RESEARCH

Associations between physical activity levels and renal recovery following acute kidney injury stage 3: a feasibility study

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Abstract

Background: Acute kidney injury (AKI) can lead to chronic kidney disease, which results in poor long-term outcomes. There is plausibility that increased levels of physical activity may promote renal recovery post-AKI. This study aimed to investigate associations between physical activity levels and renal recovery following stage 3 AKI, and to assess the feasibility of measuring physical activity levels in this population.

Methods: Forty One hospitalised patients with AKI stage 3 were enrolled. Serum creatinine and estimated glomerular filtration rate (eGFR) were collected at 12 months prior to the development of AKI, during the hospital admission when the episode of AKI stage 3 occurred, and at 1-, 3- and 6-months post discharge. All participants completed the General Practice Activity Questionnaire (GPPAQ) to assess physical activity levels. A pedometer was also worn for 7 days immediately following discharge and at 6-months post discharge to ascertain an average daily step count. Feasibility outcomes including eligibility, recruitment and retention rates, and losses to follow up were also assessed.

Results: The average ($\pm$ SD) baseline eGFR and median (IQR) serum creatinine was 71 ± 20 mL/min/1.73m^2 and 85 (49) µmol/L respectively. A threefold increase in creatinine occurred during hospitalisation 436 (265) µmol/L. Greatest renal recovery occurred prior to discharge, with recovery continuing for a further three months. Inactive individuals (low GPPAQ scores) had consistently higher serum creatinine values compared to those who were active: 1 months 122 (111) µmol/L vs 70 (0) µmol/L, 6 months 112 (57) µmol/L vs 68 (0) µmol/L. Individuals with higher step counts also displayed better renal recovery 6-months post discharge ($r = $ -0.600, $p = 0.208$).

Conclusions: Higher levels of physical activity are associated with improved renal recovery after 6- months following an episode of stage 3 AKI. A future randomised controlled trial is feasible and would be required to confirm these initial findings.

Keywords: Acute kidney injury, Physical activity, Renal recovery

Background

Patients with acute kidney injury (AKI) experience both short- and long-term adverse health outcomes [1]. The immediate complications such as electrolyte, fluid and acid–base disturbances, are well recognised and have

established management strategies [2]. In contrast, the long-term effects of AKI that are conferred through the development of chronic kidney disease (CKD), such as increased risk of cardiovascular disease, mortality and progression to end-stage kidney disease (ESKD) are not addressed to the same extent [1]. It was previously thought that kidney damage completely resolves after AKI, however it is now understood that there is often sustained renal dysfunction [3]. Despite this, there are

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currently no targeted treatments aimed at improving post-AKI renal function. Many novel therapeutic interventions such as alpha melanocyte stimulated hormone, low dose furosemide and alkaline phosphatase have been trialled [4–6] with limited success, emphasising the requirement for new treatment strategies.

Data from animal models [7–13] demonstrate that increased levels of physical activity may be protective and promote renal recovery following an episode of chemically-induced AKI. The proposed mechanism includes the anti-inflammatory effects of increased activity [9, 10] attenuating renal damage through controlling low-grade chronic inflammation that may sustain renal damage. A reduction in fibrotic [8] and oxidative pathways, [8, 10, 11, 13] and autophagy upregulation [7, 11] improve cell survival and kidney function in physically active animals post AKI. These data suggest a possible role of exercise in attenuating renal damage post AKI, thereby improving patient outcomes.

Despite these promising animal models, at present there is a paucity of data on the association between exercise and physical activity levels and AKI recovery in humans. More specifically, since an increase in AKI severity is associated with an increased risk of CKD and ESKD [14], AKI stage 3 individuals would benefit the most from an improvement in their renal function post AKI. Additionally, as patients with AKI are usually acutely unwell and no previous study has tried to enrol these participants into a physical activity study, the feasibility of conducting such a study in this patient group is unclear.

Therefore, the aims of this observational study are to: explore the associations between physical activity levels and renal recovery following an episode of AKI stage 3 and; evaluate the feasibility of a study of physical activity in the AKI population.

Methods
Study design and population
This was an observational cohort study performed at the University Hospitals of Leicester (UHL) NHS Trust in the United Kingdom. The study received ethical approval by the UK National Health Service Research Ethics Committee (WALES REC 6 ref: 18/WA/0358), and all participants provided written informed consent.

Patients were identified through an electronic AKI alert system for hospitalised patients. Inclusion criteria: aged > 18; hospitalised with AKI stage 3; measurement of renal function available within the previous 12-month (baseline) and; willing and able to provide informed consent. AKI stage 3 was defined according to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines [15]: an increase in serum creatinine equal

to 3 times baseline levels or < 0.3 mL/kg/h urine output for $\geq$ 24 h. Baseline renal function was determined by a creatinine and eGFR measurement taken within 12 months prior to their admission. Exclusion criteria: AKI of obstructive aetiology, a previous AKI episode within the last month, previous solid organ transplant, baseline eGFR < 30 ml/min/ 1.73 m2, complete renal recovery or ongoing requirement for renal replacement therapy at time of discharge.

Data collection
Physical activity
All enrolled participants completed the General Practice Physical Activity Questionnaire (GPPAQ) [16]. The GPPAQ measures current physical activity by providing a 4-level Physical Activity Index (PAI), categorising individuals into: inactive; moderately inactive; moderately active and active. All questionnaires were completed independently by the participant during their in-patient stay and all questions answered according to their abilities immediately prior to their hospital admission, to ascertain a baseline value. These questionnaires were repeated at 3- and 6-months post discharge.

All participants were given the option of wearing a YAMAX Digi-Walker SW800-SW801 (Yamax; Yamax Corporation, Tokyo, Japan) pedometer for 7 consecutive days and an average daily step count was calculated by dividing the total number of steps by days worn. Step count data were collected twice during the study: immediately after discharge and 6 months post discharge.

Renal function
Baseline participant characteristics and measures of renal function were extracted from medical records (Integrated Clinical Environment (ICE), Sunquest Information Systems, Tucson, Arizona) during the hospital admission and at time of discharge. Creatinine was measured again at 1-, 3- and 6-months post discharge.

Feasibility outcomes
The feasibility outcomes included: the number of eligible patients against the number screened; the proportion of eligible patients enrolling in the study against those that are eligible and assessment of the proportion of participants followed up to 6-months with complete outcome data.

Participant number and sample size
As a feasibility study, a power calculation to determine a sample size was not performed. In line with previous data for feasibility trials [17], approximately 40

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participants are adequate to address the proposed feasibility outcomes.

Statistical analysis

All data were assessed for normality and are presented as mean ± standard deviation (SD) or median ± inter-quartile ranges (IQR) if skewed. Categorical variables are reported as a frequency and percentage. Renal recovery was assessed by calculating the absolute differences between follow up (1- and 6-month) and baseline creatinine values. A percentage difference was also calculated by dividing the calculated absolute difference by the baseline creatinine value. There is no consensus definition of renal recovery following AKI with recovery definitions ranging between a return of serum creatinine within 10–50% [18–21] of baseline values. In line with the published literature, we defined 'good' renal recovery as serum creatinine returning to within 25% of the baseline value [22–24].

Results

Patient demographics

Forty One participants were recruited from March 2019 to December 2020. Complete questionnaire data were available from 20 patients at 6 months. All participant baseline demographic data are presented in Table 1.

Feasibility outcomes

Five hundred twenty-nine patients were screened for eligibility, with 186 (35%) individuals being eligible for enrolment (see Fig. 1). 74 (14%) patients were approached, with 44 (8%) providing informed consent to participate. 41 participants completed all baseline assessments out of which 11 (27%) also consented to monitoring their daily step count for 7 days after discharge. 38 participants were successfully discharged from hospital (3 participants died before discharge), and all were contacted to complete the questionnaires at 3- and 6-months post discharge. During follow up, 2 individuals chose to withdraw from the study and 2 participants died. In total, 20 (52%) participants completed follow up questionnaire data with measures of renal function being available for 12 and 13 participants at 3 and 6 months respectively (Fig. 1).

Renal function

All participants experienced AKI stage 3, shown through a minimum threefold increase (from 85 (49) to 436 (265) µmol/L in serum creatinine levels during hospitalisation (Fig. 2). At discharge, residual renal impairment persisted, 125 (79) µmol/L. Renal recovery continued at 3-months post discharge, 108 (42) µmol/L, but with

Table 1 Baseline Patient Demographics

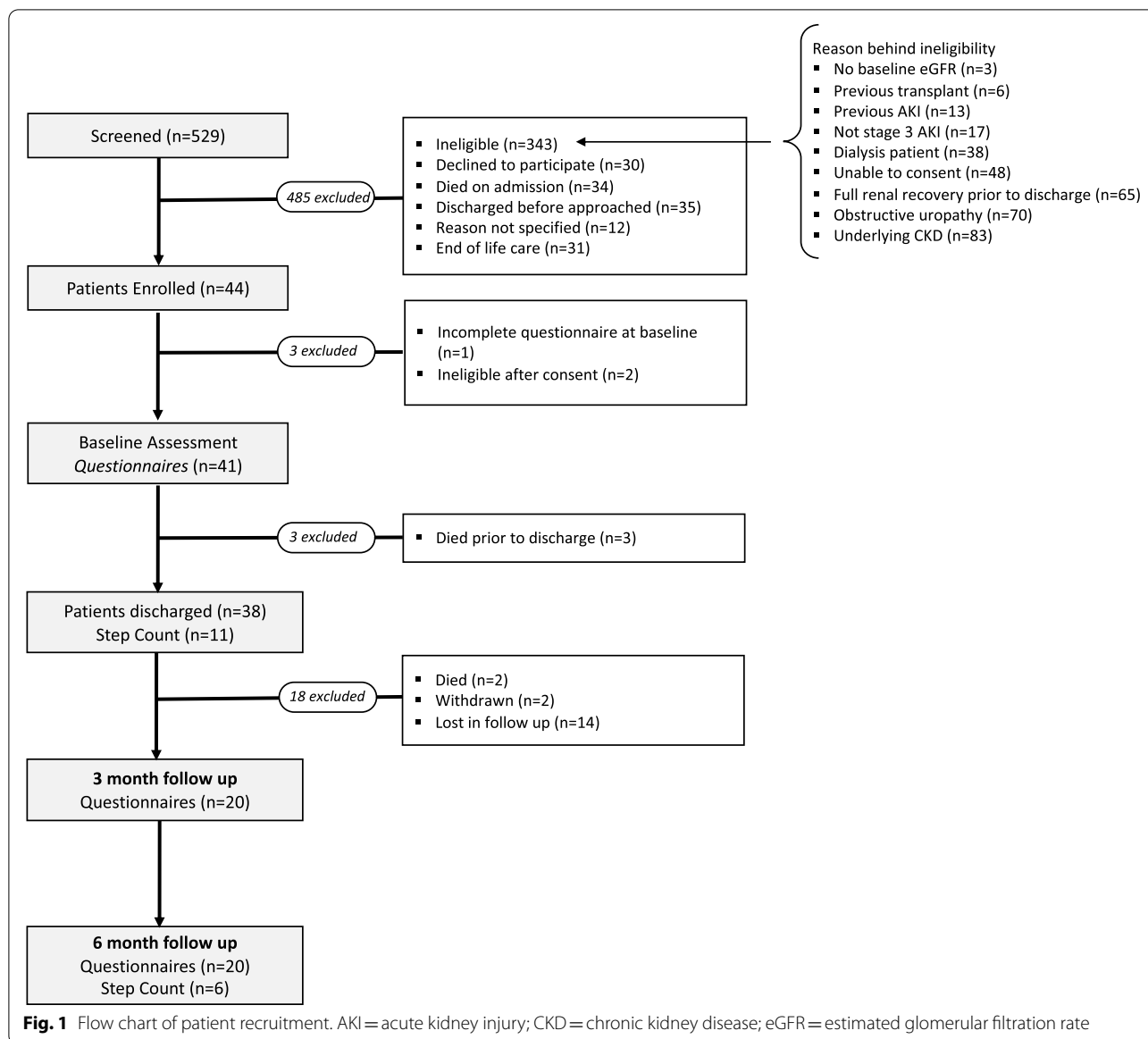| Characteristic	All $N = 41$
Age (years)	
Mean (SD)	68 (± 17)
Sex N (%)	
Male	26 (63)
Female	15 (37)
Ethnicity N (%)	
White	40 (98)
Black	1 (2)
Comorbidities N (%)	
CKD	11 (28)
Hypertension	20 (49)
Diabetes Mellitus	11 (28)
Dyslipidaemia	7 (18)
Heart Failure	3 (8)
Malignancy	6 (15)
Cause of AKI N (%)	
Sepsis	20 (49)
Dehydration	13 (32)
Drug Induced	1 (2)
Chemotherapy Induced	2 (5)
Contrast Induced	1 (2)
Post-Operative	2 (5)
Rhabdomyolysis	1 (2)
Unknown	1 (2)
Length of Admission (days)	
Mean (SD)	15 (± 10)
RRT Required	
Yes N (%)	4 (10)
No N (%)	37 (90)
ITU Admission	
Yes N (%)	8 (20)
Length of ITU Admission (days)	7 (± 6)
No N (%)	33 (80)

SD Standard deviation, *CKD* Chronic kidney disease, *AKI* Acute kidney injury, *ITU* Intensive treatment unit, *RRT* Renal replacement therapy

no further recovery being noted at 6-months, 110 (60) µmol/L (Fig. 2).

Physical activity levels

GPPAQ

The majority of participants recorded high levels of inactivity (Fig. 3). At baseline, moderately active individuals had a lower median (IQR) creatinine compared to those who were inactive, 67 (10) µmol/L vs 85 (49) µmol/L. This pattern, showing active individuals having lower creatinine values and hence better renal function, is repeated at each time point during the study, Fig. 3.

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Fig. 1 Flow chart of patient recruitment. AKI = acute kidney injury; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate

Renal function and step count data

A higher baseline renal function (lower creatinine level), taken 12-months prior to AKI, was associated with a higher step count immediately after discharge, ($r = $ -0.6636, $p = 0.03$), Fig. 4. At 1-month, those who had recovered to within 25% of their baseline creatinine had a higher average daily step count compared to those who were further away from their baseline 3712 (± 3960) vs 3085 (± 2202). Individuals with higher step counts at 6-months had better renal recovery at the same time point, ($r = $ -0.600, $p = 0.2080$) Fig. 5.

Discussion

This is the first study to measure physical activity in individuals following an episode of stage 3 AKI. We observed an association between higher levels of physical activity and improved renal function. Individuals with higher physical activity levels, assessed via the GPPAQ questionnaire, had consistently lower creatinine levels at 1- and 6-months post discharge. This association is in keeping with data from the 6-month step count as those with a higher average daily step count had greater renal recovery at 6 months post-discharge. We also observed
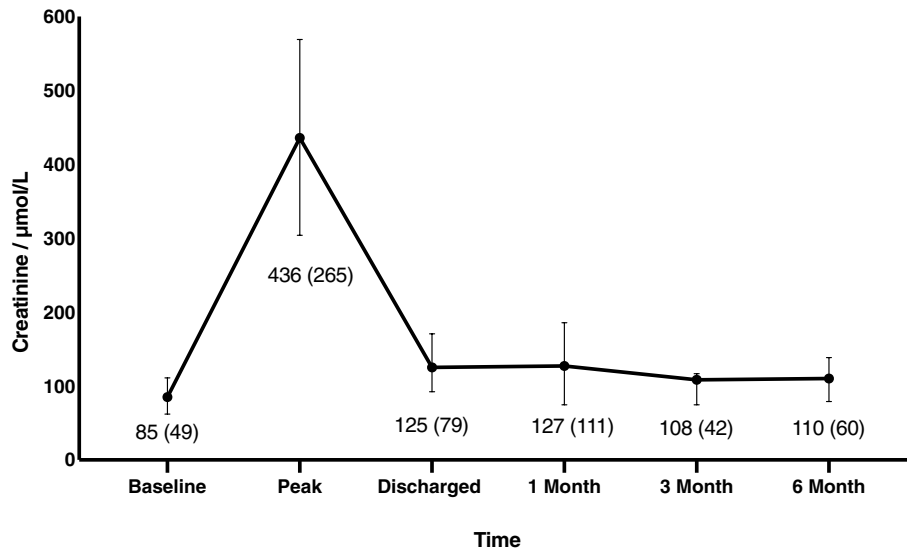
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Fig. 2 Renal Function throughout the study. Renal function estimated by creatinine is reported as median (IQR) for all participants available at each time point—baseline, discharge and 1,3- and 6-months post discharge. The error bars demonstrate IQR
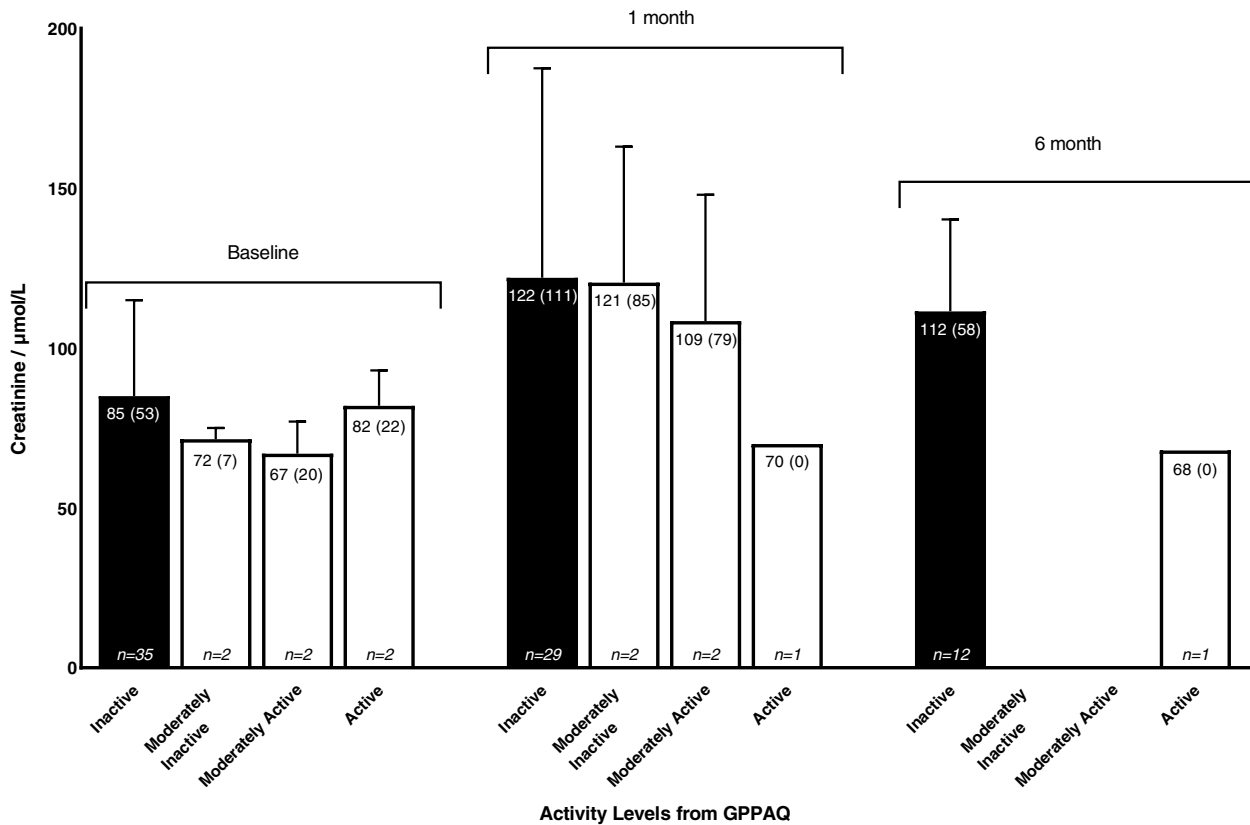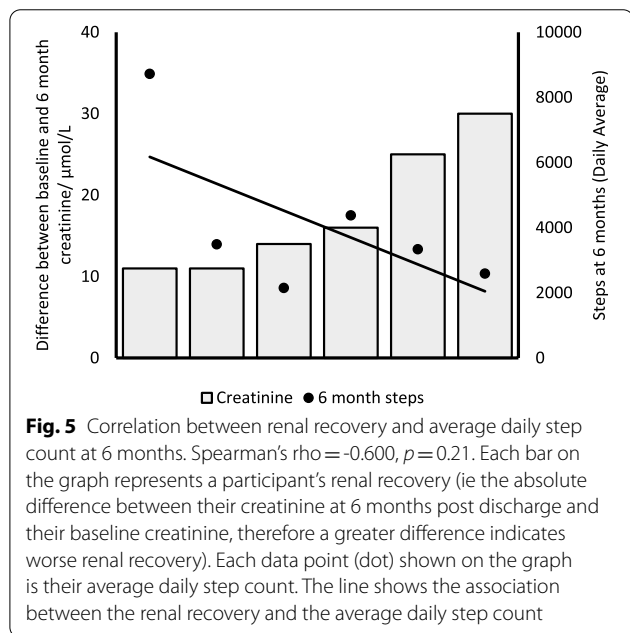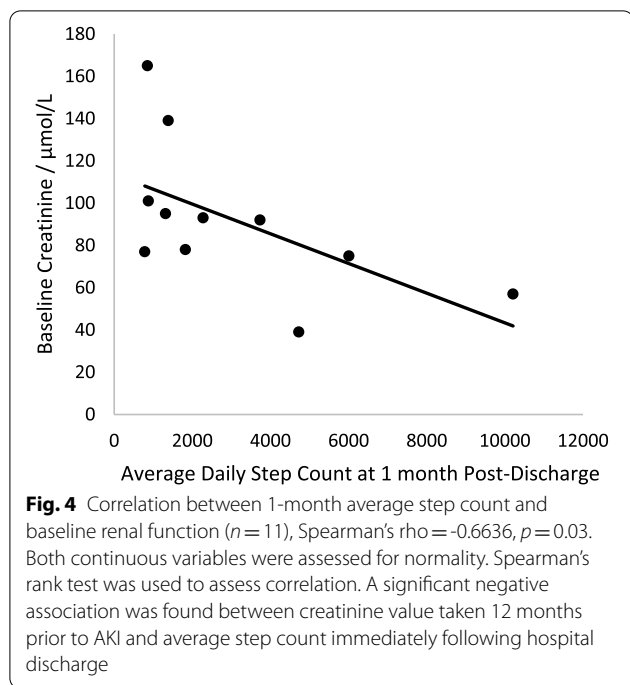

Fig. 3 Creatinine values for each activity level from the GPPAQ shown at baseline and 1 and 6 months post discharge. Median (IQR) creatinine values presented with the number of participants at each activity levels displayed at the bottom of each bar ($n=$)

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Fig. 4 Correlation between 1-month average step count and baseline renal function ($n = 11$), Spearman's rho $= -0.6636$, $p = 0.03$. Both continuous variables were assessed for normality. Spearman's rank test was used to assess correlation. A significant negative association was found between creatinine value taken 12 months prior to AKI and average step count immediately following hospital discharge

Fig. 5 Correlation between renal recovery and average daily step count at 6 months. Spearman's rho $= -0.600$, $p = 0.21$. Each bar on the graph represents a participant's renal recovery (ie the absolute difference between their creatinine at 6 months post discharge and their baseline creatinine, therefore a greater difference indicates worse renal recovery). Each data point (dot) shown on the graph is their average daily step count. The line shows the association between the renal recovery and the average daily step count

an association between higher levels of physical activity prior to AKI and better recovery in the post AKI period. We observed in patients with AKI stage 3 that renal impairment persisted at discharge with maximum renal recovery being achieved 3 months post discharge, as no further recovery was noted at 6 months. Lastly, we measured the feasibility of a study observing physical activity levels in individuals following an episode of AKI.

We screened a large number of individuals with only few meeting the eligibility criteria and being subsequently enrolled to participate. Additionally, many participants were lost to follow up at 3 and 6 months.

Numerous pre-clinical animal studies show that increasing physical activity attenuates renal damage post-AKI, highlighting the fact that there is biologically plausibility behind our findings. The transferability of these animal findings in the human setting has been questioned [25, 26]; however our results support the association between improved renal recovery in more physically active individuals [27]. Physical activity in the AKI population has not previously been reported. Furthermore, we found no studies which correlate physical activity with renal recovery in the AKI setting. However, the pattern of renal recovery observed in our study, whereby recovery continued post discharge, is well established [28]. Furthermore, it is known that those with recovery following AKI have better outcomes than those with persistent renal impairment. In addition, time to recovery is a valuable clinical parameter as those with longer recovery times have worse long-term outcomes such as a higher incidence of CKD, long term dialysis use and increase in mortality [29]. This study observed that the greatest amount of renal recovery occurred in the 3 months post-discharge, therefore any future interventions aimed at recovering renal function would be most beneficial if implemented during this time frame.

The association observed between increased levels of physical activity and improved renal recovery does not imply causation. It is possible that individuals may have been more active because of improved renal recovery. Furthermore, those who were more active prior to AKI may have had better overall health hence facilitating their faster recovery in renal function. This is supported by studies [30, 31] that report associations between poor pre-operative cardiorespiratory functioning and worse post-operative outcomes, such as longer stay in intensive care and increased short- and long-term morbidity and mortality. Additionally, randomised controlled trial (RCT) data has demonstrated that pre-operative exercise training decreases post-operative complications in patients undergoing elective abdominal aortic aneurysm repair [32] and coronary artery bypass graft surgery [33], indicating that healthier individuals prior to hospitalisation have better outcomes. It is therefore not clear whether our observations showing associations between improved recovery and renal function post AKI have implications for long-term outcomes in this population. Furthermore, it is unclear whether increasing physical activity levels (through a targeted intervention) following AKI, would lead to an improvement in renal recovery. Regardless, since our study demonstrates an

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association between increased levels of physical activity and improved renal function, this warrants further investigation.

In this study only a small number of the screened patients fulfilled our inclusion criteria. The three most common reasons for ineligibility were: underlying severe CKD, obstructive uropathy and patients achieving full renal recovery prior to discharge. A wider inclusion criteria should be considered for future studies. This can be achieved by including individuals with stage 1 and stage 2 AKI. More specifically, those with an increased risk of CKD progression following AKI should be identified and recruited. Whilst increase AKI severity is a risk factor for CKD progression, other factors such as the number of AKI insults and presence of other CKD risk factors such as diabetes mellitus and hypertension are also important to consider [34].

Out of those who were approached, the majority (59%) consented to participate. We found large losses to follow up at both 3- and 6-months post discharge. Only a small amount of these were attributed to participant death and withdrawal of consent from the study. Based on prior research, it is possible that difficulties in participant retention may be explained by our cohort belonging to an older age demographic, 68 ($\pm$17) years. Difficulties in both recruitment and retention in > 65 years have been previously demonstrated [35]. Decline in overall health, loss of interest, failure to recognise research benefit and increase frailty have previously been reported as reasons for lack of retention in research studies in this age group [35, 36]. It is plausible that our study could also have been impacted by these factors. Different strategies have been proposed on how to combat these issues. Many of which were already part of our study design, most notably the remote nature of our data collection process whereby individuals were able to complete the follow up questionnaires at home. Methods to increase retention in future studies include regular follow up phone calls to keep participants engaged in the study. Widening the inclusion criteria to the possible addition of stage 1 and stage 2 AKI individuals would also create a more age-diverse cohort hence addressing the issues seen mostly in > 65 year demographic. With the successful addition of strategies to reduce loss of follow up, our data supports that larger scale studies of physical activity would be feasible in the AKI population.

These data demonstrate that a RCT designed to investigate the effect of exercise on renal recovery post AKI is feasible. At present, there are still no effective interventions that improve renal recovery and thus reduces the long term sequalae of an episode of AKI [37]. This feasibility study provides hypothesis generating data, however due to the limitations of our sample size, the results must be interpreted with caution. A future, large scale RCT is needed to definitively test the hypothesis that a programme of exercise may have a positive impact upon renal recovery.

Limitations
A small sample size and a large proportion of patients lost to follow are the primary limitations of this study, although the design was to test feasibility rather than to show a definitive result. Loss of follow up during the study occurred due to withdrawal, patient death and lack of response to the follow-up questionnaire, the reasons behind which were not explored. Selection and recruitment bias may have resulted in the recruitment of more active individuals, limiting the generalisability of the findings. Whilst we observed an association between increased levels of physical activity and improved renal recovery, due to the observational study design, a causal relationship cannot be inferred.

Conclusion
This feasibility study demonstrates a possible association between higher levels of physical activity and improved renal recovery after 3-months following an episode of stage 3 AKI. A future randomised controlled trial is feasible and would be required to confirm these initial findings.

Abbreviations
AKI: Acute kidney injury; CKD: Chronic kidney disease; ESKD: End stage kidney disease; UHL: University Hospitals Leicester; NHS: National health service; KDIGO: Kidney Disease Improving Global Outcomes; GFR: Glomerular filtration rate; GPPAQ: General Practice Physical Activity Questionnaire; PAI: Physical Activity Index; ICE: Integrated Clinical Environment; SD: Standard deviation; IQR: Interquartile range; RCT: Randomised controlled trial; ITU: Intensive care unit.

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data within the University of Leicester and University of Leicester Hospitals Trust servers only. As such, anonymised data will be available on request once details of secure transfer and storage are clarified with those research teams.

Declarations

Ethics approval and consent to participant

Consent for publication
Not Applicable.

Competing interests
The authors declare that they have no competing interests.

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References
1. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int. 2012;81(5):442–8.
2. Doyle JF, Forni LG. Acute kidney injury: short-term and long-term effects. Crit Care. 2016;20(1):188-y.
3. Chawla LS, Bellomo R, Bihorac A, Goldstein SL, Siew ED, Bagshaw SM, et al. Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. Nat Rev Nephrol. 2017;13(4):241–57.
4. McCullough PA, Bennett-Guerrero E, Chawla LS, Beaver T, Mehta RL, Molitoris BA, et al. ABT-719 for the Prevention of Acute Kidney Injury in Patients Undergoing High-Risk Cardiac Surgery: A Randomized Phase 2b Clinical Trial. J Am Heart Assoc. 2016;5(8):https://doi.org/10.1161/JAHA.116.003549.
5. Bagshaw SM, Gibney RTN, Kruger P, Hassan I, McAlister FA, Bellomo R. The effect of low-dose furosemide in critically ill patients with early acute kidney injury: a pilot randomized blinded controlled trial (the SPARK study). J Crit Care. 2017;01(42):138–46.
6. Pickkers P, Heemskerk S, Schouten J, Laterre PF, Vincent JL, Beishuizen A, et al. Alkaline phosphatase for treatment of sepsis-induced acute kidney injury: a prospective randomized double-blind placebo-controlled trial. Crit Care. 2012;16(1):R14.
7. de Lima WV, Visona I, Schor N, Almeida WS. Preconditioning by aerobic exercise reduces acute ischemic renal injury in rats. Physiol Rep. 2019;7(14):e14176.
8. Francescato HDC, Almeida LF, Reis NG, Faleiros CM, Papoti M, Costa RS, et al. Previous exercise effects in cisplatin-induced renal lesions in rats. Kidney Blood Press Res. 2018;43(2):582–93.
9. Miyagi MY, Seelaender M, Castoldi A, de Almeida DC, Bacurau AV, Andrade-Oliveira V, et al. Long-term aerobic exercise protects against cisplatin-induced nephrotoxicity by modulating the expression of IL-6 and HO-1. PLoS One. 2014;9(10):e108543.
10. Miyagi MYS, Latancia MT, Testagrossa LA, Andrade-Oliveira V, Pereira WO, Hiyane MI, et al. Physical exercise contributes to cisplatin-induced nephrotoxicity protection with decreased CD4+ T cells activation. Mol Immunol. 2018;01(101):507–13.
11. Oliveira CS, Rodrigues AM, Nogueira GB, Nascimento MA, Punaro GR, Higa EM. Moderate aerobic exercise on the recovery phase of gentamicin-induced acute kidney injury in rats. Life Sci. 2017;15(169):37–42.
12. Sossdorf M, Fischer J, Meyer S, Dahlke K, Wissuwa B, Seidel C, et al. Physical exercise induces specific adaptations resulting in reduced organ injury and mortality during severe polymicrobial sepsis. Crit Care Med. 2013;41(10):246.
13. Zeynali F, Nematbakhsh M, Mojtahedi H, Poorshahnazari A, Talebi A, Pezeshki Z, et al. Protective role of aerobic exercise against cisplatin-induced nephrotoxicity in rats. Asian J Sports Med. 2015;6(3):e24901.
14. Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med. 2015;41(8):1411–23.
15. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Workgroup. Kidney Int Suppl. 2012;2:1-138.
16. The General Practice Physical Activity Questionnaire: A Screening tool to assess adult physical activity levels, within primary care. 2009. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/192453/GPPAQ_-_guidance.pdf.
17. Billingham SA, Whitehead AL, Julious SA. An audit of sample sizes for pilot and feasibility trials being undertaken in the United Kingdom registered in the United Kingdom clinical research network database. BMC Med Res Methodol. 2013;13:104.
18. Horne KL, Packington R, Monaghan J, Reilly T, Selby NM. Three-year outcomes after acute kidney injury: results of a prospective parallel group cohort study. BMJ Open. 2017;7(3):e015316-015316.
19. Bucaloiu ID, Kirchner HL, Norfolk ER, Hartle JE, Perkins RM. Increased risk of death and de novo chronic kidney disease following reversible acute kidney injury. Kidney Int. 2012;81(5):477–85.
20. Jones J, Holmen J, De Graauw J, Jovanovich A, Thornton S, Chonchol M. Association of complete recovery from acute kidney injury with incident CKD stage 3 and all-cause mortality. Am J Kidney Dis. 2012;60(3):402–8.
21. Bihorac A, Yavas S, Subbiah S, Hobson CE, Schold JD, Gabrielli A, et al. Long-term risk of mortality and acute kidney injury during hospitalization after major surgery. Ann Surg. 2009;249(5):851–8.
22. Pannu N, James M, Hemmelgarn B, Klarenbach S, Alberta Kidney Disease Network. Association between AKI, recovery of renal function, and long-term outcomes after hospital discharge. Clin J Am Soc Nephrol. 2013;8(2):194–202.
23. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, Acute Dialysis Quality Initiative workgroup. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the second international consensus conference of the Acute Dialysis Quality Initiative (ADQI). Crit Care. 2004;8(4):204–12.
24. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11(2):R31.
25. Bao YW, Yuan Y, Chen JH, Lin WQ. Kidney disease models: tools to identify mechanisms and potential therapeutic targets. Zool Res. 2018;39(2):72–86.
26. Skrypnyk NI, Siskind LJ, Faubel S, de Caestecker MP. Bridging translation for acute kidney injury with better preclinical modeling of human disease. Am J Physiol Renal Physiol. 2016;310(10):972.
27. Asad A, Burton JO, March DS. Exercise as a therapeutic option for acute kidney injury: mechanisms and considerations for the design of future clinical studies. BMC Nephrol. 2020;21(1):446–9.
28. Kellum JA, Sileanu FE, Bihorac A, Hoste EA, Chawla LS. Recovery after Acute Kidney Injury. Am J Respir Crit Care Med. 2017;195(6):784–91.
29. Mehta RL. Renal recovery after acute kidney injury and long-term outcomes: is time of the essence? JAMA Netw Open. 2020;3(4):e202676.
30. Moran J, Wilson F, Guinan E, McCormick P, Hussey J, Moriarty J. Role of cardiopulmonary exercise testing as a risk-assessment method in patients undergoing intra-abdominal surgery: a systematic review. Br J Anaesth. 2016;116(2):177–91.
31. Smith TB, Stonell C, Purkayastha S, Paraskevas P. Cardiopulmonary exercise testing as a risk assessment method in non cardio-pulmonary surgery: a systematic review. Anaesthesia. 2009;64(8):883–93.
32. Barakat HM, Shahin Y, Khan JA, McCollum PT, Chetter IC. Preoperative supervised exercise improves outcomes after elective abdominal aortic aneurysm repair. Ann Surg. 2016;264:47–53.
33. Arthur HM, Daniels C, McKelvie R, Hirsh J, Rush B. Effect of a preoperative intervention on preoperative and postoperative outcomes in low-risk patients awaiting elective coronary artery bypass graft surgery. A randomized, controlled trial. Ann Intern Med. 2000;133(4):253–62.

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34. Kazancioglu R. Risk factors for chronic kidney disease: an update. Kidney Int Suppl (2011). 2013;3(4):368–71.

35. Forsat ND, Palmowski A, Palmowski Y, Boers M, Buttgereit F. Recruitment and retention of older people in clinical research: a systematic literature review. J Am Geriatr Soc. 2020;68(12):2955–63.

36. Provencher V, Mortenson WB, Tanguay-Garneau L, Belanger K, Dagenais M. Challenges and strategies pertaining to recruitment and retention of frail elderly in research studies: a systematic review. Arch Gerontol Geriatr. 2014;59(1):18–24.

37. James MT, Bhatt M, Pannu N, Tonelli M. Long-term outcomes of acute kidney injury and strategies for improved care. Nat Rev Nephrol. 2020;16(4):193–205.

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