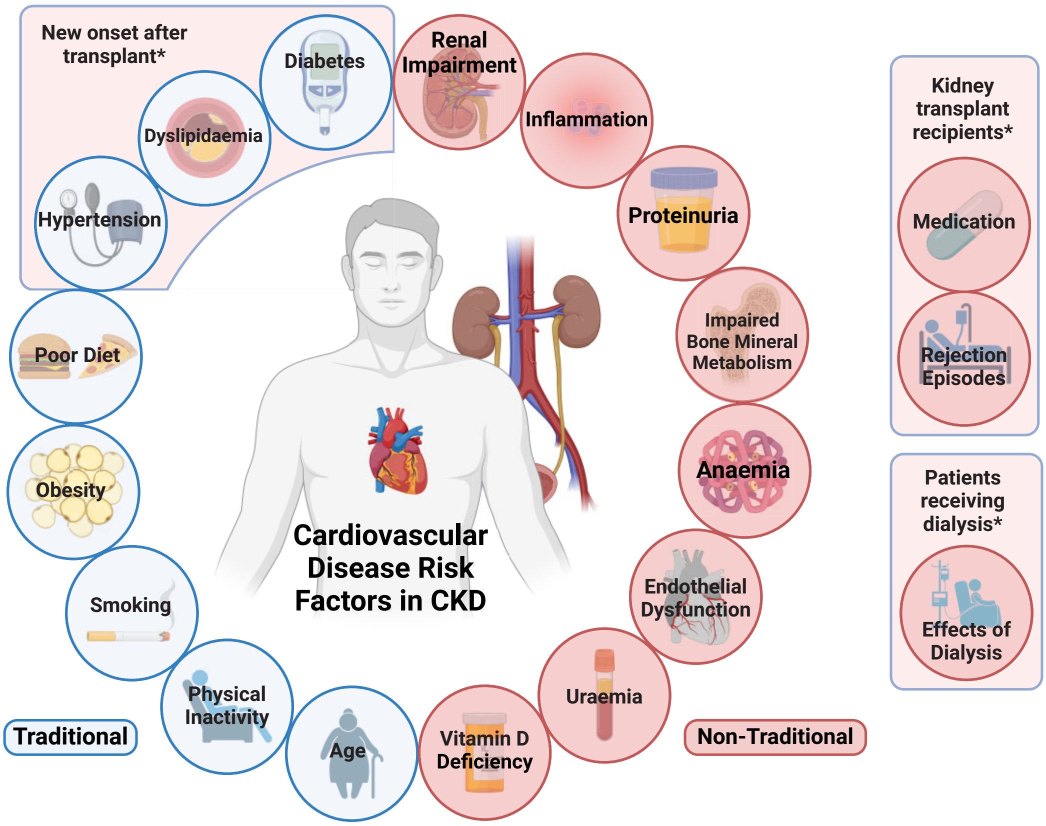

Figure 1: Cardiovascular disease risk factors in CKD. *Additional risk factors in named patient group. Created with BioRender.com.

cohort study reported up to 49% of 3 926 people with prevalent mild-to-moderate CKD were inactive [14]. The most recent umbrella review and meta-analysis compiling 31 systematic reviews assessing the therapeutic effects of exercise training across the CKD trajectory reported moderate positive effects on cardiorespiratory fitness (CRF), muscle strength, and body composition [16]. They also reported minor positive effects on muscle endurance, cardiovascular risk factors, dialysis-related symptoms, and health-related quality of life (QoL).

This review considers the available recent evidence for the association between physical activity and exercise and cardiorenal health, and the evidence surrounding the effectiveness of interventions for the prevention and management of its decline across the spectrum of CKD.

EVIDENCE OF ASSOCIATIONS BETWEEN PHYSICAL ACTIVITY AND CARDIORENAL HEALTH FROM OBSERVATIONAL STUDIES

Physical activity and the risk of CKD in the general population

A recent meta-analysis of 12 published observation cohort studies including over 1.2 million people identified that in the general population, individuals who are the most physically active have a lowered risk of CKD compared with those who are not active or are the least physically active (pooled multivariable-adj. RR, 0.91 [95% CI, 0.85–0.97]) [17]. The authors noted, however, that the quality of the evidence was low. In a combined cross-sectional and prospective observational study of ∼half a million adults in Spain, compared to physical inactivity, cross-sectional analyses at baseline showed that regular PA (OR, 0.80 [95% CI, 0.79–0.81]), but not insufficient PA (1.02 [95% CI, 0.99–1.04]) was associated with lower CKD prevalence [18]. Prospective analyses in individuals without CKD at baseline did not confirm an inverse association between PA and the odds of developing CKD during the short 2-year follow-up. In the same study in those with CKD, regular PA was associated with a lower prevalence (−45% to −7%) and incidence (−38% to −4%) of all CVD risk factors [18]. Parvathaneni *et al.* (2020) reported that in middle-aged adults, exceeding the WHO recommendation for aerobic PA (>300 min/week) resulted in a CKD risk reduction of −11% compared with −7% in those meeting the recommendations (≥150 min/week) during a 24-year follow-up [19]. In 2 668 participants with PA measured by the ActivPAL3 accelerometer, PA duration is inversely associated with endothelial dysfunction in those with and without CKD diagnosis [20].

Physical activity and cardiorenal health in non-dialysis-dependent CKD

Irrespective of PA levels, as kidney function declines, incidence of CVD, cardiovascular mortality, and cardiovascular events increases [3]. As CKD progresses, levels of PA decrease, and the number of patients categorized as inactive increases [11], leading to further increases in CVD risk. In a prospective cohort study of 3 926 people living with mild-to-moderate CKD, those in the highest compared with the lowest quartile of self-reported moderate-to-vigorous PA (MVPA) had lower risk of atherosclerotic events (HR, 0.64 [95% CI, 0.51–0.79]), incident heart failure (HR, 0.71 [95% CI, 0.58–0.87]), and all-cause and cardiovascular death (HR, 0.54 [95% CI, 0.46–0.63] and HR, 0.47 [95% CI, 0.35–0.64], respectively) [14]. Those classified as ‘inactive’ (performing 0 minutes of MVPA per week) showed the lowest levels of kidney function compared with those who were 'active' and either not meeting or meeting recommended PA levels. A cross-sectional analysis of the same study showed peripheral artery disease (PAD) severity was not associated with PA defined by total metabolic equivalent (MET) hours per week (MET-h/week). However, PAD severity was significantly associated with walking activity and walking pace [21]. Kuo *et al.* (2022) concluded after a longitudinal cohort analysis of 4 508 patients with CKD that PA of 7.5 to <15 MET-h/week is associated with lower risks of adverse cardiorenal outcomes and should be part of CKD care [22].

Physical activity and cardiorenal health in patients receiving dialysis

Studies of the association between PA and health are limited and of relatively small sample sizes within dialysis populations. An analysis of 5763 patients receiving haemodialysis assessed via the Rapid Assessment of Physical Activity questionnaire, showed an inverse association between PA levels and mortality (adj. HR of death for very active vs never/rarely active, 0.60 [95% CI, 0.47–0.77]) [23]. In a cross-sectional analysis of 20 920 patients receiving haemodialysis, PA was assessed using a single-item questionnaire and mortality risk was lower for regular (equal to or more than once/week) versus non-regular (less than once/week) exercisers (adj. HR, 0.73 [95% CI, 0.69–0.78]) [24]. However, no significant association was found between regular exercise and hospitalizations except for those due to fractures [24]. Data in 2 507 patients receiving peritoneal or haemodialysis found that regular exercise (between 2 and 3 and 4 and 5×/week) was associated with lower all-cause and cardiovascular mortality, although this benefit did not extend to those who reported daily exercise potentially indicating a shortfall in self-reported PA data [25]. However, in this study, patients who reported severe limitations in either moderate or vigorous PA experienced significantly increased cardiovascular mortality in multivariable analysis (RR, 1.59 [95% CI, 1.27–1.99; RR, 1.47 [95% CI, 1.10–1.97], respectively) [25].

Physical activity and cardiorenal health in patients with a kidney transplant

Research examining the association between PA and outcomes in kidney transplant recipients (KTRs) is limited but consistent. In a study of 4034 participants, KTRs in the lowest tertiles of PA, using modified summary scores from the Yale Physical Activity Survey, were more likely to be obese/overweight, have diabetes mellitus, and/or have prevalent CVD [26]. Independent of age, self-reported PA was inversely associated with metabolic syndrome, history of CVD, fasting insulin, and triglyceride concentration when examined in 540 KTRs [27]. The mortality of the least active group in this study was 24%, while the most active had a mortality rate of only 1.7% over 5.3 (4.7–5.7) years of follow-up. Longitudinal analysis of cardiovascular risk factors in active and sedentary KTRs showed stable allograft function in those who were active and worsening serum creatinine levels and proteinuria over time (~3 years) in those who were sedentary [28]. In this study, there was also an amelioration of all blood pressure indices, reduction in fasting blood glucose and triglyceride levels in those who were active.

Sedentary behaviour and cardiorenal health

Research has begun to focus on sedentary behaviour as a separate concept to PA: 'any waking behaviour with an energy expenditure of ≤1.5 METs, while in a sitting or reclining posture' [29]. The WHO recommends that adults limit sedentary time and in the case of high sedentary time, undertake more than the recommended volume of PA [30]. Extended periods of sedentary behaviour are becoming recognized as an independent determinant of poor outcomes [31]. In a cohort analysis of 132 122 middle-aged and older adults in China, increased sitting time was significantly associated with the risk of kidney function decline (aHR, 1.136 [95% CI, 1.036–1.247]) [32]. Greater television watching time was related to a higher CKD occurrence and lower kidney function in an analysis of 329 758 UK Biobank participants [33]. In almost half a million adults in Taiwan, prolonged occupational sitting was significantly associated with a higher risk of CKD (OR, 1.26 [95% CI, 1.21–1.31]), end stage kidney disease (HR, 1.19 [95% CI, 1.03–1.38]), and kidney-specific mortality (HR, 1.43 [95% CI, 1.07–1.91]) compared with mostly standing participants after controlling for PA and other risk factors [34]. Crucially, even a minimal level of PA of 15 min/day (90 min/week) of moderate intensity, was associated with a reduction in these risks [34]. These findings are supported by a study by Oh *et al.* (2023) who showed that the harmful effects of high sedentary time on the occurrence of CKD are mitigated by high levels of PA [35]. Sedentary time was associated with a small longitudinal decline in kidney function in 7134 adults without CKD; however, in stratified analyses, each 1-hour increase in sedentary time was associated with a significant decline in kidney function in women but not men [36]. In a small prospective cohort study, extended sedentary time increased the risk of new cardiovascular or kidney events and/or all-cause mortality in patients with diabetic kidney disease [37]. In CKD, longer sedentary bouts measured by accelerometery associated with endothelial dysfunction [20].

Summary

Table 1 presents an overview of the included studies. There is evidence to support a beneficial dose-response effect of PA in the prevention of incident CKD and growing evidence in those with prevalent CKD for the attenuation of kidney function decline, and the reduction in CVD risk, morbidity, and mortality. Larger volumes of sedentary behaviours associate with an increased risk of CKD, a faster decline in kidney function, and in those with CKD, an increased risk of CVD and mortality. Emerging observational data suggest that even in patients with high levels of sedentary behaviours, some of the detrimental effects are mitigated by even small increases in PA levels. The key disparities in these studies that make coherent interpretation and evidence synthesis difficult are the large and differing methods that have been used to determine PA and sedentary behaviours. Generally, subjective methods that infer more bias (e.g. self-reported questionnaires) are more commonly used, and ideally more studies with objective methods (e.g. device-measured) are required. Observational studies alone cannot infer causality, and commonly, people with less poor health are more active overall. Therefore, it is important to follow up these studies with rigorous interventional studies.

PHYSICAL ACTIVITY AND EXERCISE INTERVENTIONS TARGETING CARDIORENAL OUTCOMES

There is an abundance of interventional studies across the trajectory of CKD that examine a broad array of exercise interventions (aerobic, resistance, balance, etc.), targeting different behaviours (increasing PA, reducing sedentary time, and increasing specific exercise), in a variety of locations and methods of delivery (e.g. supervised vs unsupervised, and in-centre, community-based, or home-based), assessing a wide range of outcome measures. Peak

Table 1: Characteristics of included observational studies.

Author Year Country (Data origin) Study	Study type	Population	Sample size	Physical activity/sedentary behaviour measure	Key outcome(s)
Physical activity and the risk of CKD in the general population					
Seidu *et al.* 2023 Multiple N/A	Systematic review and meta-analysis	Adult, general population	1 281 727 (from 12 observational cohort studies)	Multiple Self-report: 12/12 studies	The pooled multivariable-adjusted RR [95% CI] of CKD comparing the most vs the least physically active groups was 0.91 [0.85–0.97]. 9% lower risk of CKD in the most vs least active groups Low quality of evidence reported
Castillo-Garcia *et al.* 2024 Spain N/A	Prospective cohort and cross-sectional	Adults (18–64 yrs)	517 917	Self-report: undefined questionnaire	Compared with physical inactivity, cross-sectional analyses at baseline showed that regular PA (OR, 0.80 [95% CI, 0.79–0.81]), but not insufficient PA (1.02 [0.99–1.04]) was associated with lower CKD prevalence. Prospective analyses (short 2-yr follow-up) failed to confirm this association ($P > 0.1$). CKD was associated with a higher prevalence of hypertension (+3%) and diabetes (+5%) at baseline and with a greater incidence of hypertension at follow-up (+37%). In prevalent CKD, regular PA was associated with a lower prevalence (–45% to –7%) and incidence (–38% to –4%) of all CVD risk factors
Parvathaneni *et al.* 2021 USA ARIC	Prospective cohort	Adults (45–64 yrs, Black or white)	15 792	Self-report: modified Baecke Physical Activity Questionnaire	Higher categories of PA were associated with lower risk for CKD compared with the inactive group (HRs for insufficiently active, 0.95 [95% CI, 0.88–1.02]; active, 0.93 [95% CI, 0.86–1.01]; highly active, 0.89 [95% CI, 0.81–0.97]; P for trend = 0.007). Median follow-up 24 yrs
Bellos *et al.* 2023 Netherlands Maastricht Study	Cross-sectional	Adults (40–75 yrs)	2668	Objective: ActivPAL3 accelerometer	After adjustment for clinicodemographic covariates, higher total PA was associated with a significantly lower endothelial dysfunction score both among participants with normal (model 3, β: –2.68 [95% CI, –4.07 to –1.30]) and impaired (model 3, β: –4.42 [95% CI, –7.98 to –0.87]) kidney function
Physical activity and cardiorenal health in non-dialysis-dependent CKD					
Bruinius *et al.* 2022 USA CRIC	Prospective cohort study	Adults (21–74 yrs) with eGFR 20–70 mL/min/1.73m^2	3926	Self-report: Multi-Ethnic Study of Atherosclerosis; Typical Week Physical Activity Survey	Compared with participants in the lowest MVPA quartile, the highest quartile had lower risk of atherosclerotic events (HR, 0.64 [95% CI, 0.51–0.79]), incident heart failure (HR, 0.71 [95% CI, 0.58–0.87]), and all-cause and cardiovascular death (HR, 0.54 [95% CI, 0.46–0.63], and HR, 0.47 [95% CI, 0.35–0.64], respectively). Findings were similar for analyses evaluating recommended level of PA. Median follow-up 13.4 yrs
Wang *et al.* 2016 USA CRIC	Cross-sectional	Adults (21–74 yrs) with mild-to-moderate CKD as defined by eGFR	3543	Self-report: Multi-Ethnic Study of Atherosclerosis; Typical Week Physical Activity Survey	In a multivariable linear regression model, PAD severity was not associated with PA defined by total MET-h/wk in men or women ($P = 0.432$). However, PAD severity was significantly associated with walking activity ($P = 0.037$), although this relationship did not differ by sex ($P = 0.130$). Similarly, PAD severity was significantly associated with walking pace ($P < 0.001$), although this relationship did not differ by sex ($P = 0.086$). In contrast, there was an independent association between PAD severity and SF-12 (physical function, $P = 0.018$), with a significant interaction by sex ($P < 0.001$)

Table 1: Continued

Author Year Country (Data origin) Study	Study type	Population	Sample size	Physical activity/sedentary behaviour measure	Key outcome(s)
Kuo *et al.* 2022 Taiwan N/A	Longitudinal cohort	Adults (>20 yrs) with pre-dialysis CKD: Stage 1–3A CKD patients with >1 g/d of proteinuria or Stage 3B–5 CKD patients	4508	Self-report: National Health and Nutrition Examination Survey (NHANES)	Highly active group had the lowest chance of all study outcomes, followed by low-active and inactive groups ($P < 0.001$). Multivariable Cox regression showed that only highly active group was independently associated with lower risks for all-cause mortality (HR, 0.62 [95% CI, 0.53–0.74]), ESKD (HR, 0.83 [95% CI, 0.72–0.96]), and MACE (HR, 0.63 [95% CI, 0.51–0.76]) compared with the inactive group. The risks of MACE did not further decrease once PA surpassed 15 MET-h/wk, indicating a U-shaped association. Median follow-up 686 d
Physical activity and cardiorenal health in patients receiving dialysis					
Lopes *et al.* 2014 Multiple DOPPS	Prospective cohort study	Prevalent in-centre HD patients (>17 yrs)	5763	Self-report: Rapid Assessment of Physical Activity	CVD was the main reported cause of death: 33.3% for patients infrequently or never/rarely active and 36.0% for patients sometimes to very active. An inverse association was seen between aerobic PA level and mortality. Compared with never/rarely active patients, the extensively adjusted HR was 0.89 [95% CI, 0.72–1.10] for infrequently active, 0.84 [95% CI, 0.67–1.05] for sometimes active, 0.81 [95% CI, 0.68–0.96] for often active, and 0.60 [95% CI, 0.47–0.77] for very active (P for trend < 0.001) patients. Median follow-up 1.6 yrs
Tentori *et al.* 2010 Multiple DOPPS	Cross-sectional	Prevalent in-centre HD patients (>17 yrs)	20920	Self-report: unnamed questionnaire	In models extensively adjusted for demographics, comorbidities and socioeconomic indicators, mortality risk was lower among regular exercisers (HR, 0.73 [0.69–0.78], $P < 0.0001$) and at facilities with more regular exercisers (0.92 [0.89–0.94], $P < 0.0001$ per 10% more regular exercisers). No significant association was found between regular exercise and hospitalizations except for those due to fractures
Stack *et al.* 2005 USA DMMS Wave 2	Cross-sectional	PD or HD (>15 yrs)	2507	Self-report: unnamed questionnaire	Mortality risks were greatest for those with severe limitations in either moderate (RR, 1.72 [95% CI, 1.44–2.05]) or vigorous physical activities (RR, 1.51 [95% CI, 1.20–1.90]) compared with those reporting minimal or no limitations. Conversely, mortality risks were lower for patients who exercised 2 to 3×/wk (RR, 0.74 [95% CI, 0.58–0.95]) or 4 to 5×/wk (RR, 0.70 [95% CI, 0.47–1.07]), whereas no advantage was associated with daily exercise (RR, 1.06 [95% CI, 0.86–1.30])
Physical activity and cardiorenal health in patients with a kidney transplant					
Kang *et al.* 2019 Multiple FAVORIT	Cross-sectional	Adult KTRs ≥6 mo post-transplant (35–75 yrs)	4034	Self-report: Yale Physical Activity Survey (YPAS)	More participants in the 'low' PA tertile were overweight/obese, had a history of prevalent diabetes and/or CVD, compared with more active participants (all $P < 0.001$)
Zelle *et al.* 2011 Netherlands N/A	Prospective cohort	Adult KTRs >1 yr post-transplant	540	Self-report: Tecumseh Occupational Activity Questionnaire and the Minnesota Leisure Time Physical Activity Questionnaire	Cardiovascular mortality was 11.7, 7.2, and 1.7%, respectively, according to gender-stratified tertiles of physical activity ($P = 0.001$). All-cause mortality was 24.4, 15.0, and 5.6% according to these tertiles ($P < 0.001$). In Cox regression analyses, adjustment for potential confounders including history of CVD, muscle mass, and traditional risk factors for CVD did not materially change these associations. Median follow-up 5.3 yrs

Table 1: Continued

Author Year Country (Data origin) Study	Study type	Population	Sample size	Physical activity/sedentary behaviour measure	Key outcome(s)
Totti *et al.* 2020 Italy N/A	Observational cohort	Stable adult KTRs (45–51 yrs)	54	Self-report: interview	Graft function was stable in active KTRs, while it showed a decline over time in sedentary KTRs, as indicated by the rise in serum creatinine levels ($P = 0.006$) and lower eGFR ($P = 0.050$). There was an amelioration of all blood pressure indices, reduction in fasting blood glucose and in triglyceride levels in those who were active. Three follow-ups over 3-yr period
Sedentary behaviour and cardiorenal health					
Yu *et al.* 2023 China CCDCC	Prospective cohort	Adults (>40 yrs)	132123	Self-report: International Physical Activity Questionnaire (IPAQ)	Longer sitting time was significantly associated with the risk of kidney function decline (aHR, 1.136 [95% CI, 1.036–1.247, $P = 0.007$, comparing participants with baseline sitting time in the lowest quartile with those in the highest quartile) after adjustment for potential confounders. Mean follow-up 3.8 yrs
Park *et al.* 2022 UK UK Biobank data	Observational cohort	Adults (40–69 yrs)	329758	Self-report: unnamed questionnaire	Those with a longer time spent watching television had significantly higher odds of CKD (aOR 1.091 [95% CI, 1.072–1.111]) and lower eGFR values. Using computer and driving were also inversely associated with the eGFR after adjustment for age and sex. However, computer use was not significantly associated with CKD and driving was associated with lower odds of CKD
Tsai *et al.* 2022 Taiwan N/A	Prospective cohort	Adults (>20 yrs)	455506	Self-report: unnamed questionnaire	Occupational sitting was significantly associated with a higher risk of CKD (OR, 1.26 [95% CI, 1.21–1.31]), ESKD (HR, 1.19 [95% CI: 1.03–1.38]), and kidney-specific mortality (HR, 1.43 [95% CI, 1.07–1.91]) compared with mostly standing participants after controlling for PA and other risk factors. A minimal level of PA of 15 min/d (90 min/wk) of moderate-intensity, was associated with a reduction in these risks. 13-yr follow-up
Oh *et al.* 2023 South Korea KoGES	Prospective cohort	Adults (40–69 yrs)	7988	Self-report: unnamed questionnaire	Relative to the low-sedentary time, the coefficients of annual eGFR decline were (−0.07 [59% CI, −0.19 to 0.05], $P = 0.236$) and (−0.14 [95% CI, −0.28 to −0.01], $P = 0.039$) in the moderate- and high-sedentary time groups, respectively. Incident CKD was higher with lower PA (HR: high-PA 1.00, moderate-PA 1.13 [1.00, 1.28, $P = 0.056$] and low-PA 1.25 [1.11, 1.24, $P < 0.001$]) and higher sedentary time (HR: low-sedentary time 1.00, moderate-sedentary time 1.04 [0.94, 1.16, $P = 0.440$] and high-sedentary time 1.19 [1.05, 1.34, $P = 0.007$]). The high-PA reduced the risk for the CKD development irrespective of the amount of sedentary time. Median follow-up 12 yrs
Hannah *et al.* 2021 USA HCHS/SOL	Prospective cohort	Adults (18–74 yrs)	7134	Objective: Actical version B-1	On multivariable analysis, each 1-h increase in sedentary time was associated with a longitudinal decline in eGFR (−0.06% per year [95% CI, −0.10 to −0.02]). There was a significant interaction with sex, and on stratified analyses, higher sedentary time was associated with eGFR decline in women but not men. Median follow-up 6.1 yrs

Table 1: Continued

Author Year Country (Data origin) Study	Study type	Population	Sample size	Physical activity/sedentary behaviour measure	Key outcome(s)
Chuang *et al.* 2024 USA N/A	Retrospective cohort	Adults (20–79 yrs) with reduced kidney function (eGFR <60 mL/min/1.73m^2 or receiving dialysis)	1419	Self-report: National Health and Nutrition Examination Survey (NHANES)	The crude analysis showed that individuals with sedentary lifestyle have higher risk of all-cause and CVD-related but not cancer-related mortality compared with the non-sedentary population. After adjusting for potential confounders, we showed that all-cause mortality and CVD-related mortality were 1.64-fold [95% CI, 1.26–2.12] and 1.66-fold [95% CI, 1.03–2.67] higher, respectively, in the sedentary population compared with the non-sedentary population. Median follow-up 99 mo
Bellos *et al.* 2023 Netherlands Maastricht Study	Cross-sectional	Adults (40–75 yrs)	2668	Objective: ActivPAL3 accelerometer	Positive association of endothelial dysfunction score with sedentary bout duration (β: 43.72 [95% CI, 9.85]; 77.59)

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; d, day(s); eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; h/wk, hours/week; KTR, kidney transplant recipient; MACE, major adverse cardiac event; MET, metabolic equivalent; min, minutes; mo, month(s); MVPA, moderate to vigorous physical activity; PA, physical activity; PAD, peripheral artery disease; yr(s), year(s).

oxygen consumption (VO_{2peak}) derived from cardiopulmonary exercise testing (CPET) is the gold standard measure of CRF and both its prognostic links with clinical outcomes and CVD risk in CKD have been rigorously explained [38]. However, a maximal exercise test is often unattainable in elderly, frail, and/or symptomatic patients and is a resource-intensive investigation in larger trials. The 6-minute walk test (6MWT) is well correlated with VO_{2peak} in clinical populations and is well used in randomized controlled trials (RCTs) [39, 40]. Herein we present the most recent and largest studies of exercise interventions across CKD groups and a summary is provided in Table 2.

Interventions in non-dialysis-dependent CKD

In early CKD development, traditional CVD risk factors are of predominant importance in therapeutic intervention due to their contribution to atherosclerotic vascular disease development and their detrimental impact on the vessels of the kidney leading to progression of functional decline [3]. The RENEXC trial was one of the largest self-monitored exercise trials in 151 non-dialysis-dependent (NDD) CKD patients (G3-5) combining aerobic exercise with either resistance training or balance training over 12 months [41]. Both groups experienced improvements (increased effect sizes) in physical performance: 6MWT distance (31 m and 24 m, $P < 0.001$), 30-second sit-to-stand test (both: 1 rep, $P < 0.001$); quadriceps strength (right/left: strength 1.2/0.8 kg*m, $P < 0.003$; balance 0.6/0.9, $P < 0.01$); and functional reach (both: 2 cm, $P < 0.01$) [41]. In a sub-study analysis of 112 patients, blood pressure, triglycerides, total cholesterol, high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C), IL6, CRP, and albumin were all unchanged [42]. The AWARD study was a multicentre RCT assessing the effects of 12 months of predominantly centre-based (thrice weekly in-centre for 6 months and 1 home-based and 2 centre-based for the remaining 6 months) supervised combined aerobic and resistance exercise versus education showed positive changes in CPET measured CRF at 6 months (17.9 ± 5.5 vs 15.9 ± 7.0 mL/kg/min, $P = 0.03$) although this difference was not maintained at 12 months [43]. No significant changes were found in HbA1c, blood pressure, or body mass index (BMI). A systematic review and meta-analysis of 13 RCTs of predominantly aerobic exercise therapy showed increases in kidney function, decreases in BMI, and decreases in systolic and diastolic blood pressure compared with controls [44]. Caution has been advised for the adoption of exercise purely on the basis of delaying the decline in kidney function, as the mechanisms remain unclear [45]. It is likely that the positive effects observed have been due to improvements in disease progression risk factors such as blood pressure, glucose regulation, and BMI [45], all of which double as CVD risk factors, highlighting the importance of being active in this patient group even in early stage CKD.

Interventions in patients receiving dialysis

The CYCLE-HD RCT assessed the effects of a 6-month programme of structured intra-dialytic cycling in 130 patients showing improvements in prognostically important measures of cardiovascular structure and function assessed with cardiac MRI, including reduced left ventricular mass, myocardial fibrosis, and aortic stiffness compared with standard care [46]. However, the trial reported no change in PA levels. Whilst the PEDAL multicentre trial showed no effect of 6 months of intra-dialytic cycling combined with resistance training [47], the DiaTT trial of 12 months of similar exercise in 1 211 patients did show improvements in the 6MWT and sit-to-stand 60 [48]. The increased

Table 2: Characteristics of included interventional studies.

Author Year Country (Data origin) Study	Study type Inclusion/Exclusion criteria	Sample size	Intervention	Main outcome(s)
Interventions in non-dialysis-dependent CKD				
Zhang *et al.* 2019 Multiple N/A	Systematic review and meta-analysis Inclusion: RCTs Adults (>18 yrs) Non-dialysis CKD (stage 2–5) Studies describing the effects of exercise. Exclusion: Non-randomized trials Dialysis Inappropriate statistical methods Data not mean ± SD	421 (from 13 RCTs)	Multiple	Compared with the controls, exercise therapy brought an increase in eGFR (MD = 2.62 [95% CI, 0.4–4.82], $P = 0.02$, I2 = 22%), and decreases in SBP (MD = −5.61 [95% CI, −8.99 to −2.23], $P = 0.001$, I2 = 44%), DBP (MD = −2.87 [95% CI, −3.65 to −2.08], $P < 0.00001$, I2 = 16%) and BMI (MD = −1.32 [95% CI, −2.39 to − 0.25], $P = 0.02$, I2 = 0%). Exercise therapy of short-term (< 3 mo) decreased triglyceride (TG) level ($P = 0.0006$). However, exercise therapy did not significantly affect SCr, TC, HDL, or LDL in non-dialysis CKD patients
Hellberg *et al.* 2019 Sweden RENEXC	RCT Inclusion: ≥18 yrs No contraindication for regular exercise. Exclusion: Severe orthopaedic or neurologic disorders, unstable CVD, uncontrolled hypertension, severe anaemia, severe electrolyte disturbances, inability to communicate in Swedish, inability to understand oral instructions, expectation to start KRT < 1 yr	151 (76 strength group; 75 balance group)	Both groups: 150 min/wk of self-administered exercise training for an intervention period of 12 mo. In both groups, 60 min of endurance training was part of the prescription and was combined with 90 min of either strength training (strength group) or balance training (balance group)	Endurance, measured with the 6MWT, increased after 4 mo in the strength group and after 12 mo in the balance group; stair climbing increased after 12 mo in both groups. There was a significant decrease in mGFR of 1.8 ml/min/1.73 m^2 in both groups after 12 mo, with no interaction effect. U-ACR decreased significantly in the strength group at 12 mo and was unchanged in the balance group, with a significant interaction effect. There were no significant interaction effects (treatment*time) between the strength group and the balance group for estimated effects for any of the physical performance measures after 12 mo of intervention
Zhou *et al.* 2020 Sweden RENEXC (sub-study)	As above	112 (53 strength group; 59 balance group)	As above	After 12 mo of exercise training, the abdominal aortic calcification score increased significantly in both groups; mGFR and lipoprotein (a) decreased significantly in both groups; parathyroid hormone and $1,25(OH)_2D_3$ increased significantly only in the strength group; fetuin-A increased significantly only in the balance group. Plasma triglycerides, TC, HDL, LDL, FGF23, phosphate, calcium, IL6, CRP, albumin were unchanged

Table 2: Continued

Author Year Country (Data origin) Study	Study type Inclusion/Exclusion criteria	Sample size	Intervention	Main outcome(s)
Weiner *et al.* 2023 USA AWARD	RCT Inclusion: Adults with CKD 15–<45 mL/min/1.73^2. Exclusion: >185 min/wk exercise, prior disabling stroke, severe anaemia (haemoglobin <9 g/dL), uncontrolled diabetes (glycated haemoglobin >10%), vascular claudication impairing physical functioning, dementia or severe cognitive impairment, NYHA class III/IV heart failure, and acute cardiovascular event (stroke, myocardial infarction, decompensated heart failure, or coronary revascularization) <6 mo	99 (49 exercise group; 50 control group)	Exercise: 3×/wk in-centre for 6 mo. 1 to 3 sessions at home for the second 6 mo. Progressive aerobic exercise starting with 20 min at 50–60% heart rate reserve progressing to 40 min at 70–80%. Two 10-min strength routines per wk. Control: Group-based educational sessions modelled after the successful ageing intervention in the LIFE (Lifestyle Interventions and Independence for Elders) clinical trial in older adults. Weekly for 6 mo and monthly for the second 6 mo	At 6 mo, aerobic capacity was higher among exercise participants (17.9 ± 5.5 vs 15.9 ± 7.0 mL/kg/min, $P = 0.03$), but the differences were not sustained at 12 mo. 6MWT distance improved more in the exercise group (adjusted difference: 98 feet [$P = 0.02$; $P = 0.03$ for treatment-by-time interaction]). The exercise group had greater improvements on the TUAG ($P = 0.04$) but not the SPPB ($P = 0.8$). No significant changes were found in HbA1c, blood pressure, or BMI
Interventions in patients receiving dialysis				
Graham-Brown *et al.* 2021 UK CYCLE-HD	RCT Inclusion: Adults (>18 yrs) receiving maintenance haemodialysis for >3 mo. Exclusion: Unable to participate in exercise programme, unable to undergo MRI scan, unfit to exercise according to ACSM guidance	130 (65 exercise group, 65 control group)	Exercise: 6 mo intradialytic cycling 3×/wk. Aiming for 30 min continuous cycling at RPE 12–14. 1-mo 'run-in' period. Control: 6 mo usual care	Significant reduction in left ventricular mass between groups (−11.1 g; 95% CI −15.79 to −6.43), which remained significant on sensitivity analysis (missing data imputed) (−9.92 g; 14.68 to −5.16). There were significant reductions in native T1 mapping and aortic pulse wave velocity between groups favouring the intervention. There was no increase in either ventricular ectopic beats or complex ventricular arrhythmias as a result of exercise with no significant effect on physical function or QoL
Greenwood *et al.* 2021 UK PEDAL	RCT Inclusion: Adults (>18 yrs) receiving haemodialysis for >3 mo. Exclusion: Expected survival <6 mo, clinically unstable, bilateral lower limb amputation, severe cognitive impairment, pregnancy	335 (175 exercise group, 160 control group)	Exercise: 6 mo intradialytic cycling 3×/wk. 2×/wk lower extremity muscular conditioning (3 sets of 5 repetitions) Control: 6 mo usual care	Mean difference in change KDQOL-SF PCS (Kidney Disease Quality of Life Short-Form physical component summary) from baseline to 6 mo between exercise and control was 2.4 [95% CI, −0.1 to 4.8] arbitrary units ($P = 0.055$); no improvements were observed in VO_{2peak} or secondary outcome measures (arterial stiffness, physical activity, gait speed, STS-60). Participants in the intervention group had poor compliance (47%) and poor adherence (18%) to the exercise prescription

Table 2: Continued

Author Year Country (Data origin) Study	Study type Inclusion/Exclusion criteria	Sample size	Intervention	Main outcome(s)
Anding-Rost *et al.* 2023 Germany DiaTT	RCT Inclusion: Adults (>18 yrs) receiving haemodialysis for >4 wks. Exclusion: Planned kidney transplant <12 mo, planned other dialysis <12 mo, participation in other exercise during dialysis (≥1 session/wk), unstable/uncontrolled conditions	1211 (578 exercise group, 633 control group	Exercise: Intradialytic exercise 3×/wk (60 min). Endurance exercise, 30 min cycling. Resistance exercise, 30 mins exercise bands, balls, and dumbbells (8 exercises, 2×1-min sets 12–13 RPE). Control: usual care	At 12 mo, the STS repetitions improved from 16.2 ± 7.6 to 19.2 ± 9.1 in the exercise group but declined from 16.2 ± 7.1 to 14.7 ± 7.9 in the usual care group (group difference, 3.85 repetitions; [95% CI, 2.22–5.48], $P < 0.0001$). The TUAG test (−1.1 seconds; [95% CI, −1.9 to −0.3]) and the 6MWT (37.5 m; [95% CI, 14.7–60.4]) also differed in the exercise group versus usual care group. The physical summary score and vitality subscale of the QoL questionnaire (i.e. the 36-item Short Form Health Survey) differed in the exercise group versus usual care group, but the other subscales did not change. Adverse events during dialysis sessions were similar in both groups. Median days spent in the hospital annually were 2 in the exercise group and 5 in the usual care group. Mortality and dialysis-specific adverse events were not affected
Manfredini *et al.* 2017 Italy EXCITE	RCT Inclusion: Adults (>18 yrs) on haemodialysis (>6 mo). Exclusion: Physical or clinical limitations to deambulation	296 (151 exercise group, 145 control group)	Exercise: 6 mo individualized, home-based, low-intensity personalized programme of walking exercise. Based on 6MWT performance and gradually increased throughout. Control: usual care	The distance covered during the 6MWT improved in the exercise group (mean distance ± SD: baseline, 328 ± 96 m; 6 mo, 367 ± 113 m) but not in the control group (baseline, 321 ± 107 m; 6 mo, 324 ± 116 m; $P < 0.001$ between groups). Similarly, the five times STS test time improved in the exercise group (mean time ± SD: baseline, 20.5 ± 6.0 seconds; 6 mo, 18.2 ± 5.7 seconds) but not in the control group (baseline, 20.9 ± 5.8 seconds; 6 mo, 20.2 ± 6.4 seconds; $P = 0.001$ between groups). The cognitive function score ($P = 0.04$) and quality of social interaction score ($P = 0.01$) in the kidney disease component of the KDQOL-SF improved significantly in the exercise arm compared with the control arm
Mallamaci *et al.* 2022 Italy EXCITE	Long-term observational (following above RCT) As above	227 (104 exercise group, 123 control group)	Observational period (36 mo) following the above RCT	The long-term risk for hospitalization or death was 29% lower (HR, 0.71 [95% CI, 0.50–1.00]), and in an analysis stratified by adherence to the walking exercise programme during the 6-mo trial, the subgroup with high adherence (>60% of prescribed sessions) had a 45% lower risk as compared with the control group (HR, 0.55 [95% CI, 0.35–0.87]). A Bayesian analysis showed that the posterior probability of a (HR, 0.71 [95% CI, 0.50–1.00]) for the risk of the composite outcome observed in the post-trial observational study was 93% under the conservative prior and 97% under the optimistic prior
Interventions in patients with a kidney transplant				
Wilkinson *et al.* 2022 Multiple N/A	Systematic review and meta-analysis Inclusion: RCTs Adults ≥18 yrs Received or awaiting kidney transplant. Exclusion: Unpublished materials and abstracts Dialysis and non-dialysis CKD	827 (from 16 RCTs)	Multiple	Significant improvements were observed in cardiorespiratory function (VO_{2peak}) (3.21 ml/kg/min, $P = 0.003$), 6MWT (76.3 metres, $P = 0.009$), physical function (STS-60, 4.8 repetitions, $P = 0.04$), and HDL (0.13 mg/dL, $P = 0.03$). A moderate increase in maximum heart rate was seen ($P = 0.06$). A moderate reduction in creatinine was also observed (0.14 mg/dl, $P = 0.05$). Isolated studies reported improvements in strength, bone health, lean mass, and QoL. Overall, studies had high risk of bias suggestive of publication bias

Table 2: Continued

Author Year Country (Data origin) Study	Study type Inclusion/Exclusion criteria	Sample size	Intervention	Main outcome(s)
Painter *et al.* 2002 USA N/A	RCT Inclusion: Received kidney transplant <2 mo. Exclusion: Transplant rejection Psychiatric or neurological disorder Orthopaedic/other limitations to exercise. Contraindications to exercise in line with ACSM guidelines	167 97 completed follow-up (54 exercise group, 43 control group)	Exercise: 12 mo home-based aerobic exercise that consisted of walking/cycling 4×/wk for at least 30 min (intensity set at 60–65% maximum HR, progressed up to 75–80%). Control: 12 mo usual care	At 1 yr 67% of the exercise group were exercising regularly compared with 36% of the control group ($P = 0.01$). Compared with the control group, the exercise group had significantly greater gains in VO_{2peak} ($P = 0.016$), per cent age-predicted VO_{2peak} ($P = 0.03$), and muscle strength ($P = 0.05$), and a trend towards higher self-reported physical functioning ($P = 0.06$). There were no differences between the groups in changes in body composition
Zhang *et al.* 2023 China N/A	RCT Inclusion: Adults >18 yrs Undergoing first kidney transplant Smartphone access No experience of resistance training Participating in no other research. Exclusion: Cognitive or mental disability Skeletal muscle issues hindering exercise Transplant rejection Haemodynamic instability	108 (54 exercise group, 54 control group)	Exercise: 6 mo total nurse-led programme. Pre- and post discharge. Non-ambulatory to ambulatory (after passing TUAG test). Daily combined aerobic and resistance training. Once discharged participants sent daily video to nurse. Dumbbells for resistance training	Compared with the control group, the intervention group had less fatigue and more motivation to be active in primary outcomes. Patients in the intervention group had a higher phase angle, a longer 6MWT distance, more 30-second chair stand times and decreased anxiety and depression levels in secondary outcomes. There were no significant differences in all dimensions of the QoL questionnaire between the intervention and the control group
Greenwood *et al.* 2015 UK	RCT Inclusion: Adults ≥18 yrs Kidney transplant <12 mo. Exclusion: Pregnancy Ambulatory support <50 m Unstable conditions Structured exercise participation <6 mo prior Psychiatric illness	60 (20 aerobic group [AT], 20 resistance group [RT], 20 control group [C])	Exercise: 12 wks of AT or RT 3×/wk. AT consisted of stationary bike, treadmill and elliptical trainer, 80% HR maximum, RPE 13–15. Training duration was progressed to 60 min/session. RT intensity set at 80% 1-RM for both upper and lower body exercises. Frequency built to 3 sets of 8–10 repetitions (bench press, latissimus pulldown, bicep curl, triceps pull down, leg press, knee extension, hamstring curl, and calf raises). AT group were provided with a HR monitor and the RT were provided with therabands, ankle weights and free weights. Control: usual care not referred to any exercise pathway	Analyses of covariance, adjusted for baseline values, age, and dialysis vintage pre-transplantation, revealed significant mean differences between AT and usual care in pulse wave velocity of -2.2 ± 0.4 [95% CI, -3.1–-1.3] m/s (P, 0.001) and between RT and usual care of -2.6 ± 0.4 [95% CI, -3.4–1.7] m/s (P, 0.001) at 12 wks. Secondary analyses indicated significant improvements in VO_{2peak} in the AT group and in VO_{2peak}, STS 60, and isometric muscle force in the RT group compared with usual care at 12 wks

Abbreviations: ACSM, American College of Sports Medicine; BMI, body mass index; CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1C; HDL, high-density lipoprotein; HR, heart rate; IL-6, interleukin 6; KRT, kidney replacement therapy; LDL, low-density lipoprotein; mo, month(s); MRI, magnetic resonance imaging; NYHA, New York Heart Association; PA, physical activity; QoL, quality of life; RCT, randomized controlled trial; RPE, rating of perceived exertion; SBP, systolic blood pressure; SCr, serum creatinine; SPPB, short physical performance battery; STS, sit-to-stand; TC, total cholesterol; TUAG, timed up-and-go; U-ACR, urine albumin–creatinine ratio; VO_{2peak}, peak oxygen uptake; wk(s), week(s); yr(s), year(s); 6MWT, 6-minute walk test.

duration and sample size of the DiaTT study could likely account for the observed differences between trials, especially as both studies recruited similarly older and frailer patients. Additionally, longer programmes of exercise may be needed to elicit changes in this population. There is increasing high-quality evidence for the effectiveness of intra-dialytic exercise programmes on cardiovascular health, and no indications of harm. However, these programmes are neither accessible nor acceptable to all patients and examples of effective translation into clinical care are limited, largely due to cost and complexity [49]. The EXCITE trial reported a personalized 6-month home-based walking programme improved 6MWT result [50], and reduced the risk of hospitalization, the latter of which was maintained for up to 36 months [51]. Furthermore, there are non-cardiac benefits of exercise in patients receiving dialysis that attenuate the common development of heart failure, such as reduced oxidative stress and inflammation, release of micro-RNAs from contracting muscle, improved cardiorespiratory and muscle function, and neurohormonal control [52]. Recently preliminary evidence suggests that intra-dialytic exercise may even reduce (1-year) mortality risk [53].

Interventions in patients with a kidney transplant

There has been an increase in trials assessing the effects of exercise training in KTRs. A recent systematic review and meta-analysis of 16 studies demonstrated the positive effect of exercise on physical fitness (CRF, strength, and physical function), and some markers of dyslipidaemia with no detrimental effects or safety concerns [54]. However, BMI, body weight, and glycaemic control remained unaffected and studies were highly heterogenous in sample size, duration, intervention content, outcome measure choice, and methods. An early home-based exercise trial of personalized cardiovascular exercise (walking or cycling) in 167 new KTRs showed that VO_{2peak} was significantly higher in exercise versus control at 12 months [55]. Zhang *et al.* (2023) reported significant improvements compared with control in fatigue, motivation, 30-second chair stands, and 6MWT results after an immediate post-transplant programme of exercise that was continued remotely after discharge (follow-up at 6 months, $n = 106$) [56]. Greenwood *et al.* (2015) reported improvements in VO_{2peak} in both aerobic and resistance training groups compared with control after 12-weeks of exercise training shared between centre and home-based locations [57], with mirrored improvements in pulse wave velocity.

Summary

Broadly speaking, across the whole trajectory of CKD, the literature supports that exercise interventions are effective for improving CRF and aspects of cardiorenal health. The mechanisms by which improvements are achieved appear to be different with differential effects on traditional and non-traditional risk factors for CKD progression and CVD. In dialysis, exercise interventions have shown improvements in CRF and cardiac structure and function, whilst in KTRs, interventions improve measures of physical fitness and markers of dyslipidaemia. To date, there is limited transfer of these findings into clinical care, although the evaluation of available evidence has led to the development of the first detailed clinical practice guideline for exercise and lifestyle in CKD [58]. There is a lack of large-scale multicentre RCTs, and trials exploring hard clinical outcomes, or long-term effects of exercise on cardiorenal outcomes.

CURRENT SITUATION, IMPORTANT BARRIERS, AND FUTURE PERSPECTIVES

Cardiovascular disease, CVD-related morbidity and mortality, and kidney function have well-established associations with PA and sedentary behaviour and the importance of maintaining an active life in CKD management is clear. Increasingly evidence supports the use of exercise interventions to improve CRF and cardiorenal health across the spectrum of patients with CKD. Patients with CKD are recommended to aim for 150 min of moderate intensity PA per week (or 75 min of vigorous activity or a combination of the two) with the addition of 2 days per week of activities aimed at improving muscular strength, balance, and flexibility in NDD-CKD patients, and that exercise is structured and individualized in KTRs with the aim of increasing CRF, muscle strength, and physical function [58]. These broad-reaching aims do not address the differences in CVD risk exhibited during the different stages of CKD and transplantation. We have limited understanding of the mechanisms through which exercise elicits beneficial cardiorenal effects across different populations; although potential mechanisms underlying the overall physiological benefits have been recently summarized [59]. A deeper understanding could allow for optimization of therapies to appropriately stratify patients and make best use of the limited resources available. A 2024 Clinical Consensus Statement of the European Association of Preventative Cardiology (of the European Society of Cardiology [ESC]) and the European Association of Rehabilitation in CKD with the aim of raising awareness of the importance of exercise training in CKD amongst cardiologists, nephrologists, and other healthcare professionals is timely, particularly as we begin to understand the interconnection between diseases as the number of patients presenting with multiple long-term conditions rises [52]. Whilst we have guidelines in place around the volume and broadly the intensity of exercise that patients should be achieving, we have limited evidence of how best to prescribe this whilst taking into account a plethora of concomitant risk factors and other health conditions. It is advised that whilst evidence is growing, prescription of exercise should be tailored utilizing the existing ECS 2020 Guidelines on sports cardiology and exercise in patients with CVD. Whilst it is not CKD-specific, it takes into account the presence of CVD, other conditions, and frailty, which are all likely to be present in patients living with CKD [52]. These guidelines place importance on risk stratification prior to exercise prescription with effective clinical evaluation of functional limitations to minimize the risk of harm in patients exhibiting cardiovascular risk factors.

Even with specific guidelines in mind, exercise prescription should be based on the evidence of association between small increases in PA being beneficial for the improvement of cardiorenal outcomes, and the process should involve shared decision-making between healthcare professionals and patients to aid long-term engendered changes [52]. The proposed targets may be unattainable for many patients, as in reality in a clinical setting, many patients are frail, elderly, have multiple long-term conditions, and are physically deconditioned. A knowledge of optimal therapies will inform staff and lead to correctly individualized exercise prescription. Enhanced patient motivation and behaviour change could then be supported with specific goal setting and management of expectations.

There are several further areas of missing information that limit our ability to move forward in this field. There is no single accepted way to monitor PA levels in a clinical setting, which is a fundamental starting point to exercise prescription. How adaptions to exercise training interact with baseline PA status is largely unknown. This may be helpful to identify differential responses between patient groups and to help guide personalized prescription. Additionally, we must establish the optimal modalities and doses to target specific cardiovascular and renal outcomes for different patient groups to support this aim. There is a lack of large-scale multicentre RCTs, particularly in transplantation and NDD-CKD, and trials exploring hard clinical outcomes and long-term effects of exercise on cardiorenal outcomes across all stages. However, we must also start to address the challenges of implementing programmes of exercise and PA into routine care to begin bridging the gap between research and clinical services. Without this, optimizing cardiovascular outcomes for patients with CKD will not be possible.

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AUTHORS' CONTRIBUTIONS

R.E.B., A.C.S., and M.G.B. wrote this manuscript. All authors reviewed the content and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

No new data were created or analysed for this review.

CONFLICT OF INTEREST STATEMENT

None to declare.

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