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SYSTEMATIC REVIEWS

The Efficacy and Safety of In–Intensive Care Unit Leg-Cycle Ergometry in Critically Ill Adults

A Systematic Review and Meta-analysis

Alyson Takaoka[1,2], Rucha Utgikar[2,3], Bram Rochwerg[1,2], Deborah J. Cook[1,2,3], and Michelle E. Kho[2,4,5]

[1]Department of Health Research Methods, Evidence, and Impact, [2]Faculty of Health Sciences, [3]Department of Medicine, and [4]School of Rehabilitation Science, McMaster University, Hamilton, Ontario, Canada; and [5]Physiotherapy Department, St. Joseph's Healthcare Hamilton, Hamilton, Ontario, Canada

ORCID IDs: 0000-0003-1442-080X (A.T.); 0000-0003-3170-031X (M.E.K.).

Abstract

Background: Survivors of critical illness may experience physical-function deficits after intensive care unit (ICU) discharge. In-ICU cycle ergometry may facilitate early mobilization and decrease functional impairment.

Objective: We conducted a systematic review and meta-analysis to understand the effect of in-ICU leg-cycle ergometry on patient-important and clinically relevant outcomes.

Data Sources: We searched eight electronic databases from inception until July 2019.

Data Extraction: We included randomized controlled trials (RCTs) and nonrandomized studies of critically ill adults admitted to the ICU for ⩾24 hours, comparing cycling interventions to control arms that did not receive cycling. Main outcomes included physical function, mechanical ventilation (MV) duration, length of stay (LOS), quality of life (QoL), mortality, and safety. We conducted independent duplicate-citation screening, data abstraction, and risk-of-bias assessments. We pooled RCTs using a random-effects model and calculated the risk ratio (RR), mean difference (MD), or standardized MD with 95% confidence intervals (CIs). We assessed certainty of outcomes using the Grading of Recommendations Assessment, Development, and Evaluation approach.

Results: Of 6,531 citations, we included 12 RCTs and 2 nonrandomized studies ($n = 926$). Between the cycling and control groups, there were no differences in physical function at hospital discharge (3 RCTs; $n = 225$; standardized MD, 0.07 [95% CI, −0.38 to 0.53]; very low certainty), MV duration (9 RCTs; $n = 676$; MD, 0.01 [−1.04 to 1.07] days; moderate certainty), ICU LOS (10 RCTs; $n = 511$; MD, 0.23 [−1.44 to 1.89] days; moderate certainty), hospital LOS (7 RCTs; $n = 393$, MD −0.07 [−3.87 to 3.73] days; moderate certainty), QoL at 6 months after hospital discharge (2 RCTs; $n = 103$; MD, 9.13 [13.80 to 32.05] points higher; very low certainty), or hospital mortality (7 RCTs; $n = 710$; RR 1.09 [0.82 to 1.46]; moderate-certainty). The adverse event rate in cycling sessions was 0.16% across studies (10 studies; 5 of 3,117 sessions; very low certainty).

Conclusions: Cycling initiated in the ICU is probably safe; however, we did not find any differences in physical function, MV duration, LOS, QoL, or mortality compared with those not receiving cycling. Rigorously designed RCTs are needed to improve precision and further investigate the effect of cycling on patient-important outcomes.

Keywords: intensive care unit; cycle ergometry; physiotherapy; physical function; rehabilitation

(Received in original form January 22, 2020; accepted in final form June 30, 2020)

Supported by the Canada Research Chairs Program (D.J.C. and M.E.K.); an Ontario Ministry of Research, Innovation and Science Early Researcher Award (held by M.E.K. and funding A.T. for this study); and a Hamilton Health Sciences Early Career Research Award (B.R.).

Author Contributions: M.E.K. is the lead principal investigator of the CYCLE (A Randomized Clinical Trial of Early In-bed Cycling for Mechanically Ventilated Patients) research program; she was the lead investigator for the pilot trial and conceived of this project. A.T. was the primary reviewer and performed the protocol, including the search, screening, and meta-analysis, and led manuscript preparation. R.U. was the duplicate reviewer and contributed to manuscript writing. B.R. and D.J.C. contributed to the manuscript and consulted on the methods of the project.

Correspondence and requests for reprints should be addressed to Michelle E. Kho, P.T., Ph.D., McMaster University, School of Rehabilitation Science, Faculty of Health Sciences, McMaster University, Institute of Applied Health Science, 1400 Main Street West, Rm. 403, Hamilton, ON, L8S 1C7 Canada. E-mail: khome@mcmaster.ca.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Ann Am Thorac Soc Vol 17, No 10, pp 1289–1307, Oct 2020

DOI: 10.1513/AnnalsATS.202001-059OC
Internet address: www.atsjournals.org

Survivors of critical illness face significant functional disability that can last up to 5 years after intensive care-unit (ICU) discharge (1). These impairments, including reductions in pulmonary function, muscle strength, and exercise capacity, may limit the ability to perform activities of daily living (2, 3) and have been associated with lower health-related quality of life (QoL) (4). Early rehabilitation interventions may be effective in addressing the functional deficits associated with prolonged immobilization in the ICU (5, 6).

One novel in-ICU rehabilitation strategy is cycle ergometry. Cycle ergometry is a potentially safe and feasible strategy for early ICU-based rehabilitation (7, 8) and may improve physical function and performance on the 6-minute walk test at hospital discharge (9). Through either passive or active cycling, the ergometer enables patients to start rehabilitation even while sedated and receiving mechanical ventilation (MV) (8); however, the effect of cycling remains unknown. Two recent meta-analyses examining the effects of ICU rehabilitation on patient-important outcomes (6) and safety (10) excluded interventions evaluating cycling because of inherent differences in this modality of rehabilitation compared with active out-of-bed mobilization activities. Other systematic reviews evaluated cycling as part of multicomponent rehabilitation interventions, introducing heterogeneity into analyses and limiting the opportunity to determine the unique effect of cycling alone (11, 12). To address this literature gap, we conducted a systematic review to determine the effectiveness of in-ICU leg-cycle ergometry on patient-important outcomes in critically ill adults.

Methods

Inclusion and Exclusion Criteria

This review was registered in PROSPERO (CRD 42018092132). We included studies examining adult critically ill patients (≥18 yr) admitted to an ICU for at least 24 hours, with any admitting diagnoses, who performed leg-cycle ergometry in the ICU compared with patients who performed no leg-cycle ergometry. As long as cycling was initiated in the ICU, regardless of intervention duration over the course of the ICU or hospital stay, the study was eligible for inclusion. We included studies of interventions delivered by any trained personnel and studies of cycling alone, as well as studies of cycling within a multicomponent intervention. Comparators of interest included any control groups, including other rehabilitation interventions such as electrical muscle stimulation (13) or routine ICU physiotherapy as defined by the institutions where the studies were conducted.

Outcomes of interest included physical function, duration of MV, length of stay (LOS), mortality, QoL, muscle strength, and safety. We added duration of MV as an outcome after protocol registration because of its importance for clinical decision-making (14). We used the International Classification of Functioning, Disability, and Health developed by the World Health Organization (15) model to organize our outcomes for this review. On the basis of a literature review of outcomes in ICU studies (14), and consensus by three reviewers with expertise in critical care medicine (R.U.), rehabilitation (M.E.K.), and research methodology (A.T. and M.E.K.), outcomes and time points were prioritized by patient importance and relevance to clinical decision-making (Table 1). We reviewed the Core Outcome Set for survivors of critical illness after hospital discharge for recommended instruments to measure functional outcome measures and QoL in ICU survivors (16) and prioritized inclusion of instruments validated in ICU settings, followed by the study's primary outcome measures, as the study would have been powered for this outcome.

We included both randomized and nonrandomized studies in this review. Nonrandomized observational studies with cycling and comparison arms were included to assess safety outcomes only. We did not pool randomized and nonrandomized data for any other outcomes. We included studies published in all languages and excluded studies in which the control group also received cycling. We excluded published abstracts because of an anticipated inability to assess risk of bias (RoB).

Search Methods

We consulted with a health research librarian (J. Young, M.L.I.S.) to develop our search strategy and searched the following eight databases from inception to July 18, 2019: Ovid MEDLINE Epub Ahead of Print, In-Process, and Other Non-Indexed Citations; Ovid MEDLINE(R) Daily and Ovid MEDLINE(R); Ovid Excerpta Medica Database; Cochrane Central Register of Controlled Trials; EBSCOhost Cumulative Index of Nursing and Allied Health Literature; REHABDATA; and Physiotherapy Evidence Database. We contacted cycle-ergometer manufacturers (MOTOmed and Restorative Therapies, May 2018) and searched the World Health Organization International Clinical Trials Registry Platform for ongoing studies. We searched OpenGrey for conference abstracts or thesis work and followed up on corresponding full-article publications. Citations of included articles were hand searched for any additional articles for inclusion. For search strategies, *see* the online supplement. We managed references using Covidence software (17) for title and abstract screening and Microsoft Excel for full-text screening.

Initial searches of the electronic databases were conducted by one reviewer (A.T.). Two reviewers (A.T. and R.U.) screened all titles, abstracts, and full texts independently. Disagreements were discussed between the two reviewers until consensus was reached or were resolved by a third-party reviewer (M.E.K.). Two review authors (A.T. and R.U.) independently extracted details about the study population, intervention (frequency, intensity, time from ICU admission to start, duration, and type), comparators, and outcome measures into a Microsoft Excel spreadsheet.

Data Synthesis and Analyses

Measures of treatment effect. We used pooled mean differences (MDs) for continuous outcomes (physical function, muscle strength, QoL, duration of MV, and LOS) and pooled risk ratios (RRs) for dichotomous outcomes (mortality), both with corresponding 95% confidence intervals (95% CIs). If continuous outcomes were measured using different scales, we calculated the standardized MDs. We transformed data presented as medians and interquartile ranges (IQRs) to means and standard deviations (SDs) for input into meta-analyses (18) (*see* supplement 1, Tables E2–E10 in the online supplement). If both intention-to-treat analyses and per-protocol analyses were reported, we used published intention-to-treat data in our meta-analysis to preserve randomization. Data were pooled for meta-analyses in Review Manager 5 (Cochrane Collaboration, 2014) using a random-effects model to account for heterogeneity present

Table 1. Summary of included outcome measures

WHO ICF Category	Outcome	Time Point	Measures in Order of Prioritization
Body structure and function	Muscle strength	ICU awakening	MRC-SS
		ICU discharge	MRC-SS
		Hospital discharge	MRC-SS
Activity and participation restriction	Physical function	ICU awakening	PFIT-s
			CCCPAT
			FSS-ICU
			IMS
		ICU discharge	PFIT-s
			CCCPAT
			FSS-ICU
			IMS
		Hospital discharge	DEMMI
			TUPGT
			FIM
			SPPB
			SF-36 PF
	Quality of life	Hospital discharge	SF-36
			EuroQoL (EQ-5D)
			Sickness impact profile
		After hospital discharge	SF-36
			EuroQoL (EQ-5D)
			Sickness impact profile
Other	Duration of mechanical ventilation	In ICU	Days
	Length of stay	In ICU	Days
		In hospital	Days
	Mortality	In ICU	Yes/no
		In hospital	Yes/no
		At any other time	Yes/no
	Safety	During exercise sessions	Adverse events
			Serious adverse events
			Exercise stoppage

Definition of abbreviations: CCCPAT = Chelsea Critical Care Physical Assessment Tool; DEMMI = De Morton Mobility Index; EQ-5D = EuroQol 5-Dimension health questionnaire; FIM = functional independence measure; FSS-ICU = Functional status score for the ICU; ICF = International Classification of Function, Disability, and Health; ICU = intensive care unit; IMS = ICU mobility scale; MRC-SS = Medical Research Council sum score; PF = physical function domain; PFIT-s = Physical Function in ICU Test-Scored; SF-36 = Short Form 36; SPPB = short physical performance battery; TUPGT = timed up and go test; WHO = World Health Organization.

across studies. Narrative syntheses were performed for safety outcomes that pooled randomized and nonrandomized data.

We planned 3 *a priori* subgroup analyses to compare results for all outcomes: age (≥65 vs. <65 yr) because older adults are underrepresented in critical care trials (19); time from ICU admission to initiation of cycling intervention (≥7 vs. <7 d) because of the association between longer bedrest and lesser muscle strength (20); and MV status at ICU admission (yes vs. no) as a surrogate for illness severity. We added a subgroup analysis of intervention type (cycling alone vs. multicomponent intervention) after initiating data abstraction and identifying numerous multicomponent interventions.

Heterogeneity assessment. We assessed heterogeneity among pooled studies through visual inspection of forest plots, the chi-square test (critical value $P < 0.10$) and the I^2 statistic. We assessed the I^2 value to describe heterogeneity using categories of "might not be important" (0–40%), "moderate" (30–60%), "substantial" (50–90%), or "considerable" (75–100%) (21).

RoB assessment. Two reviewers (A.T. and R.U.) independently assessed RoB for each outcome within studies, using the Cochrane Collaboration's tool for randomized studies and the Risk of Bias in Nonrandomized Studies of Interventions tool for nonrandomized studies (22). We selected these tools because of their objective and consistent methodology of assessing the overall RoB.

Certainty of evidence assessment. We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to assess the certainty of the body of evidence for each outcome on the basis of the following categories: RoB, indirectness of evidence, unexplained heterogeneity or inconsistency, imprecision of results, high probability of publication bias, and other domains, including large effect size, dose–response relationships, and plausible confounding opposing the effect (23–25). Nonrandomized studies were assigned low certainty of evidence and were upgraded for signs of high quality. Randomized studies were assigned a high certainty of evidence and downgraded for signs of low quality.

Quality of reporting assessment. We evaluated the quality of reporting for cycling interventions and control groups using the Consensus on Exercise Reporting Template (CERT) (26–28). We classified CERT scores of ≥70% as adequate, scores between 50% and 70% as moderate, and scores of ≤50% as poor (13). *Post hoc*, we

reported median (IQR) CERT scores and compared differences in intervention- and control-group reporting using Wilcoxon's signed-rank test ($\alpha = 0.05$).

We referred to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement to ensure transparent reporting in this review (29, 30).

Results

Search Results

After removal of duplicates, we identified 6,532 citations that were screened for eligibility. We encountered no non-English articles. Of these, we reviewed 122 manuscripts in full text, of which 14 ($n = 12$ randomized; $n = 2$ nonrandomized) met eligibility criteria. Of 108 excluded articles, we describe reasons for exclusion in a subset of 27 studies that involved cycling in critically ill patients (*see* supplement 1, Table E1, in the online supplement). Figure 1 illustrates the process of screening and selection of studies for inclusion in this review.

These studies included 926 critically ill patients (cycling intervention, $n = 490$; control, $n = 436$). The mean proportion of females ranged from 16.0% to 72.2%, the mean age of participants varied from 44.6 to 67.2 years, and the mean Acute Physiology and Chronic Health Evaluation II scores ranged from 17.3 to 28.0. Thirteen studies were single-center studies (9, 31–42), and one study was a multicenter study, implemented in seven institutions (43). Most studies ($n = 5$) were from Brazil (32–34, 37, 40), whereas others originated from Belgium (9, 38), Australia (39, 42), France (36), Switzerland (35), Italy (41), Canada (43), and the United States (31).

Five studies included in-bed semirecumbent or supine cycling sessions in addition to standard physiotherapy (9, 32, 33, 40, 43). Seven studies included cycling as one exercise in multicomponent interventions (31, 34–36, 39, 41, 42). All studies compared cycling with usual care; however, one study compared cycling with no therapeutic intervention (37). The duration of cycling sessions was between 20 and 60 minutes, and patients cycled at a rate of 20–30 cycles/min. Characteristics of the included studies are summarized in Table 2.

Effects of Interventions and Evidence Assessment

We summarize patient-important outcome comparisons in a GRADE evidence table (Table 3) (44) and pooled analyses in forest plots (Figures 2–6). We found no differences in physical function at hospital discharge (3 randomized controlled trials [RCTs]; standardized MD, 0.07 SDs [95% CI, −0.38 to 0.53]; very low-certainty evidence), duration of MV (9 RCTs; MD, 0.01 [−1.04 to 1.07] days; moderate-certainty evidence), ICU LOS (10 RCTs; MD, 0.23 [−1.44 to 1.89] days; moderate-certainty evidence), and hospital LOS (7 RCTs; MD, −0.07 [−3.87 to 3.73] days; moderate-certainty evidence) between cycling and control groups. Similarly, we found no differences in QoL at 6 months after hospital discharge (2 RCTs; MD, 9.13 points, Short Form 36 [SF-36] physical function domain [−13.80 to 32.05]; very low-certainty evidence), ICU mortality (7 RCTs; RR, 1.03 [0.77 to 1.37];

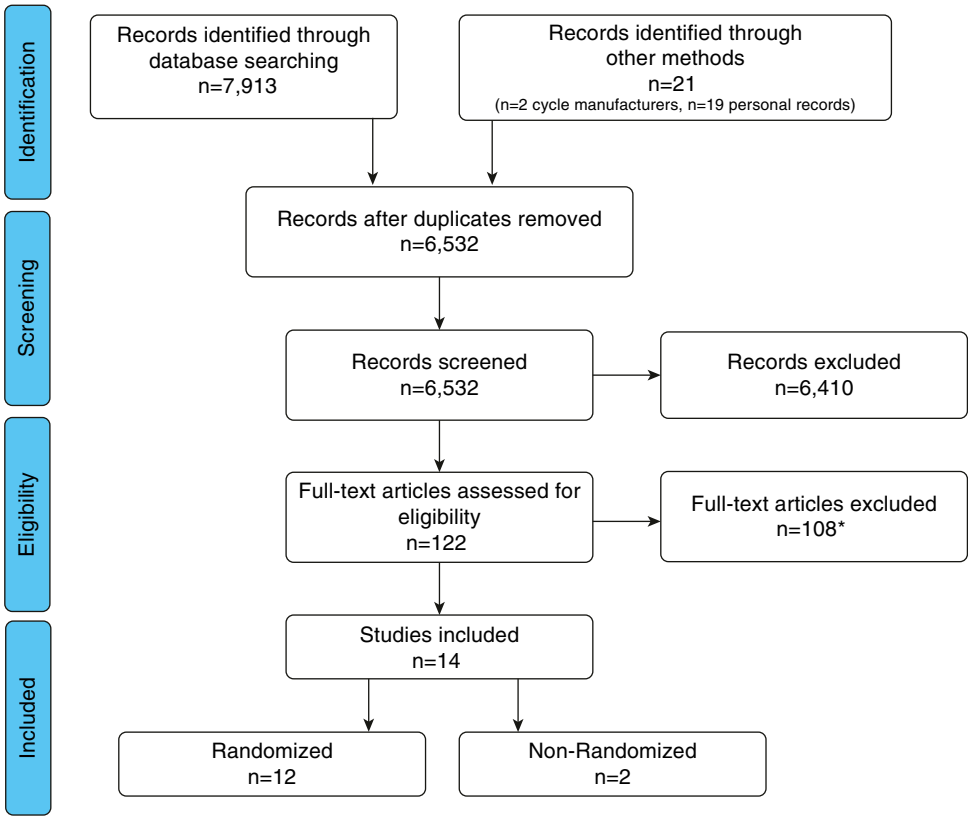


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram. We illustrate the process of screening and selecting studies for inclusion in the review. *We provide explanations for exclusion of 27 full texts in supplement 1, Table E1 (*see* online supplement).

Table 2. Summary of included studies

Author(s), yr	RCT vs. Non-RCT	Study Site	Inclusion Criteria	Participants		Intervention (*Frequency, Intensity, Time, Type*)	Comparator (*Frequency, Intensity, Time, Type*)	Outcome Measures (*Instrument; Time Point*)
				Intervention (*n*), Age [*Mean (SD)*] or [*Median (IQR)*], Female (%) or [*n (%)*], APACHE II Score, [*Mean (SD)*] or [*Median (IQR)*]	Control (*n*), Age [*Mean (SD)*] or [*Median (IQR)*], Female (%) or [*n (%)*], APACHE II Score [*Mean (SD)*] or [*Median (IQR)*]			
Bahouth *et al.*, 2018 (31)	Non-RCT	Neurocritical care unit, urban, academic hospital Baltimore, Maryland, United States	Adult patients admitted for management of primary intracranial hemorrhage	Intervention: 29 Age: 67.2 (14.1) yr Female: 59.0 APACHE II: N/A	Control: 28 Age: 62.1 (13.9) yr Female: 39 APACHE II: N/A	Frequency: 3 sessions/d Intensity: passive and/or active Time: started at mean (SD) of 2.6 (3.0) ICU days Type: multicomponent–progressive mobility algorithm. Passive (3 levels): L1, passive ROM, cycling (passive); L2, passive ROM, cycling; (passive), partial chair position; L3, passive ROM, cycling (passive), complete chair position. Or Active (8 levels): L1, lying in bed, cycling (active); L2, turning self in bed, cycling (active); L3, sitting on edge of bed, cycling (active); L4, transferring to chair; L5, standing for 1 min; L6, walking 10+ steps; L7, walking 25+ steps; L8, walking	Frequency: not reported Intensity: not reported Time: started at mean (SD) of 2.6 (3.3) ICU days Type: no algorithm	Safety
Bianchi *et al.*, 2018 (32)	RCT	ICU in Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil	Patients ⩾ 18 yr, 24–48 h of MV and up to 1 wk of ICU stay	Intervention: 18 Age: 52.3 (22.7) yr Female: 13 (72.2) APACHE II: 23.7 (7.7)	Control: 14 Age: 56.1 (23.0) yr Female: 8 (57.1) APACHE II: 23.8 (8.7)	Frequency: 1 20-min session/d, until Day 7 of MV Intensity: passive Time: not reported Type: passive, supine cycle ergometry (20 cycles/min)	Frequency: 2 30-min sessions/d Intensity: not reported Time: not reported Type: PNF, hand exercises for bronchial hygiene, Ambu bag maneuver, secretion aspiration	Duration of MV, length of stay (ICU, hospital), mortality (ICU), safety
Burtin *et al.*, 2009 (9)	RCT	Single-center medical and surgical ICU with 16-beds (10 general ICU beds, 6 cardiac beds), University Hospital, Leuven, Belgium	Critically ill patients with an expected prolonged stay	Intervention: 31 Age: 57.0 (17.0) yr Female: 29.0 APACHE II: 26.0 (6.0)	Control: 36 Age: 56.0 (16.0) yr Female: 28.0 APACHE II: 25.0 (4.0)	Frequency: 1 20-min session/d, 5 d/wk Intensity: individually adjusted intensity (L1–L6) Time: started ICU Day 5 Type: semirecumbent in-bed cycle ergometry (20 cycles/min), plus standard physiotherapy	Frequency: 5 d/wk Intensity: not reported Time: not reported Type: respiratory physiotherapy and standardized passive or active mobilization of the upper and lower extremities	Physical function (6MWD; hospital d/c), quality of life (SF-36 PF domain; hospital d/c), length of stay (ICU, hospital), mortality (hospital, 1 yr)

(Continued)

Table 2. (*Continued*)

Author(s), yr	RCT vs. Non-RCT	Study Site	Inclusion Criteria	Participants		Intervention (*Frequency, Intensity, Time, Type*)	Comparator (*Frequency, Intensity, Time, Type*)	Outcome Measures (*Instrument; Time Point*)
				Intervention (*n*), Age [*Mean (SD)*] or [*Median (IQR)*], Female (%) or [*n (%)*], APACHE II Score, [*Mean (SD)*] or [*Median (IQR)*]	Control (*n*), Age [*Mean (SD)*] or [*Median (IQR)*], Female (%) or [*n (%)*], APACHE II Score [*Mean (SD)*] or [*Median (IQR)*]			
Coutinho *et al.*, 2016 (33)	RCT	Single-center ICU. Porto Alegre Teaching Hospital, Sao Paulo, Brazil	Patients ⩾18 yr, admitted to ICU ⩾24 h and with <48 h of invasive MV, not in hospital >1 wk	Intervention: 11 Age: 61.8 (22.6) yr Female: 45.4 APACHE II: 27.8 (4.9)	Control: 14 Age: 55.2 (29.1) yr Female: 57.1 APACHE II: 23.6 (7.6)	Frequency: 30- to 45-min session/d (cycling: 20-min session/d) Intensity: not reported Time: started at median (IQR) of 2.5 (2.0–2.5) ICU days Type: supine, in-bed cycle ergometry (20 cycles/min), plus conventional PT	Frequency: 1 30-min session/d Intensity: not reported Time: not reported Type: upper and lower extremity diagonals from the PNF method (2 series of 10 repetitions for each bilateral diagonal), bronchial hygiene exercises such as vibrocompression, manual hyperinflation, and aspiration of secretions when necessary. Patients started early mobility activities such as sitting on edge of bed, sitting out of bed, standing, marching in place, and walking for up to a max of 15 min/d, if possible	Duration of MV, length of stay (ICU, hospital), mortality (hospital)

(Continued)

Table 2. (*Continued*)

Author(s), yr	RCT vs. Non-RCT	Study Site	Inclusion Criteria	Participants		Intervention (*Frequency, Intensity, Time, Type*)	Comparator (*Frequency, Intensity, Time, Type*)	Outcome Measures (*Instrument; Time Point*)
				Intervention (*n*), Age [*Mean (SD)*] or [*Median (IQR)*], Female (%) or [*n (%)*], APACHE II Score, [*Mean (SD)*] or [*Median (IQR)*]	Control (*n*), Age [*Mean (SD)*] or [*Median (IQR)*], Female (%) or [*n (%)*], APACHE II Score [*Mean (SD)*] or [*Median (IQR)*]			
Dantas *et al*., 2012 (34)	RCT	Single-center, general ICU Hospital Agamenon Magalhaes, Recife, Brazil	Mechanically ventilated patients with adequate cardiovascular and respiratory reserve, no signs of respiratory distress, and respiratory rate < 25 breaths/min, no physical exercise program before study enrollment	Intervention: 14 Age: 59.1 (15.2) yr Female: 50.0 APACHE II: 23.7 (8.5)	Control: 14 Age: 50.4 (20.5) yr Female: 71.4 APACHE II: 21.1 (7.2)	Frequency: 2 sessions/d, 7 d/wk Intensity: Cycling-Borg 12–13 Time: not reported Type: Step 1: passive stretching of the four limbs, passive joint mobilization of the four limbs (10×); Step 2: passive stretching of the four limbs, flexion/extension active-assisted exercise on the four limbs (10×); Step 3: passive stretching of the four limbs, active-resistive exercise on upper-limbs, transfer from lying to sitting position on edge of bed, lower-limb cycling; Step 4: passive stretch of the four limbs, active resistive exercise on upper-limb, lower-limb cycling, transfer from sitting to chair, orthostatic posture; Step 5: passive stretching of the four limbs, counterresistance exercise on upper-limbs, lower-limb cycling, balance training, walking	Frequency: 5 times/wk Intensity: not reported Time: not reported Type: passive mobilization of the four limbs and active-assisted exercises	Muscle strength (MRC-SS; before and after intervention), MV duration, length of stay (ICU, hospital), mortality (ICU)

(Continued)

Table 2. (*Continued*)

Author(s), yr	RCT vs. Non-RCT	Study Site	Inclusion Criteria	Participants		Intervention (*Frequency, Intensity, Time, Type*)	Comparator (*Frequency, Intensity, Time, Type*)	Outcome Measures (*Instrument; Time Point*)
				Intervention (*n*), Age [*Mean (SD)*] or [*Median (IQR)*], Female (%) or [*n (%)*], APACHE II Score, [*Mean (SD)*] or [*Median (IQR)*]	Control (*n*), Age [*Mean (SD)*] or [*Median (IQR)*], Female (%) or [*n (%)*], APACHE II Score [*Mean (SD)*] or [*Median (IQR)*]			
Eggmann *et al*., 2018 (35)	RCT	Single-center, tertiary, mixed ICU, Inselspital, Bern University Hospital, Bern, Switzerland	Patients ⩾18 yr, expected to stay on MV for ⩾72 h, independent before onset of critical	Intervention: 58 Age: 65.0 (15.0) yr Female: 22.0 (38.0) APACHE-II: 22.0 (8.0)	Control: 57 Age: 63.0 (15.0) yr Female: 16.0 (28.0) APACHE-II: 23.0 (7.0)	Frequency: not reported Intensity: endurance training: passive, motor-assisted, or active. Resistance training: 8–12 repetitions with 2–5 sets (2-min rest) on 50–70% of the estimated 1-repetition max Time: not reported Type: endurance training: passive, motor-assisted, or active in-bed-cycle; resistance training: standardized exercises for both upper and lower limbs using weights or manual resistance from the therapist	Frequency: 1 session/d, 7 d/wk Intensity: not reported Time: not reported Type: European standard physiotherapy with early mobilization, respiratory therapy (intensive rehabilitation and weaning period or retained airway secretion in extubated patients) and passive or active exercises)	Physical function (6MWD; ICU d/c, hospital d/c), duration of MV, length of stay (hospital and ICU), quality of life (SF-36; 6 mo after hospital d/c), muscle strength (MRC-SS; ICU d/c), safety
Fossat *et al*., 2018 (36)	RCT	Single-center, Centre Hospitalier Regional d'Orleans, Orleans, France	Patients ⩾18 yr, admitted to the ICU <72 h, requiring >48 h of care in the ICU, independent walking ability, Barthel Index > 55 within 15 d before ICU admission	Intervention: 159 Age: 65.0 (13.0) yr Female: 35.0 Simplified APACHE II: 47.0 (19.0)	Control: 155 Age: 66.0 (15.0) yr Female: 37.0 Simplified APACHE II: 46.0 (17.0)	Frequency: 1 15-min session/d of cycling, 1 50-min session/d of electrical stimulation, 5 d/wk Intensity: not reported Time: not reported Type: leg cycling and electrical stimulation session of the quadriceps muscles	Frequency: 5 d/wk Intensity: not reported Time: not reported Type: standardized early rehabilitation with progressive multistep program beginning with 10 passive range-of-motion exercises with each limb joint, followed by passive or active exercises and then fully active muscle exercises, transfer to the edge of the bed or to a chair, standing, and walking	Physical function (IMS; ICU d/c), duration of MV, quality of life (SF-36 physical function; 6 mo after ICU d/c), muscle strength (MRC-SS; ICU d/c), mortality (ICU, hospital, 28 d, 6 mo), safety

(*Continued*)

Table 2. (*Continued*)

Author(s), yr	RCT vs. Non-RCT	Study Site	Inclusion Criteria	Participants		Intervention (*Frequency, Intensity, Time, Type*)	Comparator (*Frequency, Intensity, Time, Type*)	Outcome Measures (*Instrument; Time Point*)
				Intervention (*n*), Age [*Mean (SD)*] or [*Median (IQR)*], Female (%) or [*n (%)*], APACHE II Score, [*Mean (SD)*] or [*Median (IQR)*]	Control (*n*), Age [*Mean (SD)*] or [*Median (IQR)*], Female (%) or [*n (%)*], APACHE II Score [*Mean (SD)*] or [*Median (IQR)*]			
Franca *et al*., 2017 (37)	RCT	Single-center ICU at Hospital Agamenom Magalhaes, Recife, Brazil	Mechanically ventilated patients with good cardiovascular and respiratory reserve	Intervention: 9 Age: 77.0 (32.5–81.0) yr Female: not reported APACHE II: 23.0 (10.0–27.0)	Control: 10 Age: 56.0 (44.0–70.5) yr Female: not reported APACHE II: 25.0 (15.5–29.5)	Frequency: 1 20-min session Intensity: not reported Time: not reported Type: passive cycle ergometry (30 cycles/min)	No therapeutic intervention	Duration of MV, length of stay (ICU), mortality (ICU)
Hickmann *et al*., 2018 (38)	RCT	Tertiary 14-bed mixed ICU, Saint-Luc University Hospital, Brussels, Belgium	Adults with septic shock, admitted to ICU for <72 h	Intervention: 9 Age: 59.0 (19.0) yr Female: 44.0 APACHE II: 20.0 (6.0)	Control: 10 Age: 57.0 (20.0) yr Female: 60.0 APACHE II: 17.0 (7.0)	Frequency: 2 30-min sessions/d for up to 7 d Intensity: not reported Time: not reported Type: continuous passive/active leg chair/bed cycling followed by passive/active limb mobilization	Frequency: 5 d/wk Intensity: not reported Time: not reported Type: manual passive/active limb mobilization	Duration of MV, length of stay (ICU), muscle strength (MRC-SS; Day 7 of protocol), mortality (28 d), safety
Kayambu *et al*., 2015 (39)	RCT	Single-center, quaternary-level, university-affiliated, general ICU, Brisbane, Queensland, Australia	Critically ill patients, aged $\geq$18 yr, with diagnosis of sepsis, severe sepsis, or septic shock, remained mechanically ventilated for $\geq$48 h	Intervention: 26 Age: 62.5 (30–83) yr Female: 16.0 APACHE II: 28.0 (7.6)	Control: 24 Age: 65.5 (37–85) yr Female: 20.0 APACHE II: 27.0 (6.8)	Frequency: 1–2 30-min sessions/d Intensity: not reported Time: $\leq$48 h of sepsis diagnosis Type: electrical muscle stimulation, passive ROM, active ROM, sitting out of bed, transfers, ambulation, and other mobilization techniques (including cycling)	Frequency: not reported Intensity: not reported Time: not reported Type: standard care including physiotherapy strategies	Physical function (PFIT-s; ICU d/c), muscle strength (MRC-SS; ICU d/c), quality-of-life (SF-36 PF domain; 6 mo after hospital d/c), ventilator-free days; length of stay (ICU, hospital), mortality (hospital, 90 d), safety

(Continued)

Table 2. (*Continued*)

Author(s), yr	RCT vs. Non-RCT	Study Site	Inclusion Criteria	Participants		Intervention (*Frequency, Intensity, Time, Type*)	Comparator (*Frequency, Intensity, Time, Type*)	Outcome Measures (*Instrument; Time Point*)
				Intervention (*n*), Age [*Mean (SD)*] or [*Median (IQR)*], Female (%) or [*n (%)*], APACHE II Score, [*Mean (SD)*] or [*Median (IQR)*]	Control (*n*), Age [*Mean (SD)*] or [*Median (IQR)*], Female (%) or [*n (%)*], APACHE II Score [*Mean (SD)*] or [*Median (IQR)*]			
Kho *et al*., 2019 (43)	RCT	Seven academic, tertiary, mixed ICUs: St. Joseph's Healthcare Hamilton, Juravinski Hospital, Hamilton General Hospital, Toronto General Hospital, London Health Sciences–Victoria, St. Michael's Hospital, Ottawa General Hospital, Ontario, Canada	Patients ⩾18 yr old with <4 d of MV and <7 d of ICU, able to ambulate independently before hospital admission	Intervention: 36 Age 60.0 (16.8) yr Female 25.0 APACHE II: 24.6 (10.0)	Control: 30 Age 63.3 (17.1) yr Female 56.7 APACHE-II: 22.1 (6.4)	Frequency: 1 30-min session/d Intensity: passive, active-assisted, or active Time: from randomization for the duration of index ICU stay (max: 28 d) Type: in-bed cycle ergometry plus routine physiotherapy	Frequency: not reported Intensity: not reported Time: not reported Type: routine PT per current institutional practice include activities to assist with optimizing airway clearance and respiratory function, and, activities to maintain/increase limb ROM and strength, in-bed and out-of-bed mobility, and ambulation	Physical function (PFIT-s); ICU awakening, ICU d/c, hospital d/c, MV duration, length of stay (ICU, hospital), quality of life (EQ-5D; hospital d/c), muscle strength (MRC-SS; ICU awakening, ICU d/c, hospital d/c), mortality (ICU, hospital)
Machado *et al*., 2017 (40)	RCT	Santa Maria University Hospital, Federal University of Santa Maria, Santa Maria, Brazil	Patients ⩾18 yr, mechanically ventilated, maintained at a light amount of sedation and hemodynamically stable	Intervention: 22 Age: 44.6 (19.2) yr Female: 57.0 APACHE II: 17.3 (6.7)	Control: 16 Age: 45.1 (18.9) yr Female: 28.0 APACHE II: 18.1 (6.4)	Frequency: 1 20-min session/d, 5 d/wk Intensity: not reported Time: started at median (IQR) of 3 (2–5) ICU days Type: supine passive cycling on a leg-cycle ergometer (20 cycles/min) plus conventional PT and respiratory therapy	Frequency: 2 30-min session/d, 7 d/wk Intensity: not reported Time: started at median (IQR) of 2 (1–3) ICU days Type: conventional physical and respiratory therapy including vibrocompression maneuvers; lung hyperinflation by the mechanical ventilator; and tracheal aspiration, when necessary; as well as passive and active-assisted motor exercises for arms and legs	Muscle strength (MRC-SS; before and after intervention), mortality (ICU), length of stay (ICU and hospital)

(*Continued*)

Table 2. (*Continued*)

Author(s), yr	RCT vs. Non-RCT	Study Site	Inclusion Criteria	Participants		Intervention (*Frequency, Intensity, Time, Type*)	Comparator (*Frequency, Intensity, Time, Type*)	Outcome Measures (*Instrument; Time Point*)
				Intervention (*n*), Age [*Mean (SD)*] or [*Median (IQR)*], Female (%) or [*n (%)*], APACHE II Score, [*Mean (SD)*] or [*Median (IQR)*]	Control (*n*), Age [*Mean (SD)*] or [*Median (IQR)*], Female (%) or [*n (%)*], APACHE II Score [*Mean (SD)*] or [*Median (IQR)*]			
Nava, 1998 (41)	RCT	Single-center RICU in a rehabilitation center, Montescano, Italy	Clinically stable patients with a diagnosis of chronic obstructive pulmonary disease admitted to the RICU within 3–5 d	Intervention: 60 No other info reported	Control: 20 No other info reported	Frequency: 2 30- to 45-min sessions/d (cycling: 20-min sessions) Intensity: cycling, <6 Borg Scale with workload of 15 W Time: started within ⩽24 h of admission to RICU Type: Step I and II, Step III: specific respiratory muscle training and cycle ergometry; ⩾5× climbing 25 stairs; Step IV: 3 wk of 2 30-min sessions/d of continuous treadmill walking	Frequency: not reported Intensity: not reported Time: not reported Type: Step I: maintaining optimal postural position (i.e., sitting upright in bed or in a chair); lifting light weights or pushing against resistance; postural drainage and cough education; Step II: rolling platform walker	Physical function (6MWD; ICU d/c), length of stay (ICU, hospital), mortality (ICU, hospital)
Parry *et al.*, 2014 (42)	Non-RCT	Single-center ICU, Melbourne, Australia	Critically ill patients ⩾18 yr of age, admitted with sepsis or severe sepsis, predicted to be mechanically ventilated for >48 h and remain in the ICU for 4 d	Intervention: 8 Age: 62.5 (17.7) yr Female: 50.0 APACHE II: 20.3 (7.9)	Control: 8 Age: 60.5 (18.6) yr Female: 50.0 APACHE II: 20.3 (7.5)	Frequency: 1 20- to 60-min sessions/d, 5 d/wk Intensity: not reported Time: started within ⩽96 h of admission and continued until ICU d/c Type: supine, active functional electrically stimulated cycling plus usual care	Frequency: ⩽15 min Intensity: not reported Time: not reported Type: usual care consisting of early mobility activities (i.e., sitting on the edge of bed, sitting out of bed, standing, marching in place, and walking)	Safety

Definition of abbreviations: 6MWD = 6-minute walk distance; APACHE II = Acute Physiology and Chronic Health Evaluation II; d = day; d/c = discharge; EQ-5D = EuroQol 5-Dimension health questionnaire; ICU = intensive care unit; IMS = ICU mobility scale; IQR = interquartile range; L = level; max = maximum; mo = month; MRC-SS = Medical Research Council sum score; MV = mechanical ventilation; N/A = not applicable; PF = physical function domain; PFIT-s = Physical Function in ICU Test- Scored; PNF = proprioceptive neuromuscular facilitation; PT = physical therapy; RCT = randomized controlled trial; RICU = respiratory ICU; ROM = range of motion; SD = standard deviation; SF-36 = Short Form 36; wk = week.

Table 3. GRADE evidence table of patient-important outcome comparisons

Certainty Assessment							No. of Patients		Effect		Certainty	Importance
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Cycling Intervention (*n*)	Control (*n*)	Relative RR (95% CI)	Absolute (95% CI)		
Physical function at hospital discharge (assessed with: Physical Function in ICU Test- Scored; 6-min walking distance)												
3	Randomized trials	Serious*	Serious†	Not serious	Serious‡	None	114	111	—	SMD, 0.07 SDs higher (0.38 lower to 0.53 higher)	⊕◯◯◯ Very low	Critical
Duration of mechanical ventilation (assessed with: days)												
9	Randomized trials	Not serious	Not serious	Not serious	Serious§	None	350	326	—	MD, 0.01 days greater (1.04 fewer to 1.07 more)	⊕⊕⊕◯ Moderate	Critical
ICU length of stay (assessed with: days)												
10	Randomized trials	Not serious	Not serious	Not serious	Serious‖	None	283	228	—	MD, 0.23 days greater (1.44 fewer to 1.89 more)	⊕⊕⊕◯ Moderate	Critical
Hospital length of stay (assessed with: days)												
7	Randomized trials	Not serious	Not serious	Not serious	Serious‖	None	205	188	—	MD, 0.07 days fewer (3.87 fewer to 3.73 more)	⊕⊕⊕◯ Moderate	Critical
Quality-of-life of life at 6 mo after hospital discharge (assessed with: SF-36 physical function domain; scale from 0 to 100)												
2	Randomized trials	Serious*	Not serious	Serious¶	Serious**	None	47	56	—	MD, 9.13 points higher (13.80 lower to 32.05 higher)	⊕◯◯◯ Very low	Critical
ICU mortality												
7	Randomized trials	Not serious	Not serious	Not serious	Serious††	None	77/339 (22.7%)	76/331 (23.0%)	1.03 (0.77 to 1.37)	7 more deaths more per 1,000 patients (from 53 fewer to 85 more)	⊕⊕⊕◯ Moderate	Critical

(Continued)

Table 3. *(Continued)*

No. of Studies	Study Design	Certainty Assessment					No. of Patients		Effect		Certainty	Importance
		Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Cycling Intervention (*n*)	Control (*n*)	Relative RR (95% CI)	Absolute (95% CI)		
Hospital mortality												
7	Randomized trials	Not serious	Not serious	Not serious	Serious††	None	96/389 (24.7%)	72/321 (22.4%)	RR, 1.09 (0.82 to 1.46)	20 more deaths per 1,000 patients (from 40 fewer to 103 more)	⊕⊕⊕○ Moderate	Critical
Safety events (assessed with: adverse events and exercise session interruptions)												
10	Randomized trials (8) and nonrandomized studies (2)	Not serious	Not serious	Not serious	Serious††	None	Adverse events occurred in 5/3,117 (0.16%) cycling sessions. Exercise interruption was reported in 6 studies and occurred in 96/2753 (3.5%) cycling sessions.				⊕○○○ Very low	Critical

Definition of abbreviations: 95% CI = 95% confidence interval; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; ICU = intensive care unit; MD = mean difference; RR = risk ratio; SF-36 = Short Form 36; SMD = standardized MD.
*Participants and physiotherapists were not blinded to group allocation and incomplete outcome assessments; therefore, the risk of bias was downgraded to serious.
†Moderate-to-substantial unexplained heterogeneity; therefore, inconsistency was downgraded to serious.
‡Optimal-information-size criterion of 400 participants for a continuous outcome not met (38) and 95% CI cover possible decrease, no effect, or increase in physical function; therefore, imprecision was downgraded to serious.
§95% CI covers a possible decrease, no effect, or increase in days of mechanical ventilation; therefore, imprecision was downgraded to serious.
‖Optimal-information-size criterion of 400 participants for a continuous outcome not met (38) and 95% CI cover possible decrease, no effect, or increase in length of stay; therefore, imprecision was downgraded to serious.
¶Studies involved cycling as part of a multicomponent intervention; therefore, indirectness was downgraded to serious.
**Optimal-information-size criterion of 400 participants for a continuous outcome not met (38) and 95% CI cover possible decrease, no effect, or increase in quality of life at 6 months after hospital discharge; therefore, imprecision was downgraded to serious.
††Optimal-information-size criterion of 300 events for a dichotomous outcome not met (38); therefore, imprecision was downgraded to serious.

moderate-certainty evidence), or hospital mortality (7 RCTs; RR, 1.09 [0.82 to 1.46]; moderate-certainty evidence). Adverse events occurred in 0.16% of cycling sessions (5 of 3,117) (8 RCTs; 2 nonrandomized studies) and exercise interruptions occurred in 3.5% of cycling sessions (96 of 2,753) (5 RCTs; 1 nonrandomized study); however, this was based on very low-certainty evidence. We report proportions of safety events in Table 4 and elaborate on study-specific definitions of safety events in supplement 1 (*see* Table E11 in the online supplement). Results of additional outcomes are summarized in supplement 1 (*see* Figures E1–E4 and Table E12 in the online supplement).

Subgroup Analyses

Subgroup analyses focusing on elderly patients (≥65 yr) and MV status (yes or no) could not be performed because of a lack of studies reporting on these subgroups. Cycling was initiated within 7 days of ICU admission in all studies, with the exception of one randomized trial (9). Five RCTs administered multicomponent interventions that included cycling (34–36, 39, 41), whereas the remaining studies evaluated cycling alone. Neither of these two analyses demonstrated credible subgroup effects and conclusions are therefore consistent across included RCTs. Results of the subgroup analyses are presented in supplement 1 (*see* Figures E5–E13 in the online supplement).

Quality of Reporting Assessment

Using the CERT guidelines (26–28) to assess the overall quality of reporting, five studies (33, 35, 36, 41, 43) were assessed as adequately reported (CERT score > 70%), six studies (9, 32, 37–40) were moderately reported (CERT score between 50% and 70%), and three studies (31, 34, 42) were poorly reported (CERT score ≤ 50%). Overall, intervention arms were adequately reported (81.8% [61.8–90.5%]) and were significantly better reported than control arms (51.3% [34.4–72.9%]) ($P = 0.002$). We found that studies tended to poorly report motivation, progression rules, and intervention fidelity in both intervention and control groups; however, control groups also tended to have poor descriptions of the exercises being

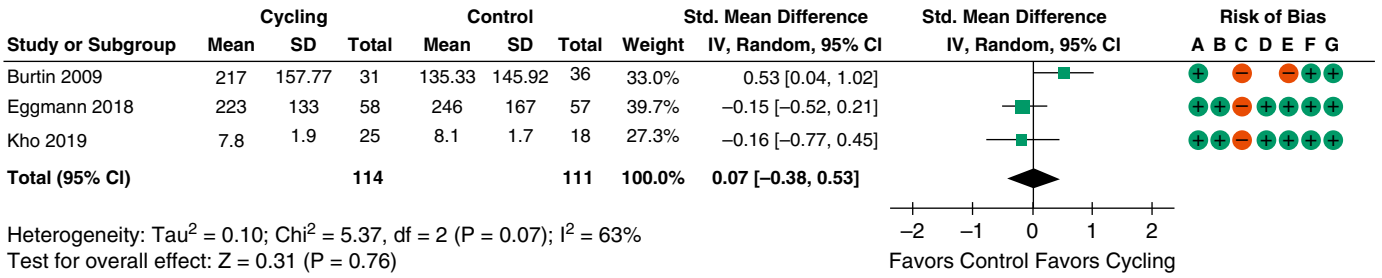


Figure 2. Forest plot of the standardized mean differences for physical function at hospital discharge in cycling and control groups measured using Physical Function in ICU Test- Scored (Kho and colleagues [43]) and 6-minute walk distance (Burtin and colleagues [9]; Eggmann and colleagues [35]). 95% CI = 95% confidence interval; A = risk of bias for random sequence generation (selection bias); B = risk of bias for allocation concealment (selection bias); C = risk of bias for blinding of participants and personnel (performance bias); D = risk of bias for blinding of outcome assessment (detection bias); df = degrees of freedom; E = risk of bias for incomplete outcome data (attrition bias); F = risk of bias for selective reporting (reporting bias); G = risk of other bias; I^2 = percentage of variation across studies due to heterogeneity; IV = inverse variance; SD = standard deviation; Std. = standardized.

administered, duration of exercise sessions, exercise tailoring, and rules for determining starting exercise amounts. Full CERT assessments are presented in supplement 2 (*see* online supplement).

Discussion

Summary of Main Results and Certainty of Evidence

Most studies are single-center trials, initiating cycling within the first 7 days of the ICU stay. Cycling initiated in the ICU is probably safe but, compared with control arms, may not improve physical function or QoL. These results, however, are limited by very low-certainty evidence, and further research is likely to change these results. Moderate-certainty evidence suggests no differences between cycling and control arms with respect to MV duration, LOS in the ICU and hospital, and mortality at ICU and hospital discharge. These findings are consistent with those of previous studies, which suggest that in-ICU rehabilitation does not have an effect on duration of MV, LOS, and risk of mortality (6).

Blinding was a consistent issue across studies included in this review. There was high risk of performance bias for performance-based outcome measures (i.e., physical function and muscle strength at all time points) and self-reported outcome measures (i.e., QoL at all time points) because of the inability to blind patients and research personnel to group allocation; however, this was less of a concern for more objective measures (i.e., MV duration, LOS, and mortality). Although most studies reported blinding of outcome assessors, some reported no blinded assessors or did not clearly report this information, placing studies at high risk or unclear risk of detection bias (9, 36).

Heterogeneity of Both Interventions and Outcome Measures

We found that studies included in our review used varying dosages, frequencies, intensities, and timing of the cycling protocol and used a range of instruments to measure outcomes at different time points. Some interventions combined cycling with other rehabilitative strategies, such as

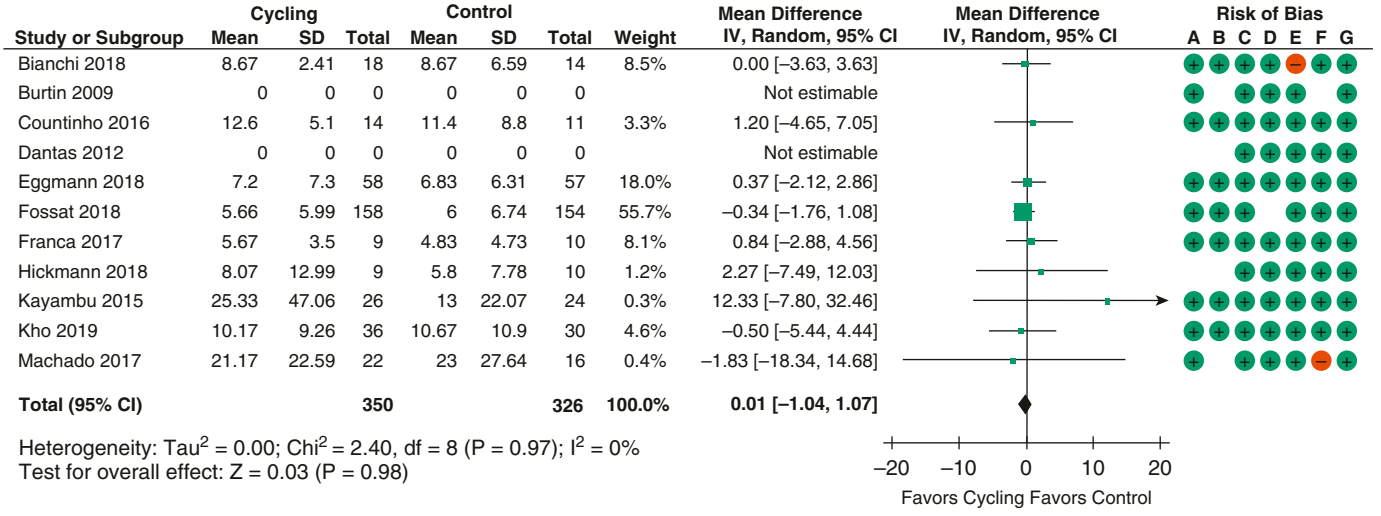


Figure 3. Forest plot of the mean differences for mechanical ventilation duration in cycling and control groups measured in days. 95% CI = 95% confidence interval; A = risk of bias for random sequence generation (selection bias); B = risk of bias for allocation concealment (selection bias); C = risk of bias for blinding of participants and personnel (performance bias); D = risk of bias for blinding of outcome assessment (detection bias); df = degrees of freedom; E = risk of bias for incomplete outcome data (attrition bias); F = risk of bias for selective reporting (reporting bias); G = risk of other bias; I^2 = percentage of variation across studies due to heterogeneity; IV = inverse variance; SD = standard deviation.

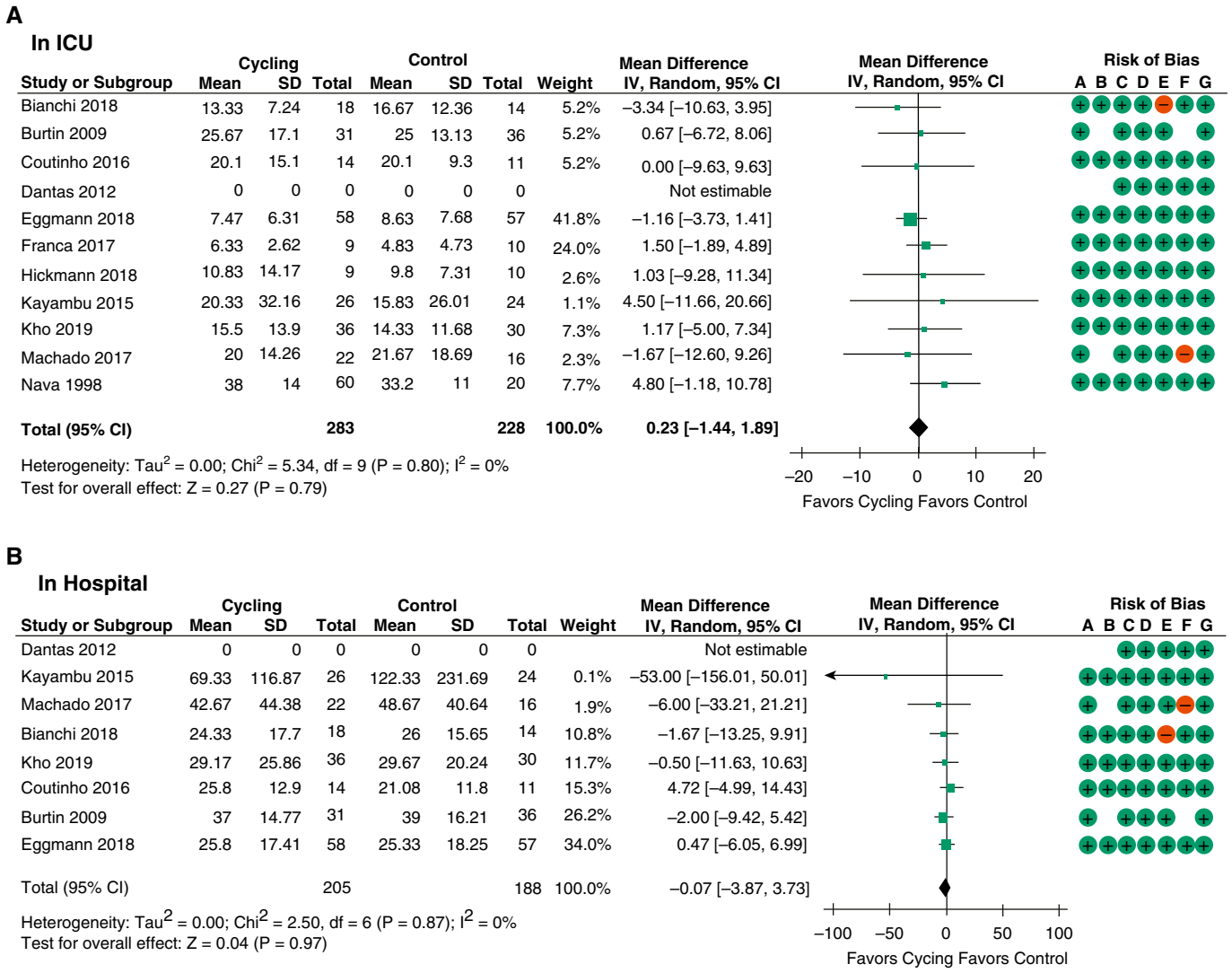


Figure 4. Forest plot of the mean differences for (*A*) ICU and (*B*) hospital length of stay in cycling and control groups measured in days. 95% CI = 95% confidence interval; A = risk of bias for random sequence generation (selection bias); B = risk of bias for allocation concealment (selection bias); C = risk of bias for blinding of participants and personnel (performance bias); D = risk of bias for blinding of outcome assessment (detection bias); df = degrees of freedom; E = risk of bias for incomplete outcome data (attrition bias); F = risk of bias for selective reporting (reporting bias); G = risk of other bias; I^2 = percentage of variation across studies due to heterogeneity; ICU = intensive care unit; IV = inverse variance; SD = standard deviation.

progressive mobility programs or functional electrical muscle stimulation. Although this may be a pragmatic approach, as ICU rehabilitation interventions are often multifaceted, it is important for future investigators to consider studying cycling alone to determine its efficacy. Furthermore, when studying cycling, measures that have been validated in the ICU should be used, and a focus should be placed on selecting patient-important outcomes and measurement time points (45).

Reporting

The findings from our CERT assessments were consistent with those published in a recent scoping review by Reid and colleagues (13), in which intervention groups were significantly better reported than control groups in ICU physical-rehabilitation interventions. Findings from the current review build on these previous data and further emphasize the need for higher-quality reporting in ICU rehabilitation studies, particularly within control arms. Transparency in reporting interventions and their implementation facilitates study-result interpretation and will be important to consider as the field of ICU rehabilitationunder advances.

Strengths and Limitations

Strengths of our study include employment of strategies to reduce bias. Two reviewers independently assessed study eligibility, abstracted data, and conducted RoB and CERT assessments. Large and topic-specific databases were searched to cover all possible electronic sources of studies. Although we were unable to generate assessments of publication bias on the basis of statistical methods because of the limited number of studies included in our review, we searched the gray literature for unpublished data to follow-up on full-text articles, set no language restrictions, and contacted cycle manufacturers for further studies.

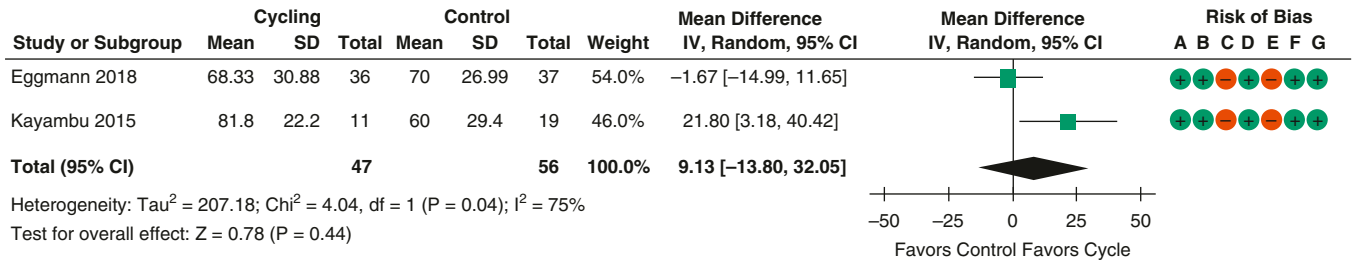
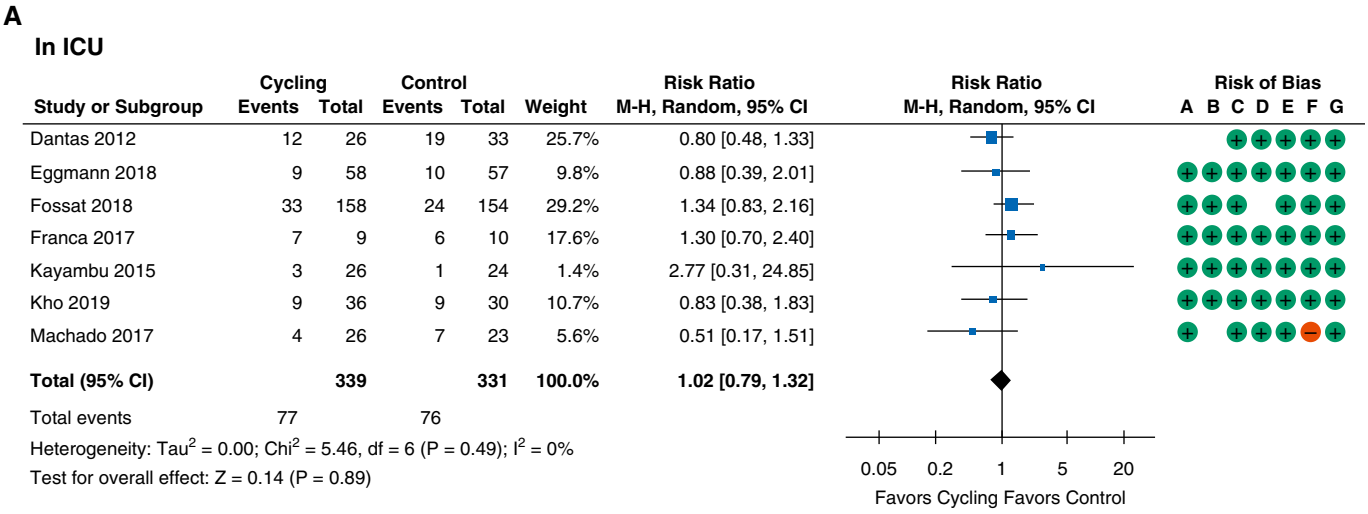


Figure 5. Forest plot of the mean difference for quality-of-life at 6 months after hospital discharge in cycling and control groups measured using the Short Form 36 physical function domain. 95% CI = 95% confidence interval; A = risk of bias for random sequence generation (selection bias); B = risk of bias for allocation concealment (selection bias); C = risk of bias for blinding of participants and personnel (performance bias); D = risk of bias for blinding of outcome assessment (detection bias); df = degrees of freedom; E = risk of bias for incomplete outcome data (attrition bias); F = risk of bias for selective reporting (reporting bias); G = risk of other bias; I^2 = percentage of variation across studies due to heterogeneity; IV = inverse variance; SD = standard deviation.

Furthermore, we identified several published protocols (46–50) and trial registrations (51–54) for studies that may be eligible for inclusion in this review and it is likely that this review will need be updated when these studies are published. We assessed RoB for included studies and contextualized pooled estimates together with certainty in these estimates using GRADE methodology. We also assessed the quality of intervention and control reporting using the CERT guidelines. This step



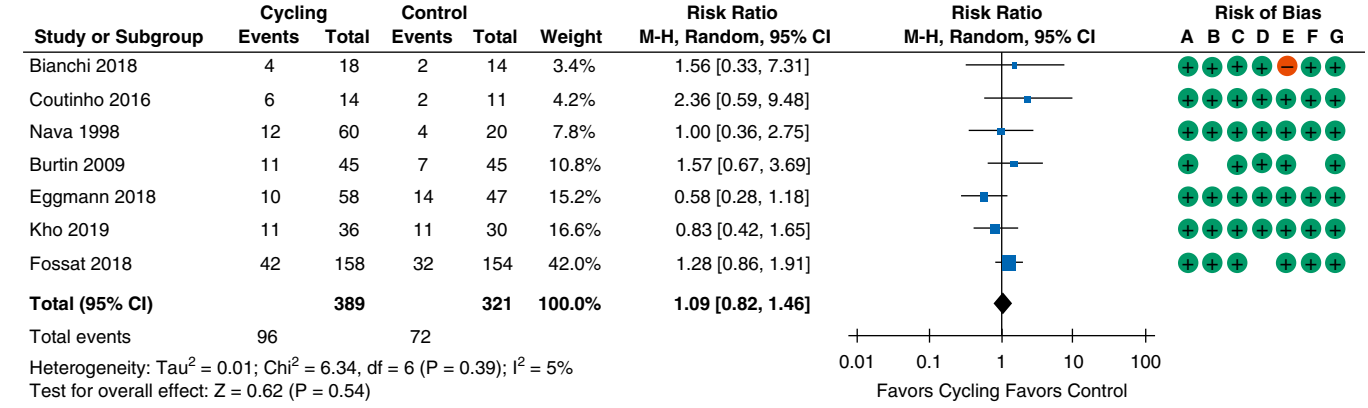


Figure 6. Forest plot of the risk ratios for mortality at (*A*) ICU and (*B*) hospital discharge in cycling and control groups. 95% CI = 95% confidence interval; A = risk of bias for random sequence generation (selection bias); B = risk of bias for allocation concealment (selection bias); C = risk of bias for blinding of participants and personnel (performance bias); D = risk of bias for blinding of outcome assessment (detection bias); df = degrees of freedom; E = risk of bias for incomplete outcome data (attrition bias); F = risk of bias for selective reporting (reporting bias); G = risk of other bias; I^2 = percentage of variation across studies due to heterogeneity; ICU = intensive care unit; M-H = Mantel-Haenszel.

Table 4. Safety outcomes

Study	Intervention			Control		
	Cycling Sessions (*n*)	Adverse Events [*n (%) of sessions*]	Exercise Interruption [*n (%) of sessions*]	Control Sessions (*n*)	Adverse events [*n (%) of sessions*]	Exercise Interruption [*n (%) of sessions*]
Randomized studies						
Bianchi *et al*., 2018 (32)	83*	0 (0.0)	Not reported	137†	0 (0.0)	Not reported
Burtin *et al*., 2009 (9)	425	0 (0.0)	16 (3.8)	Not reported	Not reported	Not reported
Eggmann *et al*., 2018 (35)	186	1 (0.54)	Unclear	377	3 (0.8)	13 (3.4)
Fossat *et al*., 2018 (36)	1,387	1 (0.07)	46 (3.3)	1,190	12 (1.0)	80 (6.7)
Hickmann *et al*., 2018 (38)	69	1 (1.4)	4 (5.8)	85	Not Reported	Not reported
Kayambu *et al*., 2015 (39)	6‡	0 (0.0)	0 (0)	235§	Not reported	Not reported
Kho *et al*., 2019 (43)	146	1 (0.68)	31 (21.2)	262	3 (2.0)	Not reported
Machado *et al*., 2017 (40)	720‖	0 (0.0)	0 (0.0)	480¶	Unclear	Unclear
Randomized total	3,022	4	97	2,766	18	93
Nonrandomized studies						
Bahouth *et al*., 2018 (31)	26**	0 (0.0)	Unclear	4††	Unclear	Unclear
Parry *et al*., 2014 (42)	69	1 (0.4)‡‡	Not reported	Not reported	Not reported	Not reported
Nonrandomized total	95	1	N/A	4	N/A	N/A
Overall total	3,117	5/3,117 (0.16)	97/2,753§§ (3.5)	2,535	18/1,966‖‖ (0.92)	93/1,567§§ (5.9)

Definition of abbreviation: N/A = not applicable.

*Estimated 83 sessions (mean number of cycling sessions per intervention-group participant = 4.6, multiplied by 18 intervention-group participants).

†Estimated 137 conventional physiotherapy sessions (mean number of exercise sessions per control-group participant = 4.9, multiplied by 2 sessions/d, multiplied by 14 control-group participants).

‡Estimated six cycling sessions as per bar graph in Figure 1 (39): total frequency and duration of physical rehabilitation received by participants in intervention and standard-care groups.

§Estimated 235 standard care sessions as per bar graph in Figure 1 (39): total frequency and duration of physical rehabilitation received by participants in intervention and standard-care groups.

‖Estimated 792 cycling sessions (median number of cycling sessions per intervention-group participant = 36.0, multiplied by 22 intervention-group participants).

¶Estimated 480 conventional physiotherapy sessions (median number of usual care sessions per control-group participant = 30.0, multiplied by 16 control-group participants).

**Estimated 26 sessions (mean number of mobilization sessions per postimplementation-group participant = 1.5 multiplied by 17 "ever-mobilized" postimplementation-group participants). Note: it is possible that not every mobilization session contained cycling.

††Estimated four mobilization sessions (mean number of mobilization sessions per preimplementation-group participant = 0.4, multiplied by nine "ever-mobilized" postimplementation-group participants).

‡‡Minor adverse event that occurred 30 minutes after intervention, whereby one subject had a transient desaturation to 86% for more than 1 minute, requiring a temporary increase in the fraction of inspired oxygen from 0.4 to 0.6 for 1 hour.

§§Denominator includes only studies that reported exercise interruption. Excludes studies with "unclear" or "not reported."

‖‖Denominator includes only studies that reported adverse events. Excludes studies with "unclear" or "not reported."

identified an important, actionable gap in the reporting of intervention and control groups in ICU rehabilitation studies.

This review had some limitations. Certain outcome data required transformation from reported medians and IQRs to means and SDs for input into meta-analyses (18). However, after conducting a *post hoc* sensitivity analysis removing transformed values from pooled data, our findings were robust (*see* supplement 1, Figures E14–E18, in the online supplement). This review precluded patient and caregiver perspectives in determining patient-important outcomes; however, this selection was based on existing literature and consensus among our interdisciplinary research team.

Investigators conducting future studies should consider blinding outcome assessors, given that blinding of research personnel and participants to group assignment is not possible when administering a cycling intervention. Future investigators are also encouraged to consult the CERT guidelines early in the trial design phase to ensure the use of research methods that facilitate adequate reporting of exercise interventions and control-group activities. Lastly, future studies could consider patient-led determination of outcomes of importance, given the increasingly recognized importance of patient input into study designs (55, 56). We also encourage investigators to focus on studying these outcomes at common time points, including patient well-being, both in the ICU and after discharge.

Conclusions

Our study suggests that cycling is a safe intervention that can be delivered in the ICU; however, the effect on patient outcomes remains uncertain. Although we did not find an effect on any of these outcomes of interest, these findings were based on moderate-certainty, low-certainty, or very-low-certainty evidence. As such, there is an urgent need for well-designed and well-reported RCTs to investigate the effect of cycling on patient-important outcomes. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank Dr. Julie Reid and Ms. Heather O'Grady for their guidance and expertise in applying the CERT tool to rehabilitation studies in the ICU; Mr. Jack Young, who kindly provided consultation on their electronic database search strategy; and Ms. Daniella Russo for her assistance with search updates.

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