**Effect of In-bed Cycling on Acute Muscle Wasting in Critically Ill Adults: A Randomized Clinical Trial**

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We would also like to thank the dedicated staff of the Princess Alexandra Hospital Physiotherapy Department and Intensive Care Unit for supporting this study.

We would like to acknowledge the support for this work from the Metro South Research Support Scheme (Small Grant and Postgraduate Scholarship), Centre for Functioning and Health Research, Metro South Health, and the Institute of Health and Biomedical Innovation and School of Public Health & Social Work, Queensland University of Technology.

Finally, we would like to thank all participants and their families and friends of those who were involved in this study, without your active participation and dedication to improving outcomes for critically ill patients this research would not have been possible.

**Authors' contributions**

Marc Nickels: Study design, participant screening and recruitment, intervention implementation, data collection, safety monitoring, analysis, manuscript preparation, critical review and approval of the manuscript.

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# Effect of In-bed Cycling on Acute Muscle Wasting in Critically Ill Adults: A Randomised Controlled Trial


## Abstract

**Purpose:** To examine whether in-bed cycling assists critically ill adults to reduce acute muscle wasting, improve function and improve quality of life following a period of critical illness.

**Materials and methods:** A single-centre, two-group, randomised controlled trial with blinded assessment of the primary outcome was conducted in a tertiary ICU. Critically ill patients expected to be mechanically ventilated for 48-hours were randomised to 30-minutes daily in-bed cycling in addition to usual-care physiotherapy (n = 37) or usual-care physiotherapy (n = 37). The primary outcome was muscle atrophy of rectus femoris cross-sectional area ($RF_{CSA}$) measured by ultrasound at Day 10 following study enrolment. Secondary outcomes included manual muscle strength, handgrip strength, ICU mobility score, six-minute walk test distance and health-related quality of life up to six-months following hospital admission.

**Results:** Analysis included the 72 participants (mean age, 56-years; male, 68%) who completed the study. There were no significant between-group differences in muscle atrophy of $RF_{CSA}$ at Day 10 (mean difference 3.4, 95% CI -6.9% to 13.6%; p=0.52), or for secondary outcomes (p-values ranged p=0.11 to p=0.95).

**Conclusions and relevance:** In-bed cycling did not reduce muscle wasting in critically ill adults, but this study provides useful effect estimates for large-scale clinical trials.

**Trial Registration:** anzctr.org.au Identifier: ACTRN12616000948493

**Introduction:**

Patients who experience critical illness often develop profound and persistent physical, cognitive and psychological deficits following an intensive care unit (ICU) admission [1-3]. Critically ill patients experience acute muscle wasting and have been reported to lose 17.7% of rectus femoris cross-sectional area ($RF_{CSA}$) in the first ten-days following ICU admission [4, 5]. This muscle atrophy is associated with a decline in functional independence and mortality in critically ill patients [6-8]. Consequently, interventions that reduce acute muscle wasting during critical illness are likely to benefit survivors of critical illness.

Randomised controlled trials (RCTs) designed to test exercise interventions with critically ill patients have reported conflicting results [9-14]. A recent systematic review concluded that early rehabilitation may improve mobility, strength, and increase the number of days alive and out of hospital over a six-month timeframe [15]. However, the initiation of exercise interventions with critically ill patients is frequently delayed [16]. In-bed cycling is a promising intervention that can be introduced before a patient can follow commands [17]. Studies have reported that cycle ergometry introduced early during a patient's ICU admission were safe and feasible [17-20]. The first RCT investigating the effectiveness of in-bed cycling with critically ill patients reported that participants who completed cycle ergometry were able to walk further in the six-minute-walk-test (6MWT), had significantly higher quadriceps force and reported better functional well-being at acute-hospital discharge [9]. This trial did not incorporate measures of muscle size or quality to provide insights regarding the effect of in-bed cycling on reducing muscle loss. An RCT by Fossat et al. (2018) compared the Medical Research Council Sum Score ($MRC_{SUM}$) for participants who completed weekday in-bed cycling with additional sessions of functional electrical stimulation sessions while in ICU in comparison to usual-care, reporting no between-group differences [20]. Recently, a preliminary trial analysed muscle biopsy specimens from 18 patients and reported that in-bed cycling was effective at preserving muscle fibre area, but did not measure functional or quality of life outcomes [21]. Before a large Phase III RCT is completed, it is important to quantify the mechanism of action prior to assessing for efficacy. Hence, there is a need to complete an early exercise intervention study with critically ill patients that incorporates both blinded measures of muscle atrophy and patient-centred outcomes.

A single-centre RCT was designed to investigate if in-bed cycling in addition to usual-care (compared with usual-care) in patients expected to require more than 48-hours of invasive mechanical ventilation was:

1. Effective in reducing muscle atrophy,
2. Associated with better functional and cognitive outcomes at ICU and acute-hospital discharge, and
3. Associated with improved quality of life measured at three and six-months following hospital admission.

**Methods:**

Ethical approval was obtained from the human research ethics committees of Metro South Health and the Queensland University of Technology. The protocol for this study has been published, and this report follows the template for intervention description and replication (TIDieR) and the CONSORT statement [22, 23].

*Study Design*

A parallel two-arm, RCT with 1:1 allocation and blinding of the primary outcome assessors, was conducted. The setting was a 26-bed tertiary mixed medical, surgical and trauma ICU in Brisbane, Australia. Participants were allocated to receive either usual-care or daily in-bed cycling in addition to usual-care (Figure 1).

*Participants*

Patients were eligible for the study if they were: (i) expected to be mechanically ventilated for more than 48-hours, (ii) recruited within 96-hours of their ICU admission, and (iii) expected to remain in the ICU for more than 48-hours from study enrolment.

Patients were excluded if they: (i) were under 18-years old, (ii) had pre-existing condition that impaired mobility, (iii) had a new neurological disorder, (iv) had injuries precluding in-bed cycling, (v) were over 135 kg (cycle ergometer maximum weight capacity), (vi) were pregnant, (vii) had uncontrolled seizures or status epilepticus, or (viii) were unlikely to survive the current hospital admission.

*Randomisation and allocation concealment*

Participants were individually randomised, using random block sizes, to either intervention or usual-care groups. Randomisation was not stratified by demographic or clinical factors. A computer-generated

randomisation sequence was created by an investigator (SMM) not involved in the screening, consenting, allocation or assessment processes. The randomised sequence was uploaded onto a secure web-based computer application, the Research Electronic Data Capture (REDCap) [24]. Group allocation was revealed to the intervention coordinating investigator (MRN) after informed consent (from the patient or surrogate decision-maker) was granted.

*Interventions*

The usual-care group received routine physiotherapy interventions that included a daily assessment of physical and respiratory status and treatment. Physical treatments were directed to functional task achievement including; sitting, standing and mobilising. In-bed cycling was not a routine intervention at the site prior to the study. Consequently, usual-care group participants were not scheduled to participate in the cycling intervention.

The cycling group received the same usual-care interventions; they also received once daily (up to six-days per week) in-bed leg cycling using a MOTOmed Letto2 (RECK-Technik GmbH & Co. KG, Betzenweiler, Germany) cycle ergometer either in the ICU or in an acute hospital ward. The intervention co-ordinator (MRN) set-up and delivered the cycling sessions. Safety guidelines adapted from previous exercise intervention studies and recommendations were used to guide these sessions [9, 25-28]. Cycling sessions were chosen as they could be delivered to participants passively and progressed to active or resisted exercise depending on participants' ability and level of consciousness. Alert participants were encouraged to exercise at a moderate to hard level of perceived exertion, with the cycle ergometer resistance added and adjusted during the cycling session to achieve an appropriate level of exertion. Cycling sessions were delivered for a maximum of 30-minutes. However, sessions could be ceased early on participant request or if safety concerns arose.

*Primary Outcome*

The primary outcome was muscle atrophy at Day 10 post-study enrolment. Muscle atrophy was calculated as the percentage change from baseline (measured within 24-hours of study enrolment) in $RF_{CSA}$ at Day 10. The scan point was on the anterior thigh one-third distance from the superior patella to the anterior superior iliac spine [29]. All ultrasound scans were performed by experienced registered sonographers blinded to the

group allocation. The investigators acknowledge prior evidence of inter-rater reliability of $RF_{CSA}$ assessments was preliminary in nature [4, 30]. It was not possible within the constraints of study resources to have multiple sonographers perform each assessment to examine inter-rater reliability specific to this study's sonographers. Instead, to minimise the risk of between-sonographer measurement error, follow-up scans were completed by the same sonographer that had performed the baseline assessment where possible, and only three sonographers completed scans in this study. Each of these three accredited, experienced sonographers had received the same training and instruction in the study methodology. Scans were measured in triplicate on the right thigh (unless inaccessible due to attachments and then the left thigh was used throughout the participant's admission), and the mean value calculated.

*Secondary Outcomes*

In addition to $RF_{CSA}$, rectus femoris thickness (RFT) and vastus intermedius thickness (VIT) were also measured by sonographers at baseline, Day 3, Day 7, Day 10 post-study enrolment, and seven-days following ICU discharge. Change in muscle thickness and $RF_{CSA}$ at these timepoints were evaluated as secondary outcomes for acute muscle wasting. The coefficient of variation of participants' ultrasound scans for each assessment parameter ($RF_{CSA}$, RFT and VIT) at each assessment timepoint was calculated. Physical outcomes measured by physiotherapy assessors blinded to group allocation were: i) manual muscle strength using the Medical Research Council sum score ($MRC_{SUM}$) of 12 tested muscles with a score range of 0 to 60, ii) handgrip strength (HGS) using a Jamar Digital Dynamometer measured bilaterally with three attempts each hand, iii) functional status measured using the Functional Status Score for the ICU, all measured at ICU discharge and one week following ICU discharge, and iv) a single 6MWT [31] measured one week following ICU discharge.

Other outcomes were: i) participants' best level of function while admitted to the ICU using the ICU Mobility Score, ii) time from ICU admission until the participants achieved functional milestones of sitting out of bed, standing, assisted mobility, and independent mobility, iii) delirium incidence and days using routinely recorded nurse recorded Confusion Assessment Method (CAM)–ICU measures, iv) participants self-rated quality of life at Day 10, three- and six-months post ICU admission using the EQ5D-5L [32]. Data were collected on: demographic information including age, gender, diagnosis code, illness severity using the Acute Physiology and Chronic Health Evaluation III and Sequential Organ Failure Assessment [33], and admission

characteristics including the length of mechanical ventilation, ICU length of stay, acute-hospital length of stay and discharge destination, mortality, and days alive and out of hospital to six-months [34].

*Sample size considerations*

A minimum sample size of 68 participants (34 per group) was based on a repeated measures design with 80% power to detect a between-group difference of 2.9% on the primary outcome, representing a relative reduction of muscle atrophy of $RF_{CSA}$ by 16% if the absolute reduction in $RF_{CSA}$ in the control group was 17.7%, as reported by Puthucheary et al. (2013). The following assumptions were made: type I error 0.05, a standard deviation (SD) of 6% and a within-patient correlation of 0.5 between assessments, after accounting for up to 20% drop-out rate including in-hospital mortality [28]. An unavoidable limitation was the absence of prior effect estimates from in-bed cycling interventions versus usual-care for informing this sample size calculation.

*Statistical analyses*

Analyses followed the intention-to-treat principle with participants analysed even if they did not complete the cycling exercises. For the six participants that died prior to hospital discharge, data collected before death were included in analyses. Participants unable to complete the 6MWT (i.e., physically incapable) scored zero meters for this outcome. Descriptive statistics and generalised linear (mixed) models (with patients as a random effect for repeated measures) were used to examine the effect of group allocation on the primary and secondary outcomes, except for the use of Cox proportional hazards (time-to-event) analyses for time to mobility milestones (stand, sit, mobilise with assistance, mobilise independently). For the generalised linear models, the distributions were: Poisson for the counts of days with delirium (using a denominator of days in ICU); Gaussian for all other continuous outcomes; and Binomial for the outcome of whether patients were classified as having ICU acquired weakness. Due to an irregular distribution of 6MWT values owing to the assignment of zero metres to patients unable to walk without assistance, bias-corrected confidence intervals derived from Bootstrap resampling (2000 replications) were used. No adjustment for multiple testing was made [35]. P less than 0.05 was considered to be statistically significant. Statistical analysis was performed using Stata 13 (Stata Statistical Software: Release 13. College Station, TX: StataCorp LLC).

**Results**

Participants were recruited from July 2016 to May 2018, with six-month follow-up extending to November 2018. Of the 99 eligible patients, 74 consented and were randomised (Figure 1). One participant withdrew from the study. An additional participant was withdrawn when it became evident that they had sustained an unexpected ischemic spinal cord injury (and was therefore ineligible). To examine whether findings were sensitive to the exclusion of the two participants who were withdrawn after randomisation, we repeated the analysis including the two withdrawn participants. All findings were consistent regardless of the inclusion or exclusion of withdrawn participants. Therefore, we have presented an intention-to-treat analysis for all patients meeting the eligibility criteria. Except for one participant, all participants randomised to in-bed cycling received the planned interventions as per the protocol. One participant in the intervention group and five participants (7%) in the usual-care group died before hospital discharge. Participant mortality was unrelated to the study interventions received.

The analysis included 72 participants who were eligible for the study. Participants were predominately male (68%) with a mean (SD) age of 56 (17) years. The most common reasons for admission to ICU were sepsis, trauma and cardiac surgery. Baseline characteristics of participants were similar between the groups (Table 1).

A total of 276-sessions of in-bed cycling were completed. Two minor transient adverse events were observed, namely increased respiratory rate and decreased peripheral capillary oxygen saturation (SpO2) representing less than 1% of completed sessions. Both groups received equivalent usual-care respiratory and rehabilitative physiotherapy while they were acute hospital inpatients (Supplementary Table 1). In-bed cycling commenced median [IQR] 2.3 [1.8 to 3.1] days following ICU admission, and participants completed median [IQR] 6 [4 to 8] sessions. The mean (SD) duration of the cycling sessions was 27 (5) minutes. In-bed cycling sessions typically progressed from passive to active assist to resisted exercise as the participant regained consciousness and strength. Three cycling participants did not complete any active cycling sessions. Thirty-three cycling participants completed 130 (130/276, 47%) in-bed cycling sessions that included active cycling for at least 100 metres.

Thirty-one participants in each group had ultrasound assessments completed at the Day 10 primary endpoint. At Day 10 both groups experienced muscle atrophy, with the cycling group losing 8.4% (19.7%)$RF_{CSA}$ in comparison to the usual-care group who lost 14.7% (21.0%)$RF_{CSA}$ (Table 2). There were no significant

between-group differences as shown by the group-by-time interaction in percentage change in $RF_{CSA}$ at Day 10 (mean difference 3.4, 95% CI,-6.9 to 13.6, p=0.52) (Table 3). Both groups continued to experience muscle atrophy after discharge from the ICU. Similar patterns of acute muscle wasting were found for RFT and VIT (Figure 2). There were no statistically significant between-group differences in any of the secondary outcomes (Table 3). Time from ICU discharge to acute hospital discharge was median [IQR] three-days shorter (Table 2) in the cycling group 6.0 [3.9 to 12.4] versus usual-care group 9.0 [5.5 to 14.5]. Six-months after hospitalisation, the in-bed cycling group participants, spent a median of an additional six-days alive and out of hospital (Table 2). Quality of life outcomes were similar at Day 10, three- and six-months post-study enrolment (Table 2).

**Discussion**

In this single-centre randomised controlled trial, there were no statistically significant between-group differences across the primary and secondary outcomes. The variation in participants' $RF_{CSA}$ measures was larger than anticipated. Therefore, a sufficiently powered study with a larger sample size is required to determine the effect of in-bed cycling on reducing acute muscle wasting and on patient-centred outcomes.

Potential reduction in muscle atrophy was not detected in this study despite indications of the beneficial effect of in-bed cycling on reducing acute muscle loss in a recent study [21]. This mechanistic RCT investigated the differences in muscle mass of 18 critically ill patients with sepsis via muscle biopsy. Samples were taken a week apart and reported that in-bed cycling assisted in preserving muscle fibre area [21]. There is some initial evidence passive cycling increases strength [36] and that a greater acute loss of $RF_{CSA}$ is associated with knee extensor weakness [37]. However, further research is required to determine if passive or active cycling is more effective at reducing muscle atrophy, and whether reductions in atrophy are associated with improved patient outcomes such as strength or walking endurance. A recent multi-centre longitudinal study found that lean muscle mass is associated with gait speed and 6MWT [7]. Consequently, if in-bed cycling does help to reduce acute muscle wasting, then improvements in function should be seen. However, no between-group statistical differences were found for 6MWT in the present study. The 6MWT is a validated measure of exercise capacity [38]. It may represent a more clinically useful marker of muscle function and cardiovascular fitness, in comparison to the assessment of muscle strength (i.e. $MRC_{SUM}$, HGS) or muscle size.

Therefore, 6MWT may be a more clinically relevant marker of response to exercise-based interventions in future studies. The present study also reported no between-group differences in $MRC_{SUM}$ for participants who completed in-bed cycling, this result was consistent with findings from a recent RCT that coupled cycling with additional electrical stimulation sessions [20].

The present study complemented findings from previous studies that in-bed cycling is feasible and can be delivered safely to critically ill patients within 72-hours of ICU admission. Total session duration was less than an hour, including safety screening, set-up, intervention delivery (30-minutes), removal and cleaning of the cycle ergometer, and could be delivered by existing clinicians. Adverse events were minor, transient and occurred in less than 1% of the delivered interventions.

The optimal dose of cycle ergometry exercise remains unknown. Most studies have compared daily in-bed cycling with variable durations of between 20- and 60-minutes [9, 14, 17-21, 27, 39]. The time to commence the intervention is also variable, with studies commencing in-bed cycling between a median of two- and five-days following admission to the ICU [9, 14, 17-21, 27, 39]. The optimal intensity of in-bed cycling is also unknown, with most studies incorporating early passive cycling and later progressing to active and resisted cycling [9, 14, 18-21, 27]. Current clinical trials are assessing the effect of in-bed cycling in combination with protein supplementation on participants' functional outcome measured by the 6MWT. Functional electrical stimulation (FES) has been incorporated in some studies to reduce muscle atrophy. Determining the optimal dose (commencement, frequency, duration, intensity) and type (standard versus FES) of in-bed cycling and complementary nutritional supplementation remains a priority for future research [40]. Patients are typically inactive throughout their hospital admission [41-43]. Cycle ergometry is an intervention that can be used to initiate early rehabilitation before a patient can follow commands [17] and can be implemented following ICU discharge to increase the activity levels of patients throughout their hospitalisation.

No between-group differences were found for quality of life at three- or six-months following hospital admission. Participants allocated to the in-bed cycling group received a median of six in-bed cycling sessions for an average duration of 27 minutes. The relatively short implementation of a single intervention may not have been enough to have a consistent clinically meaningful impact on the quality of life (and other study outcomes) several months after the cessation of this intervention. Quality of life is also influenced by factors

that may be unaffected by exercise; including non-physical-activity related health conditions, social support, coping strategies, home environment, and adaptability [3, 44]. For long-term improvements in quality of life among critical illness survivors, it is possible that multi-factorial intervention including reduced sedation, early multi-modal exercise interventions and complementary optimisation of nutrition, especially protein, may be more effective in reducing muscle wasting and loss of function underpinning negative impact on health-related quality of life [44, 45], than early exercise intervention alone. It is also possible that patients with particular clinical characteristics may have received a benefit from the in-bed cycling intervention, while others did not. Identifying patients most likely to respond to early exercise interventions remains a priority for future research, albeit that the present study was not designed for exploratory analyses of this nature.

The strengths of this study included adherence to a pre-specified study protocol [28]. All but one participant allocated to the intervention group were able to complete the minimum number of cycling sessions. Blinded assessment of the primary outcome was completed with over 85% of participants enrolled.

The study had some limitations, and as a single-centre clinical trial, results should be generalised with caution. The study was not powered to detect differences in secondary outcomes, and the greater than anticipated variability in the primary measure also meant the study was at risk of Type II error. The 6MWT was only completed once, without replication. Whilst this is common in studies involving critically ill patients [46], the potential feasibility or impact of learning effects of repeated 6MWT in hospital settings among critical illness survivors remains a priority for further research.

Another limitation was that only one sonographer completed the ultrasound assessment at each timepoint. Therefore, the inter-rater reliability of the assessors could not be evaluated. Assessment of quadriceps muscle mass with ultrasound in critically ill patients has been reported to be able to be reliably assessed within observers, but not necessarily between observers [47]. To address this issue, this study used the same accredited and experienced sonographers at follow-up assessments where possible who had received consistent training in the ultrasound methodology, all ultrasound measurements were performed in triplicate and sonographers were blinded to group allocation. The use of ultrasound in critical care studies is an emerging field, and it is important that future studies adopt recommendations to standardise assessment methods and measure the reliability and variability of assessors wherever possible [48-50]. The mean

difference in the primary outcome of percentage change in $RF_{CSA}$ of 3.4% observed in this study was greater than the 2.9% difference that the study was initially planned to be able to detect. The substantially greater variability in muscle atrophy in this sample (in comparison to the a-priori sample size estimate) should be an important consideration in the design of future studies.

## Conclusions

In-bed cycling did not reduce acute muscle wasting in critically ill adults, but this study provides useful effect estimates and learnings for large-scale clinical trials.

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**Conflicts of interest:** None to declare

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**References:**


1. Iwashyna TJ, Ely EW, Smith DM, Langa KM, (2010) Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA 304: 1787-1794
2. Herridge MS, Tansey CM, Matte A, Tomlinson G, Diaz-Granados N, Cooper A, Guest CB, Mazer CD, Mehta S, Stewart TE, Kudlow P, Cook D, Slutsky AS, Cheung AM, Canadian Critical Care Trials G, (2011) Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med 364: 1293-1304
3. Hodgson CL, Udy AA, Bailey M, Barrett J, Bellomo R, Bucknall T, Gabbe BJ, Higgins AM, Iwashyna TJ, Hunt-Smith J, Murray LJ, Myles PS, Ponsford J, Pilcher D, Walker C, Young M, Cooper DJ, (2017) The impact of disability in survivors of critical illness. Intensive Care Med 43: 992-1001
4. Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, Hopkinson NS, Phadke R, Dew T, Sidhu PS, Velloso C, Seymour J, Agley CC, Selby A, Limb M, Edwards LM, Smith K, Rowlerson A, Rennie MJ, Moxham J, Harridge SD, Hart N, Montgomery HE, (2013) Acute skeletal muscle wasting in critical illness. JAMA 310: 1591-1600
5. Hayes K, Holland AE, Pellegrino VA, Mathur S, Hodgson CL, (2018) Acute skeletal muscle wasting and relation to physical function in patients requiring extracorporeal membrane oxygenation (ECMO). J Crit Care 48: 1-8
6. Batt J, Herridge M, Dos Santos C, (2017) Mechanism of ICU-acquired weakness: skeletal muscle loss in critical illness. Intensive Care Med 43: 1844-1846
7. Chan KS, Mourtzakis M, Aronson Friedman L, Dinglas VD, Hough CL, Ely EW, Morris PE, Hopkins RO, Needham DM, National Institutes of Health National Heart L, Blood Institute Acute Respiratory Distress Syndrome N, (2018) Evaluating Muscle Mass in Survivors of Acute Respiratory Distress Syndrome: A 1-Year Multicenter Longitudinal Study. Crit Care Med 46: 1238-1246
8. Dinglas VD, Aronson Friedman L, Colantuoni E, Mendez-Tellez PA, Shanholtz CB, Ciesla ND, Pronovost PJ, Needham DM, (2017) Muscle Weakness and 5-Year Survival in Acute Respiratory Distress Syndrome Survivors. Crit Care Med 45: 446-453

9. Burtin C, Clerckx B, Robbeets C, Ferdinande P, Langer D, Troosters T, Hermans G, Decramer M, Gosselink R, (2009) Early exercise in critically ill patients enhances short-term functional recovery. Crit Care Med 37: 2499-2505

10. Kayambu G, Boots R, Paratz J, (2015) Early physical rehabilitation in intensive care patients with sepsis syndromes: a pilot randomised controlled trial. Intensive Care Med 41: 865-874

11. Morris PE, Berry MJ, Files DC, Thompson JC, Hauser J, Flores L, Dhar S, Chmelo E, Lovato J, Case LD, Bakhru RN, Sarwal A, Parry SM, Campbell P, Mote A, Winkelman C, Hite RD, Nicklas B, Chatterjee A, Young MP, (2016) Standardized Rehabilitation and Hospital Length of Stay Among Patients With Acute Respiratory Failure: A Randomized Clinical Trial. JAMA 315: 2694-2702

12. Moss M, Nordon-Craft A, Malone D, Van Pelt D, Frankel SK, Warner ML, Kriekels W, McNulty M, Fairclough DL, Schenkman M, (2016) A Randomized Trial of an Intensive Physical Therapy Program for Patients with Acute Respiratory Failure. Am J Respir Crit Care Med 193: 1101-1110

13. Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, Spears L, Miller M, Franczyk M, Deprizio D, Schmidt GA, Bowman A, Barr R, McCallister KE, Hall JB, Kress JP, (2009) Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet 373: 1874-1882

14. Eggmann S, Verra ML, Luder G, Takala J, Jakob SM, (2018) Effects of early, combined endurance and resistance training in mechanically ventilated, critically ill patients: A randomised controlled trial. PLoS One 13: e0207428

15. Tipping CJ, Harrold M, Holland A, Romero L, Nisbet T, Hodgson CL, (2017) The effects of active mobilisation and rehabilitation in ICU on mortality and function: a systematic review. Intensive Care Med 43: 171-183

16. Nickels MR, Aitken LM, Walsham J, Crampton LJ, Barnett AG, McPhail SM, (2019) Exercise interventions are delayed in critically ill patients: an historical cohort study in an Australian tertiary intensive care unit. Physiotherapy 10.1016/j.physio.2019.06.011

17. Camargo Pires-Neto R, Fogaca Kawaguchi YM, Sayuri Hirota A, Fu C, Tanaka C, Caruso P, Park M, Ribeiro Carvalho CR, (2013) Very early passive cycling exercise in mechanically ventilated critically ill patients: physiological and safety aspects--a case series. PLoS One 8: e74182

18. Kho ME, Martin RA, Toonstra AL, Zanni JM, Mantheiy EC, Nelliot A, Needham DM, (2015) Feasibility and safety of in-bed cycling for physical rehabilitation in the intensive care unit. J Crit Care 30: 1419 e1411-1415

19. Kho ME, Molloy AJ, Clarke FJ, Reid JC, Herridge MS, Karachi T, Rochwerg B, Fox-Robichaud AE, Seely AJ, Mathur S, Lo V, Burns KE, Ball IM, Pellizzari JR, Tarride JE, Rudkowski JC, Koo K, Heels-Ansdell D, Cook DJ, (2019) Multicentre pilot randomised clinical trial of early in-bed cycle ergometry with ventilated patients. BMJ Open Respir Res 6: e000383

20. Fossat G, Baudin F, Courtes L, Bobet S, Dupont A, Bretagnol A, Benzekri-Lefevre D, Kamel T, Muller G, Bercault N, Barbier F, Runge I, Nay MA, Skarzynski M, Mathonnet A, Boulain T, (2018) Effect of In-Bed Leg Cycling and Electrical Stimulation of the Quadriceps on Global Muscle Strength in Critically Ill Adults: A Randomized Clinical Trial. JAMA 320: 368-378

21. Hickmann CE, Castanares-Zapatero D, Deldicque L, Van den Bergh P, Caty G, Robert A, Roeseler J, Francaux M, Laterre PF, (2018) Impact of Very Early Physical Therapy During Septic Shock on Skeletal Muscle: A Randomized Controlled Trial. Crit Care Med 46: 1436-1443

22. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, Altman DG, Barbour V, Macdonald H, Johnston M, Lamb SE, Dixon-Woods M, McCulloch P, Wyatt JC, Chan AW, Michie S, (2014) Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ 348: g1687

23. Schulz KF, Altman DG, Moher D, Group C, (2010) CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ 340: c332

24. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG, (2009) Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 42: 377-381

25. Hodgson CL, Stiller K, Needham DM, Tipping CJ, Harrold M, Baldwin CE, Bradley S, Berney S, Caruana LR, Elliott D, Green M, Haines K, Higgins AM, Kaukonen KM, Leditschke IA, Nickels MR, Paratz J, Patman S, Skinner EH, Young PJ, Zanni JM, Denehy L, Webb SA, (2014) Expert consensus and recommendations on safety criteria for active mobilization of mechanically ventilated critically ill adults. Crit Care 18: 658

26. Kho ME, Molloy AJ, Clarke F, Herridge MS, Koo KK, Rudkowski J, Seely AJ, Pellizzari JR, Tarride JE, Mourtzakis M, Karachi T, Cook DJ, Canadian Critical Care Trials G, (2016) CYCLE pilot: a protocol for a pilot randomised study of early cycle ergometry versus routine physiotherapy in mechanically ventilated patients. BMJ Open 6: e011659

27. Kho ME, Molloy AJ, Clarke FJ, Ajami D, McCaughan M, Obrovac K, Murphy C, Camposilvan L, Herridge MS, Koo KK, Rudkowski J, Seely AJ, Zanni JM, Mourtzakis M, Piraino T, Cook DJ, Canadian Critical Care Trials G, (2016) TryCYCLE: A Prospective Study of the Safety and Feasibility of Early In-Bed Cycling in Mechanically Ventilated Patients. PLoS One 11: e0167561

28. Nickels MR, Aitken LM, Walsham J, Barnett AG, McPhail SM, (2017) Critical Care Cycling Study (CYCLIST) trial protocol: a randomised controlled trial of usual care plus additional in-bed cycling sessions versus usual care in the critically ill. BMJ Open 7: e017393

29. Tillquist M, Kutsogiannis DJ, Wischmeyer PE, Kummerlen C, Leung R, Stollery D, Karvellas CJ, Preiser JC, Bird N, Kozar R, Heyland DK, (2014) Bedside ultrasound is a practical and reliable measurement tool for assessing quadriceps muscle layer thickness. JPEN J Parenter Enteral Nutr 38: 886-890

30. Connolly B, Puthucheary Z, Montgomery H, Moxham J, Hart N, (2011) P66 Inter-observer reliability of ultrasound to measure rectus femoris cross-sectional area in critically ill patients. Thorax 66: A95-A95

31. Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, McCormack MC, Carlin BW, Sciurba FC, Pitta F, Wanger J, MacIntyre N, Kaminsky DA, Culver BH, Revill SM, Hernandes NA, Andrianopoulos V, Camillo CA, Mitchell KE, Lee AL, Hill CJ, Singh SJ, (2014) An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J 44: 1428-1446

32. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, Bonsel G, Badia X, (2011) Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 20: 1727-1736

33. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, Reinhart CK, Suter PM, Thijs LG, (1996) The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ

dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 22: 707-710

34. Ariti CA, Cleland JG, Pocock SJ, Pfeffer MA, Swedberg K, Granger CB, McMurray JJ, Michelson EL, Ostergren J, Yusuf S, (2011) Days alive and out of hospital and the patient journey in patients with heart failure: Insights from the candesartan in heart failure: assessment of reduction in mortality and morbidity (CHARM) program. Am Heart J 162: 900-906

35. Sedgwick P, (2012) Multiple significance tests: the Bonferroni correction. BMJ 344: e509-e509

36. Machado ADS, Pires-Neto RC, Carvalho MTX, Soares JC, Cardoso DM, Albuquerque IM, (2017) Effects that passive cycling exercise have on muscle strength, duration of mechanical ventilation, and length of hospital stay in critically ill patients: a randomized clinical trial. J Bras Pneumol 43: 134-139

37. Puthucheary ZA, McNelly AS, Rawal J, Connolly B, Sidhu PS, Rowlerson A, Moxham J, Harridge SD, Hart N, Montgomery HE, (2017) Rectus Femoris Cross-Sectional Area and Muscle Layer Thickness: Comparative Markers of Muscle Wasting and Weakness. Am J Respir Crit Care Med 195: 136-138

38. Chan KS, Pfoh ER, Denehy L, Elliott D, Holland AE, Dinglas VD, Needham DM, (2015) Construct validity and minimal important difference of 6-minute walk distance in survivors of acute respiratory failure. Chest 147: 1316-1326

39. Parry SM, Berney S, Warrillow S, El-Ansary D, Bryant AL, Hart N, Puthucheary Z, Koopman R, Denehy L, (2014) Functional electrical stimulation with cycling in the critically ill: a pilot case-matched control study. J Crit Care 29: 695 e691-697

40. Morris PE, Montgomery-Yates A, (2017) Mastering the design for rehabilitation strategies in ICU survivors. Thorax 72: 594-595

41. Connolly BA, Mortimore JL, Douiri A, Rose JW, Hart N, Berney SC, (2019) Low Levels of Physical Activity During Critical Illness and Weaning: The Evidence-Reality Gap. J Intensive Care Med 34: 818-827

42. Beach LJ, Fetterplace K, Edbrooke L, Parry SM, Curtis R, Rechnitzer T, Berney S, Denehy L, (2017) Measurement of physical activity levels in the Intensive Care Unit and functional outcomes: An observational study. J Crit Care 40: 189-196

458 43. Baldwin C, van Kessel G, Phillips A, Johnston K, (2017) Accelerometry Shows Inpatients With Acute
459 Medical or Surgical Conditions Spend Little Time Upright and Are Highly Sedentary: Systematic
460 Review. Phys Ther 97: 1044-1065
461 44. Heyland DK, Stapleton RD, Mourtzakis M, Hough CL, Morris P, Deutz NE, Colantuoni E, Day A, Prado
462 CM, Needham DM, (2016) Combining nutrition and exercise to optimize survival and recovery from
463 critical illness: Conceptual and methodological issues. Clin Nutr 35: 1196-1206
464 45. Heyland DK, Day A, Clarke GJ, Hough CT, Files DC, Mourtzakis M, Deutz N, Needham DM, Stapleton
465 R, (2019) Nutrition and Exercise in Critical Illness Trial (NEXIS Trial): a protocol of a multicentred,
466 randomised controlled trial of combined cycle ergometry and amino acid supplementation
467 commenced early during critical illness. BMJ Open 9: e027893
468 46. Parry SM, Nalamalapu SR, Nunna K, Rabiee A, Friedman LA, Colantuoni E, Needham DM, Dinglas
469 VD, (2019) Six-Minute Walk Distance After Critical Illness: A Systematic Review and Meta-Analysis. J
470 Intensive Care Med 10.1177/0885066619885838
471 47. Segers J, Hermans G, Charususin N, Fivez T, Vanhorebeek I, Van den Berghe G, Gosselink R, (2015)
472 Assessment of quadriceps muscle mass with ultrasound in critically ill patients: intra- and inter-
473 observer agreement and sensitivity. Intensive Care Med 41: 562-563
474 48. Mourtzakis M, Parry S, Connolly B, Puthucheary Z, (2017) Skeletal Muscle Ultrasound in Critical
475 Care: A Tool in Need of Translation. Ann Am Thorac Soc 14: 1495-1503
476 49. Parry SM, Burtin C, Denehy L, Puthucheary ZA, Bear D, (2019) Ultrasound Evaluation of Quadriceps
477 Muscle Dysfunction in Respiratory Disease. Cardiopulm Phys Ther J 30: 15-23
478 50. Weinel LM, Summers MJ, Chapple L-A, (2019) Ultrasonography to measure quadriceps muscle in
479 critically ill patients: A literature review of reported methodologies. Anaesth Intensive Care 47: 423-
480 434

481

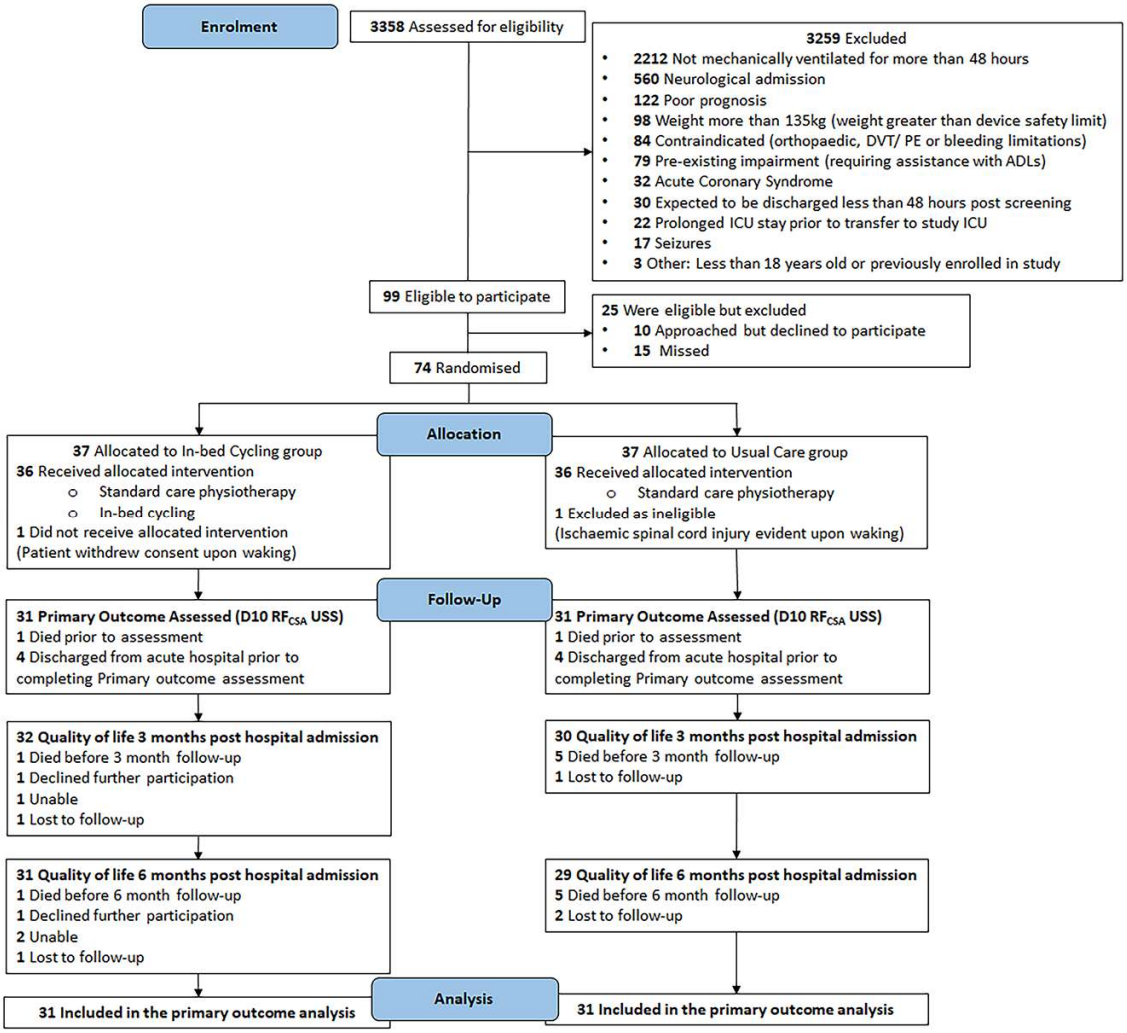


**Figure 1: CONSORT figure of participant flow through the study**

**Table 1. Patient baseline characteristics**

| Patient characteristics at baseline | In-bed cycling group, n= 36 | Usual-care group, n =36 |
|---|---|---|
| Age in years, mean (SD) | 56 (18) | 57 (16) |
| Males, n (%) | 23 (64%) | 26 (72%) |
| APACHE III score, median (IQR) | 67 (48, 82) | 65 (49, 81) |
| SOFA (worst score), median (IQR) | 9 (8, 12) | 9 (7, 11) |
| SOFA (most organs with dysfunction), median (IQR) | 3 (3, 4) | 4 (3, 5) |
| Height in centimeters, mean (SD) | 171 (11) | 173 (10) |
| Weight in kilograms, mean (SD) | 85 (16) | 88 (18) |
| BMI kg/m$^2$, mean (SD) | 29 (5) | 30 (8) |
| Primary Diagnosis on ICU Admission | | |
| Sepsis | 7 (19%) | 6 (17%) |
| Trauma | 8 (22%) | 5 (14%) |

| | | |
|---|---|---|
| Cardiac Surgery | 3 (8%) | 5 (14%) |
| Gastrointestinal | 3 (8%) | 3 (8%) |
| Pneumonia | 3 (8%) | 3 (8%) |
| Hemorrhage | 2 (6%) | 2 (6%) |
| Vascular surgery | 1 (3%) | 2 (6%) |
| Acute exacerbation of asthma | 1 (3%) | 2 (6%) |
| Airway obstruction | 2 (6%) | 1 (3%) |
| Overdose | 2 (6%) | 1 (3%) |
| Cardiac arrest | 1 (3%) | 1 (3%) |
| Malignancy | 1 (3%) | 1 (3%) |
| Other | 2 (6%) | 4 (11%) |

SD, standard deviation, n, number; APACHE III = Acute Physiology and Chronic Health Evaluation III severity of illness score (0-299); SOFA = Sequential Organ Failure Assessment; IQR, interquartile range; MV, mechanical ventilation; ICU, intensive care unit.

**Table 2. Ultrasound, secondary and clinical outcomes**

| Variable | In-bed cycling group | Usual care group | |
|---|---|---|---|
| Ultrasound | | | CV%[a] |
| Rectus femoris cross-sectional area [b] | | | |
| Day 3 | -0.3 (21.2) | -2.3 (26.2) | 5.6 |
| Day 7 | 0.9 (27.3) | -11.1 (23.6) | 4.8 |
| Day 10 | -8.4 (19.7) | -14.7 (21.0) | 5.2 |
| 7 days post ICU discharge | -12.1 (24.7) | -22.6 (23.4) | 6.3 |
| Rectus femoris thickness [b] | | | |
| Day 3 | -0.04 (24.5) | 2.5 (26.3) | 4.7 |
| Day 7 | 0.14 (23.5) | -3.0 (21.9) | 4.3 |
| Day 10 | -2.7 (17.0) | -8.0 (22.9) | 5.7 |
| 7 days post ICU discharge | -2.6 (14.2) | -7.5 (18.5) | 5.5 |
| Vastus intermedius thickness [b] | | | |
| Day 3 | 5.3 (37.1) | 1.4 (34.1) | 4.3 |
| Day 7 | -3.9 (19.3) | -4.3 (23.6) | 4.8 |
| Day 10 | -0.6 (24.7) | -7.8 (28.8) | 4.8 |
| 7 days post ICU discharge | -0.2 (22.3) | -11.6 (21.5) | 4.6 |
| Secondary Outcomes | | | |
| ICU Mobility Scale (ICU discharge) | 6 (3, 7) | 4 (3, 7) | |
| 6-minute walk test (7 days following ICU discharge) | 258 (30, 326) | 225 (57, 324) | |
| Upper limb MRC sum score (ICU discharge) | 26 (24, 28) | 27 (24, 28) | |

| | | |
|---|---|---|
| Lower limb MRC sum score (ICU discharge) | 26 (24, 28) | 28 (23, 29) |
| MRC sum score [c] (ICU discharge) | 54 (47, 57) | 54 (47, 56) |
| Upper limb MRC sum score (7 days following ICU discharge) | 28 (25, 30) | 29 (27, 30) |
| Lower limb MRC sum score (7 days following ICU discharge) | 28 (26, 30) | 29 (28, 30) |
| MRC sum score [c] (7 days following ICU discharge) | 57 (52, 60) | 58 (53, 59) |
| Handgrip strength [d] (ICU discharge) | 16.3 (10.6, 21.2) | 16.7 (10.9, 20.1) |
| Handgrip strength [d] (7 days following ICU discharge) | 21.1 (16.8, 30.8) | 22.2 (16.6, 31.3) |
| FSS ICU (ICU discharge) | 23 (18, 31) | 23 (15, 29) |
| FSS ICU (7 days following ICU discharge) | 35 (32, 35) | 35 (32, 35) |
| Functional milestones [e] (days) | | |
| Sitting out of bed | 8.4 (5.0, 13.0) | 7.8 (5.5, 11.1) |
| Standing | 8.4 (4.9, 14.8) | 7.4 (5.0, 10.7) |
| Mobilised with assistance | 9.1 (5.0, 19.7) | 8.8 (5.9, 12.7) |
| Mobilised independently | 12.8 (7.8, 26.1) | 13.4 (8.6,19.7) |
| Quality of life (EQ-5D VAS), Day 10 post admission, mean (SD) | 52 (22) | 53 (23) |
| Quality of life (EQ-5D VAS), 3-months post admission, mean (SD) | 67 (19) | 70 (17) |
| Quality of life (EQ-5D VAS), 6-months post admission, mean (SD) | 75 (18) | 73 (17) |
| Clinical outcomes | | |
| Length of MV, days | 6.3 (3.9, 9.5) | 5.5 (3.5, 10.1) |
| Delirium | | |
| Participant with delirium, n (%) | 9 (25%) | 13 (36%) |
| Delirium positive days, n (%) | 14 (3.7%) | 26 (7.0%) |
| Delirium positive days | 0 (0, 0.3) | 0 (0,1) |
| ICU length of stay [f], days | 8.4 (5.0, 13.1) | 7.7 (4.9, 11.1) |
| ICU admit to acute hospital discharge [f], days | 14.9 (9.2, 31.2) | 17.2 (12.2, 26.5) |
| ICU discharge to acute hospital discharge [g], days | 6.0 (3.9, 12.4) | 9.0 (5.5, 14.5) |
| Acute hospital stay [g], days | 17.2 (10.5, 29.7) | 17.9 (13.0, 29.4) |
| ICU discharge destination, n (%) | | |
| Acute hospital ward | 35 (97%) | 33 (92%) |
| Died in ICU | 1 (3%) | 3 (8%) |
| Acute hospital discharge destination, n (%) | | |

| | | |
|---|---|---|
| Home | 31 (86%) | 27 (75%) |
| Died in Hospital | 1 (3%) | 5 (14%) |
| Transferred to a rehabilitation facility | 4 (11%) | 4 (11%) |
| Days alive and out of hospital | | |
| Days | 162 (145, 169) | 156 (126, 166) |
| % days | 90 (81, 94)% | 87 (70, 92)% |

[a] Coefficient of variation reported as a percentage
[b] Ultrasound calculated as the percentage change from baseline, reported as mean (standard deviation)
[c] MRC Sum Score: reported for participants who completed all twelve muscle tests.
[d] Handgrip strength calculated as the average of left and right tests. If one side was unable to be tested the value of the tested side was utilized.
[e] Functional milestones calculated in days from ICU admission till first achieved functional task,
[f] Length of stay for participants who survived ICU admission
[g] Length of stay for participants who survived acute hospital admission
Participants who passed away prior to the assessment timepoint were excluded from the analysis.
Quality of life measured by EQ5D-5L Visual Analogue Scale.
CV: Coefficient of variation, ICU: intensive care unit, IQR: interquartile range, MRC: medical research council, FSS ICU: Functional status score for the intensive care unit.
Unless otherwise stated variables reported as median (interquartile range).

**Table 3. Findings from generalised linear (mixed) models expressing coefficient (beta, odds ratio, incidence rate ratio) for group effect (or group by time interaction when repeated measures) or time-to-event analyses (hazard ratio) for primary and secondary outcomes.**

| Model dependent variable | Coefficient [a] | 95% confidence intervals | *p* value |
|---|---|---|---|
| Change in rectus femoris cross-sectional area [b] | | | |
| Day 3 | Referent | | |
| Day 7 | b=8.52 | -2.01 to 19.04 | 0.11 |
| Day 10 | b=3.39 | -6.86 to 13.64 | 0.52 |
| Change in rectus femoris thickness [b] | | | |
| Day 3 | Referent | | |
| Day 7 | b=4.84 | -6.96 to 16.63 | 0.42 |
| Day 10 | b=6.60 | -4.90 to 18.10 | 0.26 |
| Change in vastus intermedius thickness [b] | | | |
| Day 3 | Referent | | |
| Day 7 | b=-3.89 | -18.88 to 11.10 | 0.61 |
| Day 10 | b=0.83 | -13.79 to 15.46 | 0.91 |
| 6-minute walk test [c d] | b=16.44 | -60.54 to 94.07 | 0.68 |
| ICU acquired weakness [e] | OR=1.79 | 0.13 to 25.62 | 0.67 |
| Handgrip strength [f] | b=-0.22 | -2.45 to 2.01 | 0.85 |
| ICU mobility scale [c] | b=0.92 | -0.24 to 2.07 | 0.12 |
| Functional status score ICU | b=-1.53 | -4.84 to 1.77 | 0.36 |
| Functional milestones [c g] | Hazard ratio | | |
| Sit out of bed | HR=1.14 | 0.70 to 1.85 | 0.59 |
| Standing | HR=1.06 | 0.65 to 1.72 | 0.81 |
| Mobilised with assistance | HR=1.05 | 0.65 to 1.70 | 0.84 |

| | | | |
|---|---|---|---|
| Mobilised independently | HR=1.23 | 0.74 to 2.03 | 0.43 |
| Delirium incidence [c] | OR=0.59 | $2.13e^{-8}$ to $1.64e^{7}$ | 0.95 |
| Delirium days [h] | IRR=0.61 | 0.25 to 1.46 | 0.27 |
| Health-related quality of life (EQ5D-5L) [i] | | | |
| Day 10 | Referent | | |
| 3-months | b=0.05 | -0.09 to 0.20 | 0.47 |
| 6-months | b=0.10 | -0.04 to 0.25 | 0.17 |

[a] Coefficients are reported for the group variable when only one assessment, or for group by time interactions when repeated measures; [b] Ultrasound calculated as a percentage change from baseline (repeated assessments), [c] Single assessment or timepoint, therefore, no coefficient for assessment and group by time, [d] Bias corrected confidence intervals generated via bootstrapping used due to irregular distribution of 6-minute walk test, [e] ICU acquired weakness: reported for participants who completed all twelve muscle tests of the Medical Research Council sum score, [f] Handgrip strength calculated as the average of left and right tests. If one side was unable to be tested the value of the tested side was utilised, [g] Functional milestones calculated in days from ICU admission till first achieved functional task, [h] Delirium days calculated for days when participants were able to be assessed while in ICU, ICU: intensive care unit, [i] EQ5D-5L: EuroQual 5-dimensions 5-levels utility score (reference: Norman R, Cronin P, Viney R. A pilot discrete choice experiment to explore preferences for EQ-5D-5L health states. Applied health economics and health policy. 2013;11(3):287-298),
ICU: intensive care unit, b: beta coefficient, OR: odds ratio, HR: hazard ratio, IRR: incident rate ratio.

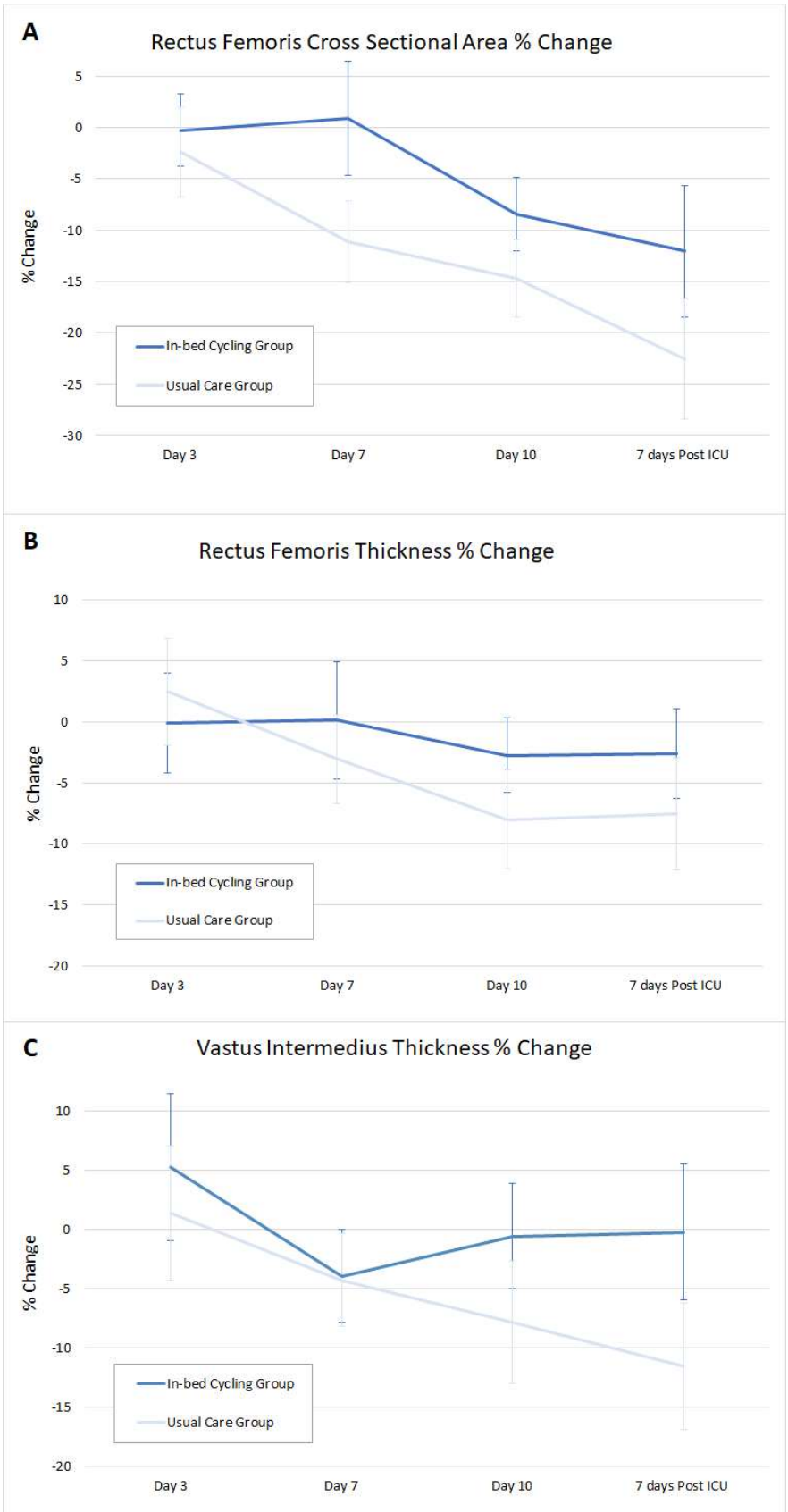


**Figure 2:** Acute muscle wasting of study participants according to group allocation at pre-specified longitudinal timepoints. Markers represent median percentage change, and error bars represent standard errors. **A** Rectus femoris cross sectional area percentage change. **B** Rectus femoris thickness percentage change. **C** Vastus intermedius percentage change. Seven days post intensive care unit (ICU) was a milestone driven timepoint, due to participants variable ICU length of stay this timepoint was not consistent amongst patients.

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**Supplementary Material 1. Physiotherapy care received according to group allocation**

| Physiotherapy Intervention | In-bed cycling group | Usual Care Group |
|---|---|---|
| ICU | | |
| Respiratory session | 10 (7, 15) | 10 (6, 15) |
| Passive range of motion | 3 (1, 5) | 3 (1, 6) |
| Active rehabilitation session | 3 (2, 5) | 3 (2, 5) |
| Acute medical or surgical ward [a] | | |
| Respiratory session | 4 (1, 5) | 3 (2, 4) |
| Rehabilitation session | 4 (3, 6) | 4 (2, 6) |

[a] Number of interventions occurring in the first week following ICU discharge,
ICU, intensive care unit.