

Exercise therapy to improve mobility, active behaviour and quality of life of chronic kidney disease patients with peripheral artery disease: study protocol for the EXACT-CKDPAD multicentre randomised controlled trial

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ABSTRACT

The combination of chronic kidney disease (CKD) and peripheral artery disease (PAD) enhances the already present high cardiovascular risk, exposing the affected patients to unfavourable long-term clinical outcomes. Physical exercise is considered an effective treatment for reducing sedentary behaviour and improving quality of life, but several barriers limit patient participation. In this parallel-design, single-blinded, randomised controlled trial, we will enrol 130 patients with concomitant CKD at stages III and IV and PAD at the claudication stage to be randomised into a 6-month exercise (Ex) or control (Co) intervention. The Ex programme will consist of two daily 10 min interval walking sessions (1 min of walking followed by 1 min of resting), with gait speed controlled via a metronome and increased approximately weekly. The Co group will receive standard nephrological care. Outcomes will be assessed before and after treatment, as well as at the 12-month follow-up. The primary outcome will be the 6 min walking distance. The secondary outcomes will include quality of life, lower limb and handgrip strength, body composition and bone mineral density, as well as circulating indexes of kidney function and long-term clinical outcomes. Since no trials have been published that purposely enrol this high-risk population (CKD-PAD), the eventual positive results will validate a simple, pain-free exercise intervention that can be carried out at home to improve patients' mobility and quality of life. Trial registration number: [NCT06621264](https://www.clinicaltrials.gov/ct2/show/study?term=NCT06621264).

INTRODUCTION

Chronic kidney disease (CKD) is one of the fastest-growing non-communicable diseases. It is responsible for 1.2 million deaths per

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The combination of chronic kidney disease (CKD) and peripheral artery disease (PAD) exposes the affected patients to a very high risk of cardiovascular morbidity and mortality. Physical exercise programmes have been effectively tested in both CKD and PAD populations, but their effectiveness on patients presenting both pathological conditions has been poorly tested.

WHAT THIS STUDY ADDS

⇒ The EXACT-CKDPAD study aims to investigate whether a simple, pain-free, home-based walking programme is feasible and effective in improving patients' mobility, quality of life and long-term clinical outcomes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ If the trial results confirm the initial hypothesis, a pain-free, simple walking programme will be made available to a wide number of patients worldwide, allowing them to carry it out at home, thereby improving their physical functioning and potentially reducing the burden on national healthcare services.

year and is projected to become the fifth leading cause of years of life lost worldwide by 2040.¹⁻³ This high risk of morbidity and mortality² is the sum of several critical factors affecting patients with CKD, who are exposed to an increased cardiovascular risk, including a higher risk of developing peripheral artery disease (PAD). In particular, PAD is related

to adverse short-term and long-term clinical outcomes,^{4 5} considering the strong association between albuminuria and amputation.⁶

Approximately one out of four patients in the world with CKD is concomitantly affected by PAD.⁷ PAD prevalence in patients with reduced kidney function is significantly higher (24%) compared with subjects (3.7%) with normal kidney function (3.7%), and on the other hand, CKD prevalence is close to 40% in patients with PAD.⁴ These considerations delineate a subgroup of patients who share the same traditional risk factors (older age, diabetes, hypertension, hyperlipidaemia, smoking, physical inactivity) but also present unique risk factors, such as increased albuminuria, inflammation, oxidative stress, endothelial dysfunction and an unbalanced metabolic panel.^{8 9} These aspects are all closely linked in terms of both cause and effect to the sedentary attitude of the patient with CKD.^{10–12} Indeed, this high-risk population is poorly engaged in multidisciplinary secondary prevention programmes,^{13 14} and the need for effective interventions with sustainable benefits is reflected in the lack of previous randomised controlled trials (RCTs) focused on improving people's mobility. In addition, reduced physical activity is associated with unfavourable outcomes in patients with CKD, including progressive deconditioning, poor control of risk factors, reduced muscle mass and fatigue up to sarcopenia.^{12 15 16} Exercise may counteract these effects in both CKD and PAD populations,^{4 16} and higher physical activity levels may contribute to better management of cardiovascular risk factors and, possibly, retard CKD progression.^{17 18} Indeed, several meta-analyses have been conducted in both populations, yielding promising results in terms of mobility, exercise capacity, quality of life, laboratory parameters and many other outcomes.^{19–29}

However, despite the effectiveness of exercise and physical activity programmes, several barriers are still present for patients' participation, both in CKD and PAD populations.^{30 31}

To this end, the search for models of exercise prescription that are connectable with nephrology services should be implemented; however, no trials are available for the global management of this condition in the CKD-PAD population.³²

In recent years, a home-based walking programme has been developed to overcome barriers to exercise among patients with CKD and PAD. It has been successfully tested with favourable effects on exercise capacity, physical functioning and quality of life in patients with CKD^{33–35} and PAD.^{36–39} We hypothesise that a very similar intervention could also be effective when both conditions are present.

Therefore, this multicentre RCT aims to test the effectiveness of a home-based pain-free exercise programme in a CKD-PAD population on mobility, quality of life, exercise capacity and long-term outcomes, including CKD progression, peripheral revascularisations and survival compared with usual care.

METHODS

Study design and setting

This study protocol is reported following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.⁴⁰ The study is designed as a multicentre, parallel-group, single-blinded, RCT. The trial is available at Clinicaltrials.gov NCT06621264.

The study will take place at Sant'Anna University Hospital of Ferrara, which will act as the coordinating centre, as well as at Grande Ospedale Metropolitano Bianchi-Melacrino-Morelli of Reggio Calabria, Ospedale Pederzoli in Peschiera del Garda, the University of Verona and Casa Sollievo della Sofferenza in San Giovanni Rotondo. All units will cooperate in the enrolment of patients and data collection.

Eligibility criteria

Patients will be included if the following criteria are respected: male and female patients aged >18 years affected by CKD at Kidney Disease Outcomes Quality Initiative (KDOQI) stages III or IV with concomitant PAD at Rutherford's stages I–III; ability to walk independently; cognitive function to give informed consent identified by a Mini Mental Status Examination score $\geq 20/30$ and absence of clinical conditions contraindicating exercise therapy (eg, unstable angina, severe heart failure at New York Heart Association class IV, anaemia with $Hb < 100 \text{ g/L}$). Exclusion criteria are major amputations; major surgery planned in the next 3 months; known comorbid conditions that may limit survival to <2 years and inability or unwillingness to comply with protocol requirements.

Each Operative Nephrology Unit database will select all potential patients. If the inclusion criteria are met, potential participants will be given a study information leaflet detailing the study's objectives, procedures, time frame, risks and potential benefits, as well as the telephone contact details of the staff involved and the Consent Form (supplementary material). Within the following week, candidates will be contacted by telephone and asked about their decision. For those who decide to participate, an appointment will be scheduled at which signed informed consent will be requested, and a baseline assessment session will be performed. The total number of subjects screened will be recorded according to the Consolidated Standards of Reporting Trials guidelines (figure 1).

Interventions

Patients randomised to both groups will receive optimisation of medical therapy and standard nephrological care. Follow-up visits and assessments for each group member will be performed by a specialised physician and an exercise physiologist

Experimental group

Patients enrolled in the experimental group will receive a detailed 6-month exercise prescription aimed at

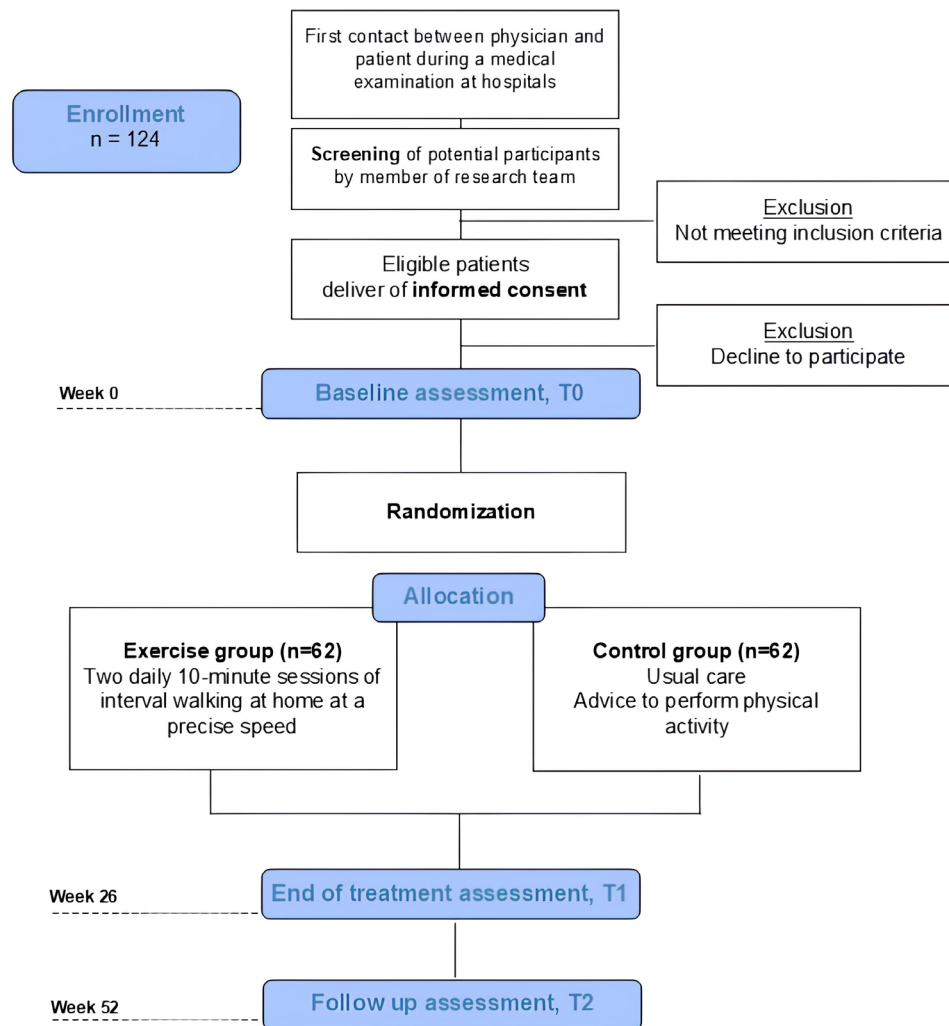


Figure 1 Flow chart of the study.

providing in-home, low-fatiguing walking training at light to moderate intensity (2–3 out of 10 on the CR10 Borg's scale). The programme consists of two daily 10 min interval walking sessions (1 min of walking followed by 1 min of resting), which will be maintained at a constant pace throughout the entire programme. Walking speed will be prescribed according to the patient's baseline walking capacity (approximately 50% lower than the habitual gait speed collected during the 6 min walking test). It will be increased weekly until reaching the habitual gait speed, following a specific scheme (table 1). Training intensity will be prescribed in step cadence and controlled by a digital metronome (https://www.youtube.com/watch?v=ki8YX_t-0jA) or a smartphone application that will lead the patient to walk at the right speed by listening to the prescribed walking pace (step/min). Each patient will be trained in the walking programme during the first visit. Training sessions will preferably be performed overground indoors at home to prevent the influence of weather or on a treadmill if patients prefer it.

Exercise prescriptions will be updated during two intermediate hospital visits in the first and third months. Patients will be provided with a digital application that has

been properly developed to track pacing and record the correct training execution. During the intermediate visit, systolic and diastolic blood pressure will be monitored. A team member will conduct periodic, approximately weekly telephone surveys to encourage patients to complete their home exercise diary and report any problems they encounter during exercise, such as pain or discomfort so that the exercise prescription can be adjusted appropriately.

Control group

Patients enrolled in the control group will receive standard CKD-PAD care, including optimal medical therapy and nutritional advice.

Concomitant care and recommendations

No restrictions of concomitant care physiotherapy or physical activity programmes are applied. Any participation in exercise programmes or changes in pharmacological therapy will be precisely recorded in both groups.

Fidelity to treatment

Several actions will be taken to maintain a high level of adherence and interest among patients enrolled in the

Table 1 Weekly walking speed progression for the exercise group

Week	Speed (steps/min)
1	60
2	60
3	63
4	63
5	66
6	66
7	69
8	69
9	72
10	72
11	76
12	76
13	80
14	76
15	80
16	84
17	84
18	88
19	88
20	92
21	84
22	84
23	88
24	92
25	96
26	100

Each training session includes a 10min interval training session with a walk:rest ratio of 1:1. The training speed is adjusted to ± 3 steps/min according to the patient's baseline capacity or other conditions that may limit walking speed.

exercise group. First, the walking programme will be explained by the physician and tried by patients during the first visit to state the feasibility and friendliness of the programme. Second, patients will be encouraged to continue participating in the programme during follow-up visits in the first and third months and will receive fortnightly phone calls from a researcher responsible for monitoring patients' health and addressing any possible doubts or concerns. Finally, next to an optimally written scheme and explanation of the programme, a properly designed training diary will be provided to each patient to record exercise execution and any potential symptoms. Patients in the control group will also receive a diary to record the physical activity performed for each day.

Outcomes

Outcome measures will be collected at baseline (T0), after 6 months (T1), which corresponds to the end of the training programme for the experimental group, and at the 12-month (T2) follow-up by healthcare professionals blinded to patients' allocation.

The primary outcome will be the measurement of the 6min walking distance (6MWD) performed during the 6min walking test.⁴¹ The variations in mobility assessed by 6MWD will be determined at the end of the programme in relation to the baseline. The patients will be instructed to walk back and forth along a 20 m corridor, aiming to cover as much distance as possible. Patients will also have to report the onset of any symptoms during the test, and the correspondent distance will be recorded as pain-free walking distance. When necessary, they will be allowed to stop as needed and restart whenever possible. Patients will also be monitored with a pulse oximeter to check their corresponding saturation. The rate of perceived exertion will be recorded on the 0–10 Borg scale at the end of the test.

Secondary outcomes will include the following:

- Lower limb perfusion. The haemodynamic severity of the disease will be assessed by the ankle-brachial index (ABI). This measure will be performed according to the published standards. The patient lies in a supine position, and blood pressure values at the ankle (from the posterior tibial and dorsalis pedis arteries) will be collected and compared with the systolic blood pressure. ABI is obtained by the ratio of the highest ankle value recorded and will be determined for both legs.⁴²
- Foot perfusion and temperature will be measured using an infrared thermal camera (FlirOne Pro, Flir, Milan, Italy). Infrared thermography is a non-invasive technique which has not yet been employed systematically in clinical trials, used for easy and reliable foot perfusion detection with promising results in patients with PAD.⁴³ A sample of five points covering the foot (anterior and posterior tibial, dorsalis pedis and plantar) will be measured and collected, as previously proposed in the literature.⁴⁴
- The five-time sit-to-stand test will assess lower limb strength. Patients will rise from a standard-height chair with their arms folded across the chest five times as quickly as possible. The total time elapsed for completing the five repetitions is the score.⁴⁵
- Handgrip strength will be measured using a standard dynamometer (Takei dynamometer). With one hand at a time, patients will be asked to perform three repetitions. The peak and mean values will be collected.
- Quality of life will be assessed by the Short-Form 36 questionnaire. This is a generic questionnaire that contains 36 questions referring to eight specific domains related to patient physical and mental health over the previous 4 weeks.⁴⁶
- Bone mineral density will be measured through phalangeal quantitative ultrasound (QUS, DBM

Sonic Bone Profiler, Igea s.r.l., Carpi) with an ultrasound signal of 1.25 MHz frequency and a methodology devoid of X-rays. QUS results are consistent with those obtained by standard DEXA.⁴⁷

- Body composition will be assessed with direct measures of height (cm), weight (kg) and waist circumference (cm), as well as lean body mass and lean body mass index through bioimpedance analysis (Akern, Italy).
- Circulating indexes of kidney function such as serum creatinine, estimated glomerular filtration rate (through the 2009 Chronic Kidney Disease Epidemiology Collaboration equation), albumin, urinary sediment and albuminuria-to-creatininuria ratio will be assessed by standard laboratory methods.
- Long-term clinical outcomes will also be recorded, including the number of patients requiring initiation of dialysis treatment within the 2-year follow-up

period, as well as all-cause hospitalisation and mortality rates among the enrolled patients. In the event of positive findings, the number of days elapsed from enrolment to the event will be recorded for additional analysis, as well as the reasons and diagnoses. Long-term outcomes will be collected up to 3 years from the enrolment.

Participants' timeline is reported in [figure 2](#).

Sample size and recruitment

The feasibility of this study is assessed by analysing the prevalence of patients with CKD-PAD in the hospitals involved in this project. We identified a cohort of over 200 patients potentially meeting the inclusion criteria. In each centre, a network of physicians, including nephrologists, internists and vascular surgeons, will be established to identify potentially eligible patients and facilitate enrolment. Every centre will identify a responsible person for

	STUDY PERIOD						
	Enrolment	Allocation	Post-allocation				Close-out
	-T ₁	T ₀	T ₁ (26 weeks)				T ₂ (52 wks)
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS:							
Exercise group							
Control group			X			X	
ASSESSMENTS:							
eGFR							
Duplex Ultrasound Examination	X	X					
Primary outcome							
6-minute walking distance			X			X	X
Secondary outcomes							
Ankle brachial Index							
Foot temperature							
5-time Sit-to-Stand							
Handgrip strength							
SF-36 questionnaire			X			X	X
Body composition							
Circulating biomarkers							
Long-term revascularizations, dialysis admissions, survival							

Figure 2 Study timeline according to Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement. eGFR, estimated glomerular filtration rate; SF-36, Short-Form 36.

enrolment to assess patients' eligibility and manage their inclusion in the randomisation list.

We calculated the sample size, hypothesising the superiority of the experimental treatment over the control group. A sample of 96 patients, 48 in each group, is needed to detect a 30 m improvement in 6 min walking distance in favour of the experimental group, assuming an SD of improvement of 30 m, with a type I error of 0.05 and a power of 90%. To account for possible dropouts, the sample size will be increased by 30%, resulting in a total of 124 patients to be enrolled.

Allocation

After the recruitment procedure at baseline, the physician responsible for enrolment in the Coordinating Centre will create the allocation sequence on a password-protected computer. An external administrator not involved in the trial will then randomise patients to one of the two groups using a computerised randomisation stratification approach to prevent selection bias. The random assignment will be communicated to investigators on the day of enrolment by accessing it on identification in an online repository. Only one coordinator of each centre will be permitted to access the participants' allocation. The randomisation scheme (1:1 ratio) will be established using permuted blocks of random sizes. The block sizes will not be disclosed to ensure concealment. Finally, the subjects will be assigned to one of two study groups: the exercise (Ex) group or the control (Co) group.

Blinding and data collection, management and analysis

Professionals in the management of the exercise programme will be responsible for outcome measurement, with one researcher assigned to each operational unit. An expert in data collection of body composition and bone mineral density will be responsible for collecting body composition parameters in every operating unit.

Two researchers blinded to the patients' allocation will be responsible for entering the data into two electronic datasets, which will be compared with check for possible mistakes in data input. A password will protect every data set.

The researchers responsible for the statistical analyses will also be blinded to the patient group assignments. He will also be responsible for data management (quality control and data checking) and data analysis according to the different research hypotheses described.

Patient's data will be treated following current regulations, including the 2016/679 European Union Act and D.Lgs. 30 June 2003, n. 196 s.m.i. Italian regulation, as well as any possible adjunctive measures deemed applicable by the Italian Data Protection Authority.

Statistical methods

Standard methods for the analysis of RCTs will be employed. All analyses will be conducted using intention-to-treat, where any subject randomised to one arm

remains in that arm regardless of whether they received the intervention.

Missing values, although we will make any effort possible to reduce their incidence, will be treated using the multiple imputation procedure. Moreover, a sensitivity analysis will be performed to assess the stability of the study's conclusions, comparing the intention-to-treat analysis with an analysis that takes into account the level of participation in the intervention arm. A p value <0.05 will be considered statistically significant. Several statistical analysis software packages, including SPSS, MedCalc and Stata, will be used.

A Shapiro-Wilk test will verify the nature and distribution of the data. At baseline, the two groups will be compared in terms of demographics and primary and secondary outcome measures. Although our initial hypothesis suggested the superiority of the exercise group over the control group, to account for the possibility that participants in the control group might achieve better outcomes than those in the intervention arm, we will use two-tailed tests of significance for all analyses. For categorical variables, the χ^2 test or Fisher's test will be employed, as appropriate. Overtime between-group differences will be analysed using t-tests for symmetrically distributed data and analogous non-parametric tests, such as the Mann-Whitney test, for skewed data. A two-way repeated measures analysis of variance (factors: treatment, time) will be run to compare differences over time for secondary outcomes. Paired-sample t-tests or Wilcoxon tests will assess the within-group variations. Suppose a significantly different distribution between the two groups in the baseline outcome level is identified. In that case, a secondary analysis will be performed using multivariate modelling, such as analysis of covariance, to adjust for these factors. For the long-term outcomes, Kaplan-Meier curves with log-rank tests and Cox proportional hazard regression models will be performed.

Harms

Potential risks, such as a major cardiac event or a fall, are expected to be rare. The intensity of the exercise proposed in this trial is low to moderate, interspersed with pauses and characterised by a low cardiovascular load. In our experience, among over 2000 patients at high cardiovascular risk with PAD, CKD, diabetes and/or stroke, programmes performing more than 400 000 home walking sessions for 6 months reported no falls or major events. Minor risks of participation, such as muscle soreness, fatigue or minor sprains or strains, are expected to occur in a small number of individuals during the training phase or assessment phase.

Anyway, all necessary procedures for the safety of the enrolled patients will be taken, including the exclusion of individuals with absolute contraindications to testing (inclusion/exclusion criteria) and careful monitoring of the testing phases by trained personnel (licensed and properly trained physical therapists/exercise physiologists). Direct supervision of trained operators will

be employed during every phase of testing in which the participant is standing and/or walking. A medical clearance will be requested before initiating the exercise intervention.

Finally, proper insurance has been subscribed to cover all possible harms that may occur.

Data monitoring, auditing and interim analyses

The study does not have a data monitoring committee. The research coordinator will conduct an interim analysis every 6 months to determine whether the study should be stopped, modified or continued. Any subsequent changes will be discussed by the research team and communicated to the funding agency and the Ethics Committee.

Confidentiality

Participant confidentiality will be rigorously maintained throughout all phases of the study. Each participant will be assigned a unique study identification number, and all data will be de-identified before analysis. Personally identifiable information, including names and medical records, will be stored separately from study data in secure, access-restricted databases. Only authorised research personnel will have access to identifiable participant data, and all team members will receive training in confidentiality and data protection procedures. Electronic data will be stored on encrypted and password-protected systems, and any physical records will be secured in locked filing cabinets in restricted-access areas. Data will be used solely for the purposes outlined in the study protocol. No identifiable information will be disclosed in any publication, presentation or report resulting from this research.

Dissemination

The results obtained from this RCT will be disseminated through multiple channels to ensure that the knowledge generated reaches relevant stakeholders, including the scientific community, healthcare professionals, policy-makers and the general public. The primary method of dissemination will be through publication in peer-reviewed scientific journals relevant to the study's field. Second, results will be presented at scientific conferences. They will be posted on clinical trial registries. Finally, a plain-language summary of the trial findings will be developed for study participants and the general public to be distributed through patient groups, hospital websites and the community.

Patients' associations will be involved in the discussion of the results obtained after the analyses performed by the research team.

CONCLUSIONS

This study will fill a knowledge gap in the literature as no trials have primarily focused on mobility in patients with concomitant CKD and PAD. This trial will propose a model of a home-based exercise program as a non-invasive alternative to manage the mobility impairment in

this population. This type of model may reduce the rate of surgical or endovascular revascularisation and achieve better short-term and long-term clinical outcomes.

This study provides an example of the management of this population by care teams employing a collaborative, multidisciplinary approach, testing the feasibility of this approach in the nephrology departments of five different Italian regions and demonstrating its potential for wider application. In the event of positive results from this rigorously conducted trial, a simple, integrated model of exercise therapy, effective and low-burden for patients and families, will be validated.

The introduction of this model into clinical practice could be beneficial for managing CKD patients with PAD, reducing sedentariness, deconditioning and walking disability, and limiting related clinical and psychological consequences.

In addition, the attempt to slow the decline of renal function and prevent entry into dialysis treatment is a further sanitary, socioeconomic and environmental potential outcome of interest, particularly considering the potential application of this programme in different settings with limited resources. The validation of this feasible exercise programme may be a turning point for the health service, which could employ a cost-effective intervention strategy centred on patient empowerment.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. The EXACT-CKPAD study protocol was approved by the Area-Vasta Emilia-Romagna Centro Ethics Committee with approval number 71/2023 (approved on 18 January 2023). Participants gave informed consent to participate in the study before taking part. The privacy of the participants and their medical records will be guaranteed by treating the data according to the Italian Law n. 196/2003, the 'Safe Harbor Act' (2000/520/CE), and the 'European Union Data Protection Directive (95/46/EC 24 October 1995)'.

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REFERENCES

- Xie Y, Bowe B, Mokdad AH, *et al.* Analysis of the Global Burden of Disease study highlights the global, regional, and national trends of chronic kidney disease epidemiology from 1990 to 2016. *Kidney Int* 2018;94:567–81.
- Bikbov B, Purcell CA, Levey AS, *et al.* Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet* 2020;395:709–33.
- Foreman KJ, Marquez N, Dolgert A, *et al.* Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016–40 for 195 countries and territories. *The Lancet* 2018;392:2052–90.
- Garimella PS, Hirsch AT. Peripheral artery disease and chronic kidney disease: clinical synergy to improve outcomes. *Adv Chronic Kidney Dis* 2014;21:460–71.
- Guerrero A, Montes R, Muñoz-Terol J, *et al.* Peripheral arterial disease in patients with stages IV and V chronic renal failure. *Nephrol Dial Transplant* 2006;21:3525–31.
- Matsushita K, Jassal SK, Sang Y, *et al.* Incorporating kidney disease measures into cardiovascular risk prediction: Development and validation in 9 million adults from 72 datasets. *EClinicalMedicine* 2020;27:100552.
- O'Hare AM, Glidden DV, Fox CS, *et al.* High prevalence of peripheral arterial disease in persons with renal insufficiency: results from the National Health and Nutrition Examination Survey 1999–2000. *Circulation* 2004;109:320–3.
- Bosevski M. Peripheral Arterial Disease and Chronic Kidney Disease. *Pril (Makedon Akad Nauk Umet Odd Med Nauki)* 2017;38:29–33.
- Al Adas Z, Lodewyk K, Robinson D, *et al.* Contrast-induced nephropathy after peripheral vascular intervention: Long-term renal outcome and risk factors for progressive renal dysfunction. *J Vasc Surg* 2019;69:913–20.
- Clyne N, Anding-Rost K. Exercise training in chronic kidney disease—effects, expectations and adherence. *Clin Kidney J* 2021;14:ii3–14.
- Johansen KL, Chertow GM, Kutner NG, *et al.* Low level of self-reported physical activity in ambulatory patients new to dialysis. *Kidney Int* 2010;78:1164–70.
- Kirkman DL, Edwards DG, Lennon-Edwards S. Exercise as an Adjunct Therapy In Chronic Kidney Disease. *Renal Nutr Forum* 2014;33:1–8.
- Tranche-Iparraguirre S, Marín-Iranzo R, Fernández-de Sanmamed R, *et al.* Peripheral arterial disease and kidney failure: a frequent association. *Nefrologia* 2012;32:313–20.
- Braithwaite J, Zuryski Y, Ludlow K, *et al.* Towards sustainable healthcare system performance in the 21st century in high-income countries: a protocol for a systematic review of the grey literature. *BMJ Open* 2019;9:e025892.
- Kelly JT, Su G, Carrero JJ. Lifestyle interventions for preventing and ameliorating CKD in primary and secondary care. *Curr Opin Nephrol Hypertens* 2021;30:538–46.
- Manfredini F, Mallamaci F, Catizone L, *et al.* The burden of physical inactivity in chronic kidney disease: is there an exit strategy? *Nephrol Dial Transplant* 2012;27:2143–5.
- Zhang L, Wang Y, Xiong L, *et al.* Exercise therapy improves eGFR, and reduces blood pressure and BMI in non-dialysis CKD patients: evidence from a meta-analysis. *BMC Nephrol* 2019;20:398.
- Neale EP, Rosario VD, Probst Y, *et al.* Lifestyle Interventions, Kidney Disease Progression, and Quality of Life: A Systematic Review and Meta-analysis. *Kidney Med* 2023;5:100643.
- Bernier-Jean A, Beruni NA, Bondonno NP, *et al.* Exercise training for adults undergoing maintenance dialysis. *Cochrane Database Syst Rev* 2022;1:CD014653.
- Traise A, Dieberg G, Pearson MJ, *et al.* The effect of exercise training in people with pre-dialysis chronic kidney disease: a systematic review with meta-analysis. *J Nephrol* 2024;37:2063–98.
- Bradshaw E, Alejmi A, Rossetti G, *et al.* Exercise and Cognitive Function in Chronic Kidney Disease: A Systematic Review and Meta-Analysis of Efficacy and Harms. *Clin J Am Soc Nephrol* 2024;19:1461–72.
- Liu C, Yang J, Li H, *et al.* Comparative efficacy of exercise modalities for general risk factors, renal function, and physical function in non-dialysis chronic kidney disease patients: a systematic review and network meta-analysis. *Ren Fail* 2024;46:2373272.
- Zhao M, Xiao M, Tan Q, *et al.* The effect of aerobic exercise on oxidative stress in patients with chronic kidney disease: a systematic review and meta-analysis with trial sequential analysis. *Ren Fail* 2023;45:2252093.
- Davies MD, Hughes F, Sandoo A, *et al.* The effect of exercise on vascular health in chronic kidney disease: a systematic review and meta-analysis of randomized controlled trials. *Am J Physiol Renal Physiol* 2023;325:F638–55.
- Zhang F, Bai Y, Zhao X, *et al.* Therapeutic effects of exercise interventions for patients with chronic kidney disease: an umbrella review of systematic reviews and meta-analyses. *BMJ Open* 2022;12:e054887.
- Thangada ND, Zhang D, Tian L, *et al.* Home-Based Walking Exercise and Supervised Treadmill Exercise in Patients With Peripheral Artery Disease: An Individual Participant Data Meta-Analysis. *JAMA Netw Open* 2023;6:e2334590.
- Peñín-Grandes S, López-Ortiz S, Maroto-Izquierdo S, *et al.* Winners do what they fear: exercise and peripheral arterial disease—an umbrella review. *Eur J Prev Cardiol* 2024;31:380–8.
- Mazzolai L, Belch J, Venermo M, *et al.* Exercise Therapy for Chronic Symptomatic Peripheral Artery Disease: A Clinical Consensus Document of the European Society of Cardiology Working Group on Aorta and Peripheral Vascular Diseases in Collaboration With the European Society of Vascular Medicine and the European Society for Vascular Surgery. *Eur J Vasc Endovasc Surg* 2024;16.
- Treat-Jacobson D, McDermott MM, Bronas UG, *et al.* Optimal Exercise Programs for Patients With Peripheral Artery Disease: A Scientific Statement From the American Heart Association. *Circulation* 2019;139:e10–33.
- Delgado C, Johansen KL. Barriers to exercise participation among dialysis patients. *Nephrol Dial Transplant* 2012;27:1152–7.
- Cetlin MD, Polonsky T, Ho K, *et al.* Barriers to participation in supervised exercise therapy reported by people with peripheral artery disease. *J Vasc Surg* 2023;77:506–14.
- DeLoach SS, Mohler ER. Peripheral arterial disease: a guide for nephrologists. *Clin J Am Soc Nephrol* 2007;2:839–46.
- Manfredini F, Mallamaci F, D'Arrigo G, *et al.* Exercise in Patients on Dialysis: A Multicenter, Randomized Clinical Trial. *J Am Soc Nephrol* 2017;28:1259–68.
- Mallamaci F, D'Arrigo G, Tripepi G, *et al.* Long-Term Effect of Physical Exercise on the Risk for Hospitalization and Death in Dialysis Patients: A Post-Trial Long-Term Observational Study. *Clin J Am Soc Nephrol* 2022;17:1176–82.
- Manfredini F, D'arrigo G, Lamberti N, *et al.* The legacy effect of a home walking exercise programme in kidney failure patients on dialysis. *Nephrol Dial Transplant* 2022;37:1974–81.
- Malagoni AM, Vagnoni E, Felisatti M, *et al.* Evaluation of patient compliance, quality of life impact and cost-effectiveness of a “test in-train out” exercise-based rehabilitation program for patients with intermittent claudication. *Circ J* 2011;75:2128–34.

- 37 Manfredini F, Traina L, Gasbarro V, *et al.* Structured pain-free exercise progressively improves ankle-brachial index and walking ability in patients with claudication and compressible arteries: an observational study. *Intern Emerg Med* 2022;17:439–49.
- 38 Lamberti N, López-Soto PJ, Guerzoni F, *et al.* Changes in exercise capacity and risk of all-cause mortality in patients with peripheral artery disease: a 10-year retrospective cohort study. *Intern Emerg Med* 2020;15:289–98.
- 39 Manfredini F, Traina L, Ficarra V, *et al.* A “test in-train out” program versus a “go home and walk” intervention for home-based exercise therapy in patients with peripheral artery disease: A randomized controlled trial. *Scand J Med Sci Sports* 2024;34:e14584.
- 40 Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al.* SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
- 41 ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;166:111–7.
- 42 Aboyans V, Criqui MH, Abraham P, *et al.* Council on Epidemiology and Prevention; Council on Clinical Cardiology; Council on Cardiovascular Nursing; Council on Cardiovascular Radiology and Intervention, and Council on Cardiovascular Surgery and Anesthesia. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. *Circulation* 2012;126:2890–909.
- 43 Piva G, Crepaldi A, Zenunaj G, *et al.* The Value of Infrared Thermography to Assess Foot and Limb Perfusion in Relation to Medical, Surgical, Exercise or Pharmacological Interventions in Peripheral Artery Disease: A Systematic Review. *Diagnostics (Basel)* 2022;12:3007.
- 44 Zenunaj G, Lamberti N, Manfredini F, *et al.* Infrared Thermography as a Diagnostic Tool for the Assessment of Patients with Symptomatic Peripheral Arterial Disease Undergoing Intrafemoral Endovascular Revascularisations. *Diagnostics (Basel)* 2021;11:1701.
- 45 Bohannon RW. Reference values for the five-repetition sit-to-stand test: a descriptive meta-analysis of data from elders. *Percept Mot Skills* 2006;103:215–22.
- 46 Apolone G, Mosconi P. The Italian SF-36 Health Survey: translation, validation and norming. *J Clin Epidemiol* 1998;51:1025–36.
- 47 Albanese CV, Cepollaro C, de Terlizzi F, *et al.* Performance of Five Phalangeal QUS Parameters in the Evaluation of Gonadal-Status, Age and Vertebral Fracture Risk Compared with DXA. *Ultrasound Med Biol* 2009;35:537–44.