Early intervention (mobilization or active exercise) for critically ill adults in the intensive care unit

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Published in:
Cochrane database of systematic reviews (Online)

DOI:
10.1002/14651858.CD010754.pub2

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Early intervention (mobilization or active exercise) for critically ill adults in the intensive care unit.
Cochrane Database of Systematic Reviews 2018, Issue 3. Art. No.: CD010754.
DOI: 10.1002/14651858.CD010754.pub2.

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TABLE OF CONTENTS

HEADER . . . 1
ABSTRACT . . . 1
PLAIN LANGUAGE SUMMARY . . . 2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON . . . 4
BACKGROUND . . . 8
OBJECTIVES . . . 9
METHODS . . . 9
Figure 1. . . . 12
Figure 2. . . . 13
RESULTS . . . 14
Figure 3. . . . 15
DISCUSSION . . . 21
AUTHORS' CONCLUSIONS . . . 23
ACKNOWLEDGEMENTS . . . 24
REFERENCES . . . 24
CHARACTERISTICS OF STUDIES . . . 28
ADDITIONAL TABLES . . . 46
APPENDICES . . . 53
WHAT'S NEW . . . 56
CONTRIBUTIONS OF AUTHORS . . . 56
DECLARATIONS OF INTEREST . . . 57
SOURCES OF SUPPORT . . . 57
DIFFERENCES BETWEEN PROTOCOL AND REVIEW . . . 58
INDEX TERMS . . . 58

[Intervention Review]

Early intervention (mobilization or active exercise) for critically ill adults in the intensive care unit

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Editorial group: Cochrane Emergency and Critical Care Group.
Publication status and date: Edited (no change to conclusions), published in Issue 12, 2018.

Citation: Doiron KA, Hoffmann TC, Beller EM. Early intervention (mobilization or active exercise) for critically ill adults in the intensive care unit. *Cochrane Database of Systematic Reviews* 2018, Issue 3. Art. No.: CD010754. DOI: 10.1002/14651858.CD010754.pub2.

ABSTRACT

Background

Survivors of critical illness often experience a multitude of problems that begin in the intensive care unit (ICU) or present and continue after discharge. These can include muscle weakness, cognitive impairments, psychological difficulties, reduced physical function such as in activities of daily living (ADLs), and decreased quality of life. Early interventions such as mobilizations or active exercise, or both, may diminish the impact of the sequelae of critical illness.

Objectives

To assess the effects of early intervention (mobilization or active exercise), commenced in the ICU, provided to critically ill adults either during or after the mechanical ventilation period, compared with delayed exercise or usual care, on improving physical function or performance, muscle strength and health-related quality of life.

Search methods

We searched CENTRAL, MEDLINE, Embase and CINAHL. We searched conference proceedings, reference lists of retrieved articles, databases of trial registries and contacted experts in the field on 31 August 2017. We did not impose restrictions on language or location of publications.

Selection criteria

We included all randomized controlled trials (RCTs) or quasi-RCTs that compared early intervention (mobilization or active exercise, or both), delivered in the ICU, with delayed exercise or usual care delivered to critically ill adults either during or after the mechanical ventilation period in the ICU.

Data collection and analysis

Two researchers independently screened titles and abstracts and assessed full-text articles against the inclusion criteria of this review. We resolved any disagreement through discussion with a third review author as required. We presented data descriptively using mean differences or medians, risk ratios and 95% confidence intervals. A meta-analysis was not possible due to the heterogeneity of the included studies. We assessed the quality of evidence with GRADE.

Main results

We included four RCTs (a total of 690 participants), in this review. Participants were adults who were mechanically ventilated in a general, medical or surgical ICU, with mean or median age in the studies ranging from 56 to 62 years. Admitting diagnoses in three of the four studies were indicative of critical illness, while participants in the fourth study had undergone cardiac surgery. Three studies included range-of-motion exercises, bed mobility activities, transfers and ambulation. The fourth study involved only upper limb exercises. Included studies were at high risk of performance bias, as they were not blinded to participants and personnel, and two of four did not blind outcome assessors. Three of four studies reported only on those participants who completed the study, with high rates of dropout. The description of intervention type, dose, intensity and frequency in the standard care control group was poor in two of four studies.

Three studies (a total of 454 participants) reported at least one measure of physical function. One study (104 participants) reported low-quality evidence of beneficial effects in the intervention group on return to independent functional status at hospital discharge (59% versus 35%, risk ratio (RR) 1.71, 95% confidence interval (CI) 1.11 to 2.64); the absolute effect is that 246 more people (95% CI 38 to 567) per 1000 would attain independent functional status when provided with early mobilization. The effects on physical functioning are uncertain for a range measures: Barthel Index scores (early mobilization: median 75 control: versus 55, low quality evidence), number of ADLs achieved at ICU (median of 3 versus 0, low quality evidence) or at hospital discharge (median of 6 versus 4, low quality evidence). The effects of early mobilization on physical function measured at ICU discharge are uncertain, as measured by the Acute Care Index of Function (ACIF) (early mobilization mean: 61.1 versus control: 55, mean difference (MD) 6.10, 95% CI -11.85 to 24.05, low quality evidence) and the Physical Function ICU Test (PFIT) score (5.6 versus 5.4, MD 0.20, 95% CI -0.98 to 1.38, low quality evidence). There is low quality evidence that early mobilization may have little or no effect on physical function measured by the Short Physical Performance Battery score at ICU discharge from one study of 184 participants (mean 1.6 in the intervention group versus 1.9 in usual care, MD -0.30, 95% CI -1.10 to 0.50), or at hospital discharge (MD 0, 95% CI -1.00 to 0.90). The fourth study, which examined postoperative cardiac surgery patients did not measure physical function as an outcome.

Adverse effects were reported across the four studies but we could not combine the data. Our certainty in the risk of adverse events with either mobilization strategy is low due to the low rate of events. One study reported that in the intervention group one out of 49 participants (2%) experienced oxygen desaturation less than 80% and one of 49 (2%) had accidental dislodgement of the radial catheter. This study also found cessation of therapy due to participant instability occurred in 19 of 498 (4%) of the intervention sessions. In another study five of 101 (5%) participants in the intervention group and five of 109 (4.6%) participants in the control group had postoperative pulmonary complications deemed to be unrelated to intervention. A third study found one of 150 participants in the intervention group had an episode of asymptomatic bradycardia, but completed the exercise session. The fourth study reported no adverse events.

Authors' conclusions

There is insufficient evidence on the effect of early mobilization of critically ill people in the ICU on physical function or performance, adverse events, muscle strength and health-related quality of life at this time. The four studies awaiting classification, and the three ongoing studies may alter the conclusions of the review once these results are available. We assessed that there is currently low-quality evidence for the effect of early mobilization of critically ill adults in the ICU due to small sample sizes, lack of blinding of participants and personnel, variation in the interventions and outcomes used to measure their effect and inadequate descriptions of the interventions delivered as usual care in the studies included in this Cochrane Review.

PLAIN LANGUAGE SUMMARY

Early intervention (movement or active exercise) for critically ill adults in the intensive care unit

Review question

Does helping critically ill adults to move or exercise early in their stay in the intensive care unit (ICU) improve their ability to perform everyday activities such as walking, and the ability to perform daily self care on discharge from hospital? We reviewed the evidence for this question, to see if there are benefits to early exercise, including the amount of time spent in the ICU or hospital, muscle strength, feelings of well-being, and also to see if there are harms, such as the occurrence of falls. The movement or exercise could include things such as moving in, or sitting out of bed, practicing standing up, walking, arm exercises, and self-care activities such as eating or brushing hair.

Background

Adults who are critically ill, and spend time in an ICU, can develop muscle weakness and other problems. This can occur because of the illness that led to their admission to the ICU, treatments associated with this illness, the impact of ongoing health conditions, and their lack of movement while in the ICU. They may also have ongoing problems when they leave ICU (or hospital) such as having trouble doing daily activities (for example dressing, bathing and mobility); feeling depressed or anxious and having difficulty returning to work.

We wanted to evaluate if assisting these people to move early in their ICU stay would allow them to be better able to look after themselves, be stronger and feel better about life.

Study characteristics

We found four studies that included a total of 690 adults who had been in the ICU. Patients were randomized to receive exercises and assistance to move early in their stay in the ICU or to usual care. All participants had been on a breathing machine at some point during their time in the ICU. Three studies included adults with critical illness involving severe disease of the lungs or severe body response to infection and one study involved adults who had undergone cardiac surgery.

Study funding sources

One study was funded by the Intensive Care Foundation, Royal Brisbane and Women's Hospital, Australia and the investigator was supported by a Postgraduate Award from Singapore.

Key results

We were unable to determine whether early movement or exercise of critically ill people in the ICU improves their ability to do daily activities, muscle strength, or quality of life. There were mixed results on the effect of early movement or exercise on physical function. One study found that on some measures of physical function, participants who received the intervention could get out of bed earlier and walk greater distances. However, the same study found no differences in the number of daily activities they could do when leaving ICU. Early movement or exercise appears safe as the number of adverse events was very low. There was no difference between groups in time spent in hospital, muscle strength or death rates.

Quality of the evidence

Overall there was low-quality evidence from these studies. The main reasons were that only a small number of studies have examined this intervention. Most studies included only a small number of participants, and participants and study staff were aware of group assignment. In addition, in two studies, staff assessing outcomes were aware of group assignment. There were also differences in participant diagnoses, interventions and the way that outcomes were measured. The four studies awaiting classification, and the three ongoing studies may alter the conclusions of the review once these results are available.

Currency of the evidence

Evidence in this review is current to August 2017.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Early intervention (mobilization or active exercise) versus usual care for critically ill adults

Patient or population: critically ill, mechanically ventilated adults
Settings: general, medical or surgical ICU in Australia/China/USA
Intervention: early intervention (mobilization or active exercise)
Control: usual care (defined as no mobilization/active exercise while in ICU, or mobilization/active exercise given later than the intervention group)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Early intervention (mobilization or active exercise)				
Physical function - return to independent functional status at hospital discharge Defined as ability to perform 6 ADLs (bathing, dressing, eating, grooming, transferring from bed to chair, using the toilet) and walk independently, measured with Functional Independence Measure	**Study population**		**RR 1.71** (1.11 to 2.64)	104 (1 study)	⊕⊕◯◯ **low**[1,2]	
	345 per 1000	**591 per 1000** (383 to 912)				
Physical function - independent ADLs total at ICU discharge Functional Independence Measure	**Study population**			104 (1 study)	⊕⊕◯◯ **low**[1,2]	

(0 - 6)					
	Median 0 (IQR 0 to 5)	Median 3 (IQR 0 to 5)			
Physical function - Independent ADL total at hospital discharge Functional Independence Measure (0 - 6)	**Study population**			104 (1 study)	⊕⊕◯◯ **low**[1,2]
	Median 4 (IQR 0 to 6)	Median 6 (IQR 0 to 6)			
Physical function Barthel score (0 - 100)	**Study population**			104 (1 study)	⊕⊕◯◯ **low**[1,2]
	Median 55 (IQR 0 to 85)	Median 75 (IQR 7.5 to 95)			
Physical performance Acute Care Index of Function score at ICU discharge (0 - 100)	**Study population**			42 (1 study)	⊕⊕◯◯ **low**[2,3]
	Mean score 55.0 (45.0 to 65.0)	Mean score 61.1 (46.2 to 76.0) **MD 6.10** (-11.85 to 24.05)			
Physical performance Physical Function ICU Test score at ICU discharge	**Study population**			42 (1 study)	⊕⊕◯◯ **low**[2,3]
	Mean score 5.4 (4.7 to 6.1)	Mean score 5.6 (4.7 to 6.5) **MD 0.20** (-0.98 to 1.38)			
Physical performance Short Physical Performance Battery score at ICU discharge	**Study population**			184 (1 study)	⊕⊕◯◯ **low**[2,3]

	Mean score 1.9 (1.3 to 2.4)	Mean score 1.6 (1.0 to 2.2) **MD -0.30** (-1.10 to 0. 50)		
Physical performance Short Physical Performance Battery score at hospital discharge	**Study population**		204 (1 study)	⊕⊕◯◯ **low**[2,3]
	Mean score 4.7 (4.0 to 5.4)	Mean score 4.7 (4.0 to 5.4) **MD 0** (-1.00 to 0.90)		
Adverse events Proportion of participants with one or more events, or proportion of intervention sessions where an event occurred (falls, accidental dislodgement of attachments, haemodynamic instability, oxygen desaturation or any other adverse events defined by study authors)		One study reported that in the intervention group 1/49 (2%) experienced oxygen desaturation < 80% and 1/49 (2%) had accidental dislodgement of the radial catheter. This study also found cessation of therapy due to patient instability occurred in 19/498 (4%) of the intervention sessions. In another study 5/101 (5%) of the intervention group and 5/109 (4.6%) of the control group had postoperative pulmonary complications. These were deemed to be unrelated to intervention. A third study found 1/150 in the intervention group had an episode	690 (4 studies)	⊕⊕◯◯ **low**[2,4]

		of asymptomatic bradycardia, but completed the exercise session. The fourth study reported no adverse events	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
ADLs: activities of daily living; **CI:** confidence interval; **ICU**: intensive care unit; **MD**: mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Low quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

[1]Downgraded one point for high risk of bias. Risk of bias was high for blinding of participants and personnel (performance bias).
[2]Downgraded for imprecision (only one small study).
[3]Downgraded one point for high risk of bias. Risk of bias was high for blinding of participants and personnel (performance bias) and incomplete outcome data (attrition bias; for all outcomes except mortality).
[4]Downgraded for imprecision, as there were very few adverse events of each type.

BACKGROUND

Description of the condition

Critically ill patients are admitted to the intensive care unit (ICU) so that physiological responses to illness and injury can be monitored and stabilised in a sophisticated manner, and respiration can be assisted with mechanical ventilation if needed. Multiple factors, including haemodynamic instability, altered sleep patterns, the presence of vascular attachments and sedation to improve patient comfort during mechanical ventilation, can limit mobilization of these patients (Adler 2012).

Intensive care unit-acquired weakness (ICUAW) may be described as clinically identified weakness that develops during an ICU admission with no other known cause except the acute illness or its treatment (Hermans 2015). ICUAW is a common complication for critically ill patients and is associated with extended duration of mechanical ventilation (DeJonghe 2002), sepsis, systemic inflammatory response syndrome, multi-organ failure and hyperglycaemia (Desai 2011). Incidence of ICUAW in this patient population has been found to be as high as 46% (95% CI 43% to 49%) (Stevens 2007). Critically ill patients can sustain loss of muscle mass within the first week of admission to the ICU (Parry 2015a; Puthucheary 2013). ICUAW has also been associated with worse acute outcomes, higher healthcare-related costs, and the persistence of weakness is associated with a higher mortality one year after ICU admission (Hermans 2014a). The long-term weakness appears to result from heterogeneous muscle pathophysiology, with both muscle atrophy and decreased contractile capacity involved (Dos Santos 2016).

Among critically ill patients in ICU, some may have or develop acute lung injury or acute respiratory distress syndrome (Herridge 2005). Patients with acute lung injury demonstrate rapid onset of infiltrates in bilateral lungs and mild to moderate hypoxaemia of noncardiac origin (Herridge 2005). In a two-year follow-up on people with this condition, the presence of ICUAW was associated with impairments in physical function; six-minute walk distance (Crapo 2002), and the physical function subscale scores of the Short F-36 survey (Ware 1992), were significantly lower (52% to 69% of predicted value) at six, 12 and 24 months' follow-up (Fan 2014). ICUAW has also been related to a higher incidence of hospital mortality (Ali 2008), and the persistence of weakness is associated with a higher mortality one year after ICU admission (Hermans 2014a).

The term 'post-intensive care syndrome' was developed to describe new or residual problems that are often experienced by survivors of critical illness. These include cognitive impairments (such as altered memory, attention and executive functioning); psychological difficulties (such as depression, anxiety and post-traumatic stress disorder) and physical impairments in pulmonary, neuromuscular and physical function (Needham 2012). These problems can affect the performance of activities of daily living (ADLs) and lead to decreased quality of life for these people. In addition, similar psychological difficulties may occur in families of people with critical illness (Needham 2012).

In an attempt to improve outcomes for the survivors of critical illness, there have been efforts to interrupt sedation (Kress 2000), to allow patients to choose their own level of sedation (Chlan 2010), and to cease sedation (Strøm 2011), for patients who are mechanically ventilated. As patients become increasingly responsive, they are better able to participate in active exercise and to mobilize outside of bed, even when mechanically ventilated. Bailey 2007, demonstrated infrequent adverse events in participants who mobilized while mechanically ventilated and concluded that early mobility of patients in the ICU is feasible and safe. To assist in the assessment of patient readiness and appropriateness to commence early mobility in the ICU, a panel of multidisciplinary experts reached consensus on safety recommendations concerning respiratory, cardiovascular, neurological, medical or surgical and other factors (Hodgson 2014).

Description of the intervention

We considered interventions that commenced earlier than the intervention received by the control group while the patient was in the ICU and may have included any of the following activities.

- Cycle ergometer: (a stationary cycle where work intensity can be adjusted by varying pedal resistance and cycling rate)
- Active-assisted exercises (exercises performed by the participant with manual assistance of another person)
- Active range-of-motion exercises (exercises moving a joint(s) through its range of motion, that are performed independently by the participant)
- Bed mobility activities (activities including rolling, bridging and transfer to upright sitting)
- ADLs (self-care tasks such as eating, bathing, dressing and toileting)
- Transfer training (repetition of transfers such as sitting to standing and bed to chair or commode)
- Pre-gait exercises (improving postural stability, static and dynamic balance and marching on the spot)
- Ambulation (gait training and walking with or without mobility aids).

(See Types of interventions for additional details.)

Characteristics of the intervention such as type, provider skills and training, timing of delivery, dose/duration, tailoring and progression of intervention, and resources used in the delivery can greatly influence an intervention's efficacy as well as the heterogeneity of the population receiving the intervention. Evaluation of the impact of the intervention across studies is dependent on adequate reporting in the included studies so that variations in its delivery may be identified and analysed. To facilitate understanding of the components of the interventions across studies, we used the

Template for Intervention Description and Replication (TIDieR) checklist to report intervention details (see Table 1).

How the intervention might work

The consequences of bed rest are well documented and include adverse effects on the cardiovascular system (through decreased functional capacity), the respiratory system (through difficulty weaning from mechanical ventilation) and the neuromuscular system (through ICUAW) (Koo 2011). Beneficial effects of exercise training are widespread and can include improvements in skeletal muscle function, respiration (increased tidal volume and oxygen transport capacity) and cardiovascular function (including prevention of age-related diastolic dysfunction and decreased oxidative stress) (Gielen 2010). Prolonged immobilization is one of the risk factors for ICUAW (Hermans 2015), and hence reducing the duration of immobilization has been suggested as one of the actions that can be taken to prevent it (Hermans 2015). It has been suggested that early mobilization might reduce muscle injury through its effect on muscle unloading (Hermans 2015), but the pathophysiological mechanisms through which this intervention might work are complex and not clearly understood. As the recovery from ICUAW can take weeks or months, its impact on function and quality of life can last for years. In a five-year follow-up study of survivors of acute respiratory distress syndrome, generalized weakness and fatigue were chief complaints and still present in many survivors at this time (Herridge 2011). Hence preventing or lessening the impact of ICUAW may have consequent effects on patients' function and quality of life in the weeks, months, and years following an ICU admission.

Why it is important to do this review

A Cochrane protocol for a systematic review (Greve 2012), and one Cochrane systematic review (Connolly 2015), relevant to the impact of mobilization of critically ill patients have been published. Greve 2012, has a focus on preventing ICU delirium and will assess the impact of any multicomponent (behavioural, cognitive, psychological, physical training) or pharmacological interventions, or both. Connolly 2015, evaluated the efficacy of exercise rehabilitation or training for functional exercise capacity and health-related quality of life in adult ICU survivors who had been mechanically ventilated longer than 24 hours. However, neither of these reviews plans to examine or has investigated mobilization delivered early in the participants' admission to ICU. The protocol (Greve 2012), has not specified the timing of the intervention while the systematic review (Connolly 2015), investigated the impact of exercise rehabilitation once participants had been discharged from the ICU.

Early mobilization and active exercise of critically ill patients are increasingly being provided in some ICUs. However, the effectiveness of early interventions that are being used is not clear. This review aims to guide clinicians and intensive care unit policy makers regarding the timing of mobilization and active exercise for critically ill patients.

OBJECTIVES

To assess the effects of early intervention (mobilization or active exercise), commenced in the ICU, provided to critically ill adults either during or after the mechanical ventilation period, compared with delayed exercise or usual care, on improving physical function and performance, muscle strength and health-related quality of life.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomized controlled trials (RCTs) or quasi-RCTs that compared early intervention (mobilization or active exercise) of critically ill participants either during or after the mechanical ventilation period in the ICU with delayed exercise or usual care (see Types of interventions).

Types of participants

We included adults who had been admitted to an ICU and were mechanically ventilated. We excluded studies with participants who had pre-existing or rapidly developing neuromuscular disease, spinal cord injury, cardiopulmonary arrest, raised intracranial pressure, advanced dementia or irreversible disorders with expected six-month mortality.

Types of interventions

Interventions

The intervention must have been conducted within the ICU and must have consisted of mobilization or active exercise, or both, that was designed to commence earlier than the care received by the control group.

We considered any combination of one or more of the following types of exercise modalities.

- Cycle ergometer
- Active-assisted exercises
- Active range-of-motion (ROM) exercises

- Bed mobility activities (e.g. bridging, rolling, lying to sitting)
- ADLs or exercises related to increasing independence with functional tasks
- Transfer training
- Pre-gait exercises (including marching on the spot)
- Ambulation
- Any other type of active exercise modality that commenced while the participant was in the ICU

Comparators

The comparator may have consisted of:

- delayed intervention (mobilization/active exercise the same as the intervention group, but given later, either in the ICU, or after the participant left the ICU);
- usual care (no mobilization/active exercise while in ICU);
- inspiratory/respiratory muscle training only.

Types of outcome measures

Primary outcomes

- Physical function (the ability to perform everyday activities such as basic ADLs) as measured by a validated scale (e.g. Barthel Index, Functional Independence Measure (FIM)) or physical performance tasks (as measured by a scale such as the Physical Function ICU Test (PFIT), Acute Care Index of Functional Status (ACIF), Short Physical Performance Battery, walking tests)
- Adverse events (falls, accidental dislodgement of attachments, haemodynamic instability, oxygen desaturation or any other adverse events defined by study authors)

Secondary outcomes

- Length of stay (ICU and hospital)
- Muscle strength (e.g. Medical Research Council (MRC) score (Medical Research Council 1942), cross-sectional diameter, handgrip strength)
- Health-related quality of life or well-being (e.g. The Medical Outcome Study (MOS) 36-item Short-Form Health Survey (SF-36) questionnaire (Ware 1992)
- Delirium
- Death from any cause at any measured time point
- Hospital costs

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 8) via the Cochrane Library, MEDLINE (Ovid SP) (1946 to August week 4, 2017), Embase (Elsevier) (2010 to August 2017) and CINAHL (1981 to August 2017).
We used the search strategy described in Appendix 1 to search CENTRAL and Appendix 2 to search MEDLINE. We combined the MEDLINE search terms with the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-and precision-maximizing version (2008 revision); Ovid format (Lefebvre 2011). We adapted the search strategy to search Embase (see Appendix 3), and CINAHL (see Appendix 4).
We did not impose a language restriction.

Searching other resources

We searched the Controlled Trials registry www.controlled-trials.com/ (August 2017) (see Appendix 5 for detailed search strategy), ClinicalTrials.gov registry clinicaltrials.gov/ (August 2017) (see Appendix 6), and the World Health Organization International Clinical Trials Registry Platform www.who.int/ictrp/en/ (August 2017) (see Appendix 7), for studies that may have been missed or unpublished and reviewed relevant conference proceedings and abstract presentations of important symposia.
We corresponded with authors of studies that had been completed but not published and with content experts to identify unpublished research and trials still under way.
We did not impose a language restriction.

Data collection and analysis

Selection of studies

Two researchers (review author, KAD and a research assistant) independently screened titles and abstracts and assessed full-text articles that were identified from the search. We resolved any disagreement through discussion or consultation with a third review author (TCH or EMB, or both) as required.

Data extraction and management

Two researchers (KAD, and a research assistant) independently used the data collection form shown in our protocol (Doiron 2013), to extract data from all included studies. We resolved any disagreement through discussion or consultation with a third review author (EMB or TCH, or both) as required.
We examined trials that met the inclusion criteria and recorded the following information.

- Methods: a description of study design, randomization and treatment setting
- Participants: number of participants, age, gender, race/ethnicity, body mass index, inclusion and exclusion criteria, ICU days before inclusion, primary presenting diagnosis, biochemical

data, health and well-being status scores and functional scale scores

- Interventions: description of experimental and comparator interventions and relevant co-interventions (e.g. medications)
- Outcomes: baseline and end of study measurement of functional status (e.g. functional independence measure (FIM) (Keith 1987), Barthel Index (Mahoney 1965)), health-related quality of life or well-being (the MOS 36-item Short-Form Health Survey (SF-36) questionnaire (Ware 1992)), and muscle strength, as well as adverse events, length of stay (ICU and hospital), delirium, death from any cause and hospital costs
- Notes: language of the study and any other information relevant to this review

We commented briefly about the reasons for exclusion of studies identified in the search strategy but not subsequently included.

Assessment of risk of bias in included studies

Two review authors (EMB and KAD) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion or by involving a third review author (TCH). We assessed the risk of bias according to the following domains.

- Allocation sequence generation
- Concealment of allocation
- Blinding of study participants and personnel
- Incomplete outcomes data
- Selective outcomes reporting
- Other biases

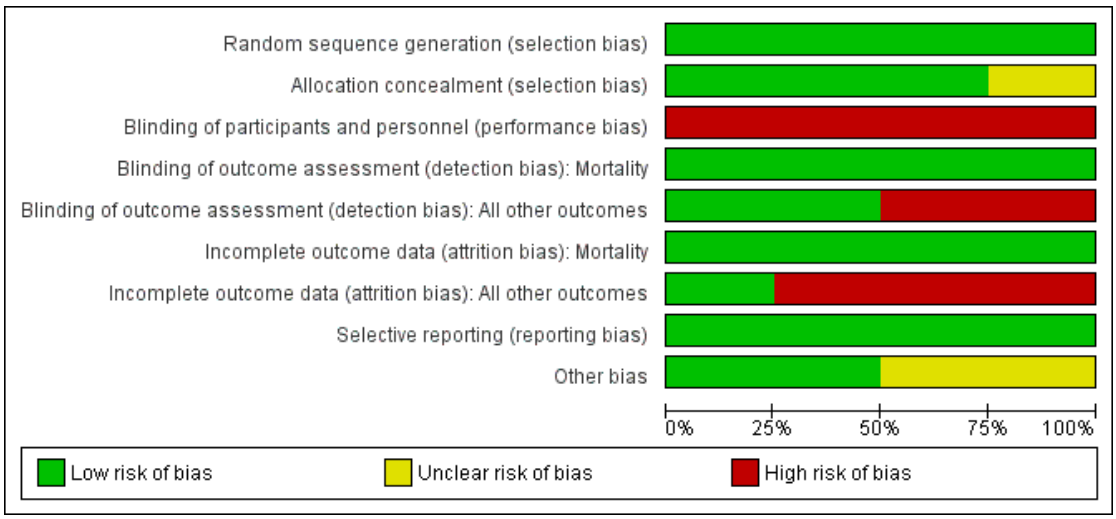
We graded each potential source of bias as yes, no or unclear according to whether the potential for bias was high, low or unknown.

We considered a trial as having a high risk of bias if we assessed either of the domains of concealment of allocation or blinding of study participants and personnel as inadequate or unclear.

We included a 'Risk of bias' summary (see Figure 1), and a 'Risk of bias' graph (see Figure 2), as part of the Characteristics of included studies table, which detailed all of the judgements made for all included studies in the review.

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



Measures of treatment effect

Primary outcomes

Functional status

Where studies reported this as a dichotomous outcome (e.g. return to independent functional status at hospital discharge), we used a risk ratio to compare the intervention group with the control group. Where studies reported ADL composite measures and functional component measures using continuous scales (e.g. Barthel Index (Mahoney 1965)), we reported results using means (standard deviations (SDs)) or medians (interquartile range).

Adverse events

We reported the proportion of participants who experienced any adverse event that was reported by the study authors. We also descriptively reported the numbers of particular types of adverse events.

Secondary outcomes

Length of stay

This was reported in days, and we therefore reported the mean difference (MD) where possible, or the median (interquartile range) in each group.

Muscle strength, health-related quality of life

These outcomes were measured using continuous scales and we reported the MD where possible, or the median (interquartile range) in each group.

Delirium

This was reported as days with delirium in the ICU and in hospital. We reported the median (interquartile range) scores in each group.

Death from any cause

This was reported as the percentage of participants in each group who died and reported as risk ratio to compare groups.

Hospital costs

None of the included studies reported this outcome. If they had done so, we planned to report the MD in costs between intervention and control groups.

Unit of analysis issues

Individual participants were the unit of analysis.

Dealing with missing data

We wrote to investigators to verify key study characteristics and details of the outcomes data as needed. We contacted a study author in Patman 2001, to identify group allocation for participants who died. We subsequently reported this information in Effects of interventions (death from any cause) and Table 2. We corresponded with authors in one study to identify the timing of the interventions received by the intervention and control groups (Kayambu 2015). We reported this information in Included studies (comparators). We also requested clarification on the methods used to calculate results from this study. We intended to conduct intention-to-treat (ITT) analysis and to impute missing standard deviations but this was not required.

Assessment of heterogeneity

We noted clinical heterogeneity in studies relating to the participants, interventions, and outcome measures. We did not measure statistical heterogeneity as we did not perform a meta-analysis.

Assessment of reporting biases

We did not create a funnel plot to investigate potential publication bias as only four studies were included in this review.

Data synthesis

If sufficient studies for meta-analysis had been found, we planned to use a random-effects model because of the varying nature of potential interventions in this review. However, as there were insufficient studies to perform a meta-analysis, we descriptively reported the results of included studies.

Subgroup analysis and investigation of heterogeneity

If heterogeneity of studies had been observed, we planned to investigate possible sources of heterogeneity such as age group, cause of ICU stay, length of mechanical ventilation, comorbidities such as diabetes and use of corticosteroids using subgroup analyses. However, as there were insufficient studies identified, we reported these factors descriptively.

Sensitivity analysis

We planned to perform a sensitivity analysis by omitting the studies judged at high risk of bias, defined as lack of concealment of allocation and blinding of study participants and personnel. However we were unable to do this as no meta-analysis was performed.

'Summary of findings' table and GRADE

We used the principles of the GRADE system (Guyatt 2008), to assess the quality of the body of evidence associated with specific outcomes (functional status and adverse events) in our review and constructed Summary of findings for the main comparison using the GRADEpro software (GRADEpro GDT 2015). The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence considers within-study risk of bias (methodological quality), the directness of the evidence, the heterogeneity of the data, the precision of effect estimates and the risk of publication bias.

Two review authors (KAD and EMB) independently performed the GRADE assessment of quality of the evidence. We resolved disagreements by consensus. We planned to consult the third review author if we had been unable to resolve disagreements. We rated the quality of the evidence for each outcome as high, moderate, low or very low.

RESULTS

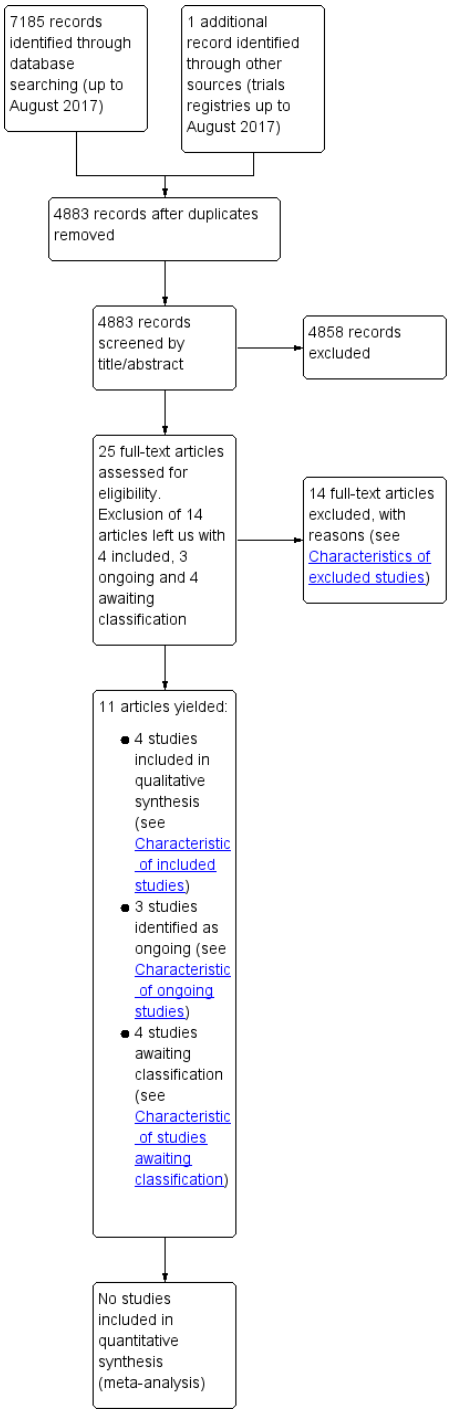
Description of studies

We included RCTs that compared early intervention (mobilization or active exercise) commenced in the ICU (either during or after the mechanical ventilation period) with delayed exercise or usual care for critically ill adults.

Results of the search

We identified a total of 7185 references from our searches of CENTRAL, MEDLINE (Ovid SP), Embase (Ovid SP) and CINAHL, and one reference after searching trials registries (to August 2017). We identified 2303 duplicates and excluded 4858 further references as they were not eligible for this review. We examined 25 full-text articles, and identified four studies that fulfilled our inclusion criteria (Kayambu 2015; Morris 2016; Patman 2001; Schweickert 2009). See Figure 3 for further information.

Figure 3. Study flow diagram



Included studies

We included four RCTs in this review (Kayambu 2015; Morris 2016; Patman 2001; Schweickert 2009).

Participants

We report participant details in the Characteristics of included studies section. The total number of participants enrolled in all four trials was 690. All were aged over 18 years; the mean or median age of participants ranged from 56 to 62 years. Sample size varied across studies; Kayambu 2015 (50 participants), Morris 2016 (300 participants), Patman 2001 (236 participants), and Schweickert 2009 (104 participants).

One study reported that all participants in the intervention group were mechanically ventilated for the duration of the intervention (Patman 2001), while the remaining three studies did not report the percentages of those who were intubated during the intervention period (Kayambu 2015; Morris 2016; Schweickert 2009).

The most common reason for ICU admission varied across the studies. In Kayambu 2015, 19 of 26 (73%) participants in the intervention group and 17 of 24 (71%) in the control group were admitted with septic shock; in Morris 2016 68% had acute respiratory failure without chronic lung disease, 31% had acute respiratory failure with chronic lung disease and 2% had an ICU diagnosis of coma; in Patman 2001, 71 of 108 (66%) participants in the intervention group and 68 of 109 (62%) of those in the control group had undergone coronary artery surgery; and in Schweickert 2009 27 of 49 (55%) participants in the intervention group and 31 of 55 (56%) in the control group were admitted with acute lung injury.

Two studies were conducted in a single ICU (Kayambu 2015; Morris 2016), one study in a surgical ICU (Patman 2001), and one study in medical ICUs at two sites (Schweickert 2009).

Please refer to the Characteristics of included studies for more detail.

Interventions

There was variation in most aspects of the interventions between the four studies: electrical muscle stimulation (EMS), tilt table therapy, arm or leg ergometry and activities ranging from passive to active to resisted range-of-motion exercises, transfers, balance training (sitting and standing) through to ambulation with assistance were part of the intervention in Kayambu 2015; passive range-of-motion, physical therapy including bed mobility, transfer training and balance training, and progressive resistance exercise using elastic resistance bands were used in Morris 2016; upper limb exercises were performed with the intervention group in the trial by Patman 2001; and activities ranging from passive to active-assisted exercises through to transfer training, ADL tasks and ambulation were implemented in Schweickert 2009.

The time to commencement of the intervention was variable across studies. in Kayambu 2015 the intervention group commenced therapy within 48 hours of admission to ICU and in Morris 2016 a median of 1 day after admission to ICU. In Patman 2001 the intervention group commenced therapy during the first 24 hours of intubation and in Schweickert 2009 at a median of 1.5 days, interquartile range (IQR) (1.0 to 2.1) after intubation had commenced.

Frequency and duration of the delivery of the intervention also varied across studies. Kayambu 2015 reported that the intervention was delivered for 30 minutes, once or twice per day until the participant was discharged from the ICU and that participants remained in the study for a mean of 11.4 days. In Morris 2016, the intervention sessions were given three times per day, with a goal of achievement of repetitions, rather than a specified time for each session. The intervention was continued until discharge from hospital. In the study by Patman 2001, the intervention was delivered as required during the intubated phase, which lasted 24 hours (participants were withdrawn from the study if mechanical ventilation was required for more than 24 hours). No further details regarding the frequency and duration of the intervention were provided. Schweickert 2009 reported that the intervention was delivered every morning until participants returned to their previous level of function or were discharged. Information on the discharge location (ICU or hospital) was not stated. Study authors reported that the median duration of therapy for the intervention group during mechanical ventilation was 0.32 hours per day, IQR (0.17 to 0.48) and a median of 0.21 hours per day IQR (0.08 to 0.33) while not being ventilated.

The intervention was provided by physiotherapists in Kayambu 2015, Morris 2016 and Patman 2001; and by a physiotherapist and an occupational therapist in Schweickert 2009. (Refer to the Characteristics of included studies for more detail.) Key characteristics of the interventions in each trial are listed in Table 1, according to the TIDieR components (Hoffmann 2014).

Comparators

Information about the timing of treatment in the control group was reported in three studies (Morris 2016, Patman 2001; Schweickert 2009). In Morris 2016, the usual care group participants could receive weekday physical therapy if it was ordered by the clinical team. This started a median of seven days after admission, compared with one day in the intervention group. The control group received physical therapy on a mean 11.7% of study days, compared with 87.1% in the intervention group. In Patman

2001, participants received the same intervention as those in the intervention group but 24 hours later (after they were extubated from mechanical ventilation). In Schweickert 2009, participants in the control group received physical and occupational therapy as ordered by the primary care team and active physiotherapy treatment occurred only after they had been mechanically ventilated for two weeks. Study authors reported that the control group received an intervention a median of 7.4 days after intubation. After correspondence with study authors, Kayambu 2015 reported that 10 of 24 (42%) participants in the control group received the same intervention as those in the intervention group (with the exception of EMS, tilt table therapy and arm or leg ergometry) at the same time as those in the intervention group (within 48 hours of admission) while 14 out of 24 (58%) of the participants in this group received it later (after 48 hours of admission).
Refer to the Characteristics of included studies for more detail.

Primary outcomes

Physical function and performance

Three studies measured physical function or performance, and each used different measures (Kayambu 2015; Morris 2016; Schweickert 2009). Kayambu 2015, used the acute care index of function (ACIF) (Van Dillen 1988), and the physical function ICU test (PFIT) (Skinner 2009), and Morris 2016 used the Short Physical Performance Battery score (SPPB). Schweickert 2009 reported the percentage of participants returning to independent functional status at discharge, the number of independent ADLs achieved at ICU and hospital discharge, the time from intubation to out of bed, standing, marching in place, transferring to a chair, and walking, and the Barthel Index. These study authors used the functional independence measure (FIM) (Keith 1987), to measure return to independent functional status and ADLs. Schweickert 2009 also measured time to achieve milestones (e.g. time from intubation to marching in place) and walking distance achieved at hospital discharge.

Adverse events

All studies reported adverse events but only two studies defined this outcome (Patman 2001; Schweickert 2009). Patman 2001 used the presence of four or more of the following criteria to identify the incidence of postoperative pulmonary complications: oral temperature greater than 38˚ C, hypoxia (oxygen saturation < 92% on room air), abnormal findings on chest X-ray reported by blinded experienced senior radiologists, abnormal white cell count (< 2 or > 10 x 10^9 cells per litre) and positive sputum culture on microscopy. Schweickert 2009 described adverse events as a fall to knees, endotracheal tube removal, systolic blood pressure more than 200 mmHg, diastolic blood pressure less than 90 mmHg, and desaturation to less than 80% . In the protocol for their study, Kayambu 2015 reported that an adverse event checklist would be used to assist in clinical decisions regarding cessation or modification of the intervention but did not provide further details. Morris 2016 collected adverse events of any kind, and classified them by severity and likelihood of being related to the intervention sessions.

Secondary outcomes

Length of stay (LOS) ICU or hospital

This outcome was reported by all four included studies.

Muscle strength

Three studies reported muscle strength (Kayambu 2015; Morris 2016; Schweickert 2009). Kayambu 2015 at ICU discharge, Morris 2016 at ICU discharge, hospital discharge and at follow-up visits, and Schweickert 2009 at hospital discharge. Kayambu 2015 and Schweickert 2009 used the Medical Research Council score (Medical Research Council 1942), to measure this outcome. Morris 2016 used dynamometer and hand grip strength; Schweickert 2009 measured hand-grip strength and reported the incidence of ICUAW at hospital discharge.

Health-related quality of life

THis outcome was reported by two studies. Kayambu 2015 used the 36-item Short Form Health Survey (SF-36) questionnaire (Ware 1992), for 11 of 26 (42%) of the participants in the intervention group and 19 of 24 (79%) of the participants in the control group to measure physical function, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health at six months post-hospital discharge. Morris 2016 used the SF-36 physical health summary score and mental health summary scores at hospital discharge and follow-up visits.

Delirium

Two studies reported the number of ICU days and the number of hospital days with delirium (Morris 2016; Schweickert 2009).

Death from any cause

All four included studies reported death from any cause using the percentage in the intervention group compared with the percentage in the control group. Kayambu 2015 and Patman 2001 reported ICU mortality, and Schweickert 2009 reported hospital mortality. Morris 2016 reported six-month mortality and Kayambu 2015 reported 90-day mortality.

Hospital costs

None of the included studies reported costs.

Funding

One study was funded by the Intensive Care Foundation and the principal investigator was supported by a postgraduate award from Singapore (Kayambu 2015); two studies did not report funding (Morris 2016; Patman 2001) and one study author declared that no funding was received (Schweickert 2009).
For further descriptive information, see Characteristics of included studies.

Excluded studies

We excluded 14 studies for the reasons identified in the Characteristics of excluded studies table. These included study design, comparators and timing of the intervention between groups. One study was not a RCT (Morris 2008), one study was conducted in a respiratory care centre (not the ICU) (Chen 2012); four studies used comparators that did not match those in this review; active or passive ROM, or both (Burtin 2009); passive chair transfer (Collings 2015); active and passive mobilization (Médrinal 2013), and active intervention once versus twice per day (Yosef-Brauner 2015). Seven studies did not compare early versus later interventions (Brummel 2014; Chiang 2006; Denehy 2013; ISRCTN20436833; Moss 2016; Nava 1998; NCT01058421; Porta 2005).

Awaiting classification

We identified four studies that are awaiting classification (Dong 2014; Files 2013; Malicdem 2010; Susa 2004). The reasons we placed these studies in this category varied. The contact author in one study declined to clarify methods and eligibility criteria as they expected to publish their results (Files 2013), and we have not received a response to our correspondence regarding eligibility criteria or timing of intervention from authors in the remaining three studies (Dong 2014; Malicdem 2010; Susa 2004). See Characteristics of studies awaiting classification for further information.

Ongoing studies

We identified three ongoing studies in trial registries (NCT01927510; NCT01960868; RBR-6sz5dj). One study has been completed but not yet published (NCT01927510), and we were unable to identify publications for the remaining two studies (NCT01960868; RBR-6sz5dj). In addition, study authors did not respond to our correspondence regarding the status of their trials. See Characteristics of ongoing studies for further information.

Risk of bias in included studies

See Figure 1 for 'Risk of bias summary' and Figure 2 for 'Risk of bias' graph for the studies included in this review.

Allocation

All four studies demonstrated adequate random sequence generation and allocation concealment except Morris 2016, which was unclear for allocation concealment, and therefore we considered them at low risk of selection bias.

Blinding

Blinding of participants and personnel

Although (Kayambu 2015), stated that they blinded participants, we considered all studies to be at high risk of performance bias as these interventions could not have been blinded for either participants or trial personnel in the ICU.

Blinding of outcome assessment

Two studies (Morris 2016; Patman 2001), demonstrated a high risk of detection bias for all outcomes except mortality; both reported that the outcome assessor was aware of group allocation. Kayambu 2015 and Schweickert 2009 blinded outcome assessors; therefore we considered these studies to be at low risk of detection bias. As the event of mortality would have been evaluated by personnel outside all of the studies, we considered them all to be at low risk of detection bias for this outcome.

Incomplete outcome data

Three studies demonstrated a high risk of attrition bias for all outcomes except mortality (Kayambu 2015; Morris 2016; Patman 2001). These studies reported results only for participants who completed the study, rather than for all randomized participants. Morris 2016 achieved outcome measurement in approximately 67% of those randomized. In addition, we noted a high dropout rate for the intervention group in the study conducted by Kayambu 2015. Only one study demonstrated a low risk of attrition bias (Schweickert 2009), as study authors presented outcome data for all outcomes including mortality for all enrolled participants.

Selective reporting

We considered all included studies to have a low risk of bias for selective reporting.
Kayambu 2015 and Morris 2016 reported all outcomes specified in the protocols for their study, and the remaining two studies reported all outcomes specified in the methods section of the text (Patman 2001; Schweickert 2009).

Other potential sources of bias

Two studies demonstrated an unclear risk of bias associated with the reporting of standard care as the control condition was not well described (Kayambu 2015; Schweickert 2009). These studies compared the intervention with standard care and the components of care delivered to the control group was not discussed in Schweickert 2009. Therefore we feel that elements of the intervention may have been delivered to the control groups. Although Kayambu 2015 described the components of the intervention delivered to standard care, the frequency and duration of the exercise strategy were not well explained and the dosage and intensity were not reported.

Effects of interventions

See: **Summary of findings for the main comparison** Early intervention (mobilization or active exercise) versus usual care for critically ill adults

Primary outcomes

1. Physical function and performance (the ability to perform everyday activities such as basic ADLs, and physical performance tasks)

Three studies, involving a total of 454 participants, reported aspects of physical functional status (Kayambu 2015; Morris 2016; Schweickert 2009).

Kayambu 2015, reported results for 42 of 50 (84%) of the participants for the acute care index of function (ACIF) and the physical function ICU test (PFIT) at discharge from ICU, and there was no clear difference between groups. However the evidence is of low quality, due to high risk of performance and attrition biases and imprecision (one small study); ACIF: (61.1 versus 55, MD 6.10, 95% CI -11.85 to 24.05; P = 0.45), and PFIT (5.6 versus 5.4, MD 0.20, 95% CI -0.98 to 1.38; P = 0.61).

Morris 2016 reported SPPB score as a measure of physical performance, with a mean score of 1.6 in the intervention group and 1.9 in the control group (MD -0.3, 95% CI -1.1 to 0.5; P = 0.46) at ICU discharge, and a MD of 0 (95% CI -1.0 to 0.9) at hospital discharge.

The study by Schweickert 2009, reported a number of outcomes associated with functional status for all of the 104 participants in this study. More of those in the intervention group returned to independent functional status at hospital discharge (59% versus 35%, RR 1.71, 95% CI 1.11 to 2.64; P = 0.01). Participants in the intervention group achieved a greater number of independently performed ADL on discharge from the ICU (median of 3 versus 0; P = 0.15) and hospital (median of 6 versus 4; P = 0.06), but these results were not statistically significantly different. There was no clear difference between the intervention and control groups for the Barthel Index score at hospital discharge (median score of 75 versus 55; P = 0.05). Schweickert 2009, reported other outcomes related to physical performance, with results favouring the intervention group for time from intubation to out of bed (median of 1.7 versus 6.6 days), standing (median of 3.2 versus 6 days), marching in place (median of 3.3 versus 6.2 days), transferring to a chair (median of 3.1 versus 6.2 days) and walking (median of 3.8 versus 7.3 days). Results for each of these outcomes were clinical important in size. Study authors also reported a difference favouring the intervention group for the greatest walking distance at hospital discharge (median of 33.4 versus 0 metres; P = 0.004). Study samples were generally small, there was no blinding of participants or personnel, there was heterogeneity in the interventions and the outcomes used to measure their effect and inadequate descriptions of the interventions delivered as standard care for this outcome. Therefore we downgraded evidence to low. See Table 3 for further information about physical function and performance outcomes.

2. Adverse events (falls, accidental dislodgement of attachments, haemodynamic instability, oxygen desaturation or any other adverse events stated by trial authors)

All studies reported adverse events for a total of 690 participants and the incidence was low.

Kayambu 2015, reported that no adverse events occurred during exercise sessions.

Morris 2016, reported no adverse events specific to physical therapy (e.g. endotracheal removal, vascular access device removal, fall, cardiac arrest). There were four events in the intervention group and three in the control group considered severe, and one life-threatening event in the intervention group. All were deemed unrelated to physical therapy. There was also an episode of asymptomatic bradycardia lasting less than one minute, with the participant completing the exercise session afterwards.

Schweickert 2009, reported the following serious adverse events for the intervention group: accidental dislodgement of the radial arterial catheter in one of 49 (2%) participants, and one of 49 (2%) participants experienced oxygen desaturation less than 80%. This study also reported cessation of therapy due to patient instability in 19 of 498 (4%) of the intervention sessions.

Patman 2001, reported 10 serious adverse events in that five of 101 (5%) participants in the intervention group compared to five of 109 (4.6%) participants in the control group met the criteria for postoperative pulmonary complications, however these were deemed unrelated to intervention.

As there was no blinding of participants and personnel, and heterogeneity in the interventions, small numbers of participants and inadequate descriptions of the interventions delivered as standard care, there was low-quality evidence for this outcome.

Secondary outcomes

1a Length of stay (ICU)

All studies involving a total of 690 participants reported length of stay in the ICU.

Schweickert 2009 (104 participants), reported that those in the intervention group stayed a shorter time in the ICU (median of 5.9 versus 7.9 days; P = 0.08). Morris 2016, reported similar times in ICU for the two groups (7.5 versus 8.0, median difference 0, 95% CI -2.5 to 2.0; P = 0.68). In contrast, two studies involving a total of 260 participants reported that those in the intervention group stayed longer in the ICU: Patman 2001; (42.7 versus 36.7 days, MD 6, 95% CI -3.58 to 15.58; P = 0.56), and Kayambu 2015; (median of 12 versus 8.5 days; P = 0.43).

As there was no blinding of participants and personnel, heterogeneity in the interventions, small numbers of participants and inadequate descriptions of the interventions delivered as standard care, there was low-quality evidence for this outcome.

1b Length of stay (hospital)

All four included studies reported length of stay in the hospital. Participants in the intervention group spent less time in hospital in two studies involving a total of 260 participants but the evidence was of low quality so we cannot be sure of this result: Patman 2001 (9.2 versus 9.6 days, MD -0.40, 95% CI -1.97 to 1.17; P = 0.25) and Kayambu 2015 (median of 41 versus 45 days; P = 0.80). Morris 2016 found that both groups spent similar time in hospital (10.0 days, median difference 0, 95% CI -1.5 to 3.0; P = 0.41. Schweickert 2009 reported on 104 participants and found no clear difference between groups (median of 13.5 versus 12.9 days; P = 0.93).

As there was no blinding of participants and personnel, heterogeneity in the interventions and the outcomes used to measure their effect, small numbers of participants and inadequate descriptions of the interventions delivered as standard care, there was low-quality evidence for this outcome.

See Table 4 for further information for length of stay in the ICU and hospital.

2. Muscle strength (Medical Research Council (MRC) score, cross-sectional diameter)

Two studies involving a total of 146 participants used the MRC sum score to measure muscle strength (Kayambu 2015; Schweickert 2009). Kayambu 2015 reported results for 42 of 50 (84%) participants and found that those in the intervention group attained slightly higher MRC scores at ICU discharge (51.9 versus 47.3, MD 4.60, 95% CI -3.11 to 12.31; P = 0.24) but with a confidence interval that suggests the effect could favour either intervention or control. The study by Schweickert 2009 involved 104 participants and the intervention group scored higher in this outcome (median of 52 versus 48; P = 0.38) but not statistically significantly so. Two studies involving 404 participants measured hand grip strength using dynamometry (Morris 2016; Schweickert 2009). There were no clear differences between groups for this outcome. Schweickert 2009 reported that the percentage of participants who had ICU-acquired paresis at hospital discharge was lower in the intervention group but we cannot be sure of this effect, due to small numbers of participants; (15/49 (31%) versus 27/55 (49%), RR 0.62, 95% CI 0.38 to 1.03; P = 0.09).

As there was no blinding of participants and personnel, heterogeneity in the interventions and the outcomes used to measure their effect, small numbers of participants and inadequate descriptions of the interventions delivered as standard care, there was low-quality evidence for this outcome.

See Table 5 for further information on muscle strength.

3. Health-related quality of life or well-being (e.g. MOS 36-item Short-Form Health Survey (SF-36) questionnaire)

Two studies involving 350 participants reported this outcome. Kayambu 2015 reported results for eight subsets of the SF-36 questionnaire at six months post-hospital discharge for 30 of 50 (60%) participants. Participants in the intervention group achieved clinically meaningfully higher scores in physical function; (81.8 versus 60, MD 21.8, 95% CI 0.81 to 42.79; P = 0.04); and role physical; (61.4 versus 17.1, MD 44.3, 95% CI 14.79 to 73.81; P = 0.005). There were no important between-group differences for the remaining six domains of the SF-36 in this study. Morris 2016 reported results for the physical function summary score and the mental health summary score of the SF-36 at hospital discharge and at follow-up visits. There were no clinically meaningful differences between groups at any time point except at six months, where the intervention group had significantly higher scores. However, no mention was made of adjusting for repeated testing on this measure. The MD in physical function score at six months was 12.2 units, a clinically important difference.

As there was no blinding of participants and personnel, heterogeneity in the interventions small numbers of participants and inadequate descriptions of the interventions delivered as standard care, there was low-quality evidence for this outcome.

See Table 6 for further information for health-related quality of life outcomes at 6 months.

4. Delirium

Two studies involving 404 participants (Morris 2016; Schweickert 2009), reported this outcome in the ICU, and one study reported this outcome for the entire hospital stay (Schweickert 2009). Schweickert 2009 found that those in the intervention group spent a lower number of days with delirium while in ICU; (median of 2 versus 4 days; P = 0.03) and in hospital; (median of 2 versus 4 days;

P = 0.02). However, Morris 2016 found no difference between groups (median of 0 versus 0 days; P = 0.71).
As there was no blinding of participants and personnel, heterogeneity in the interventions, small numbers of participants and inadequate descriptions of the interventions delivered as standard care, there was low-quality evidence for this outcome.
See Table 7 for further information about delirium.

5. Death from any cause

Two studies involving a total of 260 participants measured the percentage of participants who died in the ICU, but the numbers were too small to be confident in this result (Kayambu 2015 3/26 (12%) versus 1/24 (4%), RR 2.77, 95% CI 0.31 to 24.85; P = 0.36, and Patman 2001 (0/101 (0%) versus 3/109 (2.8%), RR 0.16, 95% CI 0.008 to 3.03; P = 0.22). One study involving a total of 104 participants measured mortality while participants were in the hospital (Schweickert 2009). There was no clear difference between groups, but again the numbers are too small to be confident of this result (9/49 (18%) versus 14/55 (25%), RR 0.72, 95% CI 0.34 to 1.52; P = 0.53). One study involving 50 participants measured 90-day mortality (Kayambu 2015), and reported that the percentage of those in the intervention group who died within 90 days of admission to this study was 8/26 (31%) versus 2/24 (8%) in the control group (RR 3.69, 95% CI 0.87 to 15.69; P = 0.08). Morris 2016 reported only on the proportion alive and hospital-readmission-free at six months (48.7% versus 44.7%, RR 1.09, 95% CI 0.86 to 1.39; P = 0.69). As there was heterogeneity in the interventions, small numbers of participants and inadequate descriptions of the interventions delivered as standard care, there was low-quality evidence for this outcome.
See Table 2 for further information about this outcome.

6. Hospital costs

No studies measured this outcome.

7. Other outcomes not pre-specified in this review - Duration of intubation/mechanical ventilation

Three studies, including a total of 390 participants, reported duration of mechanical ventilation. Schweickert 2009 found that those in the intervention group spent less time on mechanical ventilation and this difference was of clinically important size (median of 3.4 versus 6.1 days; P = 0.02). Two studies reported that those in the intervention group spent a longer time intubated but there were no clear differences between groups (Kayambu 2015; Patman 2001). Patman 2001 reported results for 210 of 236 (89%) participants; (13 versus 12.7 hours, MD 0.20, 95% CI -1.1 to 1.65; P = 0.85) and Kayambu 2015 on 50 participants; (median of 8 versus 7 days; P = 0.22).
As there was no blinding of participants and personnel, heterogeneity in the interventions, small numbers of participants and inadequate descriptions of the interventions delivered as standard care, there was low-quality evidence for this outcome.
See Table 8 for further information about this outcome.
As this outcome was not listed in the protocol for this review (Doiron 2013), we have indicated this change in the section Differences between protocol and review.

DISCUSSION

Summary of main results

There were mixed results for the effect of early mobilization or active exercise on the primary outcome of physical function or performance. Benefits from the intervention were found for return to independent functional status at hospital discharge in one study, and for greatest walking distance at hospital discharge and time from intubation to functional mobility in the same study (Schweickert 2009). However, no significant effect was found for other measures of this outcome in this study, including the number of independent ADLs achieved at ICU or hospital discharge and the Barthel Index Score at hospital discharge. The other two studies that measured physical performance status did not find any clinically important differences between groups, although confidence intervals were wide, and quality of evidence was low.
All four studies measured adverse events. Three studies reported a low incidence of adverse events in the intervention groups (Morris 2016; Patman 2001; Schweickert 2009), and one study (Kayambu 2015), reported no adverse events. This finding appears to support the safety and feasibility of early mobilization for mechanically ventilated, critically ill patients in the ICU, however the quality of the evidence was low due to small numbers of participants and events, and this result requires confirmation in other studies.
Length of stay in the ICU and in hospital was measured in all studies but no differences between groups were observed. In the three studies that measured muscle strength (Kayambu 2015; Morris 2016; Schweickert 2009), no significant differences were reported except at six months, favouring the intervention group, in one study (Schweickert 2009). Two studies (Kayambu 2015; Morris 2016), measured health-related quality of life and found significant differences favouring the intervention group in two of the 36-item Short Form Health Survey subscales in one study (Kayambu 2015) but not the other. Schweickert 2009 was the only study that measured delirium and reported a significant difference with the intervention group having less time with delirium while in the ICU and hospital. No differences in mortality were found by any of the studies.

Overall completeness and applicability of evidence

There are limitations in the applicability of the existing evidence and its completeness. Admission diagnoses in three of the studies signified critical illness and the majority of the participants were intubated for longer than three days (Kayambu 2015; Morris 2016; Schweickert 2009). While participants in the study by Patman 2001 were considered routine ICU patients after cardiac surgery, they were withdrawn from the study if mechanical ventilation was required for more than 24 hours. This is the only included study in which participants were withdrawn from the study on the basis of a predefined length of mechanical ventilation. This study also used only a small range of interventions and did not measure any functional outcomes (Patman 2001). Hence, the results from this study and its contribution to the body of evidence should be interpreted with these differences in mind (Patman 2001).

The sample size was small in all studies and less than the calculated minimum needed in Kayambu 2015. There were differences in the content of the interventions, the providers, the timing, dosage, tailoring, and exercise progression across all studies. No two studies tested the same intervention. Additional evidence from multicentre RCTs is needed to inform clinical decision-making about the effectiveness of early mobilization and active exercise in the critically ill population. The limited range of and variation in the interventions trialled does not allow us to draw conclusions about the essential components of interventions. There was no agreement between the studies on what is 'early' intervention, and 'late', however the studies all began exercise in the intervention group at a median of one day after admission to ICU. The comparator of 'late' ranged from a median of two days to seven days.

There was also heterogeneity in the types of outcome measures used to evaluate the impact of early mobilization and active exercise across the studies. Three studies measured functional status, however they used different measurement tools and methods (Kayambu 2015; Morris 2016; Schweickert 2009). Schweickert 2009 reported on a number of outcomes of interest to clinicians, but used the functional independence measure (FIM) (Keith 1987), and the Barthel Index (Mahoney 1965), to measure functional status. As no studies have investigated the reliability and validity of the FIM and the Barthel Index in critically ill patients (Adler 2012; Tipping 2012), caution is needed in the interpretation of these results. A scoping review looking at outcome measures in critical illness found eight measures of physical activity limitation used in 25 studies (Turnbull 2016). There is a project registered with the COMET initiative (www.comet-initiative.org), aimed at attaining consensus on a core outcome set for trials of physical rehabilitation after critical illness. As muscle weakness contributes to impaired physical function and the ability to perform ADLs, interventions to achieve significant gains in muscle strength are potentially important (Mehrholz 2015). The review by Turnbull (Turnbull 2016), found that 43% of studies investigating ICU survivorship used the MRC scale to measure muscle strength.

Thus further investigation is required to examine the type, frequency, intensity and dosage of early mobilization required in this population. No studies reported on costs or cost-savings of providing the intervention.

Quality of the evidence

Meta-analyses of data from the four studies in this review were not possible, as different measures of the primary outcome were used in each study. Risk of bias was low for methods used to randomize and allocate participants in three studies and unclear in the fourth. All studies were at high risk of performance bias due to the lack of blinding of participants and personnel. This finding was a contributing factor to the downgrading of the quality of evidence to low for all functional status outcomes in Summary of findings for the main comparison, as they are subjectively measured. While it is understandable that blinding of participants and personnel is challenging in the ICU environment, this introduces the potential for altered participant response to the interventions and adjustment of the intervention by study personnel (Schultz 2002). Risk of detection and attrition bias was low in all studies for mortality but high in two for the subjectively rated outcomes due to lack of blinding of outcome assessors. This introduces the potential for amplification of estimates of treatment effect, and therefore results from studies with detection bias need to be interpreted with caution. Risk of reporting bias was low across all studies. We downgraded the quality of evidence for all outcomes for imprecision, as the results came from only one small study for most outcomes, and there was a very small number of events for the outcome of adverse events. There were too few studies to assess inconsistency of results or publication bias. The reported studies used direct patient-related outcomes of physical function and performance.

Potential biases in the review process

We completed a comprehensive search in multiple stages, two review authors independently screened references and all review authors screened full-text articles before they were chosen for inclusion in the review. Data entry and calculations were checked by two review authors. However, we did not search conference proceedings unless citations were found in the search. We added the outcome of duration of mechanical ventilation to the review as we thought it would be of interest to clinicians working with critically ill adults in the ICU. We are unsure of what level of physiotherapy or exercise intervention the control group received in one study (Patman 2001). We were unable to correspond with the authors of some of the studies in Characteristics of studies awaiting classification (Malicdem 2010; Susa 2004) and Characteristics of ongoing studies (NCT01960868; RBR-6sz5dj).

Agreements and disagreements with other studies or reviews

We found nine systematic reviews examining mobilization of patients in the ICU (Adler 2012; Castro-Avila 2015; Choi 2008; Hermans 2014b; Kayambu 2013; Li 2013; Pinheiro 2012; Stiller 2013; Thomas 2011). Five of these reviews included observational study designs as well as RCTs, and four included other settings, such as high-dependency units, respiratory intensive care units and respiratory care centres.

All reviews included studies that used active exercise. However, in contrast to this Cochrane Review, additional interventions were included; inspiratory muscle training (Adler 2012; Choi 2008; Thomas 2011), breathing exercises (Choi 2008; Li 2013), chest physiotherapy (Li 2013; Stiller 2013), and electrical muscle stimulation (Choi 2008; Pinheiro 2012; Thomas 2011). We examined passive interventions only if delivered in combination with active mobilization or active exercise. Interventions were delivered at a variety of stages (early and late) during participant admission in most of the reviews and one examined participants who received interventions only after being intubated for prolonged periods (Choi 2008). In contrast, we included only studies delivering interventions earlier than those received in standard care. All of the reviews included the primary outcomes specified in this current review (functional status and adverse events).

All reviews supported the use of early mobility for increasing walking distance, and two reviews found improved return to independent functional status (Li 2013; Thomas 2011). Similarly, we found improvements in these outcomes in the only study that measured them (Schweickert 2009). We found no difference between the groups in other measures of functional status, as used by Kayambu 2015 and Morris 2016. All reviews reported a low incidence of adverse events as did this Cochrane Review. In the six reviews that reported length of stay, only one (Choi 2008), found no difference between groups for length of stay. Five reviews reported increased muscle strength (Adler 2012; Choi 2008; Kayambu 2013; Pinheiro 2012; Thomas 2011). These results were found in RCTs in which the interventions were cycle ergometers and electrical muscle stimulation, retrospective studies and a quasi-RCT. In contrast, none of the RCTs that measured muscle strength in this Cochrane Review found a significant difference between groups (Kayambu 2015; Morris 2016; Schweickert 2009). Six reviews reported health-related quality of life and all found improvements in the physical function item of the SF-36 (Adler 2012; Castro-Avila 2015; Kayambu 2013; Li 2013; Pinheiro 2012; Thomas 2011). We also found improvements in the physical function and role physical components of this outcome in two RCTs that measured it (Kayambu 2015; Morris 2016). Two of the reviews reported decreased delirium in the ICU and hospital, which is similar to the result reported in this review (Adler 2012; Thomas 2011). Four reviews, reported no significant differences between groups for mortality at hospital discharge (Hermans 2014b; Kayambu 2013; Li 2013; Pinheiro 2012). We also found no significant differences between groups for ICU, hospital or 90-day mortality. Our review concentrated on the timing of exercise intervention. Some of the other reviews included studies that evaluated different intensities of exercise interventions, or a combination of timing and intensity.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence for the effectiveness of early mobilization of mechanically ventilated, critically ill patients in the intensive care unit (ICU) on measures of physical function and performance is inconsistent and uncertain due to its low quality. The evidence on adverse events is also of low quality. There is wide variation in the type, timing, intensity and progression of the interventions delivered to this population (Jolley 2014), and there is insufficient, high-quality evidence to disentangle these factors currently. We assessed that there is currently low-quality evidence for the effect of early mobilization of critically ill adults in the ICU due to small sample sizes, lack of blinding of participants and personnel, variation in the interventions and outcomes used to measure their effect and inadequate descriptions of the interventions delivered as usual care in the studies included in this Cochrane Review. The four studies awaiting classification, and the three ongoing studies may alter the conclusions of the review once these results are available.

Implications for research

Results from ongoing studies across multiple sites will provide some evidence regarding the impact of this intervention in critically ill patients in the ICU (NCT01927510; NCT01960868; RBR-6sz5dj). However, these three studies are small. We have also identified four studies awaiting classification which may also contribute to the volume of evidence in this area (Dong 2014; Files 2013; Malicdem 2010; Susa 2004). Although the interventions in these studies are not well described at this stage, all contain some of the outcomes specified in this review, and will potentially contribute data from a further 500 participants. We hope to be able to assess and include these studies in an update of this review. In order to be confident of the safety of early intervention, more randomized controlled trials with larger sample sizes, clearly reported interventions and control conditions, and blinded outcome assessment are needed. Standardization of outcome measures between studies would permit meta-analysis of outcomes. It is also important to disentangle early intervention from intensity of intervention in the design of new studies, in order to be able to confidently recommend either early intervention, or more intensive intervention, irrespective of timing.

ACKNOWLEDGEMENTS

We would like to thank Bronagh Blackwood (content editor), Vibeke E Horstmann (statistical editor), Linda Denehy, Sue Berney, Tom J Overend, Andrea Lemos (peer reviewers) and Odie Geiger (consumer referee) for their help and editorial advice during the preparation of this systematic review.

We would like to thank Matthew Zacharias (content editor), Cathal Walsh (statistical editor), Andrea Lemos, Andrezza L Bezzera, Linda Denehy and Sue Berney (peer reviewers) for their help and editorial advice during the preparation of the Cochrane protocol (Doiron 2013).

We would like to thank Karen Hovhannisyan, former Trials Search Co-ordinator, Cochrane Anaesthesia, Critical and Emergency Care (ACE), and Sarah Thorning, previous Trials Search Co-ordinator, Cochrane Acute Respiratory Infections, for their assistance in identifying search terms for this review, and Justin Clark, Information Specialist at the Centre for Research in Evidence-Based Practice for running search updates. We also thank Leanne McGregor and Rebecca Sims (research assistants at Centre for Research in Evidence-Based Practice, Bond University) for their assistance with screening search results and initial data extraction.

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Doiron KA, Hoffmann T, Beller EM. Early intervention (mobilization or active exercise) for critically ill patients in the intensive care unit. *Cochrane Database of Systematic Reviews* 2013, Issue 10. DOI: 10.1002/14651858.CD010754

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Kayambu 2015

Methods	Single-centre, parallel-group RCT **Trial dates:** December 2010-August 2012 **Objective:** to assess the impact of early physical rehabilitation therapy on physical function and self-reported quality of life in patients admitted to the ICU with sepsis syndromes compared to standard care **Randomization:** participants were randomly assigned to either the intervention or control groups using computer-generated randomization **Consent:** study authors obtained consent from each participant's next of kin or substitute decision maker
Participants	**Inclusion criteria:** ≥ 18 years, mechanically ventilated ≥ 48 h, diagnosed with sepsis (≥ 2 criteria of a systemic inflammatory response plus confirmed or strongly suspected infection), severe sepsis (sepsis with organ failure), or septic shock (severe sepsis with hypotension not responding to the provision of fluid) **Exclusion criteria:** head injuries, burns, spinal injuries, multiple fractured lower limbs and patients diagnosed with septic shock who were unresponsive to maximal treatment, moribund or had an expected mortality within 48 h **Participants:** 50 participants were randomized; 26 (M:F 18:8, median age 62.5 years) to the intervention group and 24 (M:F 14:10, median age 65.5 years) to the control group. Baseline characteristics were similar across groups with the exception of DNR status; 9/26 (35%) of those in the intervention group compared to 4/24 (17%) in the control group were given a DNR order. The primary diagnosis on admission to the ICU for both the intervention and standard care groups was septic shock
Interventions	**Intervention group** **What (materials and procedures):** specific equipment used during the interventions was not reported. Interventions included arm or leg ergometry; passive, active and active resisted ROM exercises; sitting up in bed; sitting out of bed; sitting and standing balance exercises; sit to stand, marching on the spot, ambulation with assistance, tilt table therapy and electrical muscle stimulation (vastus medialis, vastus lateralis, tibialis anterior, brachioradialis) **Who provided:** the ICU research physiotherapist; study authors did not report reimbursement of trial personnel, their expertise/usual role, assessment of competence and components of training (if needed) to perform the interventions **Where:** a single, quaternary-level, university-affiliated, general ICU in a hospital in Brisbane, Australia **When and how much:** 30 min 1-2 times daily within 48 h of being diagnosed with sepsis until discharge from the ICU **Tailoring:** study authors stated that interventions were individualised but no further information was reported. Interventions were planned, administered and progressed at the discretion of the physiotherapist and the participant's acuity of illness and level of co-operation based on the Ramsay sedation score To ensure that interventions were delivered safely, data from participant Intellivue bedside monitors MO70 (Phillips) was collected every 10 s and printed out for ten min prior,

	during and postinterventions; the intra-arterial line was put to zero 10 min prior to the intervention and withdrawal criteria were developed to assist decision making regarding cessation or modification of the intervention **Modifications:** not reported **Fidelity (strategies to improve):** not reported **Fidelity (extent):** there no withdrawals during the conduct of the trial and all participants adhered to the intervention for an average of 11.4 days. Study authors reported the frequency and duration of interventions received by the intervention and the control group but this is difficult to interpret **Control group** **What (materials and procedures):** specific equipment used during the interventions was not reported. Interventions included passive, active and active resisted ROM exercises; sitting up in bed; sitting out of bed; sitting and standing balance exercises; sit to stand; marching on the spot and ambulation with assistance **Who provided:** ICU therapists who were not involved in the research team; study authors did not report reimbursement of trial personnel, their expertise/usual role, assessment of competence and components of training (if needed) to perform the interventions **Where:** same location as the intervention group **When and how much:** study authors confirmed via email that participants in the control group received the intervention less regularly and later than those in the intervention group; 10/24 (42%) participants received usual care within 48 h of diagnosis of sepsis after ICU admission while 14/24 (58%) subjects received it 48 h after sepsis was diagnosed in ICU **Tailoring:** not reported **Modification:** not reported **Fidelity (strategies to improve):** not reported **Fidelity (extent):** same as the intervention group
Outcomes	• Physical function (acute care index of function) at ICU discharge • Self-reported health-related quality of life (SF-36 medical short-form) at 6 months post-hospital discharge • Exercise capacity (physical functional ICU test) at ICU discharge • Muscle strength (MRC score) at ICU discharge • Psychological: anxiety (hospital anxiety and depression scale) at ICU discharge • Pro- and anti-inflammatory biomarkers; cytokines (interleukin-6, interleukin-10) and tumour necrosis factor-α on days 1, 3, 5 and 7 of ICU admission and at ICU discharge • Fat-free mass at recruitment, week 1 ICU admission and at ICU discharge • Blood lactate before and 30 min postintervention
Potential conflicts of interest	This study was funded by the Intensive Care Foundation and the principal investigator was supported by a postgraduate award from Singapore (no further details were reported) . Study authors declared that there were no conflicts of interest
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Kayambu 2015 (*Continued*)

Random sequence generation (selection bias)	Low risk	Participants were assigned to either the intervention or control groups using computer-generated randomization
Allocation concealment (selection bias)	Low risk	Sequencing of randomization was generated and serial numbers were assigned by research staff not involved in the study. Reidentifiable serial numbers were concealed from research staff for group allocation and protected by an electronic password
Blinding of participants and personnel (performance bias) All other outcomes	High risk	Study authors stated that participants but not treating therapists were blinded. However, we considered this study to be at high risk of bias as we feel that the interventions could not have been blinded for either participants or personnel
Blinding of outcome assessment (detection bias) Mortality	Low risk	The incidence of mortality would have been evaluated by personnel outside this study
Blinding of outcome assessment (detection bias) All other outcomes	Low risk	Investigators blinded outcome assessors, substitute decision makers and health care staff
Incomplete outcome data (attrition bias) Mortality	Low risk	Mortality is an objective outcome and appeared to be measured on all participants in this study
Incomplete outcome data (attrition bias) All other outcomes	High risk	All other outcomes were reported only for the remaining participants in the intervention and control groups. More participants withdrew from the intervention group than the control group both during admission and after hospital discharge. For example, there was a loss of 15/26 (58%) participants from the intervention group compared to 5/24 (21%) in the control group at 6 months post-hospital discharge
Selective reporting (reporting bias)	Low risk	All outcomes specified in the protocol for this study were reported
Other bias	Unclear risk	This study described the components, frequency and duration of the exercise strategy delivered as standard care but the dosage and intensity was unknown. Therefore we

		considered this study to have an unclear bias associated with the reporting of standard care

Morris 2016

Methods	A single-centre parallel-group RCT conducted in an ICU in Winston-Salem, North Carolina, USA to investigate the impact on hospital length of stay of standardized rehabilitation therapy initiated in the ICU versus usual care
Participants	300 participants. Mean (SD) age: 56 (15) years. Intervention group: 55 (17) years; usual care: 58 (14) years **Inclusion criteria**: age ≥ 18 years, mechanically ventilated via an endotracheal tube or Bipap, PaO_2/FIO ratio < 300 **Exclusion criteria**: inability to walk without assistance prior to acute ICU illness (use of a cane or walker not exclusion), cognitive impairment prior to acute ICU illness (non-verbal), acute stroke, BMI > 50, neuromuscular disease that could impair weaning, hip fracture, unstable cervical spine or pathological fracture, mechanically ventilated > 80 h, current hospitalization or transferring hospital stay > 7 days, moribund, DNR/DNI on admission, involvement in other research study
Interventions	**Intervention group** **What (materials and procedures):** passive ROM included 5 repetitions for each upper and lower extremity joint. Physiotherapy included bed mobility, transfer training, and balance training. The exercises included transfer to the edge of the bed; safe transfers to and from bed, chair, or commode; seated balance activities; pre-gait standing activities (forward and lateral weight shifting, marching in place); and ambulation. Progressive resistance exercise included dorsiflexion, knee flexion and extension, hip flexion, elbow flexion and extension, and shoulder flexion. Resistance was added through the use of elastic resistance bands (TheraBand, Hygienic Corporation). Both the physiotherapy and resistance training targeted lower extremity functional tasks and ADL (further details are available in the supplement of the article) **Who provided:** the rehabilitation team consisted of a physiotherapist, an ICU nurse, and a nursing assistant; study authors did not report their expertise/usual role, assessment of competence and components of training (if needed) to perform the interventions **Where:** a single medical centre in North Carolina, USA **When and how much:** 3 separate sessions every day of hospitalization for 7 days per week, from enrolment through to hospital discharge **Tailoring:** the participant's level of consciousness determined whether they were considered suitable to receive the physiotherapy or progressive resistance exercise, as did their ability to complete the exercises. When participants were unconscious, the 3 sessions consisted of passive ROM. As consciousness was gained, physiotherapy and progressive resistance exercise was commenced. Participants did not need to be free of mechanical ventilation to begin any of the exercise sessions **Modifications:** not reported **Fidelity (strategies to improve):** not reported **Fidelity (extent):** the mean percentage of study days that participants received therapy was 87.1% (SD 18.4%) for passive ROM; 54.6% (SD 27.2%) for physiotherapy; and

	35.7% (SD 23%) for progressive resistive exercise. The median days of delivery of therapy per participant was 8.0 (IQR, 5.0-14.0) for passive ROM, 5.0 (IQR, 3.0-8.0) for physiotherapy, and 3.0 (IQR, 1.0-5.0) for progressive resistance exercise **Control group:** usual care, which could include physical therapy if ordered, between Monday and Friday. The mean percentage of study days that participants received physiotherapy was 11.7% (SD, 14.5%). The median days of delivery of physiotherapy for the usual care group was 1.0 (IQR, 0.0-8.0)
Outcomes	• Length of stay in hospital • Functional capacity (SPPB, muscle strength, FPI, physical functioning scale of SF-36 (SF-36 PFS) • QoL (SF-36 PHS, SF-36 MHS), MMSE • Adverse events (deaths, device removals, reintubations, patient falls during physical therapy)
Potential conflicts of interest	The study was supported by the National Institutes of Health, National Institute of Nursing Research, and the National Heart, Lung & Blood Institute. The study authors reported that the sponsors did not participate in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned, using a computer-generated variably sized approach (in block sizes of 2, 4, 6, or 8), to standardized rehabilitation therapy or usual care
Allocation concealment (selection bias)	Unclear risk	No description of any allocation concealment
Blinding of participants and personnel (performance bias) All other outcomes	High risk	Physiotherapists delivering the intervention and participants receiving the intervention were not blinded
Blinding of outcome assessment (detection bias) Mortality	Low risk	The incidence of mortality would have been evaluated by personnel outside this study
Blinding of outcome assessment (detection bias) All other outcomes	High risk	The research team were not involved in the decision for hospital discharge, however it appears that study personnel measured other outcomes

Morris 2016 (*Continued*)

Incomplete outcome data (attrition bias) Mortality	Low risk	Mortality is an objective outcome and appeared to be measured on all participants in this study
Incomplete outcome data (attrition bias) All other outcomes	High risk	All data available for primary outcome (LOS), however only 55% of patients completed 6-month follow-up
Selective reporting (reporting bias)	Low risk	Study authors reported all outcomes specified in the methods section of the text and in the protocol
Other bias	Low risk	

Patman 2001

Methods	Single-centre, parallel-group RCT **Trial dates:** May 1998-May 1999 **Objective:** to investigate the impact of an active physiotherapy intervention to participants in the intubation period after cardiac surgery compared to usual care **Randomization:** by an independent person who utilized a randomized numbers table (Portney 1993) **Consent:** the requirement for participant consent was waived
Participants	**Inclusion criteria:** all participants admitted consecutively to the ICU following elective or semi-urgent cardiac surgery. No further details were provided **Exclusion criteria:** participants with a history of a condition that could affect their participation in the intervention (e.g. severe asthma, chronic airflow limitation, bronchiectasis or ankylosing spondylitis), and the following findings occurring in the postoperative phase: unstable cardiovascular status (systolic blood pressure < 100 and > 180 mmHg or mean arterial pressure < 60 or > 110 mmHg), arrhythmias compromising cardiovascular function, excessive blood loss (> 100 mL/h) or neurological complications **Participants:** 236 participants were randomized; 108 to the intervention group and 128 to the control group. 7 participants in the intervention group and 19 in the control group were withdrawn as they required mechanical ventilation > 24 h. Outcomes were reported for 101 (M:F 81:20, mean age 62.8 years) in the intervention group and 109 (M:F 77:32, mean age 63.9 years) in the control group. Baseline characteristics across groups were similar with the exception of the percentage of current smokers; 46/101 (46%) of those in the intervention group versus 14/109 (13%) of the control group continued to smoke pre-admission. The most common diagnosis on ICU admission was coronary artery surgery
Interventions	**Intervention group** **What (materials and procedures):** specific equipment used during the interventions was not reported. Physiotherapy interventions included positioning, manual hyperinflation, endotracheal suctioning, thoracic expansion exercises and upper limb exercises **Who provided:** a team of physiotherapists under the direct guidance of the principal investigator; study authors did not report reimbursement of trial personnel, their ex-

	pertise/usual role, assessment of competence and components of training (if needed) to perform the interventions **Where:** surgical intensive care unit (ICU) in a major tertiary hospital in Perth, Australia **When and how much:** interventions were delivered during the intubated phase of the postoperative period; participants received a mean of 1.84 interventions **Tailoring:** interventions were not specifically standardised or controlled **Modifications:** not reported **Fidelity (strategies to improve):** not reported **Fidelity (extent):** not reported **Control group** **What (materials and procedures):** nursed in the supine and then semi-erect position; endotracheal suctioning as required **Who provided:** nursing staff **Where:** same as intervention group **When and how much:** not reported **Tailoring:** not reported **Modifications:** not reported **Fidelity (strategies to improve):** not reported **Fidelity (extent):** not reported
Outcomes	• Length of intubation period from admission to ICU to extubation (h) • Length of ICU stay (h) • Length of postoperative hospital stay (days) • Incidence of postoperative pulmonary complications (number of participants affected)* *no information on the timing of this measurement was reported
Potential conflicts of interest	Study authors did not report if funding had been obtained during this study or if there were any conflicts of interest
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were assigned to either the intervention or control group using a random number table in this study
Allocation concealment (selection bias)	Low risk	Participants were randomized by an independent person and nursing and medical staff were blind to group allocation
Blinding of participants and personnel (performance bias) All other outcomes	High risk	Physiotherapists delivering the intervention and participants receiving the intervention were not blinded

Patman 2001 (*Continued*)

Blinding of outcome assessment (detection bias) Mortality	Low risk	The incidence of mortality would have been evaluated by personnel outside this study
Blinding of outcome assessment (detection bias) All other outcomes	High risk	Measurement of all other outcomes was performed on a daily basis by the principal investigator who was not blinded to group allocation
Incomplete outcome data (attrition bias) Mortality	Low risk	Mortality is an objective outcome and appeared to be measured on all participants in this study
Incomplete outcome data (attrition bias) All other outcomes	High risk	Although study authors reported that participants withdrawn when mechanical ventilation exceeded 24 h would be included in the ITT analysis, outcomes were reported only for the remaining participants in the intervention and control groups
Selective reporting (reporting bias)	Low risk	Study authors reported all outcomes specified in the methods section of the text
Other bias	Low risk	

Schweickert 2009

Methods	Multi-centre, parallel-group, RCT **Trial dates:** June 2005-October 2007 **Objective:** to investigate the efficacy of combining daily interruption of sedation with physical and occupational therapy on functional and neuropsychiatric outcomes in patients receiving mechanical ventilation in intensive care compared to usual care **Randomization:** in a 1:1 ratio using a computer-generated, permuted block randomization scheme to either exercise and mobilization - physical and occupational therapy (intervention group) or to standard care as ordered by the primary care team (the control group) **Consent:** study authors obtained written consent from participants or authorised representatives
Participants	**Inclusion criteria:** adults (≥ 18 years of age), mechanically ventilated for < 72 h and expected to continue for at least 24 h who met criteria for baseline functional independence (defined a priori as a Barthel Index score ≥ 70 obtained from a proxy describing patient function 2 weeks before admission) **Exclusion criteria:** rapidly developing neuromuscular disease, cardiopulmonary arrest, irreversible disorders with 6-month mortality estimated at > 50%, raised intracranial pressure, absent limbs, or enrolment in another trial **Participants:** 104 participants were randomized; 49 (M:F 20:29, aged a median of 57.7 years) to the intervention group and 55 (M:F 32:23, aged a median of 54.4 years) to

	the control group. Baseline characteristics across groups were similar and the primary diagnosis on admission to the ICU was acute lung injury. Many participants developed sepsis - 42/49 (86%) in the intervention group and 45/55 ((82%) in the control group
Interventions	**Intervention group** **What (materials and procedures):** specific equipment was not reported. Interventions included passive, active-assisted and active ROM exercises, bed mobility activities, sitting balance exercises, ADL, exercises to promote increased independence with functional tasks, transfer training, pre-gait exercises, and ambulation **Who provided:** an occupational and a physical therapist; study authors did not report reimbursement of trial personnel, their expertise/usual role and assessment of competence/components of training (if needed) to perform the interventions **Where:** 2 medical ICUs at 2 medical centres in Chicago, IL and Iowa City, IA, USA **When and how much:** each morning within 48-72 h of intubation (a median of 1.5 days after intubation) until return to previous level of function or discharge from the ICU. The median duration of the intervention during mechanical ventilation was 0.32 h per day and after extubation was a median of 0.21 h per day **Tailoring:** interventions were synchronized with daily interruption of sedation or narcotics and progression of interventions depended on patient tolerance and stability. Interventions were discontinued or not initiated in the presence of signs of clinical instability. Participants received daily independent neurological assessments through the use of the Richmond agitation-sedation scale (RASS) for level of arousal and the confusion assessment method (CAM) for the ICU for delirium and coma **Modifications:** not reported **Fidelity (strategies to improve):** not reported **Fidelity (extent):** therapy occurred on 87% of the days on the study for all participants in the intervention group. Reasons for therapy interruption with participants included instability, inability to attend therapy and a change in the care goals to comfort measures only **Control group** **What:** standard care as ordered by the primary care team (study authors confirmed via email that the interventions were based on the findings of a physical and occupational therapy assessment and on each participant's deficits) **Who provided:** physical and occupational therapists **When and how much:** participants usually received the intervention a median of 7.4 days after intubation (study authors confirmed via email that this was typically after extubation or tracheostomy). The median duration of the intervention during mechanical ventilation was 0 h per day and after extubation was a median of 0.19 h per day **Tailoring:** interventions were synchronized with daily interruption of sedation or narcotics and progression of interventions depended on participant tolerance and stability **Modifications:** not reported **Fidelity (strategies to improve):** not reported **Fidelity (extent):** therapy occurred on 95% of the days on the study for 22/55 (40%) of participants in the control group. Reasons for interruption of therapy were the same as those for the intervention group
Outcomes	• Return to independent functional status at hospital discharge (number of participants) • Independent ADLs every 48 h and at ICU and hospital discharge (number of

	participants) (score ≥ 5 on the Functional Independence Measure) • Greatest walking distance every 48 h and at hospital discharge (m) • 4Time from intubation to milestones achieved for out of bed, standing, marching in place, transferring to a chair and walking (days) every 48 h • Barthel Index score at hospital discharge • Adverse events • Length of ICU stay (days) and length of hospital stay (days) • MRC score every 48 h and at hospital discharge • Handgrip strength (kg-force) every 48 h and at ICU and hospital discharge • ICU-acquired paresis when participant was awake and attentive and at hospital discharge (number of participants) - study authors associated a score of ≤ 48/60 on the MRC score with the presence of this condition. • Hospital mortality (percentage) • Hospital delirium in ICU and hospital (days) • Duration of mechanical ventilation (days) • Ventilator-free days • Destination after hospital discharge
Potential conflicts of interest	Study authors reported that no funding was received for this study, and declared that there were no conflicts of interest
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	At both sites, a computer-generated, permuted block randomization scheme was used to allocate participants to each study group
Allocation concealment (selection bias)	Low risk	Each assignment was designated in a consecutively numbered, sealed, opaque envelope by an investigator with no further involvement in the trial
Blinding of participants and personnel (performance bias) All other outcomes	High risk	It was not possible to blind the physical and occupational therapists providing the interventions or the participants in this study
Blinding of outcome assessment (detection bias) Mortality	Low risk	The incidence of mortality would have been evaluated by personnel outside this study
Blinding of outcome assessment (detection bias) All other outcomes	Low risk	All other outcomes were assessed by physical and occupational therapists who were unaware of randomization assignment. Before each assessment, the participants and

		any visitors were instructed (via a structured introductory statement) not to discuss previous interventions. Furthermore, assessments occurred in the afternoon at a time distant from the morning therapy intervention
Incomplete outcome data (attrition bias) Mortality	Low risk	Mortality is an objective outcome and appeared to be measured on all participants in this study
Incomplete outcome data (attrition bias) All other outcomes	Low risk	Data were analysed by an ITT approach for 104 participants (total participants randomized to the intervention and control groups). Participants who died during the study were assigned scores of 0 for ventilator-free days, strength testing (MRC examination and hand grip), ADL total, walk distance, and Barthel Index score
Selective reporting (reporting bias)	Low risk	Study authors reported all outcomes specified in the methods section of the text
Other bias	Unclear risk	Study authors defined the control condition as 'standard care with physical and occupational therapy delivered as ordered by the primary care team and explained that neither site designated a physical therapist to patients mechanically ventilated for < 2 weeks'. As the timing and components of care were not discussed and as elements of the intervention may have been delivered to the control group in this study, we feel there is an unclear risk of bias associated with this description of standard care

ADL: activities of daily living; **APACHE**: Acute Physiology and Chronic Health Evaluation; **BMI**: body mass index; **CAM**: confusion assessment method; **DNI**: do not intubate; **DNR**: do not resuscitate; **ECG**: electrocardiogram **F**: female; **FiO_2**: fraction of inspired oxygen; **FPI**: Functional Performance Inventory; **ICU**: intensive care unit; **IQR**: interquartile range; **LOS**: length of stay; **M**: male; **MMSE**: Mini-Mental State Examiniation; **MO70**: model 70; **MRC**: Medical Research Council; **PHS**: physical health summary; **PaO_2**: partial pressure of oxygen; **QoL**: quality of life; **RASS**: Richmond Agitation-Sedation Scale; **RCT**: randomized controlled trial; **ROM**: range of motion; **SD**: standard deviation; **SF-36**: Short Form 36; **SPPB**: Short Physical Performance Battery

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Brummel 2014	While the control group may have received the intervention later than the intervention group, this was not incorporated into the study design
Burtin 2009	Comparators did not match those in this review
Chen 2012	Usual care consisted of encouragement to exercise, which participants may or may not have done
Chiang 2006	There was no difference in the timing of the intervention between groups
Collings 2015	Comparators did not match those in this review
Denehy 2013	There was no difference in the timing of mobilization between groups
ISRCTN20436833	There was no difference in the timing of the intervention between groups
Morris 2008	Not a RCT
Moss 2016	Trial of intensity, not timing
Médrinal 2013	Comparators did not match those in this review
Nava 1998	There was no difference in the timing of the intervention between groups
NCT01058421	There was no difference in the timing of the intervention between groups
Porta 2005	Comparators did not match those in this review plus there was no difference in the timing of the intervention between groups
Yosef-Brauner 2015	Comparators did not match those in this review

RCT: randomized controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Dong 2014

Methods	Single-centre, parallel-group RCT **Trial dates:** May 2010-May 2012 **Objective:** to assess the feasibility and effects of early rehabilitation therapy in mechanically ventilated patients in the ICU compared to routine care **Randomization:** Participants were randomly assigned in a 1:1 ratio to either the rehabilitation or control group - further details were not reported **Consent:** obtained from participants or their authorized representatives
Participants	**Inclusion criteria:** age > 18 years, mechanically ventilated > 48 h but < 72 h with duration of expected mechanical ventilation ≥ 1 week, clear consciousness, cardiovascular and respiratory stability and absence of an unstable fracture **Exclusion criteria:** inability to independently perform functional activities, requiring long-term mechanical ventilation, rapid development of neuromuscular disease, irreversible disorders with an estimated 6-month mortality of > 50%, increased intracranial pressure, absent limbs, preadmission glucocorticoids applied for at least 20 days, ICU admission after cardiopulmonary resuscitation, tumour radiotherapy and chemotherapy within 6 months of admission and acute myocardial infarction or unstable ischaemia within 3 weeks of admission **Participants:** 60 participants were randomized; 30 (M:F 21:9, mean age of 55.3 years) to the intervention group and 30 (M:F 20:10, mean age 55.5 years) to the control group. Baseline characteristics across groups was similar and the primary diagnosis for both groups on admission to the ICU was acute respiratory distress syndrome
Interventions	**Intervention group** **What (materials and procedures):** specific equipment used during the interventions was not reported. Interventions included transfer from supine to edge of bed, sitting to standing, bed to chair and walking at the bedside **Who provided: 1** physician and 1 nurse; study authors did not report reimbursement of trial personnel, their expertise/usual role, assessment of competence and components of training (if needed) to perform the interventions **Where:** ICU in a hospital in Qingdao, China **When and how much:** twice daily within 48-72 h of tracheal intubation or tracheostomy until return to previous level of function or discharge from the ICU (discharge destination was confirmed via email communication with study authors) **Tailoring:** intervention training time and intensity was adjusted in response to participant status and progression of activities depended on participant tolerance and stability. While the interventions were occurring, each participant's position was changed every 2 h passively or actively. Where possible, sedation was given only at night but if needed during the day was ceased 1-2 h before the intervention was delivered; the intervention was delivered once the participants could follow instructions. Enteral nutrition was stopped during the intervention and participants' oxygen saturation, ECG and blood pressure were monitored if necessary. Interventions were discontinued or not initiated in the presence of signs of clinical instability **Modifications:** not reported **Fidelity (strategies to improve):** not reported **Fidelity (extent):** not reported **Control group** Study authors reported that participants in the control group received routine care and gave no further details
Outcomes	• Days to first out of bed • Duration of mechanical ventilation (days) • Length of ICU stay (days - confirmed via email with study authors) • APACHE II score on ICU admission and discharge • Highest FiO_2* • Lowest PaO_2/FiO_2* • Hospital mortality (percentage) * no information on the timing of these measurements was reported

Dong 2014 (*Continued*)

Notes	

Files 2013

Methods	Single-centre RCT in the USA investigating the impact of rehabilitation on patients with acute respiratory failure in the ICU
Participants	100 participants with acute respiratory failure were randomized to receive early rehabilitation or usual care. Participants were divided into two cohorts of 50 but study authors did not describe the allocation of participants within each group
Interventions	Participants in cohort 1 received early rehabilitation once per day versus usual care and cohort 2 received early rehabilitation twice per day (with the second session including resistance training) versus usual care. Components of the intervention were not reported and usual care did not include early rehabilitation. Details regarding the number of participants receiving the intervention versus usual care in each cohort were not reported
Outcomes	• Days from enrolment to first intervention • Duration of mechanical ventilation (days) • Length of stay in ICU (days) • Length of stay in hospital (days) • Physical function (SPPB), • Strength (grip-strength, dynamometry) • Cytokines (Interleukin-6, Interleukin-8 and tumour necrosis factor-α) • Adverse events • Deaths (site of participants' death is not known)
Notes	Elizabeth Chmelo (one of the authors of this study) was contacted by email to clarify its method and eligibility. However, she declined to provide more information as she hoped the study would be submitted for publication soon

Malicdem 2010

Methods	Single-centre RCT conducted in an ICU in The Philippine Heart Centre, Quezon City, Philippines investigating the outcome of pulmonary rehabilitation on difficult-to-wean patients
Participants	24 participants were randomized; 12 to the intervention group and 12 to the control group
Interventions	**Intervention group**: breathing exercises, cycle ergometry and upper body exercises **Control group**: usual care (further details are not known)
Outcomes	• Time off the ventilator (unit of measure is unknown) • Duration of mechanical ventilation (days) • Length of stay in hospital (unit of measure is unknown) • ADLs • Percentage of participants developing dependence on mechanical ventilation

Malicdem 2010 (*Continued*)

Notes	Searches failed to identify publications associated with this study and therefore we contacted study authors regarding publication of this study. We have not received a reply

Susa 2004

Methods	Single-centre RCT conducted in a hospital in Trecenta, Italy to evaluate the feasibility and effectiveness of a multi-faceted intensive rehabilitation program on participants post-major colorectal surgery. This trial started in December 2000 and finished in December 2002
Participants	40 participants were randomized; 20 (M:F 14/6, mean age 66 years) to the intervention group and 20 (M:F 13:7, mean age 69 years) to the control group
Interventions	**Intervention group**: assistance with mobilization 24 to 48 h after surgery **Control group**: mobilized to a chair after the first 48 h
Outcomes	• Blood pressure • Heart rate • Pain scale at rest and on movement • Ramsay scale • Respiratory rate • Tidal volume • Forced vital capacity • Partial pressure of arterial carbon dioxide throughout the time participants were mechanically ventilated • Time to independent mobilization • Length of stay • Patient satisfaction. The unit of measure is not known for these outcomes.
Notes	We contacted study authors regarding details about the participants and the intervention and we did not receive a response

ADLs: activities of daily living; **APACHE**: Acute Physiology and Chronic Health Evaluation; **F:** female; **FiO_2**: fraction of inspired oxygen; **ICU**: intensive care unit; **M**: male; **PaO_2**: partial pressure of oxygen; **SPPB**: Short Physical Performance Battery

Characteristics of ongoing studies *[ordered by study ID]*

NCT01927510

Trial name or title	Pilot randomized controlled trial of early mobilisation in critically ill patients to improve functional recovery and quality of life
Methods	Multi-centre, parallel-group, pilot RCT conducted across five facilities in Australia and New Zealand to investigate the impact of early mobilization of critically ill patients in the ICU on functional recovery

NCT01927510 (*Continued*)

Participants	Study investigators plan to recruit 50 participants. **Inclusion criteria**: > 18 years old, admitted to the ICU, mechanically ventilated 48 h, written informed consent from next of kin or as per each individual ethics committee if delayed or telephone consent is unacceptable **Exclusion criteria**: instability (cardiovascular or respiratory), acute brain injury, acute spinal cord injury, Guillain-Barré Syndrome, second ICU admission during a single hospital admission, unable to follow simple verbal commands in English, death inevitable and imminent, inability to walk without assistance prior to onset of acute illness necessitating ICU admission, cognitive impairment prior to current acute illness, agitation which precludes safe implementation of intervention, written rest-in-bed orders due to documented injury or process that precludes mobilization, deemed unsafe to commence the intervention by treating clinician, has met all the inclusion criteria with no concomitant exclusion criteria for a period of more than 48 h
Interventions	**Intervention group**: early mobilization **Control group**: standard care
Outcomes	• Daily level of activity in ICU (ICU Mobility Scale 0-10) • Daily duration (min) of active mobilization at extubation • Duration of active mobilization at ICU discharge • Duration of active mobilization at ICU discharge to ward • Proportion of participants achieving the highest level of mobilization each day at extubation (ICU Moblity Scale 0-10) • Physical function at 6 months postrandomization (Instrumental Activities of Daily Living) • Recruitment rates • Staff utilisation costs during the ICU admission • Ventilator- and ICU-free days at day 28 • Health-related QoL (EQ5D) at 6 months post-ICU admission • Return to previous work level at 6 months postrandomization
Starting date	August 2013
Contact information	Carol Hodgson, PhD Monash University
Notes	From ClinicalTrials.gov

NCT01960868

Trial name or title	Early rehabilitation is feasible and safe in ICU in liver transplanted patients
Methods	Single-centre, parallel-group RCT being conducted in an ICU in Marseille, France to investigate the impact of early mobilization on length of stay and to validate the feasibility of this intervention with patients with liver transplantation
Participants	Study investigators plan to recruit 40 participants **Inclusion criteria**: age > 18 years, needing a liver transplant, informed consent provided **Exclusion criteria**: declining to consent, major contraindications to the intervention (paralysis neuromyopathy majeure), haemodynamic instability or severe infection, pregnancy, nursing mothers, persons deprived of their liberty by a judicial or administrative decision or under legal protection, urgent need for liver transplant

NCT01960868 (*Continued*)

Interventions	**Intervention group**: experimental physical therapy 5 days per week from 1 to several times per day **Control group**: standard physical therapy
Outcomes	• Muscle strength (MRC score) at 12 months • Length of stay in the ICU
Starting date	October 2013
Contact information	Loic Mondoloni (loic.mondoloni@ap-hm.fr) Assistance Publique Hopitaux De Maseille
Notes	We contacted the study author but did not receive a response From ClinicalTrials.gov

RBR-6sz5dj

Trial name or title	Use of game therapy to assess functionality and upper limb muscle strength in critical patients
Methods	Single-centre, parallel-group RCT being conducted in an ICU in Curitiba, Brazil to investigate the impact of game therapy on function and upper limb muscle strength in critically ill patients
Participants	Study investigators planned to recruit 15 participants admitted to the ICU with loss of muscle strength in the upper limbs **Inclusion criteria**: admitted to ICU, minimum age ≥ 16 years, Glasgow Coma Scale 15, handgrip dynamometry < normal for their age and sex, able to actively carry out the proposed activity, absence of thrombosis in the upper limbs, fractures, dislocations, muscle strains or ligament requiring the use of immobilizers in upper limbs, unable to mobilize the upper limbs, recent thoracotomy (< 40 days), absence of visual impairment (blindness); not pregnant, absence of upper-limb amputation, absence of diagnosis of neuromuscular disease, trauma, spinal cord tumours or abscesses, hemiplegia/paresis, encephalopathy plexus injury or brain injury **Exclusion criteria**: haemodynamically unstable (MAP < 60 mmHg or > 130 mmHg), refusal to do 1 or 2 daily sessions of the proposed activity, decreased level of consciousness, 30% worsening of dynamometry measure (when measured every 7 days)
Interventions	**Intervention group**: 2 sets of 15 repetitions of active ROM exercises to the upper limbs using Gameterapia Nintendo® Wii game with a Samsung 26-inch (66cm) screen and the game Wii Sports Tennis **Control group**: not reported
Outcomes	Hand grip strength (dynamometer), range of motion (goniometer), motivation (satisfaction survey)
Starting date	May 2011
Contact information	Maira Maturana (mairamaturana@yahoo.com.br) Curitiba, Brazil

RBR-6sz5dj (*Continued*)

Notes	We contacted the study author and did not receive a response From Registro Brasileiro de Ensaios Clinicos via the International Clinical Trials Registry Platform World Health Organization

DNI: do not intubate; **DNR**: do not resuscitate; **EQ5D**: EuroQol 5 domains; **ICU**: intensive care unit; **MAP**: mean arterial pressure; **MRC**: Medical Research Council; **QoL**: quality of life: **RCT**: randomized controlled trial; **ROM**: range of motion

ADDITIONAL TABLES

Table 1. Characteristics of each intervention - summarized using TIDieR criteria*

Item	Morris 2016	Kayambu 2015	Patman 2001	Schweickert 2009
Brief name	Standardized rehabilitation therapy	Early physical rehabilitation in ICU	Physiotherapy	Early physical and occupational therapy in mechanically ventilated, critically ill patients
What (Materials and Procedures)	3 exercise types: • passive ROM: 5 repetitions for each upper and lower extremity joint; • physiotherapy: bed mobility, transfer training, and balance training. These exercises included transfer to the edge of the bed; safe transfers to/from bed, chair, or commode; seated balance activities; pre-gait standing activities (forward and lateral weight shifting, marching in place); and ambulation; • progressive resistance exercise: included dorsiflexion, knee flexion and extension, hip flexion, elbow flexion and extension, and shoulder	Specific equipment not reported. Procedures mentioned include: arm or leg ergometry; passive, active and resisted ROM exercises; bed mobility activities; sitting and standing balance exercises; transfer training; pre-gait exercises; ambulation with assistance; electrical muscle stimulation; and Tilt table	Specific equipment was not reported. Procedures mentioned include: positioning; manual hyperinflation; endotracheal suctioning; thoracic expansion exercises; and upper limb exercises	Specific equipment was not reported. Procedures mentioned included: passive, active-assisted and active ROM exercises; bed mobility activities; sitting balance exercises; ADL exercises to promote increased independence with functional tasks; transfer training; pre-gait exercises; and ambulation

Table 1. Characteristics of each intervention - summarized using TIDieR criteria* (*Continued*)

	extension. Resistance was added through the use of elastic resistance bands (TheraBand, Hygienic Corporation). Both the physiotherapy and resistance training targeted lower extremity functional tasks and ADLs. See trial protocol (supplement to article) for more details			
Who provided	Physiotherapist, ICU nurse, and nursing assistant	ICU research physiotherapist	Team of physiotherapists under the guidance of the principal investigator	An occupational therapist and a physical therapist
Where	One medical ICU, Medical Centre, North Carolina, USA	Quaternary-level general ICU, Australia	Surgical ICU, Perth, Australia	Two medical ICUs: Chicago, USA and Iowa City, USA
When and how much	3 separate sessions every day of hospitalization for 7 days per week, from enrolment through to hospital discharge	30 min 1-2 times/day within 48 h of diagnosis of sepsis until discharge from the ICU	1-2 interventions during the first 24 h of mechanical ventilation	Interventions were synchronized with daily interruption of sedation. Each morning within 48-72 h of intubation until return to previous level of function or discharge from the ICU
Tailoring and progression	The participant's level of consciousness determined whether they were considered suitable to receive the physiotherapy or progressive resistance exercise, as did their ability to complete the exercises. When participants were unconscious, the 3 sessions consisted of passive ROM. As consciousness was gained, physiotherapy and progressive resistance exercise was commenced. Participants did not need to be free of mechanical venti-	Interventions were tailored, planned, administered and progressed at the discretion of the physiotherapist, participant acuity of illness and level of co-operation	Not reported	Progression of interventions depended on participant tolerance and stability

Table 1. Characteristics of each intervention - summarized using TIDieR criteria* (*Continued*)

	lation to begin any of the exercise sessions			
Modification of intervention throughout trial	Not reported	Not reported	Not reported	Not reported
Fidelity (strategies to improve)	Not reported	Not reported	Not reported	Not reported
Fidelity (extent)	The mean percentage of study days that participants received therapy was 87.1% (SD 18.4%) for passive ROM; 54.6% (SD 27.2%) for physiotherapy; and 35.7% (SD 23%) for progressive resistive exercise. The median days of delivery of therapy per participant was 8.0 (IQR, 5.0-14.0) for passive ROM, 5.0 (IQR, 3.0-8.0) for physiotherapy, and 3.0 (IQR, 1.0-5.0) for progressive resistance exercise	All participants adhered and remained enrolled for an average of 11.4 days. No further details.	Not reported	Therapy occurred on 87% of the days on the study for all participants in the intervention group and on 95% of the days on the study for 22/55 (40%) of participants in the control group

*See Hoffmann 2014 for TIDieR criteria

ADLs: activities of daily living; **ICU**: intensive care unit; **ROM**: range of motion

Table 2. Death/Survival

	n (%) in intervention group	n (%) in control group	Risk ratio (95% CI)	P value	Reference of studies
ICU mortality	3/26 (12%)	1/24 (4%)	RR 2.77 (0.31 to 24.85)	0.36	Kayambu 2015
ICU mortality	0/101 (0%)	3/109 (2.8%)	RR 0.16 (0.008 to 3.03)	0.22	Patman 2001
Hospital mortality	9/49 (18%)	14/55 (25%)	RR 0.72 (0.34 to 1.52)	0.53	Schweickert 2009
90-day mortality	8/26 (31%)	2/24 (8%)	RR 3.69 (0.87 to 15.69)	0.08	Kayambu 2015

Table 2. Death/Survival (*Continued*)

6-month hospital-free survival	73/150 (48.7%)	67/150 (44.7%)	RR 1.09 (0.86 to 1.39)	0.69	Morris 2016

CI: confidence interval; **ICU**: intensive care unit; **n**: number; **RR**: risk ratio

Table 3. Functional status measures

Outcome measure	Intervention group	Control group	Effect size (95% CI) where possible	P value	Reference of studies
Return to independent functional status at hospital discharge - n (%) in each group	29/49 (59%)	19/55 (35%)	RR 1.71 (1.11 to 2.64)	0.01	Schweickert 2009
Independent ADL total at ICU discharge - median (IQR)	3 (0-5)	0 (0-5)		0.15	Schweickert 2009
Independent ADL total at hospital discharge - median (IQR)	6 (0-6)	4 (0-6)		0.06	Schweickert 2009
Acute Care Index of Function (ACIF) at ICU discharge - mean (SD)	61.1 (33.1)	55 (24.4)	MD 6.10 (-11.85 to 24.05)	0.45	Kayambu 2015
Physical Function ICU Test (PFIT) at ICU discharge - mean (SD)	5.6 (2.1)	5.4 (1.7)	MD 0.20 (-0.98 to 1.38)	0.61	Kayambu 2015
Short Physical Performance Battery at ICU discharge - mean (SD)	1.6 (3.1)	1.9 (2.8)	MD -0.3 (-1.1 to 0.5)	0.46	Morris 2016
Time from intubation to out of bed (days) - median (IQR)	1.7 (1.1 to 3.0)	6.6 (4.2-8.3)		< 0.0001	Schweickert 2009

Table 3. Functional status measures (*Continued*)

Time from intubation to standing (days) - median (IQR)	3.2 (1.5 to 5.6)	6.0 (4.5-8.9)		< 0.0001	Schweickert 2009
Time from intubation to marching in place (days) - median (IQR)	3.3 (1.6 to 5.8)	6.2 (4.6-9.6)		< 0.0001	Schweickert 2009
Time from intubation to transferring to a chair (days) - median (IQR)	3.1 1.8 to 4.5)	6.2 (4.5-8.4)		< 0.0001	Schweickert 2009
Time from intubation to walking (days) - median (IQR)	3.8 (1.9 to 5.8)	7.3 (4.9-9.6)		< 0.0001	Schweickert 2009
Barthel Index score at hospital discharge (score 0-100) - median (IQR)	75 (7.5 to 95)	55 (0-85)		0.05	Schweickert 2009
Greatest walking distance (metres) at hospital discharge - median (IQR) (metres)	33.4 (0 to 91.4)	0 (0-30.4)		0.004	Schweickert 2009

ADL: activities of daily living; **CI**: confidence interval; **ICU**: intensive care unit; **IQR**: interquartile range; **MD**: mean difference; **n**: number; **RR**: risk ratio; **SD**: standard deviation

Table 4. Length of stay (ICU and hospital)

Outcome measure	Intervention group	Control group	Mean difference (95% CI) where possible	P value	Reference of studies
Mean (SD) LOS (h) in ICU - mean (SD)	42.7 (42.4)	36.7 (26.8)	6.00 (-3.58 to 15.58)	0.56	Patman 2001

Table 4. Length of stay (ICU and hospital) (*Continued*)

Median (IQR) LOS (days) in ICU - median (IQR)	12.0 (4-45)	8.5 (3-36)		0.43	Kayambu 2015
	7.5 (4-14)	8.0 (4-13)		0.68	Morris 2016
	5.9 (4.5-13.2)	7.9 (6.1-12.9)		0.08	Schweickert 2009
Mean (SD) LOS (days) in hospital - mean (SD)	9.2 (4.5)	9.6 (6.7)	-0.40 (-1.97 to 1.17)	0.25	Patman 2001
Median (IQR) LOS (days) in hospital - median (IQR)	41 (9-158)	45 (14-308)		0.80	Kayambu 2015
	10.0 (6-17)	10.0 (7-16)		0.41	Morris 2016
	13.5 (8.0-23.1)	12.9 (8.9-19.8)		0.93	Schweickert 2009

CI: confidence interval; **ICU**: intensive care unit; **IQR**: interquartile range; **LOS**: length of stay; **SD**: standard deviation

Table 5. Muscle strength

	Intervention group	Control group	Effect size (95% CI) where possible	P value	Reference of studies
Muscle strength (MRC score, 0-60) at ICU discharge - mean (SD)	51.9 (10.5)	47.3 (13.6)	MD 4.60 (-3.11 to 12.31)	0.24	Kayambu 2015
Hand-grip strength (kg) at ICU discharge - mean (SD)	20.0	20.9	MD -0.8 (-4.0 to 2.3)	0.60	Morris 2016
Muscle strength (MRC score, 0-60) at hospital discharge - median (IQR)	52 (25-58)	48 (0-58)		0.38	Schweickert 2009
Hand-grip strength (kg) at hospital discharge - median (IQR)	39 (10-58)	35 (0-57)		0.67	Schweickert 2009
Hand-grip strength (kg) at hospital discharge	22.6 (10.4)	24.3 (16.3)	MD -1.7 (-4.6 to 1.2)	0.25	Morris 2016

Table 5. Muscle strength (*Continued*)

- mean (SD)					
ICU-acquired paresis at hospital discharge - n (%)	15/49 (31%)	27/55 (49%)	RR 0.62 (0.38 to 1.03)	0.09	Schweickert 2009

CI: confidence interval; **ICU**: intensive care unit; **IQR**: interquartile range; **MD**: mean difference; **MRC**: medical research council; **SD**: standard deviation

Table 6. Health-related quality of life

Outcome measure at 6 months' follow-up	Mean (SD) of intervention group	Mean (SD) of control group	Mean difference (95% CI)	P value	Reference of studies
SF-36 physical function	81.8 (22.2)	60.0 (29.4)	21.8 (0.81 to 42.79)	0.04	Kayambu 2015
	55.9 (27.3)	43.6 (27.7)	12.2 (3.9 to 20.7)	0.001	Morris 2016
SF-36 role physical	61.4 (43.8)	17.1 (34.4)	44.3 (14.79 to 73.81)	0.005	Kayambu 2015
SF-36 bodily pain	70.9 (20.7)	64.7 (22.5)	6.20 (-10.78 to 23.18)	0.46	Kayambu 2015
SF-36 general health	50.5 (11.9)	41.8 (11.3)	8.70 (-0.24 to 17.64)	0.06	Kayambu 2015
SF-36 vitality	45.9 (12.0)	39.2 (7.7)	6.70 (-0.22 to 13.62)	0.07	Kayambu 2015
SF-36 social functioning	71.6 (37.1)	73.7 (37.2)	-2.10 (-30.94 to 26.74)	0.88	Kayambu 2015
SF-36 role emotional	63.6 (40.7)	33.3 (45.8)	30.30 (-3.88 to 64.48)	0.08	Kayambu 2015
SF-36 mental health	38.6 (11.5)	37.3 (7.4)	1.30 (-5.75 to 8.35)	0.71	Kayambu 2015
	48.8	46.4	2.4 (-1.2 to 6.0)	0.19	Morris 2016

CI: confidence interval; **SD**: standard deviation; **SF-36**: Short Form 36

Table 7. Delirium

	Intervention group	Control group	P value	Reference of studies
ICU (days) with delirium - median (IQR)	2.0 (0.0-6.0)	4.0 (2.0-7.0)	0.03	Schweickert 2009
	0 (0 -12.5)	0 (0-9.1)	0.71	Morris 2016
Hospital (days) with delirium - median (IQR)	2.0 (0.0-6.0)	4.0 (2.0-8.0)	0.02	Schweickert 2009

ICU: intensive care unit; **IQR**: interquartile range

Table 8. Other outcomes not specified in this review

	Intervention group	Control group	Mean difference (95% CI) where possible	P value	Reference of studies
Duration (h) of mechanical ventilation - mean (SD)	13 (4.8)	12.7 (4.7)	0.20 (-1.1 to 1.65)	0.85	Patman 2001
Duration (days) of mechanical ventilation - median (IQR)	8.0 (4-64)	7.0 (2-30)		0.22	Kayambu 2015
	3.4 (2.3-7.3)	6.1 (4.0-9.6)		0.02	Schweickert 2009

Abbreviations: CI: confidence interval. IQR: interquartile range. SD: standard deviation.

APPENDICES

Appendix 1. CENTRAL, Cochrane Library search strategy

([mh "Intensive Care Units"] OR [mh ^"Critical Illness"] OR [mh "Critical Care"] OR (critical* NEAR3 (ill* OR care*)):ti,ab OR "intensive care":ti,ab OR (icu OR icuaw):ti,ab)
AND
([mh "Exercise Therapy"] OR [mh "Physical Therapy Modalities"] OR [mh "Occupational Therapy"] OR (mobilizat* OR mobilisat* OR mobility):ti,ab OR exercis*:ti,ab OR (therap* NEAR3 (physical OR exercise OR occupation*)):ti,ab OR ((bed OR "daily living") NEAR3 activit*):ti,ab OR (training OR pregait OR pre-gait OR walk* OR adl OR physiotherap* OR ambulation):ti,ab OR ((cycle OR bicycle) NEAR1 ergomet*):ti,ab)

Appendix 2. MEDLINE (Ovid SP) search strategy

(exp Intensive Care Units/ OR Critical Illness/ OR exp Critical Care/ OR (critical* adj3 (ill* or care*)).tw. OR intensive care.tw. OR (icu or icuaw).tw.)
AND
(exp Exercise Therapy/ OR exp Physical Therapy Modalities/ OR Occupational Therapy/ OR (mobilizat* or mobilisat* or mobility).tw. OR exercis*.tw. OR (therap* adj3 (physical or exercise or occupation*)).tw. OR ((bed or daily living) adj3 activit*).tw. OR (training or pregait or pre-gait or walk* or adl or physiotherap* or ambulation).tw. OR ((cycle or bicycle) adj1 ergomet*).tw.)
AND
((randomized controlled trial OR controlled clinical trial).pt. OR randomized.ab. OR randomised.ab. OR placebo.ab. OR drug therapy.fs. OR randomly.ab. OR trial.ab. OR groups.ab.) not (exp animals/ not humans.sh.)

Appendix 3. Embase (Ovid SP) search strategy

(icu:ab,ti OR icuaw:ab,ti OR 'intensive care':ab,ti OR ((critical* NEAR/3 (ill* OR care)):ab,ti) OR 'intensive care'/exp OR 'critical illness'/de OR 'intensive care unit'/de)
AND
(training:ab,ti OR pregait:ab,ti OR 'pre-gait':ab,ti OR walk*:ab,ti OR adl:ab,ti OR physiotherapy*:ab,ti OR (((cycle OR bicycle) NEAR/1 ergomet*):ab,ti) OR ambulation:ab,ti OR (((bed OR 'daily living') NEAR/3 activity):ab,ti) OR ((therap* NEAR/3 (physical* OR exercise OR occupation*)):ab,ti) OR exercis*:ab,ti OR mobiliz*:ab,ti OR mobilis*:ab,ti OR mobility:ab,ti OR 'occupational therapy'/de OR 'physiotherapy'/exp OR 'kinesiotherapy'/exp)
AND
((random*:ab,ti OR placebo*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR allocat*:ab,ti OR trial:ti OR ((doubl* NEXT/1 blind*):ab,ti) OR 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp) NOT (('animal'/exp OR 'animal'/de OR 'nonhuman'/exp OR 'nonhuman'/de OR 'animal experiment'/exp OR 'animal experiment'/de) NOT (('animal'/exp OR 'animal'/de OR 'nonhuman'/exp OR 'nonhuman'/de OR 'animal experiment'/exp OR 'animal experiment'/de) AND 'human'/de)))

Appendix 4. CINAHL (EBSCOhost) search strategy

TI ((cycle or bicycle) N1 ergomet*) OR AB ((cycle or bicycle) N1 ergomet*) OR TI (training or pregait or pre-gait or walk* or adl or physiotherap* or ambulation) OR AB (training or pregait or pre-gait or walk* or adl or physiotherap* or ambulation) TI ((bed or daily living) N3 activit*) OR AB ((bed or daily living) N3 activit*) TI (therap* N3 (physical or exercise or occupation*)) OR AB (therap* N3 (physical or exercise or occupation*)) TI exercis* OR AB exercis* TI (mobilizat* or mobilisat* or mobility) OR AB (mobilizat* or mobilisat* or mobility) (MH "Occupational Therapy+") (MH "Physical Therapy+") (MH "Therapeutic Exercise+")
AND
TI (icu or icuaw) OR AB (icu or icuaw) OR TI intensive care OR AB intensive care OR TI (critical* N3 (ill* or care*)) OR AB (critical* N3 (ill* or care*)) OR (MH "Critical Care") OR (MH "Critical Illness") OR (MH "Intensive Care Units+")
AND
(MH "Quantitative Studies") OR TI placebo* OR AB placebo* OR (MH "Placebos") OR (MH "Random Assignment") OR TI random* OR AB random* OR TI ((singl* or doubl* or tripl* or trebl*) W1 (blind* or mask*)) OR AB ((singl* or doubl* or tripl* or trebl*) W1 (blind* or mask*)) OR TI clinic* trial* OR AB clinic* trial* OR PT clinical trial OR (MH "Clinical Trials+")

Appendix 5. Controlled Trials Registry search strategy

intensive care unit AND critically ill AND mobilisation
intensive care unit AND critically ill AND mobilization
intensive care unit AND critically ill AND exercise
intensive care unit AND critically ill AND physiotherapy
intensive care unit AND critically ill AND physical therapy
intensive care unit AND mechanical ventilation AND mobilisation
intensive care unit AND mechanical ventilation AND mobilization
intensive care unit AND mechanical ventilation AND exercise
intensive care unit AND mechanical ventilation AND physiotherapy
intensive care unit AND mechanical ventilation AND physical therapy
ICU AND critically ill AND mobilisation
ICU AND critically ill AND mobilization
ICU AND critically ill AND exercise
ICU AND critically ill AND physiotherapy
ICU AND critically ill AND physical therapy
ICU AND mechanical ventilation AND mobilisationICU AND mechanical ventilation AND mobilization
ICU AND mechanical ventilation AND exercise
ICU AND mechanical ventilation AND physiotherapy
ICU AND mechanical ventilation AND physical therapy

Appendix 6. ClinicalTrials.gov Registry search strategy

critically ill AND mobilisation
critically ill AND mobilization
critically ill AND exercise
critically ill AND physiotherapy
critically ill AND physical therapy
mechanical ventilation AND mobilisation
mechanical ventilation AND mobilization
mechanical ventilation AND exercise
mechanical ventilation AND physiotherapy
mechanical ventilation AND physical therapy
intensive care unit AND mobilisation
intensive care unit AND mobilization
intensive care unit AND exercise
intensive care unit AND physiotherapy
intensive care unit AND physical therapy
ICU AND mobilisation
ICU AND mobilization
ICU AND exercise
ICU AND physiotherapy
ICU AND physical therapy

Appendix 7. WHO International Clinical Trials Registry Platform search strategy

critically ill AND mobilisation
critically ill AND mobilization
critically ill AND exercise
critically ill AND physiotherapy
critically ill AND physical therapy
mechanical ventilation AND mobilisation
mechanical ventilation AND mobilization
mechanical ventilation AND exercise
mechanical ventilation AND physiotherapy
mechanical ventilation AND physical therapy
intensive care unit AND mobilisation
intensive care unit AND mobilization
intensive care unit AND exercise
intensive care unit AND physiotherapy
intensive care unit AND physical therapy
ICU AND mobilisation
ICU AND mobilization
ICU AND exercise
ICU AND physiotherapy
ICU AND physical therapy

Appendix 8. Original search strategy from protocol MEDLINE (Ovid SP)

1. exp Respiration, Artificial/ or (mechanical* adj3 ventila*).af.
2. exp Exercise Therapy/ or exp Physical Therapy Modalities/ or exp Occupational Therapy/ or mobilizat*.mp. or mobilisat*.mp. or mobility.mp or exercis*.mp. or (therap* adj3 (physical or exercise or occupational)).mp. or ((bed or daily living) adj3 activit*).mp. or training.mp. or pre?gait.mp. or walk*.mp. or ADL*.ti,ab. or physiotherap*.mp.
3. exp Intensive Care Units/ or ICU.mp. or exp Critical Illness/ or exp Critical Care/ or (critical* adj3 (ill* or care)).mp. or intensive care.mp. or ICUAW.mp.
4. 1 and 2 and 3

WHAT'S NEW

Date	Event	Description
20 December 2018	Amended	Editorial team changed to Cochrane Emergency and Critical Care

CONTRIBUTIONS OF AUTHORS

Conceiving the review: Katherine A Doiron (KAD), Tammy C Hoffmann (TCH)

Co-ordinating the review: KAD

Undertaking manual searches: KAD

Screening search results: KAD, research assistant

Organizing retrieval of papers: KAD

Screening retrieved papers against inclusion criteria: KAD, research assistant

Appraising quality of papers: KAD, Elaine M Beller (EMB), TCH

Abstracting data from papers: KAD, EMB, research assistant

Writing to authors of papers for additional information: KAD

Providing additional data about papers: KAD

Obtaining and screening data on unpublished studies: KAD

Providing data management for the review: KAD, EMB

Entering data into Review Manager 5 (RevMan 5) (RevMan 2014): KAD

Entering RevMan 5 statistical data: EMB, KAD

Performing other statistical analysis not using RevMan 5: not applicable

Interpreting data: KAD, EMB

Making statistical inferences: KAD, EMB

Writing the review: KAD, TCH, EMB

Securing funding for the review: no funding received

Performing previous work that was the foundation of the present study: none

Serving as guarantor for the review (one review author): KAD

Taking responsibility for reading and checking the review before submission: EMB

DECLARATIONS OF INTEREST

Katherine A Doiron: none known

Tammy C Hoffmann: none known

Elaine M Beller: work on this review was supported by an Australia Fellowship Grant from the National Health and Medical Research Council (NHMRC), Australia, to the Centre for Evidence-Based Practice, Bond University.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied, Other.

External sources

- National Health and Medical Research Council (NHMRC), Australia.

Elaine M Beller's work on this review was supported by an Australia Fellowship Grant from the NHMRC, Australia, to the Centre for Evidence-Based Practice, Bond University.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes to the published protocol (Doiron 2013).

- We changed the title from 'Early intervention (mobilization or active exercise) for critically ill patients in the intensive care unit' to 'Early intervention (mobilization or active exercise) for critically ill adults in the intensive care unit' because we only assessed studies investigating the adult population in this clinical setting.

- We changed 'participants' to 'adults' in the objective section in the Abstract and the Objectives section in the review.

- We expanded the initial search strategy because the first search (Appendix 8), did not return an expected study.

- We removed the Acute Physiology and Chronic Health Evaluation (APACHE) score and SOFA score from the examples listed for the outcome Health-related quality of life or well-being (see Types of outcome measures and Data extraction and management), because they do not measure quality of life.

- We clarified the definition of our primary outcome.

- We removed length of stay in the ICU and hospital from the 'Summary of findings' table as they are not primary outcomes in this review (see Summary of findings for the main comparison).

- We added the outcome 'duration of mechanical ventilation' to Table 8 (Other outcomes not specified in this review) because most included studies reported this outcome and we felt this to be of interest to clinicians.

- We intended to conduct intention-to-treat (ITT) analysis and impute missing standard deviations but this was not required.

- If we had done a meta-analysis, we planned to use the I^2 statistic (Higgins 2003) to measure heterogeneity in the participants, interventions and outcomes. As there were insufficient studies to do a meta-analysis, we reported possible sources of heterogeneity descriptively.

- We planned to investigate possible sources of heterogeneity such as age group, cause of ICU stay, length of mechanical ventilation, comorbidities such as diabetes and use of corticosteroids using subgroup analyses. However, as there were insufficient studies identified, we reported these factors descriptively.

INDEX TERMS

Medical Subject Headings (MeSH)

*Early Ambulation [adverse effects]; *Exercise; *Intensive Care Units; Activities of Daily Living; Critical Illness [*rehabilitation]; Muscle Strength; Quality of Life; Randomized Controlled Trials as Topic; Respiration, Artificial

MeSH check words

Adult; Humans