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

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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.

Leanne Aitken: Study design, safety monitoring, analysis, manuscript preparation, critical review and approval of the manuscript.

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

2

3 **Abstract**

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

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

13 **Results:** Analysis included the 72 participants (mean age, 56-years; male, 68%) who completed the study.
14 There were no significant between-group differences in muscle atrophy of RF_{CSA} at Day 10 (mean difference
15 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).

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

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

19 **Introduction:**

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

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

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

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

50

51 **Methods:**

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

55 *Study Design*

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

59 *Participants*

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

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

67 *Randomisation and allocation concealment*

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

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

75 *Interventions*

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

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

92 *Primary Outcome*

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

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

106 *Secondary Outcomes*

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

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

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

126 *Sample size considerations*

127 A minimum sample size of 68 participants (34 per group) was based on a repeated measures design with 80%
128 power to detect a between-group difference of 2.9% on the primary outcome, representing a relative
129 reduction of muscle atrophy of RF_{CSA} by 16% if the absolute reduction in RF_{CSA} in the control group was 17.7%,
130 as reported by Puthuchery et al. (2013). The following assumptions were made: type I error 0.05, a standard
131 deviation (SD) of 6% and a within-patient correlation of 0.5 between assessments, after accounting for up to
132 20% drop-out rate including in-hospital mortality [28]. An unavoidable limitation was the absence of prior
133 effect estimates from in-bed cycling interventions versus usual-care for informing this sample size calculation.

134 *Statistical analyses*

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

149

150 **Results**

151 Participants were recruited from July 2016 to May 2018, with six-month follow-up extending to November
152 2018. Of the 99 eligible patients, 74 consented and were randomised (Figure 1). One participant withdrew
153 from the study. An additional participant was withdrawn when it became evident that they had sustained an
154 unexpected ischemic spinal cord injury (and was therefore ineligible). To examine whether findings were
155 sensitive to the exclusion of the two participants who were withdrawn after randomisation, we repeated the
156 analysis including the two withdrawn participants. All findings were consistent regardless of the inclusion or
157 exclusion of withdrawn participants. Therefore, we have presented an intention-to-treat analysis for all
158 patients meeting the eligibility criteria. Except for one participant, all participants randomised to in-bed
159 cycling received the planned interventions as per the protocol. One participant in the intervention group and
160 five participants (7%) in the usual-care group died before hospital discharge. Participant mortality was
161 unrelated to the study interventions received.

162 The analysis included 72 participants who were eligible for the study. Participants were predominately male
163 (68%) with a mean (SD) age of 56 (17) years. The most common reasons for admission to ICU were sepsis,
164 trauma and cardiac surgery. Baseline characteristics of participants were similar between the groups
165 (Table 1).

166 A total of 276-sessions of in-bed cycling were completed. Two minor transient adverse events were observed,
167 namely increased respiratory rate and decreased peripheral capillary oxygen saturation (SpO₂) representing
168 less than 1% of completed sessions. Both groups received equivalent usual-care respiratory and rehabilitative
169 physiotherapy while they were acute hospital inpatients (Supplementary Table 1). In-bed cycling commenced
170 median [IQR] 2.3 [1.8 to 3.1] days following ICU admission, and participants completed median [IQR] 6 [4 to 8]
171 sessions. The mean (SD) duration of the cycling sessions was 27 (5) minutes. In-bed cycling sessions typically
172 progressed from passive to active assist to resisted exercise as the participant regained consciousness and
173 strength. Three cycling participants did not complete any active cycling sessions. Thirty-three cycling
174 participants completed 130 (130/276, 47%) in-bed cycling sessions that included active cycling for at least
175 100 metres.

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

179 between-group differences as shown by the group-by-time interaction in percentage change in RF_{CSA} at
180 Day 10 (mean difference 3.4, 95% CI, -6.9 to 13.6, p=0.52) (Table 3). Both groups continued to experience
181 muscle atrophy after discharge from the ICU. Similar patterns of acute muscle wasting were found for RFT
182 and VIT (Figure 2). There were no statistically significant between-group differences in any of the secondary
183 outcomes (Table 3). Time from ICU discharge to acute hospital discharge was median [IQR] three-days
184 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
185 after hospitalisation, the in-bed cycling group participants, spent a median of an additional six-days alive and
186 out of hospital (Table 2). Quality of life outcomes were similar at Day 10, three- and six-months post-study
187 enrolment (Table 2).

188

189 **Discussion**

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

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

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

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

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

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

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

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

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

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

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

265

266 **Conclusions**

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

269

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278

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280

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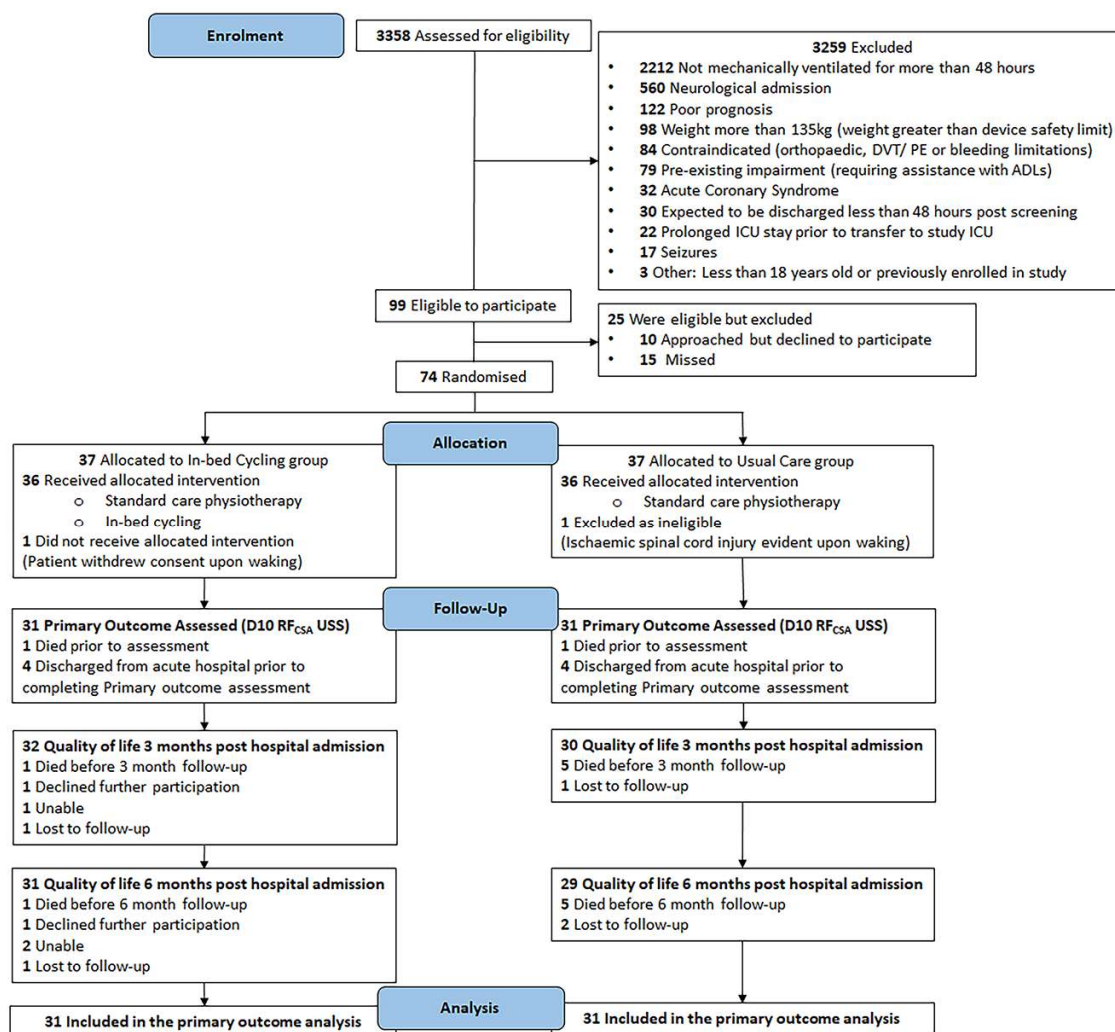
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482

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

484

485 **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%)

486 SD, standard deviation, n, number; APACHE III = Acute Physiology and Chronic Health Evaluation III severity
487 of illness score (0-299); SOFA = Sequential Organ Failure Assessment; IQR, interquartile range; MV,
488 mechanical ventilation; ICU, intensive care unit.
489

490

491 **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)
<hr/>		
Clinical outcomes		
<hr/>		
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)%

492 ^a Coefficient of variation reported as a percentage
493 ^b Ultrasound calculated as the percentage change from baseline, reported as mean (standard deviation)
494 ^c MRC Sum Score: reported for participants who completed all twelve muscle tests.
495 ^d Handgrip strength calculated as the average of left and right tests. If one side was unable to be tested the
496 value of the tested side was utilized.
497 ^e Functional milestones calculated in days from ICU admission till first achieved functional task,
498 ^f Length of stay for participants who survived ICU admission
499 ^g Length of stay for participants who survived acute hospital admission
500 Participants who passed away prior to the assessment timepoint were excluded from the analysis.
501 Quality of life measured by EQ5D-5L Visual Analogue Scale.
502 CV: Coefficient of variation, ICU: intensive care unit, IQR: interquartile range, MRC: medical research
503 council, FSS ICU: Functional status score for the intensive care unit.
504 Unless otherwise stated variables reported as median (interquartile range).
505

506 **Table 3. Findings from generalised linear (mixed) models expressing coefficient (beta, odds ratio, incidence**
507 **rate ratio) for group effect (or group by time interaction when repeated measures) or time-to-event analyses**
508 **(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}			
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

509 ^a Coefficients are reported for the group variable when only one assessment, or for group by time interactions when
510 repeated measures; ^b Ultrasound calculated as a percentage change from baseline (repeated assessments), ^c Single
511 assessment or timepoint, therefore, no coefficient for assessment and group by time, ^d Bias corrected confidence
512 intervals generated via bootstrapping used due to irregular distribution of 6-minute walk test, ^e ICU acquired weakness:
513 reported for participants who completed all twelve muscle tests of the Medical Research Council sum score, ^f Handgrip
514 strength calculated as the average of left and right tests. If one side was unable to be tested the value of the tested side
515 was utilised, ^g Functional milestones calculated in days from ICU admission till first achieved functional task, ^h Delirium
516 days calculated for days when participants were able to be assessed while in ICU, ICU: intensive care unit, ⁱ EQ5D-5L:
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520 ICU: intensive care unit, b: beta coefficient, OR: odds ratio, HR: hazard ratio, IRR: incident rate ratio.

521

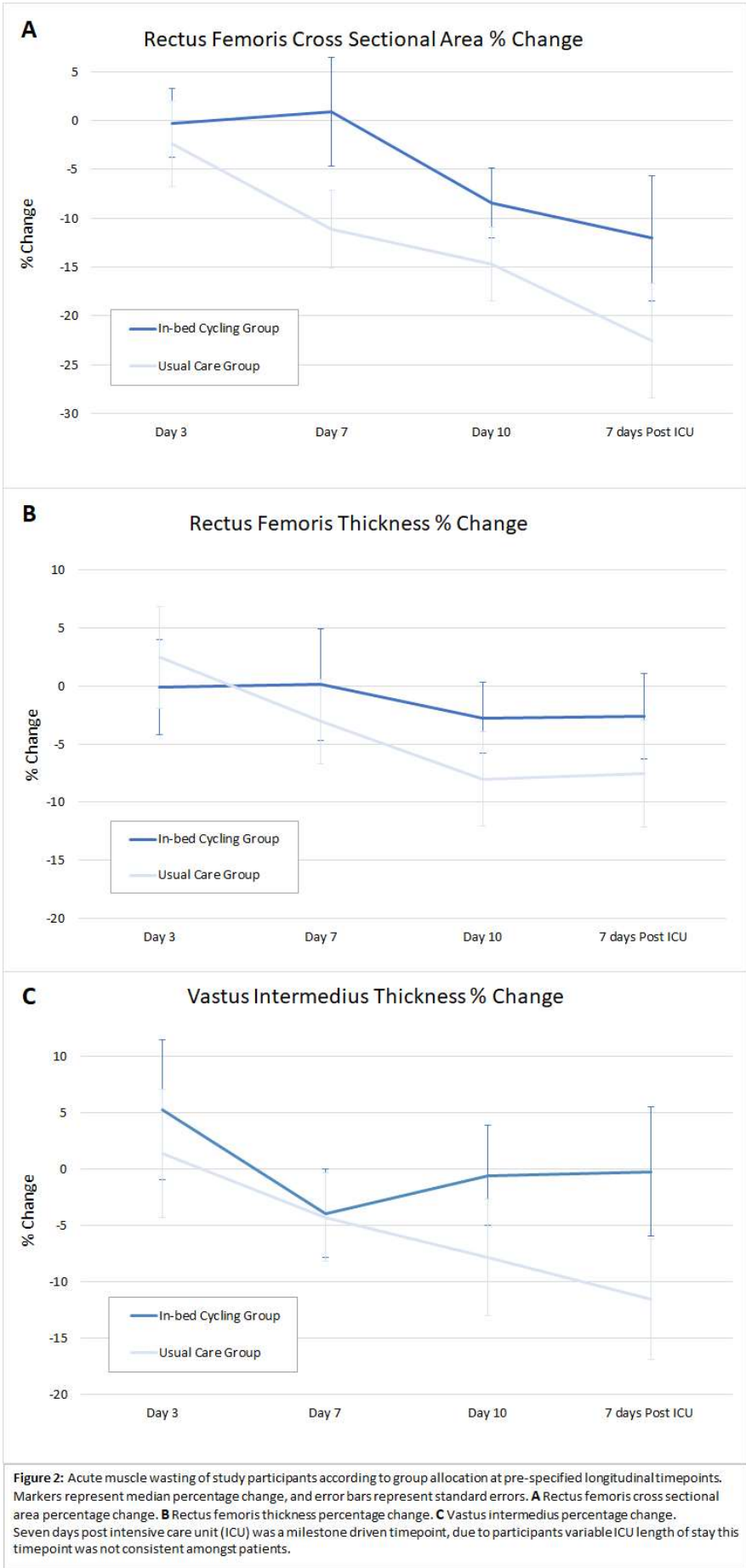


Figure 2: Acute muscle wasting of study participants according to group allocation at pre-specified longitudinal timepoints. Markers represent median percentage change, and error bars represent standard errors. **A** Rectus femoris cross sectional area percentage change. **B** Rectus femoris thickness 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.

524 **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)

525 ^a Number of interventions occurring in the first week following ICU discharge,
 526 ICU, intensive care unit.

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