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Research – meta-analysis

Does enhanced physical rehabilitation following intensive care unit discharge improve outcomes in patients who received mechanical ventilation? A systematic review and meta-analysis

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Abbreviations

ADL, activities of daily living; APACHE, Acute Physiology And Chronic Health Evaluation; CI, confidence interval; EMBASE, Excerpta Medica Database; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; ICU, intensive care unit; MCS, mental component summary; PCS, physical component summary; PEDro, Physiotherapy Evidence Database; PICS, post-intensive care syndrome; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; QOL, quality of life; RCT, randomised controlled trial; RR, risk ratio; WHO ICTRP, World Health Organization International Clinical Trials Registry Platform

Abstract

Objective: We aimed to determine whether enhanced physical rehabilitation following intensive care unit (ICU) discharge improves clinically relevant outcomes such as activity-of-daily-living (ADL), quality of life (QOL), and mortality among patients who received mechanical ventilation.

Design: Systematic review and meta-analysis.

Data sources: Randomised controlled trials published in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Excerpta Medica Database (EMBASE), Physiotherapy Evidence Database (PEDro), and World Health Organization International Clinical Trials Registry Platform between inception and December 2017.

Outcomes: Primary outcomes included ADL, QOL, and mortality. Secondary outcomes included functional exercise capacity, pain, return-to-work rate, muscle strength, duration of delirium, and incidence of adverse events. The quality of evidence was determined using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Results: Ten trials (enrolling 1110 patients) compared physical rehabilitation to usual care or no intervention after ICU discharge (four studies) or hospital discharge (six studies). Regarding QOL, the mean difference [95% confidence interval] between the

intervention and control groups regarding physical and mental component summary scores of Short Form 36 was -0.45 [-2.46 to 1.55] and -0.73 [-3.18 to 1.73], respectively (certainty of evidence: moderate). Rehabilitation did not significantly decrease long-term mortality (relative risk: 1.05 [0.66–1.66]; $I^2 = 0\%$; 907 patients; certainty of evidence, moderate). Adverse events were evaluated in three trials (153 patients), with 18 and 5 events reported for the intervention and control groups, respectively (certainty of evidence: low). The analysed trials did not report short- or long-term data on ADL function, functional exercise capacity, pain, return-to-work rate, muscle strength, or delirium.

Conclusions: Enhanced physical rehabilitation following ICU discharge did not improve QOL or mortality among patients who received mechanical ventilation. Implementing an intensive physical rehabilitation program for all ICU survivors requiring mechanical ventilation is unnecessary.

Trial registration: PROSPERO, CRD42017080532 (registered: 28 December 2017).

Keywords: rehabilitation, critical illness, post-intensive care syndrome, exercise, quality of life, mortality

Article Summary

Strengths and limitations of this study

- This is the first meta-analysis focused on enhanced physical rehabilitation to review randomised controlled trials in which the study intervention was conducted only after intensive care unit discharge.
- The findings are based on moderate certainty of evidence.
- The main limitations of this meta-analysis include the fact that (i) none of the included studies had a follow-up >6 months and that (ii) medical resources and costs associated with each intervention were not considered.
- We employed rigorous methodology that followed a written, a priori protocol developed according to the PRISMA statement, and used the Grading of Recommendations Assessment, Development and Evaluation approach in the review process.

Introduction

In critically ill patients, rehabilitation mainly aims to enhance quality of life (QOL) by improving activities of daily living (ADL) function,[1, 2] which may be severely impaired also due to post-intensive care syndrome (PICS).[3-5] According to the guidelines issued by the National Institute for Health and Care Excellence, provision of rehabilitation should be seamlessly integrated with the patient's transition from the intensive care unit (ICU) to the ward and then to out-of-hospital care.[6] However, at the time the guideline was issued, there was little evidence from clinical trials to support the use of enhanced physical rehabilitation following ICU discharge. Some experts do recommend physical rehabilitation following ICU discharge to improve ADL function and QOL.[7] Regarding sepsis survivors, the findings of a large observational study suggested that physical rehabilitation following ICU discharge improves long-term mortality.[8, 9]

A recent meta-analysis by Connolly et al.[10] focused on randomised controlled trials (RCTs) regarding the effectiveness of enhanced exercise rehabilitation following ICU discharge in adult ICU survivors who had been mechanically ventilated for longer than 24 hours. Despite the comprehensive search, only six RCTs with conflicting results were included, and no clear effect of the intervention on clinically

relevant outcomes such as QOL, mortality, functional exercise capacity, or incidence of adverse events could be established at the time. Additionally, some clinically relevant outcomes such as ADL, pain, return-to-work rate, muscle strength, and duration of delirium were not considered in their review.[10] Several RCTs assessing the effect of enhanced physical rehabilitation following ICU discharge on clinically relevant outcomes[11-15] have been published since Connolly and colleagues conducted their Cochrane review.[10] Therefore, in the present study, we aimed to re-evaluate the available literature and determine whether enhanced physical rehabilitation following ICU discharge improves clinically relevant outcomes among critically ill adults who received mechanical ventilation.

Materials and methods

Compliance with reporting guidelines

Using a pre-specified protocol (PROSPERO registry ID: CRD42017080532),[16] we conducted a systematic review of the relevant literature in agreement with the recommendations listed in the Cochrane Handbook[17] and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[18] We confirmed that this systematic review is PRISMA-compliant by

consulting the PRISMA 2009 checklist[19] (details provided in online supplementary file 1).

Research question and eligibility criteria

The research question was: "Does enhanced physical rehabilitation following ICU discharge result in improved clinically relevant outcomes such as QOL, ADL, and mortality (compared to those achievable with usual care) among patients who received mechanical ventilation?" We included all published and unpublished prospective RCTs involving adult human subjects (age ≥ 18 years) who had been discharged from an ICU or critical care environment after a stay of at least 48 hours during which mechanical ventilation was provided for at least 24 hours. Crossover trials, as well as cluster-, quasi-, and non-randomised trials were excluded. Studies were included regardless of the intervention setting (in-hospital or out-of-hospital), follow-up duration, and country of origin. We included patients of any sex and race, but excluded those receiving palliative care and those with head injury, spinal cord injury, or unstable fracture diminishing mobility.

Intervention was defined as any protocolized rehabilitation following ICU discharge, designed to either commence earlier and/or be more intensive than the care received by the control group. To determine whether enhanced physical rehabilitation

following ICU discharge improved clinically relevant outcomes, we excluded studies in which earlier and/or more intensive ICU physical rehabilitation (compared to the care received by the control group) was provided to patients in the intervention group. Any combination of one or more of the following activities was considered as a form of enhanced physical rehabilitation: neuromuscular stimulation, inspiratory or respiratory muscle training, passive range-of-motion exercise, cycle ergometer exercise, active-assisted exercises, active range-of-motion exercises, bed mobility activities (e.g., bridging, rolling, lying-to-sitting exercise), ADL training, transfer training, pre-gait exercises (including marching in place), and walking exercise.

Outcomes of interest

The primary outcomes were QOL, ADL function, and mortality. Secondary outcomes included functional exercise capacity, pain, return-to-work rate, muscle strength, duration of delirium, and incidence of adverse events (defined by the trialists).

Search strategy and selection of studies

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE via PubMed, Excerpta Medica Database (EMBASE) via Elsevier, the Physiotherapy Evidence Database (PEDro), and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) via their dedicated search

portal. The search was performed in December 2017 using a set of suitable search terms (details provided in online supplementary file 2). We hand-searched reference lists for the guideline for rehabilitation after critical illness.[6] We attempted to identify other relevant research by hand-searching the reference lists of the studies returned by the search and those of articles citing such studies (based on citation information from the Web of Science). If the database entry for a candidate study did not contain the necessary information, we contacted the study authors. Two reviewers (ST and KY) independently screened the title and abstract of each study returned by the search to determine whether the inclusion criteria were met. The two reviewers performed a full-text review to assess the eligibility of each candidate study. Disagreement was resolved by discussion between the two reviewers, occasionally with arbitration by a third reviewer (YK).

Data abstraction and quality assessment

Two reviewers (ST and KY) independently abstracted trial-level data using pre-specified forms. Disagreements regarding data extraction were resolved through discussions. Where necessary, we contacted the authors of studies that did not provide sufficient information. The risk of bias in each study was assessed independently by two reviewers (ST and KY) using the Cochrane risk-of-bias assessment tool.[17]

Differences in opinion regarding the assessment of risk of bias were resolved through discussion between the two reviewers, occasionally with arbitration by a third reviewer (KY).

Data analysis

All analyses were conducted using the Cochrane Review Manager software (RevMan 5.3; Cochrane Collaboration, Copenhagen, Denmark). For the dichotomous variables of mortality and return-to-work rate, pooled risk ratios (RRs) with 95% confidence intervals (CIs) are provided. For continuous outcomes including QOL scores, ADL function scores, pain, muscle strength, and duration of delirium (expressed in days of ICU or hospital stay), the standardized mean differences, or the mean differences with 95% CIs were calculated, as recommended by the Cochrane Handbook.[17] Adverse events were narratively summarized because their definition likely varied across studies. We used the random-effects models for all analyses.

We calculated I^2 as a measure of variation across studies that is due to heterogeneity rather than chance, and interpreted the values as follows: 0%–40%, negligible heterogeneity; 30%–60%, mild-to-moderate heterogeneity; 50%–90%, moderate-to-substantial heterogeneity; 75%–100%, considerable heterogeneity. If heterogeneity was identified for an outcome ($I^2 > 50\%$), we investigated the underlying

reasons and conducted the χ^2 test, with a *P*-value of <0.10 being considered to indicate statistical significance. We investigated reporting bias by checking the WHO ICTRP to detect trials that had been completed but not published at the time of the review.

We planned the following pre-specified sensitivity analyses for the primary outcomes: (i) exclusion of studies using imputed statistics, and (ii) exclusion of studies with high or unclear risk of bias. We also carried out pre-specified subgroup analyses according to the type of rehabilitation involved (neuromuscular stimulation versus other types of rehabilitation), rehabilitation provision in the ICU (received versus did not receive protocolized physical rehabilitation in the ICU), timing of commencement of the intervention (in-hospital or after hospital discharge), intervention duration (≤8 versus >8 weeks), treatment frequency (<5 versus ≥5 times/week), and type of control (no intervention versus usual rehabilitation). Statistical significance was set at $P < 0.05$. We created a summary-of-findings table that included an overall grading of the certainty of evidence for each of the main outcomes, which was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[20, 21]

Patient and public involvement

The patients or public were not involved in this meta-analysis.

Results

Characteristics of trials on rehabilitation in ICU survivors

Among the 3589 hits retrieved following database and manual searches, we identified 10 unique RCTs[11–13, 15, 22–27] that fulfilled all eligibility criteria and were included in the qualitative synthesis (Fig. 1; details provided in online supplementary file 3). The 10 RCTs provided a pooled sample of 1110 critically ill patients with an ICU stay of >48 hours during which mechanical ventilation was provided for at least 24 hours. Eight studies were performed in the United Kingdom, one in Australia, and one in India. The mean or median age in the analysed studies ranged from 40.5 to 68.5 years, while the mean or median Acute Physiology And Chronic Health Evaluation (APACHE) II score ranged from 15.2 to 31. Only one study included participants with PICS symptoms or ICU-acquired weakness.[11] Three RCTs[25–27] did not have sufficient outcome data for meta-analysis (details provided in online supplementary file 4), leaving a total pooled sample of 1000 patients (506 patients in the intervention groups; 494 controls) represented across 7 studies to be included in the quantitative synthesis. Of the 10 trials analysed, 6 evaluated the effect of physical rehabilitation including self-directed exercise and/or supervised exercise

following hospital discharge, while 4[12, 22–24] focused on rehabilitation started during hospitalization. The duration of intervention ranged from 6 weeks to 3 months, while the frequency of intervention ranged from 3 times per week to once daily. No study considered intensive intervention (>30 minutes of active rehabilitation daily) or intervention with neuromuscular stimulation.

Most studies were at high or unclear risk of bias (details provided in online supplementary file 5). All 10 studies demonstrated adequate random sequence generation and allocation concealment, but participants and personnel were not blinded to the intervention. One study[11] demonstrated a high risk of detection bias for all outcomes except mortality, and another study[27] did not report whether or not the outcome assessor was aware of group allocation. Four studies had high risk of selective reporting bias, and two studies had unclear risk of bias because the protocols were not published. High or unclear risk of other bias was noted for all studies because of insufficient information regarding the intervention and control protocols.

Primary outcomes

QOL was measured in 8 trials (see online supplementary file 3), but the short- and long-term physical component summary (PCS) scores and mental component summary (MCS) scores in Short Form 36 were only available in 3 trials,[22–24]

whereas the other five trials measured these outcomes at a different time or did not report PCS or MCS scores. ADL function was measured in 1 trial,[11] but the short- and long-term data were not available. Short-term mortality was reported in 2 trials,[11, 13] while long-term mortality was reported in 5 trials.[12, 15, 22–24]

The mean differences between intervention and control regarding PCS and MCS scores characterizing QOL were -0.45 (95% CI, -2.46 to 1.55) and -0.73 (95% CI, -3.18 to 1.73), respectively (Fig. 2A and 2B, respectively). Rehabilitation did not significantly decrease short-term mortality (RR, 0.71; 95% CI, 0.05–9.80, I^2 = 33%; n = 93) (Fig. 2C) or long-term mortality (RR, 1.05; 95% CI, 0.66–1.66, I^2 = 0%; n = 907) (Fig. 2D). The certainty of evidence for QOL and long-term mortality was moderate, while that for short-term mortality was low (Table 1).

We could not carry out all pre-specified sensitivity analyses because there was no study using imputed statistics, and we judged that the risk of bias of all included studies was similar in terms of random sequence generation, allocation concealment, incomplete outcome data, and other bias. The pre-specified subgroup analyses for the primary outcomes revealed no significant differences among sub-groups (see details provided in online supplementary file 6).

Secondary outcomes

Functional exercise capacity was measured in 2 trials,[11, 24] pain was measured in 1 trial,[12] and muscle strength was measured in 1 trial,[11] but short- and long-term data were not available. No trials evaluated return-to-work rate or incidence of delirium.

Adverse events were measured in 3 trials.[11, 13, 15] Two studies[11, 13] reported no adverse events. One study[15] reported 18 events in the intervention group and 5 events in the control group. Among the 18 adverse events reported in the intervention group, 12 were mild or moderate (musculoskeletal pain higher than expected or muscle soreness potentially indicating injury, 3 cases; any pain higher than expected, 1 case; cardiac symptoms or chest pain, 1 case; any other event considered by the researcher to be of concern, 7 cases; 6 of 12 events were considered to be related or possibly related to study participation), while 6 were serious (hospitalization or prolonged hospitalization, with 1 event related/possibly related to study participation). In the control group, there was 1 adverse event (musculoskeletal pain higher than expected, muscle soreness potentially indicating injury, related/possibly related to study participation) and 4 serious adverse events (hospitalization or prolonged hospitalization, with 1 event related/possibly related to study participation). The certainty of evidence for adverse events was low (Table 1).

Discussion

The results of this up-to-date review covering 10 RCTs and 1110 patients suggest that enhanced rehabilitation following ICU discharge could not improve QOL or reduce short- or long-term mortality among patients who received mechanical ventilation. We could not confirm the effect of enhanced physical rehabilitation even though all included studies exhibited performance bias potentially increasing the observed effect of the intervention. Furthermore, despite the large sample size in the meta-analysis for QOL and long-term mortality, limited data for these outcomes were available, and the certainty of evidence was only moderate.

Furthermore, subgroup meta-analyses revealed no differences among subgroups defined according to the nature or timing of the intervention. The previous review by Connolly et al.[10] did not conduct meta-analysis due to the limited number of included studies. A recent systematic review of ICU rehabilitation[28, 29] also reported no significant difference in QOL between the intervention and control groups. Thus, neither enhanced rehabilitation in the ICU nor rehabilitation following ICU discharge is likely to be superior to usual care in terms of QOL outcomes. In addition, we found no benefit in terms of short- or long-term mortality regardless of timing of

commencement, which is consistent with previous findings that ICU rehabilitation did not decrease mortality at ICU discharge, at hospital discharge, or at 6 months after discharge.[28, 30] On the other hand, rehabilitation may be detrimental in acute conditions. Specifically, intensive physical rehabilitation started within 48 hours of admission for exacerbations of chronic respiratory disease increased mortality at 12 months,[31] whereas higher-dose, physical rehabilitation very early after stroke decreased the odds of a favourable outcomes at 3 months.[32] Thus, implementation of an intensive rehabilitation program may not be indicated for all ICU survivors requiring mechanical ventilation. Though physical rehabilitation is relatively safe, it is labour intensive.[33] Our present findings do not support the allocation of additional resources to ensure intensive rehabilitation following ICU discharge, and rather indicate that physical rehabilitation staff resources might be better allocated to the management of non-severe patients such as those undergoing elective surgery and not requiring ICU admission.[34–36]

Subgroup analysis in a previous systematic review[28] indicated that, compared with low-dose rehabilitation, high-dose active rehabilitation for >30 minutes daily was associated with significantly higher QOL. Dose-response analysis of early physical rehabilitation[35] in stroke patients enrolled in A Very Early Rehabilitation

Trial (AVERT)[32] determined that intervention in such acute cases improved the odds of a favourable outcome with each episode of activity per day. Our present review did not include studies comparing high-dose rehabilitation and usual care, and thus the QOL effect of high-dose rehabilitation remains unclear. Additionally, we could not perform subgroup analysis for PICS symptoms with effect on QOL[3–5] or for sepsis, which is a risk factor for PICS.[37, 38] It remains unclear which population of critically ill patients may truly benefit from intensive physical rehabilitation.

The studies included in our review did not cover all important outcomes included in the core outcome set of rehabilitation after critical illness,[7] including ADL function, functional exercise capacity, pain, return-to-work rate, muscle strength, or delirium incidence. Nonetheless, our findings regarding QOL and mortality suggest that, even if future studies report improvement in these other aspects, the amount of improvement would likely be too small to affect QOL.

The present review has several strengths. First, we employed rigorous methodology that followed a written, a priori protocol developed according to the PRISMA statement, including a comprehensive search for evidence. Second, we performed duplicate assessment of eligibility, risk of bias, and data abstraction. Third, we used the GRADE approach for assessing the certainty of evidence. In addition, we

only included RCTs, most of which were multicentre studies. We could thus conduct an intention-to-treat analysis to understand the effect of intensive physical rehabilitation or usual care, which gives a pragmatic estimate of the benefit of a change in treatment policy.

This systematic review has two potential limitations. Firstly, none of the included studies had a follow-up >6 months, and thus we could not account for later outcomes. A previous study reported that, in patients with exacerbations of chronic respiratory disease, intensive physical rehabilitation increased mortality at 12 months.[31] Since we found no evidence of mortality benefit at 6 months, we believe that the conclusions of this review would not change even if further data on harm outcomes were available. Lastly, we could not take into account the medical resources and costs associated with each intervention. However, since studies included in this review compare rehabilitation intervention against usual care or no intervention, it is obvious that intensive physical rehabilitation would be associated with increased medical resources and costs.

Taken together, the findings of the present meta-analysis indicate that enhanced physical rehabilitation following ICU discharge does not improve QOL or mortality among patients who received mechanical ventilation. It is unnecessary to

362 implement an intensive physical rehabilitation program for all ICU survivors requiring

363 mechanical ventilation.

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Author contributions

ST and KY designed the study, were involved in the systematic review process, analysed and interpreted the data, and drafted the manuscript. MB, HT, YK, and YT participated in the systematic review process, critically reviewed the initial manuscript, and approved the final manuscript as submitted. All authors read and approved the final manuscript.

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Declaration of interests

None.

Data sharing statement

All data associated with this manuscript are included in the main text and supplementary materials.

Supplementary data

Supplementary data to this article can be found online.

Online supplementary file 1: PRISMA 2009 checklist

Online supplementary file 2: Search strategies

Online supplementary file 3: Characteristics of the studies analysed in this review

Online supplementary file 4: Characteristics of studies excluded from qualitative and quantitative synthesis

Online supplementary file 5: Assessment of risk of bias in the trials analysed

Online supplementary file 6: Subgroup analysis for quality of life and mortality

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37. Stevens RD, Dowdy DW, Michaels RK, et al. Neuromuscular dysfunction acquired in critical illness: a systematic review. *Intensive Care Med* 2007;33:1876–91.

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Figure legends

Fig 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram

Fig 2 Forest plot for quality of life and mortality

535 **Tables**

536 Table 1. Findings from ten trials focused on post-ICU rehabilitation of critically ill patients who received mechanical ventilation

537

Overview of study design						
Patients or study population: adult patients who have been discharged from an ICU or critical care environment during which mechanical ventilation was provided for at least 24 hours **Setting:** any **Intervention:** protocolized physical rehabilitation following ICU discharge, designed to be more intensive than the care received by the control group. **Comparison:** no intervention or usual care						
Outcome	**Illustrative comparative risks[*] (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Assumed risk Control	Corresponding risk Intervention				
Quality of life SF-36: physical component summary score	**Study population**	**MD: -0.45** (-2.46 to 1.55)		475 (3 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	
Quality of life	**Study population**	**MD: -0.73**		475 (3 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	

SF-36: mental component summary score		(-3.18 to 1.73)			
Mortality Short term	**Study population**		**RR: 0.71** (0.05 to 9.80)	93 (2 RCTs)	⨁⨁⊖⊖ **Low**[b,c]
	43 per 1000	**31 per 1000** (2 to 426)			
Mortality Long term	**Study population**		**RR: 1.05** (0.66 to 1.66)	907 (5 RCTs)	⨁⨁⨁⊖ **Moderate**[d]
	71 per 1000	**75 per 1000** (47 to 119)			
Adverse events	**Study population**			153 (3 RCTs)	⨁⨁⊖⊖ **Low**[ef]
	Two studies reported no adverse events. One study reported 18 and 5 events in the intervention and control groups, respectively.				

*The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect (and its 95% CI) estimated for the intervention group.

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

CI, confidence interval; RR, risk ratio; ICU, intensive care unit; SF-36, Short Form 36; MD, mean difference; RCT, randomised controlled trial

[a]Downgraded one point because of high risk of bias associated with the lack of information regarding the dose of physical rehabilitation and adherence in the intervention group (other bias).

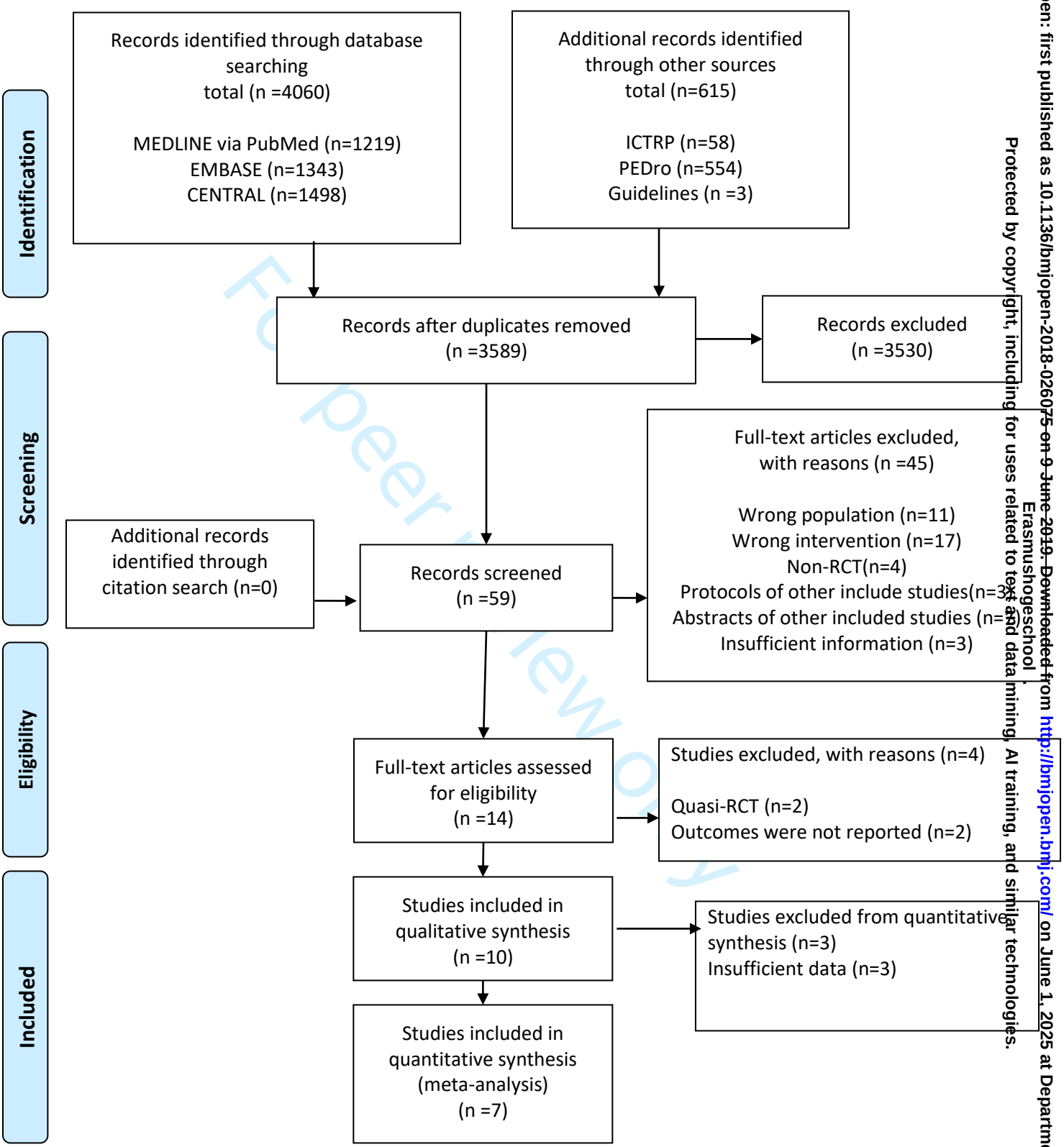
[b]Downgraded one point because of high risk of bias associated with the fact that the intervention included nutritional therapy but the study provided very little detail regarding the therapy received in the control group (other bias).

[c]Downgraded because of imprecision (only two small studies).

[d]Downgraded one point because of high risk of bias associated with the lack of information regarding the dose of physical rehabilitation and adherence in the intervention group, as well as with the fact that the intervention included nutritional therapy but the study provided very little detail regarding the therapy received in the control group (other bias).

[e]Downgraded one point because of high risk of bias associated with the fact that very little detail was given regarding the therapy received in the control group, and the adherence in the intervention group was 70% (other bias).

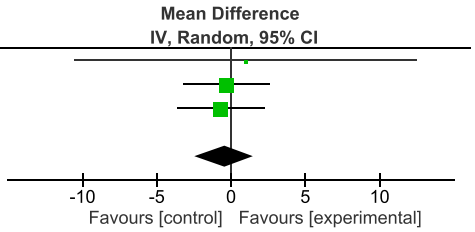
[f]Downgraded because of imprecision (only three small studies).



2-A Quality of life: physical component summary

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Jones 2003	49	31	58	48	28	44	3.0%	1.00 [-10.49, 12.49]	2003
Cuthbertson 2009	39.8	9.5	102	40.1	11.7	110	49.1%	-0.30 [-3.16, 2.56]	2009
Elliott 2011	42.6	10	76	43.3	8.6	85	47.8%	-0.70 [-3.60, 2.20]	2011
Total (95% CI)			**236**			**239**	**100.0%**	**-0.45 [-2.46, 1.55]**	

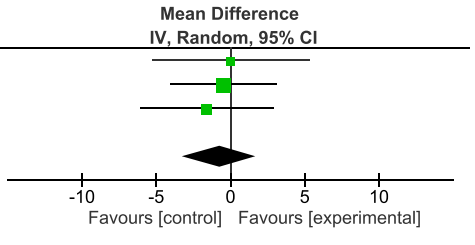
Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 2 (P = 0.95); I² = 0%
Test for overall effect: Z = 0.44 (P = 0.66)



2-B Quality of life: mental component summary

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Jones 2003	63	14	58	63	13	44	21.7%	0.00 [-5.27, 5.27]	2003
Cuthbertson 2009	44.7	14.2	102	45.2	12	110	47.8%	-0.50 [-4.05, 3.05]	2009
Elliott 2011	46.3	15.1	76	47.9	13.5	85	30.5%	-1.60 [-6.05, 2.85]	2011
Total (95% CI)			**236**			**239**	**100.0%**	**-0.73 [-3.18, 1.73]**	

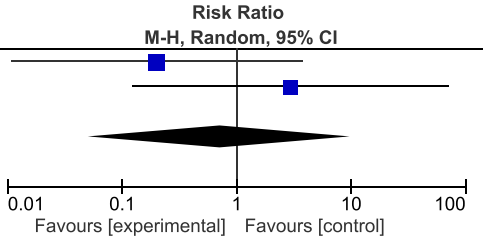
Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 2 (P = 0.89); I² = 0%
Test for overall effect: Z = 0.58 (P = 0.56)



2-C Short term mortality

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Connolly B 2015	0	10	2	10	52.7%	0.20 [0.01, 3.70]	2015
McWilliams 2016	1	37	0	36	47.3%	2.92 [0.12, 69.43]	2016
Total (95% CI)		**47**		**46**	**100.0%**	**0.71 [0.05, 9.80]**	
Total events	1		2				

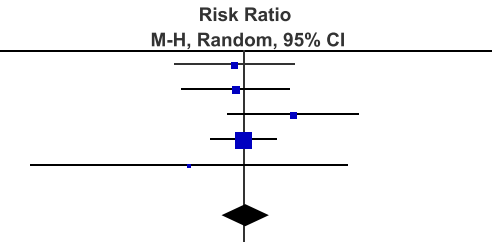
Heterogeneity: Tau² = 1.18; Chi² = 1.49, df = 1 (P = 0.22); I² = 33%
Test for overall effect: Z = 0.26 (P = 0.80)



2-D Long term mortality

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Jones 2003	5	69	5	57	15.1%	0.83 [0.25, 2.71]	2003
Cuthbertson 2009	6	143	7	143	18.8%	0.86 [0.30, 2.49]	2009
Elliott 2011	8	97	3	98	12.7%	2.69 [0.74, 9.85]	2011
Walsh 2015	16	120	16	120	51.3%	1.00 [0.52, 1.91]	2015
McDowell 2017	0	30	1	30	2.1%	0.33 [0.01, 7.87]	2017
Total (95% CI)		**459**		**448**	**100.0%**	**1.05 [0.66, 1.66]**	
Total events	35		32				

Heterogeneity: Tau² = 0.00; Chi² = 2.86, df = 4 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.19 (P = 0.85)



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4, 5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	7, 8
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	8
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	8
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8, 9
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	9, 10
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	9, 10
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8, 9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	9-11
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10, 11
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	12
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	12

PRISMA 2009 Checklist

Checklist item 9			
Section/topic	**#**		**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	12-13
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicateng which were pre-specified.	12-13
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	14
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	14, 15
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	15
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	15-17
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	15-17
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12-13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	16
DISCUSSION			
Summary of evidence	14	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	23

The cochrane central register of controlled trials (CENTRAL)

#1 MeSH descriptor:[critical care]explode all trees
#2 MeSH descriptor:[intensive care unit]explode all trees
#3 MeSH descriptor:[critical illness]explode all trees
#4 MeSH descriptor:[ventilator weaning]explode all trees
#5 MeSH descriptor:[Respiratory Distress Syndrome, Adult]explode all trees
#6 MeSH descriptor:[Sepsis]explode all trees
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#44 "lying to sitting":ti,ab,kw
#45 marching:ti,ab,kw
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MEDLINE via PubMed

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EMBASE

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#53 #21 AND #51 AND #52

PEDro

Advance search

Abstract & Title: critical illness OR critical care OR intensive care unit OR acute respiratory distress syndrome OR ards OR sepsis OR septic OR ventilator

Method: clinical trial

The world health organization international clinical trials platform search portal (WHO ICTRP)

#1 Conditions: (critical illness OR critical care OR intensive care unit OR acute respiratory distress syndrome OR ARDS OR sepsis OR ventilator)
#2 Intervention: (rehabilitation OR exercsie OR training OR mobilization OR mobilisation OR physical therapy OR physiotherapy OR occupational therapy OR neuromuscular electrical stimulation OR cycle ergometer OR ADL or activity of daily living OR ambulation OR walking)
#3 #1 AND #2

Online supplementary file 3. Characteristics of the studies analysed in this review

Author, year, country	No. of participants	Study type	Intervention (a, Timing of commencement; b, Contents; c, Duration; d, Frequency)	Control	Outcomes	Notes
Jones et al., 2003, UK	126	Multi-centre RCT	a: in-hospital b: routine follow-up plus rehabilitation package consisting of 93 pages of text c: 6 weeks d: every day*	No intervention	HRQoL, Mortality, Depression symptoms, PTSD-related symptoms	ICU rehabilitation before randomisation*
Cuthbertson et al., 2009, UK	286	Multi-centre RCT	a: in-hospital b: manual based, self-directed, physical rehabilitation program developed by physiotherapists and introduced by a study nurse c: continued for 3 months after discharge d: unknown	No intervention	HRQoL, Mortality, Quality-adjusted life years, Incidence and severity of PTSD, Anxiety and depression symptoms, Cost effectiveness	ICU rehabilitation before randomisation*
Elliott et al., 2011, Australia	195	Multi-centre RCT	a: after hospital discharge b: home-based physical rehabilitation program focused on strength training and walking c: 8 weeks	No intervention	HRQoL, Mortality, Physical function	No ICU rehabilitation before randomisation*

			d: 5 times/week			
Salisbury et al., 2010, UK	16	Single-centre pilot RCT	a: in-hospital b: enhanced physiotherapy and dietetic rehabilitation package c: unknown d: unknown	Standard care	Physical outcomes, Nutritional outcome, Breathlessness on the Visual analogue scale scores for breathlessness, fatigue, joint stiffness, pain, and appetite	
Batterham et al., 2014, UK	59	Multi-centre RCT	a: after hospital discharge b: hospital-based, physiotherapist-led, supervised exercise c: 8 weeks d: 2 times/week	No intervention	HRQoL, Oxygen uptake, Mood disorder	
Connolly et al., 2015, UK	20	Two-centre pilot RCT	a: after hospital discharge b: exercise-base rehabilitation session of 40 minutes c: 8 weeks d: 3 times/week (2 times supervised, 1 time unsupervised)	No intervention	HRQoL, ADL, Mortality, Physical function, Muscle strength, Adverse events, Anxiety and depression symptoms	ICU rehabilitation before randomisation*
Walsh et al., 2015, UK	240	Two-centre RCT	a: in-hospital b: mobilization exercise and relevant dietetic, occupational, and	Standard care	Mobility index, HRQoL, Anxiety and depression symptoms, Self-reported	ICU rehabilitation before randomisation

			speech/language therapy c: from ICU discharge until hospital discharge but no longer than 3 months d: unknown		symptom scores (using visual analogue scales) for fatigue, breathlessness, appetite, pain, and joint stiffness, Mortality	
McWilliams et al., 2016, UK	73	Single-centre RCT	a: after hospital discharge b: outpatient-based exercise and education program c: 7 weeks d: 3 times/week (1 supervised, 2 self-directed titrated)	No intervention	Exercise capacity, HRQoL, Mortality, Adverse events*	ICU rehabilitation before randomisation*
Shelly et al., 2017, India	35	RCT	a: after hospital discharge b: home□based respiratory and mobility training c: 4 weeks d: 5 times/week	No intervention	HRQoL	
McDowell et al., 2017, UK	60	Multi-centre RCT	a: after hospital discharge b: standard care plus personalized exercise program c: 6 weeks d: 3 times/week (2 supervised and 1 unsupervised)	No intervention	HRQoL, Mortality, Adverse events, Mobility index, Hand function, Exercise capacity, Breathlessness, Anxiety and depression	

		symptoms, Readiness to exercise, Self-efficacy to exercise

*Unpublished data

ICU, intensive care unit; RCT, randomised controlled trial; HRQoL, health-related quality of life; PTSD, post-traumatic stress disorder; ADL, activity of daily living

Online supplementary file 4: Characteristics of studies excluded from qualitative and quantitative synthesis

Study	Reason for exclusion
Chiang et al., Phys Ther. 2006;86:1271-81	Quasi-RCT
Patsaki et al., J Crit Care. 2017;40:76-82	Quasi-RCT
Avelino et al., Am J Respir Crit Care Med. 2015;191:A6352	Outcomes were not reported in the publication abstract. The full study will be considered when the review is updated.
Chen et al., Am J Respir Crit Care Med. 2017;195:A2337	Outcomes were not reported in the publication abstract. The full study will be considered when the review is updated.
Salisbury et al., Clin Rehabil. 2010;24:489-500	Insufficient outcome data for meta-analysis
Batterham et al., Br J Anaesth. 2014;113:130-7	Insufficient outcome data for meta-analysis
Shelly et al., Indian J Crit Care Med. 2017;21:89-93	Insufficient outcome data for meta-analysis

RCT, randomised controlled trial

Online supplementary file 5. Assessment of risk of bias in the analysed trials

Trial	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Jones et al., 2003 (22)	Low[a]	Low[a]	High	Low	Low	Unclear[a]	Unclear[b]
Cuthbertson et al., 2009 (23)	Low	Low	High	Low	Low	Low	Unclear[b]
Elliott et al., 2011 (24)	Low	Low	High	Low	Low	High	Unclear[c]
Salisbury et al., 2010 (25)	Low	Low	High	Low	Low	Unclear	High[d]
Batterham et al., 2014 (26)	Low	Low	High	Low	Low	High	Unclear[e]
Connolly et al., 2015 (11)	Low	Low	High	High	Low	High	Unclear[e]
Walsh et al., 2015 (12)	Low	Low	High	Low	Low	High	High[d]
McWilliams et al., 2016 (13)	Low	Low	High	Low	Low	Low	Unclear[e]
Shelly et al., 2017 (27)	Low	Low	High	Unclear	Low	Low	Unclear[e]
McDowell et al., 2017 (15)	Low	Low	High	Low	Low	Low	High[f]

[a]Unpublished data (reply from the authors: the randomization was undertaken the old-fashioned way, with 6 slips of paper, 3 marked interventions and 3 controls, put in 6 sequentially numbered opaque envelopes and sealed and shuffled to mix them, but protocol was not published)

[b]Dose of physical rehabilitation was unknown

[c]Adherence to the intervention was unknown

[d]Intervention included nutritional therapy

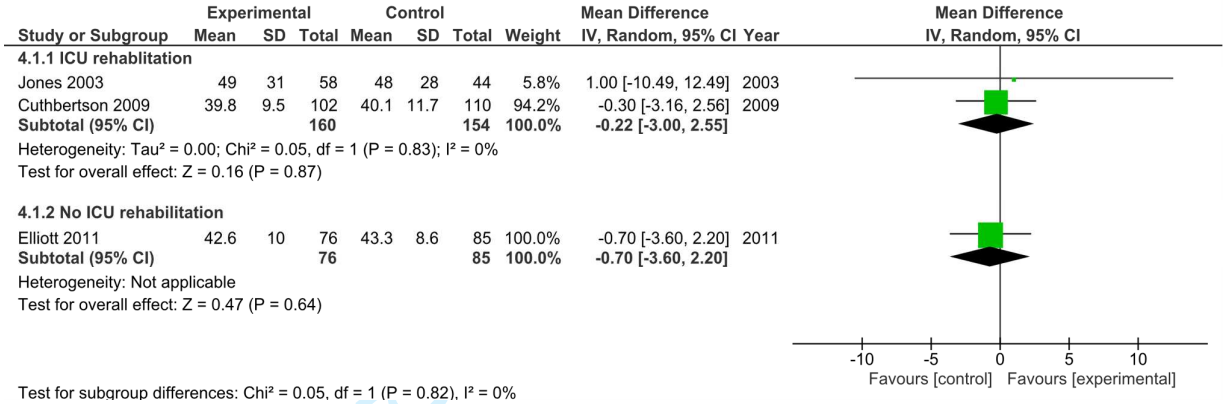
[e]Very little detail given regarding the therapy received in the control group

[f]Adherence to the intervention was 70%

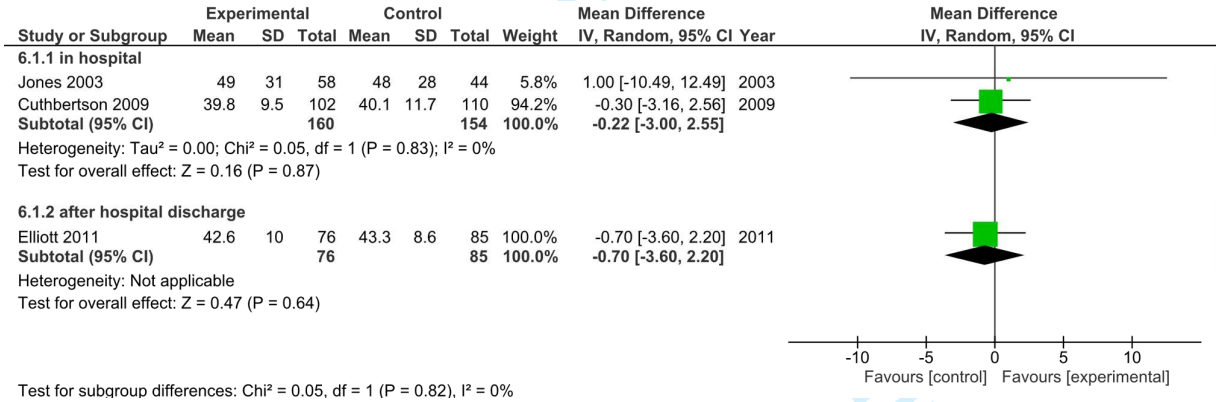
Online supplementary file 6: Subgroup analysis

A Quality of life: physical component summary

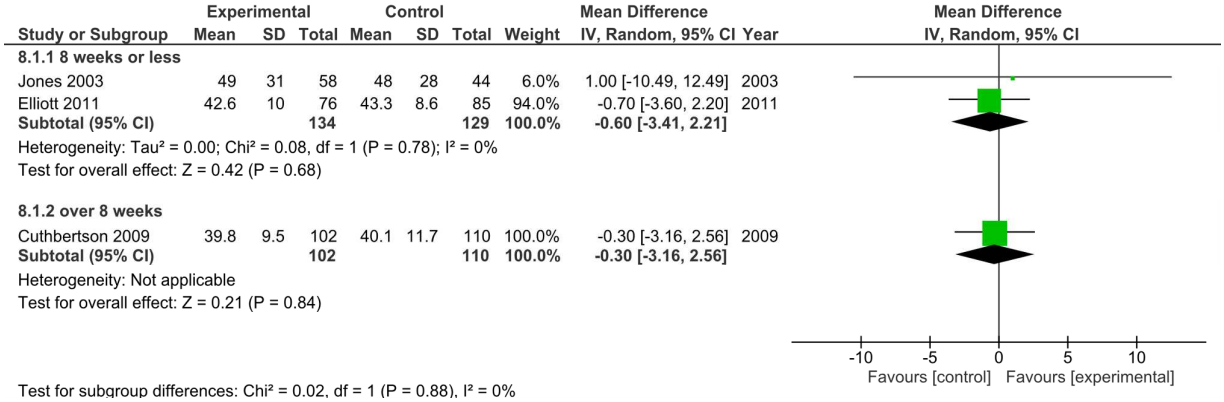
A-1 Rehabilitation practice in ICU (ICU rehabilitation before randomisation ve No ICU rehabilitation before randomisation)



A-2 The timing of the commencement of the intervention (in hospital vs after hospital discharge)

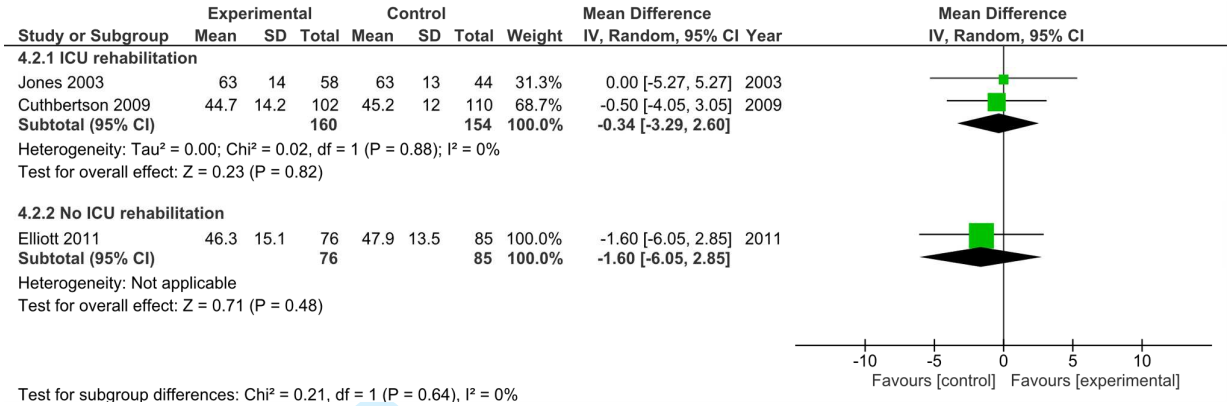


A-3. The intervention duration (8 weeks or less, and over 8 weeks)

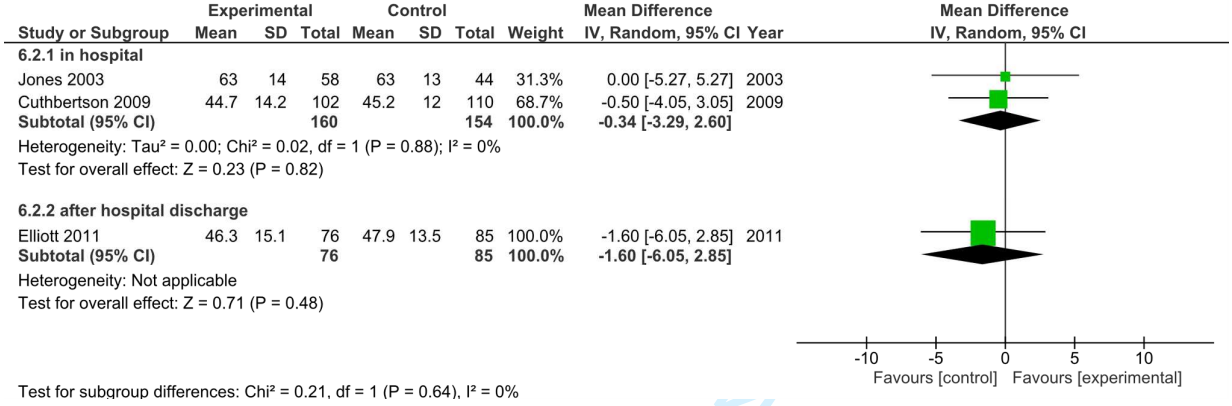


B Quality of life: mental component summary

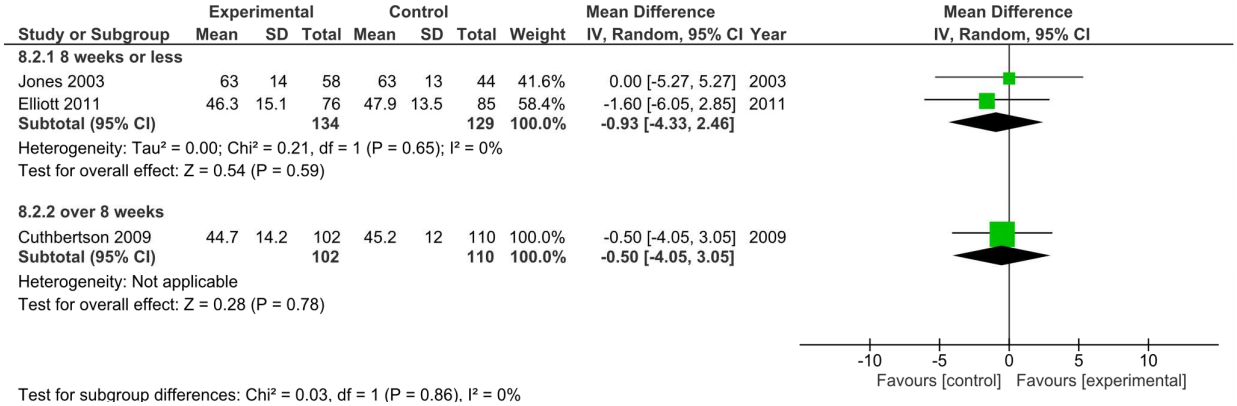
B-1. Rehabilitation practice in ICU (ICU rehabilitation before randomization ve No ICU rehabilitation before randomization)



B-2. The timing of the commencement of the intervention (in hospital vs after hospital discharge)



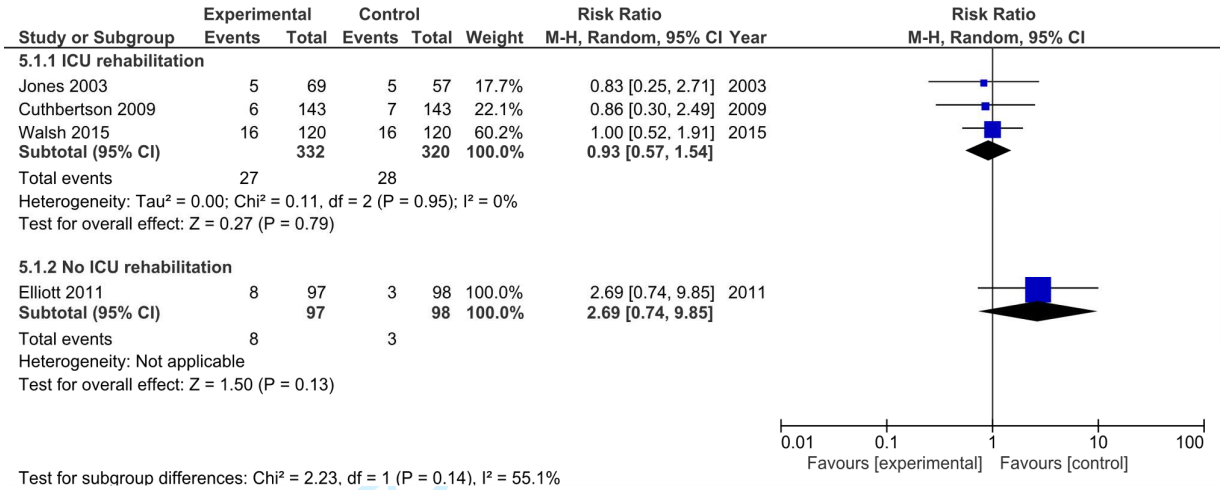
B-3. The intervention duration (8 weeks or less, and over 8 weeks)



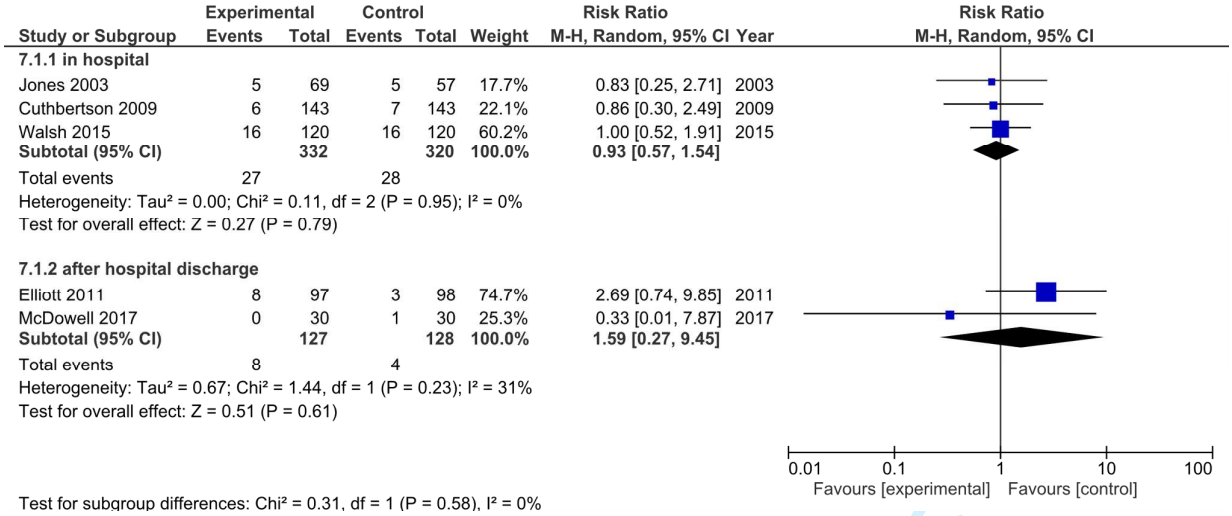
QOL: quality of life, PCS: physical component score, MCS: mental component score,

C Long term mortality

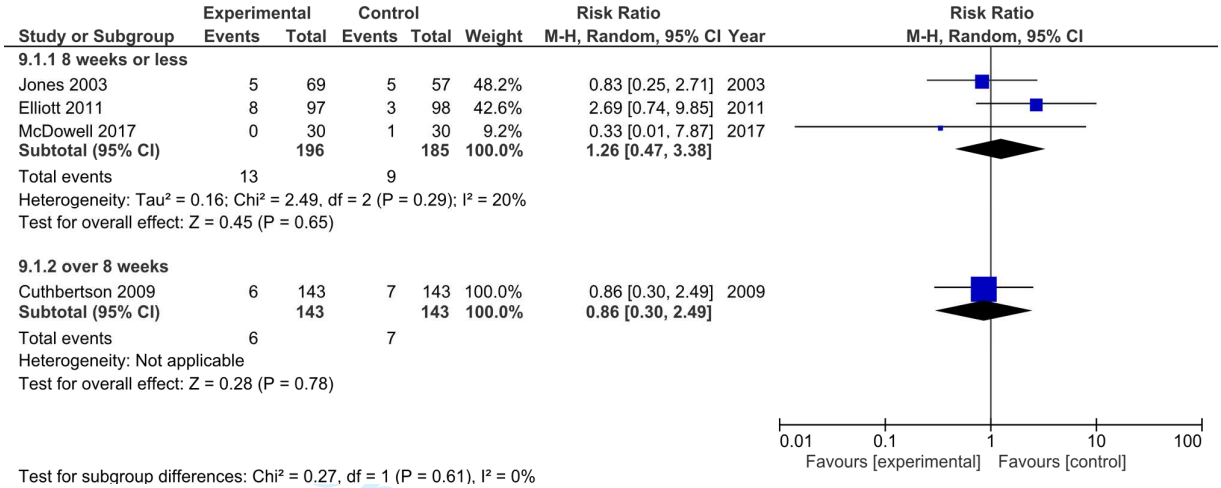
C-1. Rehabilitation practice in ICU (ICU rehabilitation before randomization ve No ICU rehabilitation before randomization)



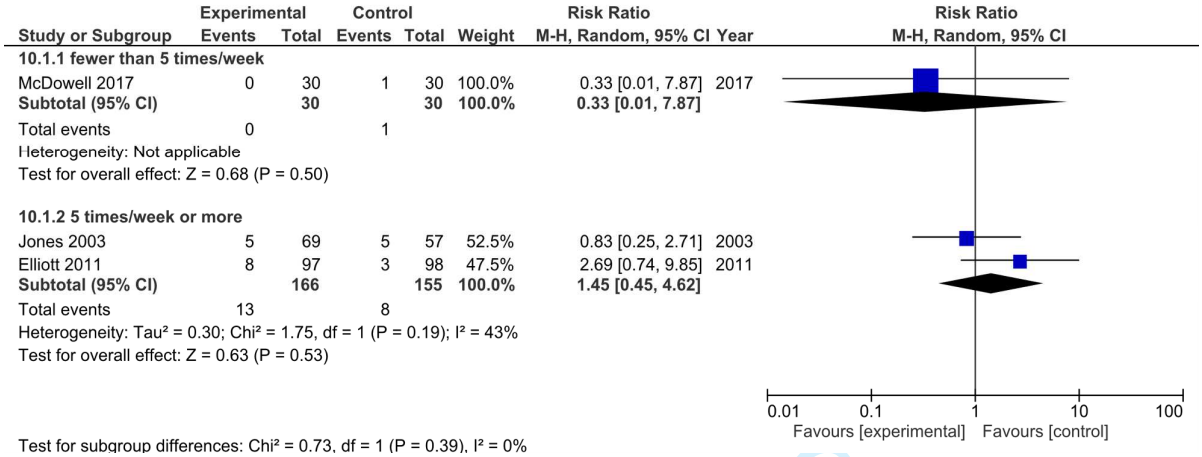
C-2 The timing of the commencement of the intervention (in hospital vs after hospital discharge)



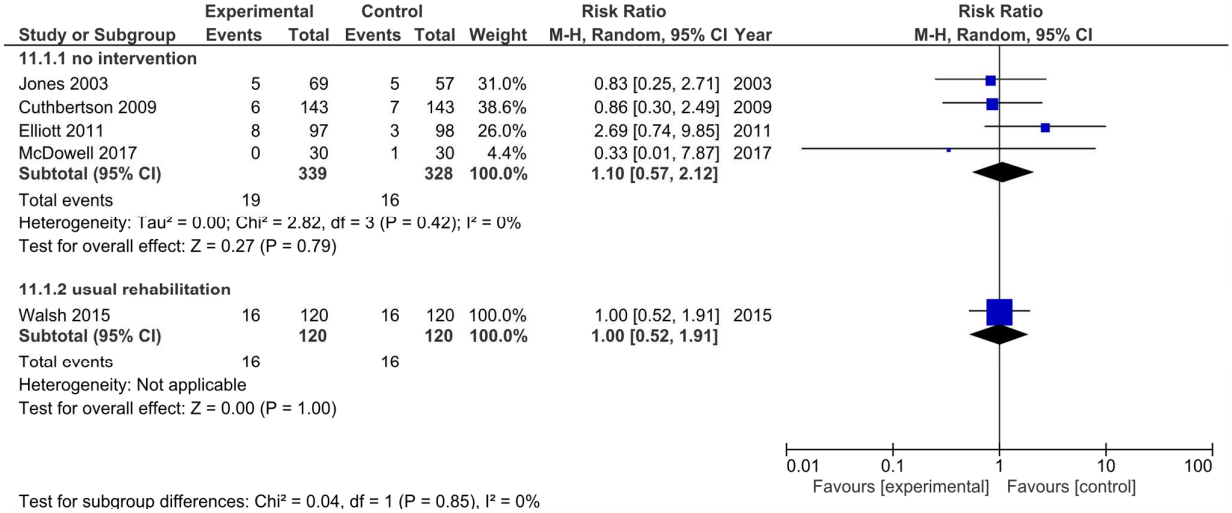
C -3. The intervention duration (8 weeks or less, and over 8 weeks)



D-4 Treatment frequency (fewer than 5 times/week vs 5 times/week or more)



D-5 Type of control (no intervention and usual rehabilitation)



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Does enhanced physical rehabilitation following intensive care unit discharge improve outcomes in patients who received mechanical ventilation? A systematic review and meta-analysis

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Keywords:	critical illness, rehabilitation, post-intensive care syndrome, exercise, quality of life, mortality

Research – meta-analysis

Does enhanced physical rehabilitation following intensive care unit discharge improve outcomes in patients who received mechanical ventilation? A systematic review and meta-analysis

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Abbreviations

ADL, activities of daily living; APACHE, Acute Physiology And Chronic Health Evaluation; CI, confidence interval; EMBASE, Excerpta Medica Database; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; ICU, intensive care unit; MCS, mental component summary; PCS, physical component summary; PEDro, Physiotherapy Evidence Database; PICS, post-intensive care syndrome; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; QOL, quality of life; RCT, randomised controlled trial; RR, risk ratio; WHO ICTRP, World Health Organization International Clinical Trials Registry Platform

Abstract

Objective: We aimed to determine whether enhanced physical rehabilitation following intensive care unit (ICU) discharge improves clinically relevant outcomes, such as activity-of-daily-living (ADL), quality of life (QOL), and mortality among patients who received mechanical ventilation.

Design: Systematic review and meta-analysis using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Data sources: MEDLINE, Embase, CENTRAL, PEDro, and World Health Organization International Clinical Trials Registry Platform searched through January 2019.

Eligibility criteria for selecting studies: We included randomised controlled trials assessing the effect of rehabilitation following ICU discharge, designed to either commence earlier and/or be more intensive for adult patients who received mechanical ventilation.

Data extraction and synthesis: Two independent reviewers extracted data and assessed risk of bias. Standard mean differences (SMDs) with 95% confidence intervals (CIs) were calculated for QOL and pooled risk ratios (RRs) with 95% CIs are provided for mortality. We calculated I^2 for assessing heterogeneity. GRADE assessed the certainty of the evidence.

Results: Ten trials (enrolling 1110 patients) compared physical rehabilitation to usual care or no intervention after ICU discharge. Regarding QOL, the SMD [95% CI] between the intervention and control groups for the physical and mental component summary scores was 0.06 [-0.12 to 0.24] and -0.04 [-0.20 to 0.11], respectively. Rehabilitation did not significantly decrease long-term mortality (RR: 1.05 [0.66–1.66]). The analysed trials did not report on ADL. The certainty of the evidence was graded as moderate for QOL and mortality.

Conclusions: Enhanced physical rehabilitation following ICU discharge may make little or no difference to QOL or mortality among patients who received mechanical ventilation. With regard to the wide CI, we believe further studies are needed to confirm the efficacy of rehabilitation.

Trial registration: PROSPERO, CRD42017080532 (registered: 28 December 2017).

Keywords: rehabilitation, critical illness, post-intensive care syndrome, exercise, quality of life, mortality

Article Summary

Strengths and limitations of this study

- This is the first meta-analysis focused on enhanced physical rehabilitation to review randomised controlled trials in which the study intervention was conducted only after intensive care unit discharge.
- The findings are based on moderate certainty of evidence.
- The main limitations of this meta-analysis are that (i) none of the included studies had a follow-up >6 months and (ii) medical resources and costs associated with each intervention were not considered.
- We employed rigorous methodology that followed a written priori protocol developed according to the Preferred Reporting Items for Systematic Reviews and Meta- (PRISMA) statement, and used the Grading of Recommendations Assessment, Development and Evaluation approach in the review process.

Introduction

In critically ill patients, rehabilitation mainly aims to enhance quality of life (QOL) by improving activities of daily living (ADL) function,[1, 2] which may be severely impaired also due to post-intensive care syndrome (PICS).[3-5] According to the guidelines issued by the National Institute for Health and Care Excellence, provision of rehabilitation should be seamlessly integrated with the patient's transition from the intensive care unit (ICU) to the ward and then to out-of-hospital care.[6] However, at the time the guidelines were issued, there was little evidence from clinical trials to support the use of enhanced physical rehabilitation following ICU discharge. Some experts do recommend physical rehabilitation following ICU discharge to improve ADL function and QOL.[7] With regards to sepsis survivors, the findings of a large observational study suggested that physical rehabilitation following ICU discharge improves long-term mortality.[8, 9]

A recent meta-analysis by Connolly et al.[10] focused on randomised controlled trials (RCTs) regarding the effectiveness of enhanced exercise rehabilitation following ICU discharge in adult ICU survivors who had been mechanically ventilated for longer than 24 hours. Despite the comprehensive search, only 6 RCTs with conflicting results were included, and no clear effect of the intervention on clinically

relevant outcomes such as QOL, mortality, functional exercise capacity, or incidence of adverse events could be established at the time. Additionally, some clinically relevant outcomes such as ADL, pain, return-to-work rate, muscle strength, and duration of delirium were not considered in their review.[10] Several RCTs assessing the effect of enhanced physical rehabilitation following ICU discharge on clinically relevant outcomes[11-15] have been published since Connolly and colleagues conducted their Cochrane review.[10] Therefore, in the present study, we aimed to re-evaluate the available literature and determine whether enhanced physical rehabilitation following ICU discharge improves clinically relevant outcomes among critically ill adults who received mechanical ventilation.

Materials and methods

Compliance with reporting guidelines

Using a pre-specified protocol (PROSPERO registry ID: CRD42017080532),[16] we conducted a systematic review of the relevant literature in agreement with the recommendations listed in the Cochrane Handbook[17] and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[18] We confirmed that this systematic review was PRISMA-compliant by

consulting the PRISMA 2009 checklist[19] (details provided in online supplementary file 1).

Research question and eligibility criteria

The research question was: "Does enhanced physical rehabilitation following ICU discharge result in improved clinically relevant outcomes such as QOL, ADL, and mortality (compared to those achievable with usual care) among patients who received mechanical ventilation?" We included all published and unpublished prospective RCTs involving adult human subjects (age ≥18 years) who had been discharged from an ICU or critical care environment after a stay of at least 48 hours during which mechanical ventilation was provided for at least 24 hours. Crossover trials, as well as cluster-, quasi-, and non-randomised trials were excluded. Studies were included regardless of the intervention setting (in-hospital or out-of-hospital), follow-up duration, and country of origin. We included patients of any sex and race, but excluded those receiving palliative care and those with head or spinal cord injuries, or unstable fracture diminishing mobility.

Intervention was defined as any protocoled rehabilitation following ICU discharge, designed to either commence earlier and/or be more intensive than the care received by the control group. To determine whether enhanced physical rehabilitation following ICU discharge improved clinically relevant outcomes, we excluded studies in

which earlier and/or more intensive ICU physical rehabilitation (compared to the care received by the control group) was provided to patients in the intervention group. We excluded studies in which enhanced rehabilitation was provided in the ICU; however, we did not exclude studies in which the same rehabilitation program was provided in the ICU as standard care for both intervention group and control group. Any combination of 1 or more of the following activities was considered as a form of enhanced physical rehabilitation: neuromuscular stimulation, inspiratory or respiratory muscle training, passive range-of-motion exercise, cycle ergometer exercise, active-assisted exercises, active range-of-motion exercises, bed mobility activities (e.g., bridging, rolling, lying-to-sitting exercise), ADL training, transfer training, pre-gait exercises (including marching in place), and walking exercise.

Outcomes of interest

The primary outcomes were QOL, ADL function, and mortality. Secondary outcomes included functional exercise capacity, pain, return-to-work rate, muscle strength, duration of delirium, and incidence of adverse events (defined by the trialists). We divided the timing for the measurements of the outcomes into the short-term (28-35 days) and the long-term (6 months).

Search strategy and selection of studies

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE via PubMed, Excerpta Medica Database (EMBASE) via Elsevier, the Physiotherapy Evidence Database (PEDro), and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) via their dedicated search portal. The search was performed in December 2017 and updated in January 2019 using a set of suitable search terms (details provided in online supplementary file 2). We hand-searched reference lists for the guidelines for rehabilitation after critical illness.[6] We attempted to identify other relevant research by hand-searching the reference lists of the studies returned by the search and those of articles citing such studies (based on citation information from the Web of Science). If the database entry for a candidate study did not contain the necessary information, we contacted the study authors. Two reviewers (ST and KY) independently screened the title and abstract of each study returned by the search to determine whether the inclusion criteria were met. The 2 reviewers performed a full-text review to assess the eligibility of each candidate study. Disagreement was resolved by discussion between the 2 reviewers, occasionally with arbitration by a third reviewer (YK).

Data abstraction and quality assessment

Two reviewers (ST and KY) independently abstracted trial-level data using pre-

specified forms. Disagreements regarding data extraction were resolved through discussions. Where necessary, we contacted the authors of studies that did not provide sufficient information. The risk of bias in each study was assessed independently by 2 reviewers (ST and KY) using the Cochrane risk-of-bias assessment tool.[17] Differences in opinion regarding the assessment of risk of bias were resolved through discussion between the 2 reviewers, occasionally with arbitration by a third reviewer (KY).

Data analysis

All analyses were conducted using the Cochrane Review Manager software (RevMan 5.3; Cochrane Collaboration, Copenhagen, Denmark). For the dichotomous variables of mortality and return-to-work rate, pooled risk ratios (RRs) with 95% confidence intervals (CIs) are provided. For continuous outcomes including QOL scores, ADL function scores, pain, muscle strength, and duration of delirium (expressed in days of ICU or hospital stay), the standardized mean differences, or the mean differences with 95% CIs were calculated, as recommended by the Cochrane Handbook.[17] Adverse events were narratively summarised because their definition likely varied across studies. We used the random-effects models for all analyses.

We calculated I^2 as a measure of variation across studies that is due to heterogeneity rather than chance, and interpreted the values as follows: 0%–40%,

negligible heterogeneity; 30%–60%, mild-to-moderate heterogeneity; 50%–90%, moderate-to-substantial heterogeneity; 75%–100%, considerable heterogeneity. If heterogeneity was identified for an outcome (I^2 >50%), we investigated the underlying reasons and conducted the χ^2 test, with a *P*-value of <0.10 being considered to be statistically significant. We investigated reporting bias by checking the WHO ICTRP to detect trials that had been completed but not published at the time of the review.

We planned the following pre-specified sensitivity analyses for the primary outcomes: (i) exclusion of studies using imputed statistics, and (ii) exclusion of studies with high or unclear risk of bias. We also carried out pre-specified subgroup analyses according to the type of rehabilitation involved (neuromuscular stimulation versus other types of rehabilitation), rehabilitation provision in the ICU (received versus did not receive protocoled physical rehabilitation in the ICU), timing of commencement of the intervention (in-hospital or after hospital discharge), intervention duration (≤8 versus >8 weeks), treatment frequency (<5 versus ≥5 times/week), and type of control (no intervention versus standard rehabilitation). Statistical significance was set at *P*<0.05. We created a summary-of-findings table that included an overall grading of the certainty of evidence for each of the main outcomes, which was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[20,

21]

Patient and public involvement

The patients or public were not involved in this meta-analysis.

Results

Characteristics of trials on rehabilitation in ICU survivors

After removing duplicates, we identified 3,589 records during the search conducted in December 2017 and updated the electronic searches in January 2019. We identified 10 unique RCTs[11–13, 15, 22–27] that fulfilled all eligibility criteria and were included in the qualitative synthesis (Fig. 1; details provided in online supplementary file 3). The 10 RCTs provided a pooled sample of 1110 critically ill patients with an ICU stay of >48 hours during which mechanical ventilation was provided for at least 24 hours. Eight studies were performed in the United Kingdom, one in Australia, and one in India. The mean or median age in the analysed studies ranged from 40.5 to 68.5 years, while the mean or median Acute Physiology and Chronic Health Evaluation (APACHE) II score ranged from 15.2 to 31. Only 1 study included participants with PICS symptoms or ICU-acquired weakness.[11] Three RCTs[25–27] did not have sufficient outcome data for meta-analysis (details provided in online

supplementary file 4), leaving a total pooled sample of 1000 patients (506 patients in the intervention groups; 494 controls) represented across 7 studies to be included in the quantitative synthesis. Of the 10 trials analysed, 6 evaluated the effect of physical rehabilitation including self-directed exercise and/or supervised exercise following hospital discharge, while 4[12, 22–24] focused on rehabilitation started during hospitalisation. The duration of intervention ranged from 6 weeks to 3 months, while the frequency of intervention ranged from 3 times per week to once daily. No study considered intensive intervention (>30 minutes of active rehabilitation daily) or intervention with neuromuscular stimulation. Two studies [12, 23] had a follow-up >6 months. We did not identify any ongoing studies.

Most studies were at high or had an unclear risk of bias, as determined using the Cochrane risk-of-bias assessment tool[17] (details provided in online supplementary file 5). All 10 studies demonstrated adequate random sequence generation and allocation concealment, but participants and personnel were not blinded to the intervention. One study[11] demonstrated a high risk of detection bias for all outcomes except mortality, and another study[27] did not report whether or not the outcome assessor was aware of group allocation. Five studies had high risk of incomplete outcome data. Four studies had high risk of selective reporting bias, and 2 studies had unclear risk of bias because the

protocols were not published. High or unclear risk of other bias was noted for all studies because of insufficient information regarding the intervention and control protocols.

Primary outcomes

QOL was measured in 9 trials (see online supplementary file 3), but the short- and long-term QOL score were only available in four trials,[12, 22–24] whereas the other 5 trials measured these outcomes at a different time or had insufficient outcome data for meta-analysis. ADL function was measured in 1 trial,[11] but the short- and long-term data were not available. Short-term mortality was reported in 2 trials,[11, 13] while long-term mortality was reported in 5 trials.[12, 15, 22–24]

The SMD between intervention and control regarding PCS and MCS scores measured by SF-36 or SF-12 characterising QOL were 0.06 (95% CI, -0.12 to 0.24) and -0.04 (95% CI, -0.20 to 0.11), respectively (Fig. 2A and 2B, respectively). Rehabilitation did not significantly decrease short-term mortality (RR, 0.71; 95% CI, 0.05–9.80, I^2 = 33%; n = 93) (Fig. 2C) or long-term mortality (RR, 1.05; 95% CI, 0.66–1.66, I^2 = 0%; n = 907) (Fig. 2D). The certainty of evidence for QOL and long-term mortality was moderate, while that for short-term mortality was low (Table 1). We performed additional analysis regarding follow-up at 12 months, and enhanced physical rehabilitation also did not increase QOL score or decrease mortality (see detail provided in online

supplementary file 6).

We could not carry out all pre-specified sensitivity analyses because there was no study using imputed statistics, and we judged that the risk of bias of all included studies was similar in terms of random sequence generation, allocation concealment, incomplete outcome data, and other bias. The pre-specified subgroup analyses for the primary outcomes revealed no significant differences among sub-groups (see details provided in online supplementary file 7).

Secondary outcomes

Functional exercise capacity was measured in 2 trials,[11, 24] pain was measured in 1 trial,[12] and muscle strength was measured in 1 trial,[11] but short- and long-term data were not available. No trials evaluated return-to-work rate or incidence of delirium.

Adverse events were measured in 3 trials.[11, 13, 15] Two studies[11, 13] reported no adverse events. One study[15] reported 18 events in the intervention group and 5 events in the control group. Among the 18 adverse events reported in the intervention group, 12 were mild or moderate (musculoskeletal pain higher than expected or muscle soreness potentially indicating injury, 3 cases; any pain higher than expected, 1 case; cardiac symptoms or chest pain, 1 case; any other event considered by the researcher to be of concern, 7 cases; 6 of 12 events were considered to be related or

possibly related to study participation), while 6 were serious (hospitalisation or prolonged hospitalisation, with 1 event related/possibly related to study participation). In the control group, there was 1 adverse event (musculoskeletal pain higher than expected, muscle soreness potentially indicating injury, related/possibly related to study participation) and 4 serious adverse events (hospitalisation or prolonged hospitalisation, with 1 event related/possibly related to study participation). The certainty of evidence for adverse events was low (Table 1).

Discussion

The results of this up-to-date review covering 10 RCTs and 1110 patients suggest that enhanced rehabilitation following ICU discharge might not improve QOL or reduce mortality among patients who received mechanical ventilation at the 6 or 12 month follow-ups. We could not confirm the effect of enhanced physical rehabilitation even though all included studies exhibited performance bias potentially increasing the observed effect of the intervention. Furthermore, despite the large sample size in the meta-analysis for QOL and long-term mortality, limited data for these outcomes were available, and the certainty of evidence was only low or moderate.

Furthermore, subgroup meta-analyses revealed no differences among subgroups defined according to the nature or timing of the intervention. The previous review by Connolly et al.[10] did not conduct meta-analysis due to the limited number of included studies. A recent systematic review of ICU rehabilitation[28, 29] also reported no significant difference in QOL between the intervention and control groups. Thus, neither enhanced rehabilitation in the ICU nor rehabilitation following ICU discharge appear to be superior to standard care in terms of QOL outcomes. In addition, we found no benefit in terms of short- or long-term mortality regardless of timing of commencement, which is consistent with previous findings that ICU rehabilitation did not decrease mortality at ICU discharge, at hospital discharge, or at 6 months after discharge.[28, 30] On the other hand, rehabilitation may be detrimental in acute conditions. Specifically, intensive physical rehabilitation started within 48 hours of admission for exacerbations of chronic respiratory disease increased mortality at 12 months,[31] and higher-dose physical rehabilitation very early after stroke decreased favourable outcomes at 3 months.[32] Thus, implementation of an intensive rehabilitation programs might not be indicated for all ICU survivors who received mechanical ventilation.

Subgroup analysis in a previous systematic review[28] indicated that, compared with low-dose rehabilitation, high-dose active rehabilitation for >30 minutes daily was associated with significantly higher QOL. Dose-response analysis of early physical rehabilitation[33] in stroke patients enrolled in A Very Early Rehabilitation Trial (AVERT)[32] determined that intervention in such acute cases improved the odds of a favourable outcome with each episode of activity per day. This review did not include studies comparing high-dose rehabilitation and usual care, and thus the QOL effect of high-dose rehabilitation remains unclear. Additionally, we could not perform subgroup analysis for PICS symptoms with effect on QOL[3–5] or for sepsis, which is a risk factor for PICS.[34, 35] It remains unclear which population of critically ill patients may truly benefit from intensive physical rehabilitation.

The studies included in our review did not cover all important outcomes included in the core outcome set of rehabilitation after critical illness,[7] including ADL function, functional exercise capacity, pain, return-to-work rate, muscle strength, or delirium incidence. Nonetheless, our findings regarding QOL and mortality suggest that, even if future studies report improvement in these other aspects, the amount of improvement would likely be too small to affect QOL.

The present review has several strengths. First, we employed rigorous

methodology that followed a written, a priori protocol developed according to the PRISMA statement, including a comprehensive search for evidence. Second, we performed duplicate assessment of eligibility, risk of bias, and data abstraction. Third, we used the GRADE approach for assessing the certainty of evidence. In addition, we only included RCTs, most of which were multicentre studies. We could thus conduct an intention-to-treat analysis to understand the effect of intensive physical rehabilitation or standard care, which gives a pragmatic estimate of the benefit of a change in treatment policy. Fourth, ICU survivors are heterogeneous in nature. To confirm the effect of enhanced physical rehabilitation for a particular group, we selected studies including only participants with an ICU stay of >48 hours during which mechanical ventilation was provided for at least 24 hours.

This systematic review has 4 potential limitations. Firstly, few studies [12, 23] had a follow-up >6 months, and we could not consider enough with a following up of greater than 6 months. Further studies and updated reviews with follow-up beyond 6 months are needed. Secondly, ideally the mortality outcomes should be reported as a time to event data, however, no included study reported the death as a time to event data. Further studies reporting as time to event data for mortality are needed. Thirdly, we could not take into account the medical resources and costs associated with each

intervention. However, since studies included in this review compare rehabilitation intervention against standard care or no intervention, it is obvious that intensive physical rehabilitation would be associated with increased medical resources and costs. Lastly, we could not consider psychological aspects in our review. However, effect of intervention for the general population is more clinically important than for that of highly self-motivated individuals, and we clarified that enhanced physical rehabilitation following ICU discharge may make little or no difference for the general population including highly self-motivated individuals.

Taken together, the findings of the present meta-analysis indicate that enhanced physical rehabilitation following ICU discharge may make little or no difference to QOL or mortality among patients who received mechanical ventilation. With regards to the wide CI, we believe further studies are needed to confirm the efficacy of rehabilitation.

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Author contributions

ST and KY designed the study, were involved in the systematic review process, analysed and interpreted the data, and drafted the manuscript. MB, HT, YK, and YT participated in the systematic review process, critically reviewed the initial manuscript, and approved the final manuscript as submitted. All authors read and approved the final manuscript.

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Declaration of interests

None.

Data sharing statement

All data associated with this manuscript are included in the main text and supplementary materials.

Supplementary data

Supplementary data to this article can be found online.

Online supplementary file 1: PRISMA 2009 checklist

Online supplementary file 2: Search strategies

Online supplementary file 3: Characteristics of the studies analysed in this review

Online supplementary file 4: Characteristics of studies excluded from qualitative and quantitative synthesis

Online supplementary file 5: Assessment of risk of bias in the trials analysed

Online supplementary file 6: Additional meta-analysis for quality of life and mortality at 12 months

Online supplementary file 7: Subgroup analysis for quality of life and mortality

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Figure legends

Fig 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram

Fig 2 Forest plot for quality of life and mortality

Tables

Table 1. Findings from ten trials focused on post-ICU rehabilitation of critically ill patients who received mechanical ventilation

Overview of study design						
Patients or study population: adult patients who have been discharged from an ICU or critical care environment during which mechanical ventilation was provided for at least 24 hours **Setting:** any **Intervention:** protocolized physical rehabilitation following ICU discharge, designed to be more intensive than the care received by the control group. **Comparison:** no intervention or usual care						
Outcome	**Illustrative comparative risks[*] (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Assumed risk Control	Corresponding risk Intervention				
Quality of life Physical component summary score (6 months)	**Study population**	**SMD: 0.06** (-0.12 to 0.24)		649 (4 RCTs)	⨁⨁⨁◯ **Moderate**[a]	
	Study population			639	⨁⨁⨁◯	

Quality of life Mental component summary score (6 months)		**SMD: -0.04** (-0.20 to 0.11)		(4 RCTs)	**Moderate**[a]
Mortality Short term (28-35 days)	**Study population** **43 per 1000**	**31 per 1000** (2 to 426)	**RR: 0.71** (0.05 to 9.80)	93 (2 RCTs)	⨁⨁⨁◯ **Low**[b]
Mortality Long term (6 months)	**Study population** **71 per 1000**	**75 per 1000** (47 to 119)	**RR: 1.05** (0.66 to 1.66)	907 (5 RCTs)	⨁⨁⨁◯ **Moderate**[d]
Adverse events	**Study population** Two studies reported no adverse events. One study reported 18 and 5 events in the intervention and control groups, respectively.			153 (3 RCTs)	⨁⨁◯⨁ **Low**[ef]

*The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect (and its 95% CI) estimated for the intervention group.

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

CI, confidence interval; RR, risk ratio; ICU, intensive care unit; SF-36, Short Form 36; SMD, standardized mean difference; RCT, randomised controlled trial

[a]Downgraded one point because of high risk of bias associated with the lack of information regarding the dose of physical rehabilitation and adherence in the intervention group (other bias).

[b]Downgraded one point because of high risk of bias associated with the fact that the intervention included nutritional therapy but the study provided very little detail regarding the therapy received in the control group (other bias).

[c]Downgraded because of imprecision (only two small studies).

[d]Downgraded one point because of high risk of bias associated with the incomplete outcome and data the lack of information regarding the dose of physical rehabilitation and adherence in the intervention group, as well as with the fact that the intervention included nutritional therapy but the study provided very little detail regarding the therapy received in the control group (other bias).

[e]Downgraded one point because of high risk of bias associated with the fact that very little detail was given regarding the therapy received in the control group, and the adherence in the intervention group was 70% (other bias).

[f]Downgraded because of imprecision (only three small studies).

136/bmjopen-2018-026075 on 6 June 2019. Downloaded from

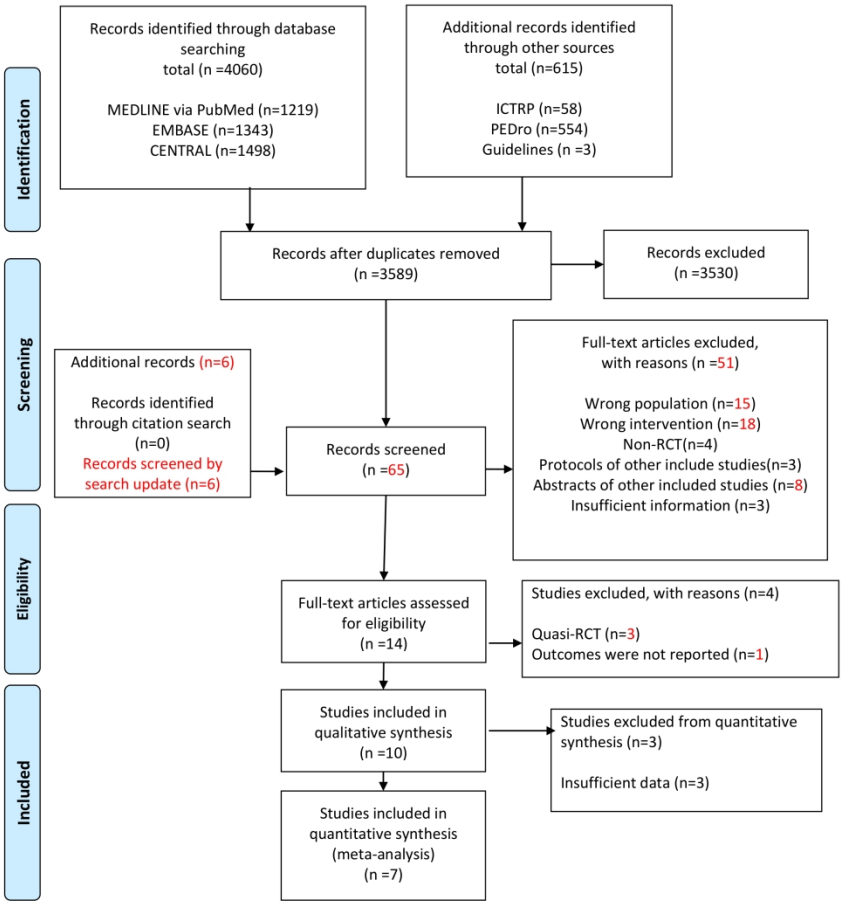

Fig 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram

215x279mm (300 x 300 DPI)

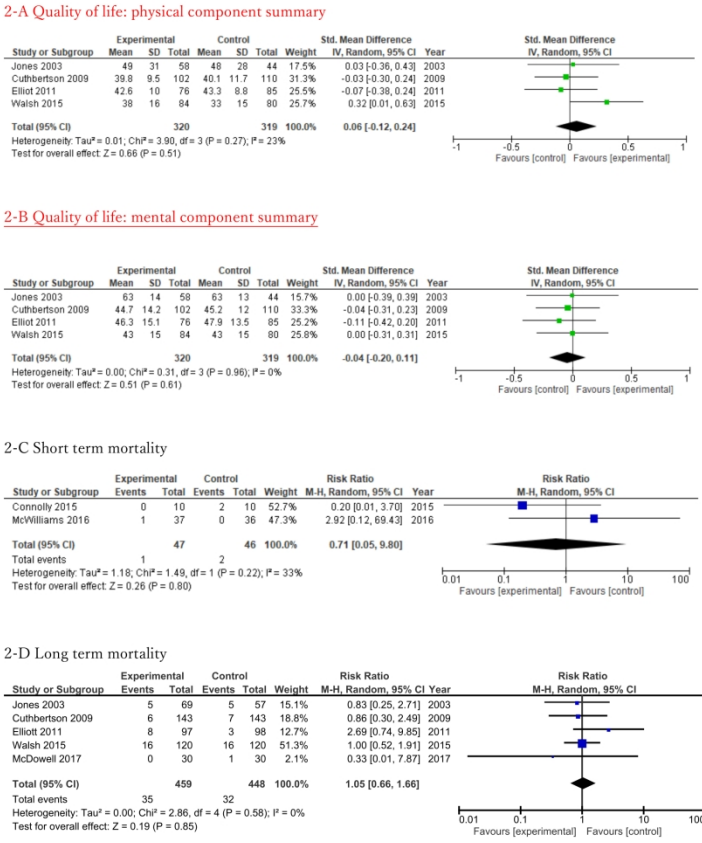

Fig 2 Forest plot for quality of life and mortality

209x297mm (300 x 300 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4, 5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	7, 8
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	8
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	8
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	9, 10
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	11
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	11
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	11
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	11, 12
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	10
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	11, 12
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	12
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	13

PRISMA 2009 Checklist

Checklist item 9			
Section/topic	**#**		**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	13
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicateng which were pre-specified.	13
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	14
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	14, 15
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	15, 16
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	16-18
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	16-18
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	15
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	17
DISCUSSION			
Summary of evidence	14	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	18, 19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21, 22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	24

Online supplementary file 2: Search strategies

The cochrane central register of controlled trials (CENTRAL)

#1 MeSH descriptor:[critical care]explode all trees
#2 MeSH descriptor:[intensive care unit]explode all trees
#3 MeSH descriptor:[critical illness]explode all trees
#4 MeSH descriptor:[ventilator weaning]explode all trees
#5 MeSH descriptor:[Respiratory Distress Syndrome, Adult]explode all trees
#6 MeSH descriptor:[Sepsis]explode all trees
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#9 "intensive care unit":ti,ab,kw
#10 ICU:ti,ab,kw
#11 "critical illness":ti,ab,kw
#12 ventilator:ti,ab,kw
#13 ARDS:ti,ab,kw
#14 "acute respiratory distress syndrome":ti,ab,kw
#15 sepsis:ti,ab,kw
#16 CIN:ti,ab,kw
#17 CIM:ti,ab,kw
#18 CIPN:ti,ab,kw
#19 CIPNM:ti,ab,kw
#20 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#21 #7 OR #20
#22 MeSH descriptor:[Exercise]explode all trees
#23 MeSH descriptor:[Exercise therapy]explode all trees
#24 MeSH descriptor:[Rehabilitation]explode all trees
#25 MeSH descriptor:[Physical fitness]explode all trees
#26 MeSH descriptor:[Physical Therapy Modalities]explode all trees
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#29 rehabilitation:ti,ab,kw
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#31 training:ti,ab,kw

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#33 mobilisation:ti,ab,kw
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#36 "occupational therapy":ti,ab,kw
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#38 "neuromuscular electrical stimulation":ti,ab,kw
#39 "respiratory muscle training":ti,ab,kw
#40 "inspiratory muscle training":ti,ab,kw
#41 "cycle ergometer":ti,ab,kw
#42 bridging:ti,ab,kw
#43 rolling:ti,ab,kw
#44 "lying to sitting":ti,ab,kw
#45 marching:ti,ab,kw
#46 ambulation:ti,ab,kw
#47 "activities of daily living":ti,ab,kw
#48 ADL:ti,ab,kw
#49 walking:ti,ab,kw
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#51 #27 OR #50
#52 #21 AND #51

MEDLINE via PubMed

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#4 ventilator weaning[mh]
#5 Respiratory Distress Syndrome, Adult[mh]
#6 Sepsis[mh]
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#23 Exercise therapy[mh]
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#49 walking[tiab]
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#54 randomized [tiab]
#55 placebo [tiab]
#56 clinical trials as topic [mesh: noexp]
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#58 trial [ti]
#59 #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58
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#61 #59 NOT #60
#62 #21 AND #51 AND #61

EMBASE

#1 "critical care"/exp
#2 "intensive care unit"/exp
#3 "critical illness"/exp
#4 "ventilator weaning"/exp
#5 "Respiratory Distress Syndrome, Adult"/exp
#6 Sepsis/exp
#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
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#10 ICU:ab,ti
#11 "critical illness":ab,ti
#12 ventilator:ab,ti
#13 ARDS:ab,ti
#14 "acute respiratory distress syndrome":ab,ti
#15 sepsis:ab,ti
#16 CIN:ab,ti
#17 CIM:ab,ti
#18 CIPN:ab,ti
#19 CIPNM:ab,ti
#20 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#21 #7 OR #20
#22 Exercise/exp
#23 "Exercise therapy"/exp
#24 Rehabilitation/exp
#25 "Physical fitness"/exp
#26 "Physical Therapy Modalities"/exp
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#28 exercise:ab,ti
#29 rehabilitation:ab,ti
#30 "physical fitness":ab,ti
#31 training:ab,ti
#32 mobilization:ab,ti
#33 mobilisation:ab,ti

#34 "physical therapy":ab,ti
#35 physiotherapy:ab,ti
#36 "occupational therapy":ab,ti
#37 "electrical muscle stimulation":ab,ti
#38 "neuromuscular electrical stimulation":ab,ti
#39 "respiratory muscle training":ab,ti
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#41 "cycle ergometer":ab,ti
#42 bridging:ab,ti
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#44 "lying to sitting":ab,ti
#45 marching:ab,ti
#46 ambulation:ab,ti
#47 "activities of daily living":ab,ti
#48 ADL:ab,ti
#49 walking:ab,ti
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#51 #27 OR #50
#52 random*:ab,ti OR (clinical NEXT/1 trial*) OR 'health care quality'/exp
#53 #21 AND #51 AND #52

PEDro

Advance search

Abstract & Title: critical illness OR critical care OR intensive care unit OR acute respiratory distress syndrome OR ards OR sepsis OR septic OR ventilator

Method: clinical trial

The world health organization international clinical trials platform search portal (WHO ICTRP)

#1 Conditions: (critical illness OR critical care OR intensive care unit OR acute respiratory distress syndrome OR ARDS OR sepsis OR ventilator)

#2 Intervention: (rehabilitation OR exercise OR training OR mobilization OR mobilisation OR physical therapy OR physiotherapy OR occupational therapy OR neuromuscular electrical stimulation OR cycle ergometer OR ADL or activity of daily living OR ambulation OR walking)

#3 #1 AND #2

Online supplementary file 3. Characteristics of the studies analysed in this review

Author, year, country	No. of participants	Study type	Intervention (a, Timing of commencement; b, Contents; c, Duration; d, Frequency)	Control	Outcomes	Notes
Jones et al., 2003, UK	126	Multi-centre RCT	a: in-hospital b: routine follow-up plus rehabilitation package consisting of 93 pages of text c: 6 weeks d: every day*	No intervention	HRQoL, Mortality, Depression symptoms, PTSD-related symptoms	ICU rehabilitation before randomisation*
Cuthbertson et al., 2009, UK	286	Multi-centre RCT	a: in-hospital b: manual based, self-directed, physical rehabilitation program developed by physiotherapists and introduced by a study nurse c: continued for 3 months after discharge d: unknown	No intervention	HRQoL, Mortality, Quality-adjusted life years, Incidence and severity of PTSD, Anxiety and depression symptoms, Cost-effectiveness	ICU rehabilitation before randomisation*
Elliott et al., 2011, Australia	195	Multi-centre RCT	a: after hospital discharge b: home-based physical rehabilitation program focused on strength training and walking c: 8 weeks d: 5 times/week	No intervention	HRQoL, Mortality, Physical function	No ICU rehabilitation before randomisation*

Salisbury et al., 2010, UK	16	Single-centre pilot RCT	a: in-hospital b: enhanced physiotherapy and dietetic rehabilitation package c: unknown d: unknown	Standard care	Physical outcomes, Nutritional outcome, Breathlessness on the Visual analogue scale scores for breathlessness, fatigue, joint stiffness, pain, and appetite	
Batterham et al., 2014, UK	59	Multi-centre RCT	a: after hospital discharge b: hospital-based, physiotherapist-led, supervised exercise c: 8 weeks d: 2 times/week	No intervention	HRQoL, Oxygen uptake, Mood disorder	
Connolly et al., 2015, UK	20	Two-centre pilot RCT	a: after hospital discharge b: exercise-base rehabilitation session of 40 minutes c: 8 weeks d: 3 times/week (2 times supervised, 1 time unsupervised)	No intervention	HRQoL, ADL, Mortality, Physical function, Muscle strength, Adverse events, Anxiety and depression symptoms	ICU rehabilitation before randomisation*
Walsh et al., 2015, UK	240	Two-centre RCT	a: in-hospital b: mobilization exercise and relevant dietetic, occupational, and speech/language therapy c: from ICU discharge until hospital	Standard care	Mobility index, HRQoL, Anxiety and depression symptoms, Self-reported symptom scores (using visual analogue scales)	ICU rehabilitation before randomisation

			discharge but no longer than 3 months d: unknown		for fatigue, breathlessness, appetite, pain, and joint stiffness, Mortality	
McWilliams et al., 2016, UK	73	Single-centre RCT	a: after hospital discharge b: outpatient-based exercise and education program c: 7 weeks d: 3 times/week (1 supervised, 2 self-directed titrated)	No intervention	Exercise capacity, HRQoL, Mortality, Adverse events	ICU rehabilitation before randomisation*
Shelly et al., 2017, India	35	RCT	a: after hospital discharge b: home-based respiratory and mobility training c: 4 weeks d: 5 times/week	No intervention	HRQoL	
McDowell et al., 2017, UK	60	Multi-centre RCT	a: after hospital discharge b: standard care plus personalized exercise program c: 6 weeks d: 3 times/week (2 supervised and 1 unsupervised)	No intervention	HRQoL, Mortality, Adverse events, Mobility index, Hand function, Exercise capacity, Breathlessness, Anxiety and depression symptoms, Readiness to exercise, Self-efficacy to	

	exercise

*Unpublished data

ICU, intensive care unit; RCT, randomised controlled trial; HRQoL, health-related quality of life; PTSD, post-traumatic stress disorder; ADL, activity of daily living

Online supplementary file 4: Characteristics of studies excluded from qualitative and quantitative synthesis

Study	Reason for exclusion
Chiang et al., Phys Ther. 2006;86:1271-81	Quasi-RCT
Patsaki et al., J Crit Care. 2017;40:76-82	Quasi-RCT
Verceles et al., J Crit Care. 2018; 47: 204-10	Quasi-RCT
Chen et al., Am J Respir Crit Care Med. 2017;195:A2337	Outcomes were not reported in the publication abstract. The full study will be considered when the review is updated.
Salisbury et al., Clin Rehabil. 2010;24:489-500	Insufficient outcome data for meta-analysis
Batterham et al., Br J Anaesth. 2014;113:130-7	Insufficient outcome data for meta-analysis
Shelly et al., Indian J Crit Care Med. 2017;21:89-93	Insufficient outcome data for meta-analysis

RCT, randomised controlled trial

Online supplementary file 5. Assessment of risk of bias in the analysed trials using the Cochrane risk-of-bias assessment tool

Trial	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Jones et al., 2003 (22)	Low[a]	Low[a]	High	Low	High	Unclear[a]	Unclear[b]
Cuthbertson et al., 2009 (23)	Low	Low	High	Low	High	Low	Unclear[b]
Elliott et al., 2011 (24)	Low	Low	High	Low	High	High	Unclear[c]
Salisbury et al., 2010 (25)	Low	Low	High	Low	Low	Unclear	High[d]
Batterham et al., 2014 (26)	Low	Low	High	Low	Low	High	Unclear[e]
Connolly et al., 2015 (11)	Low	Low	High	High	Low	High	Unclear[e]
Walsh et al., 2015 (12)	Low	Low	High	Low	High	High	High[d]
McWilliams et al., 2016 (13)	Low	Low	High	Low	Low	Low	Unclear[e]
Shelly et al., 2017 (27)	Low	Low	High	Unclear	Low	Low	Unclear[e]
McDowell et al., 2017 (15)	Low	Low	High	Low	High	Low	High[f]

[a]Unpublished data (reply from the authors: the randomization was undertaken the old-fashioned way, with 6 slips of paper, 3 marked interventions and 3 controls, put in 6 sequentially numbered opaque envelopes and sealed and shuffled to mix them, but protocol was not published)

[b]Dose of physical rehabilitation was unknown

[c]Adherence to the intervention was unknown

[d]Intervention included nutritional therapy

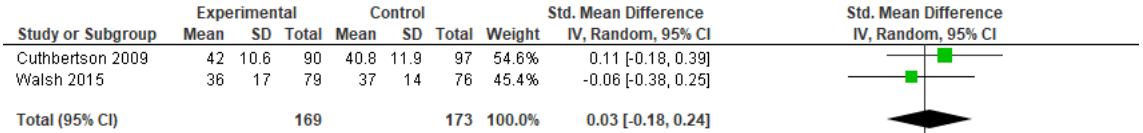
[e]Very little detail given regarding the therapy received in the control group

[f]Adherence to the intervention was 70%

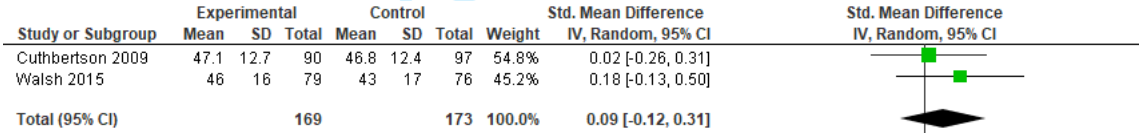
10.1136/bmjopen-2018-026075 on 9 June 2019.

Online supplementary file 6: Additional meta-analysis for quality of life and mortality at 12 months

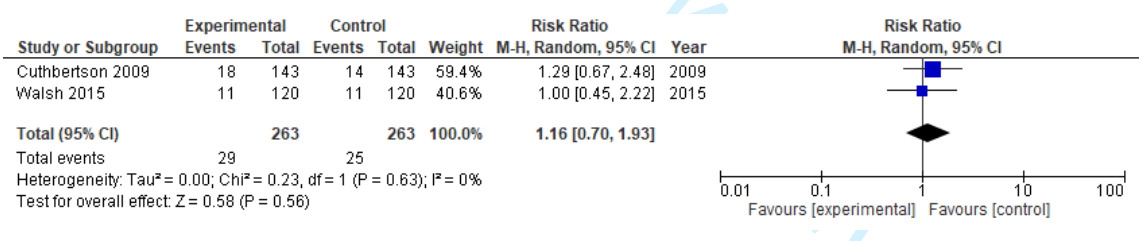
Quality of life: physical component summary



Quality of life: mental component summary



Mortality

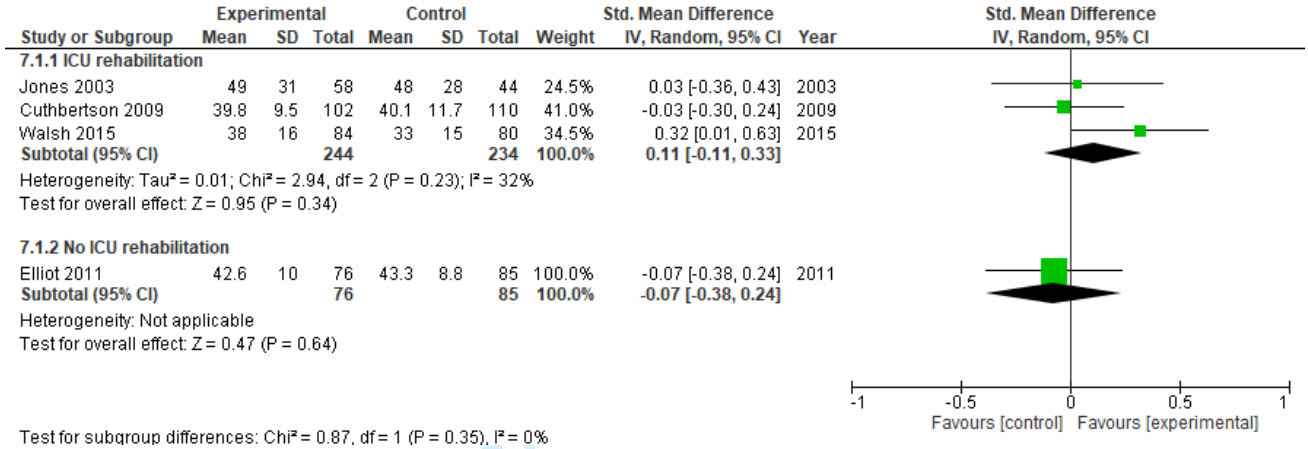


We converted median (inter quartile range) of QOL score in Walsh's study to mean (standard deviation).

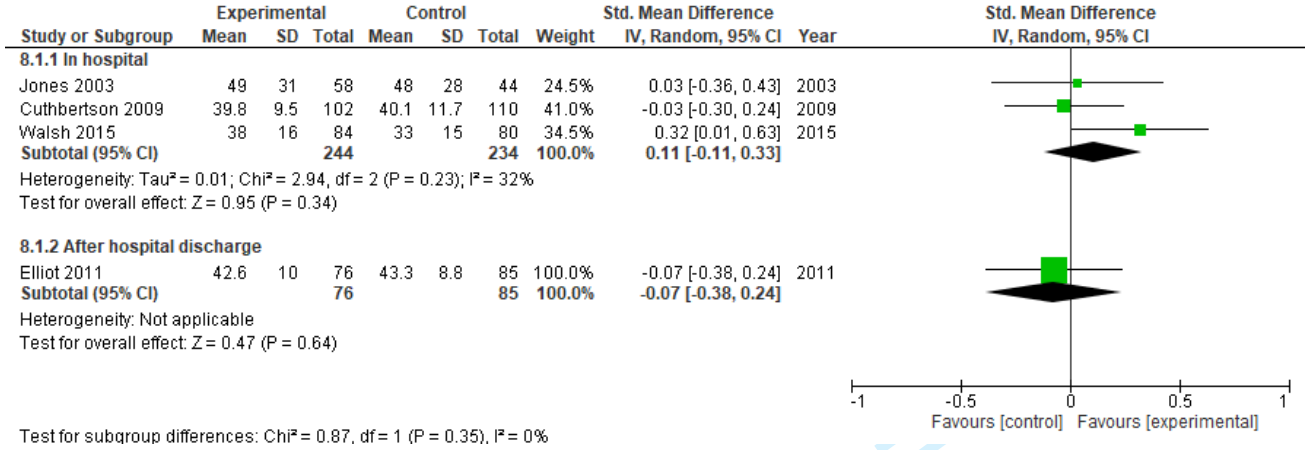
Online supplementary file 7: Subgroup analysis

A Quality of life: physical component summary

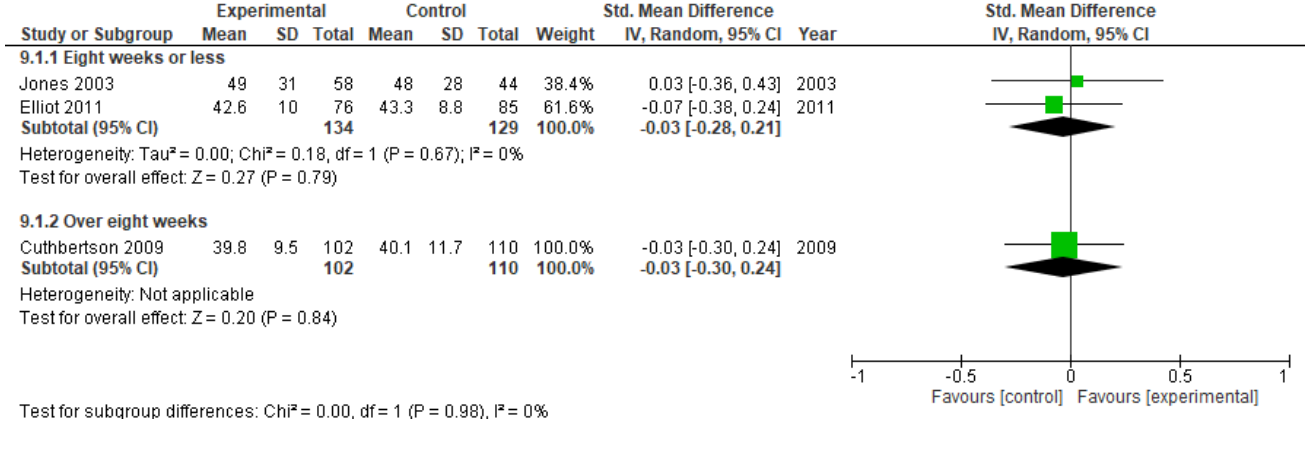
A-1 Rehabilitation practice in ICU (ICU rehabilitation before randomisation ve No ICU rehabilitation before randomisation)



A-2 The timing of the commencement of the intervention (in hospital vs after hospital discharge)

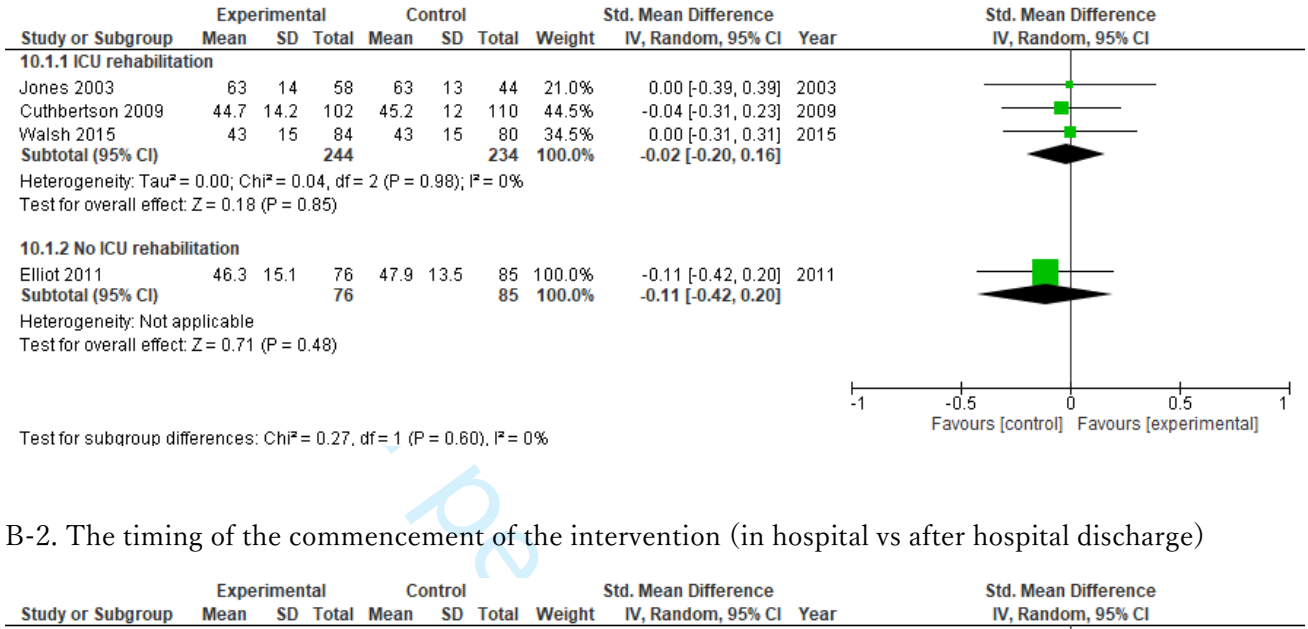


A-3. The intervention duration (eight weeks or less, and over eight weeks)

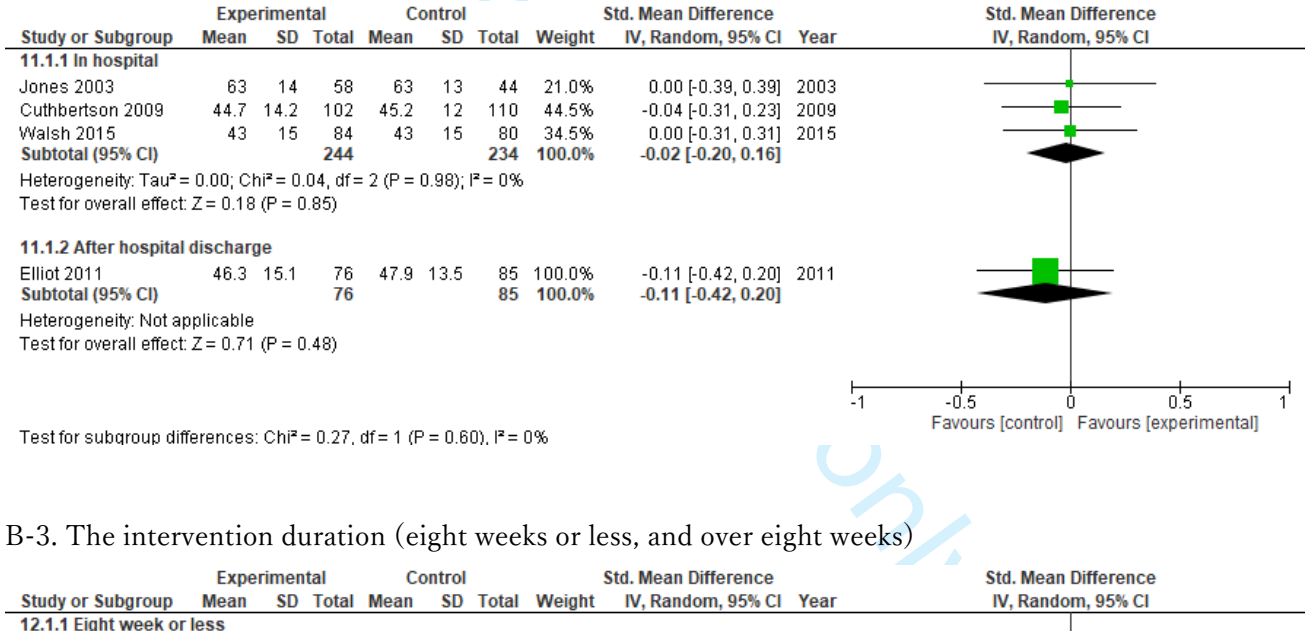


B Quality of life: mental component summary

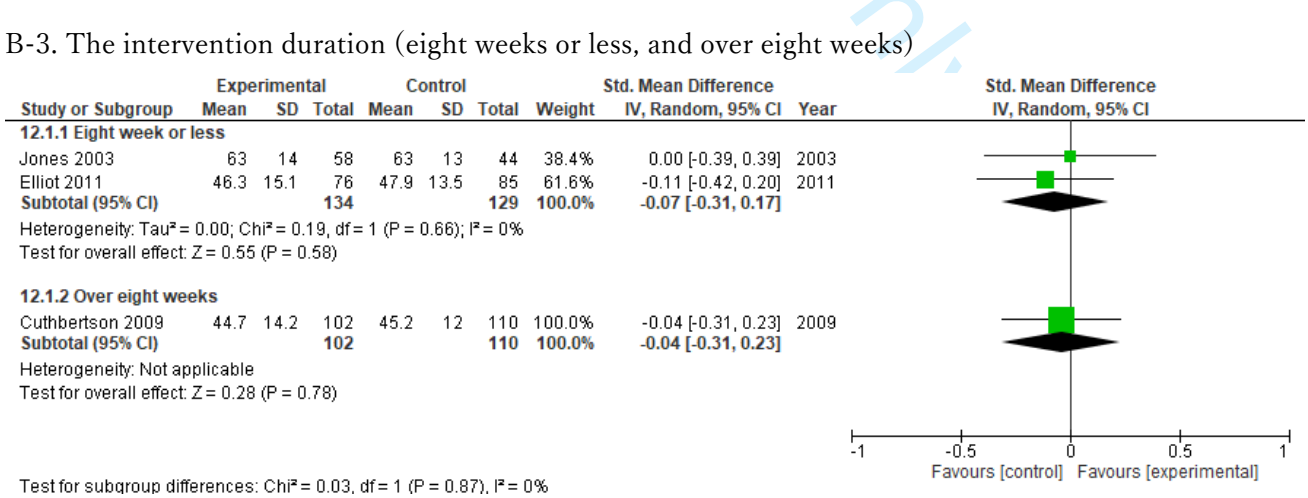
B-1. Rehabilitation practice in ICU (ICU rehabilitation before randomization ve No ICU rehabilitation before randomization)



B-2. The timing of the commencement of the intervention (in hospital vs after hospital discharge)



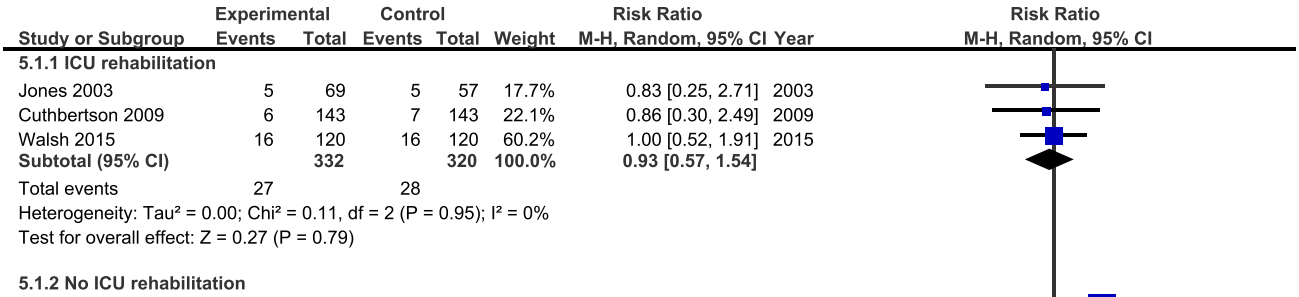
B-3. The intervention duration (eight weeks or less, and over eight weeks)



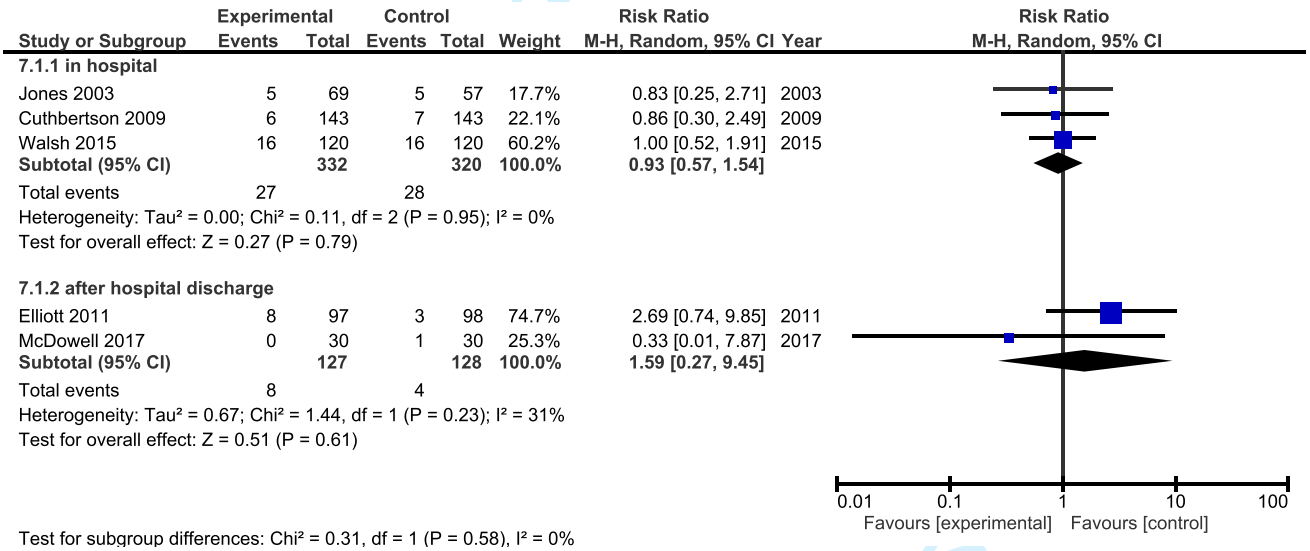
We converted median (inter quartile range) of QOL score in Walsh's study to mean (standard deviation).

C Long term mortality

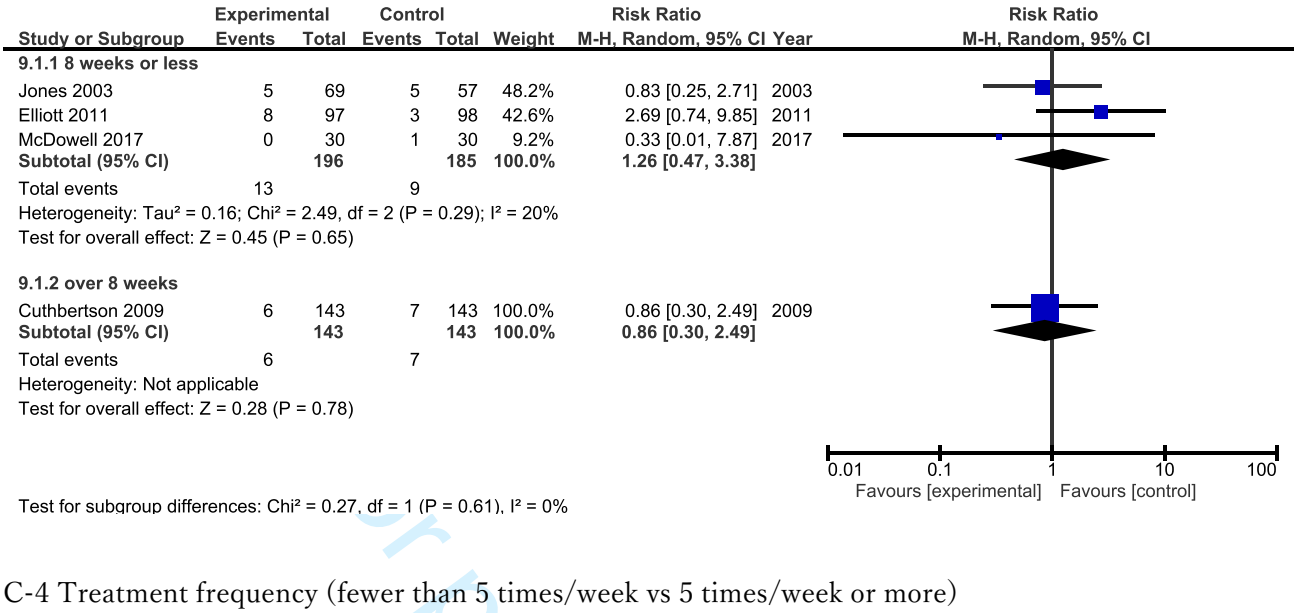
C-1. Rehabilitation practice in ICU (ICU rehabilitation before randomization ve No ICU rehabilitation before randomization)



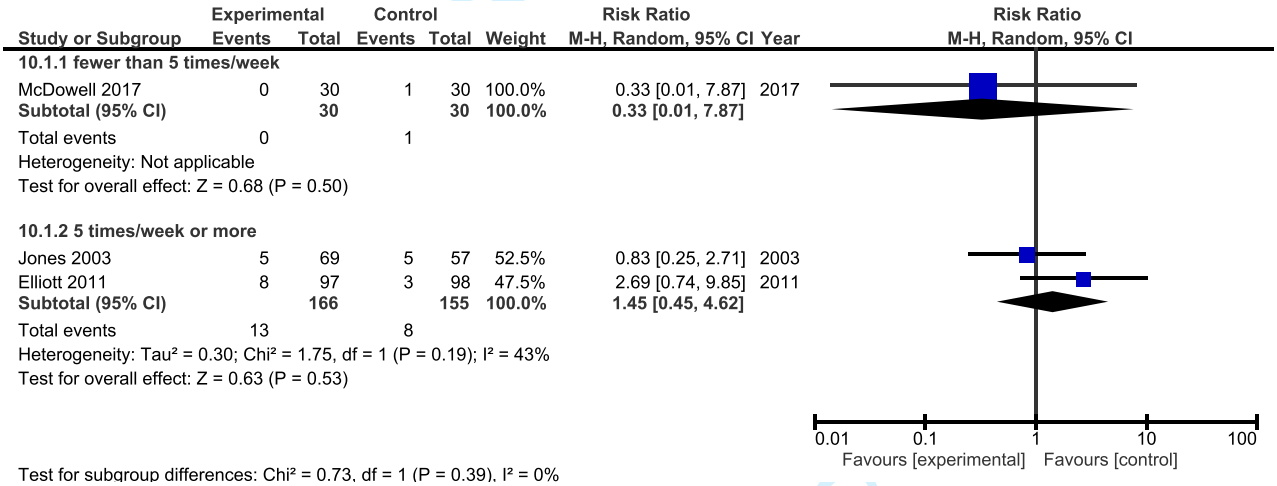
C-2 The timing of the commencement of the intervention (in hospital vs after hospital discharge)



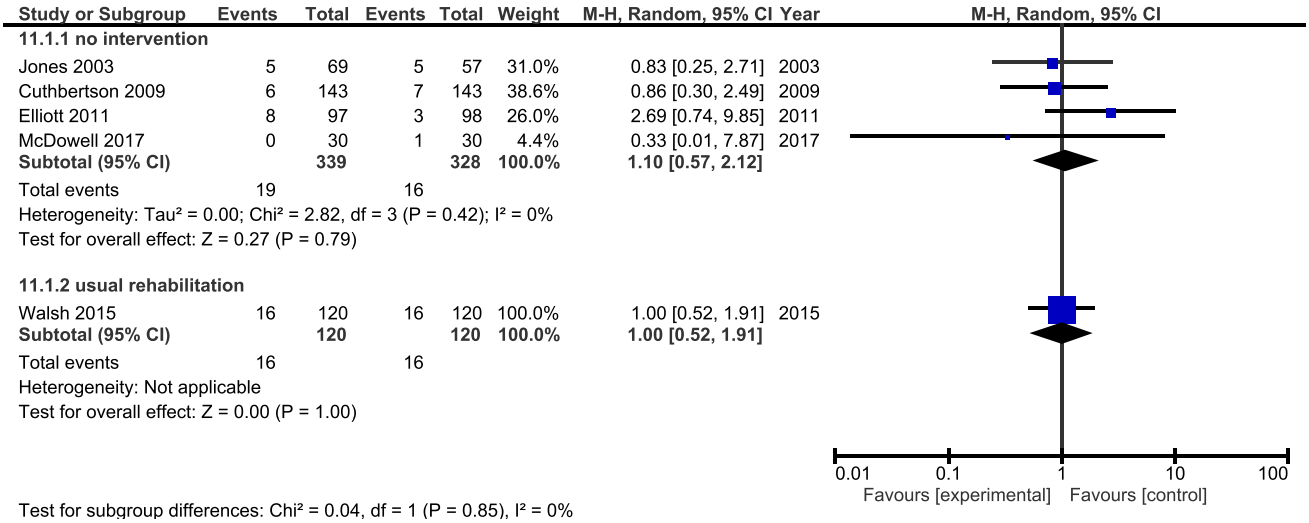
C -3. The intervention duration (8 weeks or less, and over 8 weeks)



C-4 Treatment frequency (fewer than 5 times/week vs 5 times/week or more)



C-5 Type of control (no intervention and usual rehabilitation)



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Does enhanced physical rehabilitation following intensive care unit discharge improve outcomes in patients who received mechanical ventilation? A systematic review and meta-analysis

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Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Intensive care
Keywords:	critical illness, rehabilitation, post-intensive care syndrome, exercise, quality of life, mortality

Research – meta-analysis

Does enhanced physical rehabilitation following intensive care unit discharge improve outcomes in patients who received mechanical ventilation? A systematic review and meta-analysis

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Declaration of interests: None.

Word count: 3288 words

Abbreviations

ADL, activities of daily living; APACHE, Acute Physiology And Chronic Health Evaluation; CI, confidence interval; EMBASE, Excerpta Medica Database; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; ICU, intensive care unit; PEDro, Physiotherapy Evidence Database; PICS, post-intensive care syndrome; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; QOL, quality of life; RCT, randomised controlled trial; RR, risk ratio; WHO ICTRP, World Health Organization International Clinical Trials Registry Platform

Abstract

Objective: We aimed to determine whether enhanced physical rehabilitation following intensive care unit (ICU) discharge improves activities-of-daily-living function, quality of life (QOL), and mortality among patients who received mechanical ventilation in the ICU.

Design: Systematic review and meta-analysis using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Data sources: MEDLINE, Embase, CENTRAL, PEDro, and World Health Organization International Clinical Trials Registry Platform searched through January 2019.

Eligibility criteria for selecting studies: We included randomised controlled trials assessing the effect of post-ICU rehabilitation designed to either commence earlier and/or be more intensive than the protocol employed in the control group. Only adults who received mechanical ventilation for >24 hours were included.

Data extraction and synthesis: Two independent reviewers extracted data and assessed risk of bias. Standard mean differences (SMDs) with 95% confidence intervals (CIs) were calculated for QOL, and pooled risk ratios (RRs) with 95% CIs are provided for mortality. We assessed heterogeneity based on I^2 and the certainty of evidence based on the GRADE approach.

Results: Ten trials (enrolling 1,110 patients) compared physical rehabilitation to usual care or no intervention after ICU discharge. Regarding QOL, the SMD [95% CI] between the intervention and control groups for the physical and mental component summary scores was 0.06 [-0.12 to 0.24] and -0.04 [-0.20 to 0.11], respectively. Rehabilitation did not significantly decrease long-term mortality (RR: 1.05 [0.66–1.66]). The analysed trials did not report activities-of-daily-living data. The certainty of the evidence for QOL and mortality was moderate.

Conclusions: Enhanced physical rehabilitation following ICU discharge may make little or no difference to QOL or mortality among patients who received mechanical ventilation in the ICU. Given the wide CIs, further studies are needed to confirm the efficacy of intensive post-ICU rehabilitation in selected populations.

Trial registration: PROSPERO, CRD42017080532 (registered: 28 December 2017).

Keywords: rehabilitation, critical illness, post-intensive care syndrome, exercise, quality of life, mortality

Article Summary

Strengths and limitations of this study

- This is the first meta-analysis focused on enhanced physical rehabilitation to review randomised controlled trials in which the study intervention was conducted only after intensive care unit discharge.
- The conclusions are based on moderate-certainty evidence.
- The main limitations of this meta-analysis are that (i) none of the included studies had a follow-up >6 months and (ii) medical resources and costs associated with each intervention were not considered.
- We employed rigorous methodology that followed a protocol developed *a priori* according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, and used the Grading of Recommendations Assessment, Development and Evaluation approach in the review process.

Introduction

In critically ill patients, rehabilitation mainly aims to enhance quality of life (QOL) by improving activities-of-daily-living (ADL) function,[1, 2] which may be severely impaired also due to post-intensive care syndrome (PICS).[3-5] According to the guidelines issued by the National Institute for Health and Care Excellence, provision of rehabilitation should be seamlessly integrated with the patient's transition from the intensive care unit (ICU) to the ward and then to out-of-hospital care.[6] However, at the time the guidelines were issued, there was little evidence from clinical trials to support the use of enhanced physical rehabilitation following ICU discharge. Some experts do recommend physical rehabilitation following ICU discharge to improve ADL function and QOL.[7] With regards to sepsis survivors, the findings of a large observational study suggested that physical rehabilitation following ICU discharge improves long-term mortality.[8, 9]

A recent systematic review by Connolly et al.[10] focused on randomised controlled trials (RCTs) regarding the effectiveness of enhanced exercise rehabilitation following ICU discharge in adult ICU survivors who had been mechanically ventilated for longer than 24 hours in the ICU. Despite the comprehensive search, this previous systematic review included only 6 RCTs with conflicting results, and no clear effect of

the intervention on QOL, mortality, functional exercise capacity, or incidence of adverse events could be established at the time. Additionally, ADL, pain, return-to-work rate, muscle strength, and duration of delirium were not considered in that review.[10] Several RCTs assessing the effect of enhanced physical rehabilitation following ICU discharge on clinically relevant outcomes[11-15] have been published since Connolly and colleagues conducted their Cochrane review.[10] Therefore, in the present study, we aimed to re-evaluate the available literature and determine whether enhanced physical rehabilitation following ICU discharge improves clinically relevant outcomes among critically ill adults who received mechanical ventilation.

Materials and methods

Compliance with reporting guidelines

Using a pre-specified protocol (PROSPERO registry ID: CRD42017080532),[16] we conducted a systematic review of the relevant literature in agreement with the recommendations listed in the Cochrane Handbook[17] and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[18] We confirmed that this systematic review was PRISMA-compliant by consulting the PRISMA 2009 checklist[19] (details provided in online supplementary file

1). ***Research question and eligibility criteria***

The research question addressed in this study was: "Does enhanced physical rehabilitation following ICU discharge result in improved QOL, ADL function, and mortality (compared to those achievable with usual care) among patients who received mechanical ventilation in the ICU?" We included all published and unpublished prospective RCTs involving adult human subjects (age ≥18 years) who had been discharged from an ICU or critical care environment after a stay of at least 48 hours during which mechanical ventilation was provided for at least 24 hours. Crossover trials, as well as cluster-, quasi-, and non-randomised trials were excluded. Studies were included regardless of the intervention setting (in-hospital or out-of-hospital), follow-up duration, and country of origin. We included patients of any sex and race, but excluded those receiving palliative care and those with head or spinal cord injuries, or unstable fracture diminishing mobility.

Intervention was defined as any protocolised rehabilitation following ICU discharge, designed to either commence earlier and/or be more intensive than the care received by the control group. To determine whether enhanced physical rehabilitation following ICU discharge improved clinically relevant outcomes, we excluded studies in

which the patients in the intervention group received earlier and/or more intensive physical rehabilitation (compared to the care received by the control group) during their stay in the ICU. However, while we excluded studies in which enhanced rehabilitation was provided in the ICU, we did not exclude studies in which the same rehabilitation program was provided in the ICU as standard care for both the intervention group and the control group. Protocolised rehabilitation consisting of one or more of the following activities was considered as a form of enhanced physical rehabilitation: neuromuscular stimulation, inspiratory or respiratory muscle training, passive range-of-motion exercise, cycle ergometer exercise, active-assisted exercises, active range-of-motion exercises, bed mobility activities (e.g., bridging, rolling, lying-to-sitting exercise), ADL training, transfer training, pre-gait exercises (including marching in place), and walking exercise.

Outcomes of interest

The primary outcomes were QOL, ADL function, and mortality. Secondary outcomes included functional exercise capacity, pain, return-to-work rate, muscle strength, duration of delirium, and incidence of adverse events (defined by the trialists). We defined the intervention outcomes according to the timing of their evaluation post-intervention, as short-term (evaluated at 28–35 days) or long-term (evaluated at 6 months).

Search strategy and selection of studies

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE via PubMed, Excerpta Medica Database (EMBASE) via Elsevier, the Physiotherapy Evidence Database (PEDro), and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) via their dedicated search portal. The search, which employed a set of suitable search terms (details provided in online supplementary file 2), was performed in December 2017 and updated in January 2019. We hand-searched reference lists for the guidelines for rehabilitation after critical illness.[6] We attempted to identify other relevant research by hand-searching the reference lists of the studies returned by the search and those of articles citing such studies (based on citation information from the Web of Science). If the database entry for a candidate study did not contain the necessary information, we contacted the study authors. Two reviewers (ST and KY) independently screened the title and abstract of each study returned by the search to determine whether the inclusion criteria were met. The two reviewers performed a full-text review to assess the eligibility of each candidate study. Disagreement was resolved by discussion between the two reviewers, occasionally with arbitration by a third reviewer (YK).

Data abstraction and quality assessment

Two reviewers (ST and KY) independently abstracted trial-level data using pre-

specified forms. Disagreements regarding data extraction were resolved through discussions. Where necessary, we contacted the authors of studies that did not provide sufficient information. The risk of bias in each study was assessed independently by two reviewers (ST and KY) using the Cochrane risk-of-bias assessment tool.[17] Differences in opinion regarding the assessment of risk of bias were resolved through discussion between the two reviewers, occasionally with arbitration by a third reviewer (KY).

Data analysis

All analyses were conducted using the Cochrane Review Manager software (RevMan 5.3; Cochrane Collaboration, Copenhagen, Denmark). For the dichotomous variables of mortality and return-to-work rate, pooled risk ratios (RRs) with 95% confidence intervals (CIs) are provided. For continuous outcomes including QOL scores, ADL function scores, pain, muscle strength, and duration of delirium (expressed in days of ICU or hospital stay), the standardized mean differences, or the mean differences with 95% CIs were calculated, as recommended by the Cochrane Handbook.[17] Adverse events were narratively summarised because their definition often varies across studies. We used the random-effects models for all analyses.

We calculated I^2 as a measure of variation across studies that is due to heterogeneity rather than chance, and interpreted the values as follows: 0%–40%,

negligible heterogeneity; 30%–60%, mild-to-moderate heterogeneity; 50%–90%, moderate-to-substantial heterogeneity; 75%–100%, considerable heterogeneity. If heterogeneity was identified for an outcome (I^2 >50%), we investigated the underlying reasons and conducted the χ^2 test, with a *P*-value of <0.10 being considered to indicate statistical significance. We investigated reporting bias by checking the WHO ICTRP to detect trials that had been completed but not published at the time of the review.

We planned the following pre-specified sensitivity analyses for the primary outcomes: (i) exclusion of studies using imputed statistics, and (ii) exclusion of studies with high or unclear risk of bias. We also carried out pre-specified subgroup analyses according to the type of rehabilitation involved (neuromuscular stimulation versus other types of rehabilitation), rehabilitation provision in the ICU (received versus did not receive protocolised physical rehabilitation in the ICU), timing of commencement of the intervention (in-hospital or after hospital discharge), intervention duration (≤8 versus >8 weeks), treatment frequency (<5 versus ≥5 times/week), and type of control (no intervention versus standard rehabilitation). Statistical significance was also set at *P*<0.05.

We created a summary-of-findings table that included an overall grading of the certainty of evidence for each of the main outcomes, which was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[20,

21]

Patient and public involvement

The patients or public were not involved in this meta-analysis.

Results

Characteristics of trials on rehabilitation in ICU survivors

After removing duplicates, we identified 3,589 records during the search conducted in December 2017 and updated the electronic searches in January 2019. We identified 10 unique RCTs[11–13, 15, 22–27] that fulfilled all eligibility criteria and were included in the qualitative synthesis (Fig. 1; details provided in online supplementary file 3). The 10 RCTs provided a pooled sample of 1,110 critically ill patients with an ICU stay of >48 hours during which mechanical ventilation was provided for at least 24 hours. Eight studies were performed in the United Kingdom, one in Australia, and one in India. The mean or median age in the analysed studies ranged from 40.5 to 68.5 years, while the mean or median Acute Physiology and Chronic Health Evaluation (APACHE) II score ranged from 15.2 to 31. Only 1 RCT included participants with PICS symptoms or ICU-acquired weakness.[11] Three RCTs[25–27] did not have sufficient outcome data for meta-analysis (details provided in online

supplementary file 4), leaving a total pooled sample of 1,000 patients (506 patients in the intervention groups; 494 controls) represented across 7 studies to be included in the quantitative synthesis. Of the 10 trials analysed, 6 evaluated the effect of physical rehabilitation including self-directed exercise and/or supervised exercise following hospital discharge, while 4[12, 22–24] focused on rehabilitation started during hospitalisation. The duration of intervention ranged from 6 weeks to 3 months, while the frequency of intervention ranged from 3 times per week to once daily. No study considered intensive intervention (>30 minutes of active rehabilitation daily) or intervention with neuromuscular stimulation. Two studies [12, 23] had a follow-up >6 months. We did not identify any ongoing studies.

Most studies were at high or unclear risk of bias, as determined using the Cochrane risk-of-bias assessment tool[17] (details provided in online supplementary file 5). All 10 studies demonstrated adequate random sequence generation and allocation concealment, but participants and personnel were not blinded to the intervention. One study[11] demonstrated a high risk of detection bias for all outcomes except mortality, and another study[27] did not report whether or not the outcome assessor was aware of group allocation. Five studies had high risk of incomplete outcome data. Four studies had high risk of selective reporting bias, and 2 studies had unclear risk of bias because the

protocols were not published. High or unclear risk of other bias was noted for all studies because of insufficient information regarding the intervention and control protocols.

Primary outcomes

QOL was measured in 9 trials (see online supplementary file 3), but the short- and long-term QOL scores were only available in four trials,[12, 22–24] whereas the other 5 trials measured these outcomes at a different time or had insufficient outcome data for meta-analysis. ADL function was measured in 1 trial,[11] but the short- and long-term data were not available. Short-term mortality was reported in 2 trials,[11, 13] while long-term mortality was reported in 5 trials.[12, 15, 22–24]

The standard mean deviation between intervention and control regarding the physical and mental component summary scores measured using QOL questionnaires (SF-36 or SF-12) were 0.06 (95% CI, -0.12 to 0.24) and -0.04 (95% CI, -0.20 to 0.11), respectively (Fig. 2A and 2B, respectively). Rehabilitation did not significantly decrease short-term mortality (RR, 0.71; 95% CI, 0.05–9.80, I^2 = 33%; n = 93) (Fig. 2C) or long-term mortality (RR, 1.05; 95% CI, 0.66–1.66, I^2 = 0%; n = 907) (Fig. 2D). The certainty of evidence for QOL and long-term mortality was moderate, while that for short-term mortality was low (Table 1). The lack of benefit of enhanced physical rehabilitation after ICU discharge was confirmed upon additional analysis of QOL scores and mortality at

12 months post-intervention (see details provided in online supplementary file 6).

We could not carry out all pre-specified sensitivity analyses because there was no study using imputed statistics, and we judged that the risk of bias of all included studies was similar in terms of random sequence generation, allocation concealment, incomplete outcome data, and other bias. The pre-specified subgroup analyses for the primary outcomes revealed no significant differences among sub-groups (see details provided in online supplementary file 7).

Secondary outcomes

Functional exercise capacity was measured in 2 trials,[11, 24] pain was measured in 1 trial,[12] and muscle strength was measured in 1 trial,[11] but short- and long-term data were not available. No trials evaluated return-to-work rate or incidence of delirium.

Adverse events were measured in 3 trials.[11, 13, 15] Two studies[11, 13] reported no adverse events. One study[15] reported 18 events in the intervention group and 5 events in the control group. Among the 18 adverse events reported in the intervention group, 12 were mild or moderate (musculoskeletal pain higher than expected or muscle soreness potentially indicating injury, 3 cases; any pain higher than expected, 1 case; cardiac symptoms or chest pain, 1 case; any other event considered by the researcher to be of concern, 7 cases; 6 of 12 events were considered to be related or

possibly related to study participation), while 6 were serious (hospitalisation or prolonged hospitalisation, with 1 event related/possibly related to study participation). In the control group, there was 1 adverse event (musculoskeletal pain higher than expected, muscle soreness potentially indicating injury, related/possibly related to study participation) and 4 serious adverse events (hospitalisation or prolonged hospitalisation, with 1 event related/possibly related to study participation). The certainty of evidence for adverse events was low (Table 1).

Discussion

The results of this up-to-date review covering 10 RCTs and 1,110 patients suggest that enhanced rehabilitation following ICU discharge might not improve QOL or reduce mortality at 6 or 12 months post-intervention among patients who received mechanical ventilation in the ICU. We could not confirm the effect of enhanced physical rehabilitation even though all included studies exhibited performance bias potentially increasing the observed effect of the intervention. Furthermore, despite the large sample size in the meta-analysis for QOL and long-term mortality, limited data for these outcomes were available, and the certainty of evidence was only low or moderate.

Furthermore, subgroup meta-analyses revealed no differences among subgroups defined according to the nature or timing of the intervention. The previous review by Connolly et al.[10] did not conduct meta-analysis due to the limited number of included studies. A recent systematic review of ICU rehabilitation[28, 29] also reported no significant difference in QOL between the intervention and control groups. Thus, neither enhanced rehabilitation in the ICU nor rehabilitation following ICU discharge appear to be superior to standard care in terms of QOL outcomes. In addition, we found no benefit in terms of short- or long-term mortality regardless of timing of commencement, which is consistent with previous findings that ICU rehabilitation did not decrease mortality at ICU discharge, at hospital discharge, or at 6 months after discharge.[28, 30] On the other hand, rehabilitation may be detrimental in acute conditions. Specifically, intensive physical rehabilitation started within 48 hours of admission for exacerbations of chronic respiratory disease increased mortality at 12 months,[31] and higher-dose physical rehabilitation very early after stroke decreased favourable outcomes at 3 months.[32] Thus, implementation of an intensive rehabilitation program might not be indicated in all patients who received mechanical ventilation in the ICU.

Subgroup analysis in a previous systematic review[28] indicated that, compared with low-dose rehabilitation, high-dose active rehabilitation for >30 minutes daily was associated with significantly higher QOL. Dose-response analysis of early physical rehabilitation[33] in stroke patients enrolled in A Very Early Rehabilitation Trial (AVERT)[32] determined that intervention in such acute cases improved the odds of a favourable outcome with each episode of activity per day. Our present review did not include studies comparing high-dose rehabilitation and usual care, and thus the QOL effect of high-dose rehabilitation remains unclear. Additionally, we could not perform subgroup analysis for PICS symptoms with effect on QOL[3–5] or for sepsis, which is a risk factor for PICS.[34, 35] It remains unclear which population of critically ill patients may truly benefit from intensive physical rehabilitation.

The studies included in our review did not cover all important outcomes included in the core outcome set of rehabilitation after critical illness,[7] including ADL function, functional exercise capacity, pain, return-to-work rate, muscle strength, or delirium incidence. Nonetheless, our findings regarding QOL and mortality suggest that, even if future studies report improvement in these other aspects, the amount of improvement would likely be too small to affect QOL.

The present review has several strengths. First, we employed rigorous

methodology that followed a written protocol developed *a priori* according to the PRISMA statement, including a comprehensive search for evidence. Second, we performed duplicate assessment of eligibility, risk of bias, and data abstraction. Third, we used the GRADE approach for assessing the certainty of evidence. In addition, we only included RCTs, most of which were multicentre studies. We could thus conduct an intention-to-treat analysis to understand the effect of intensive physical rehabilitation or standard care, which gives a pragmatic estimate of the benefit of a change in treatment policy. Fourth, the cohorts of ICU survivors are heterogeneous in terms of demographics and pathologies. To confirm the effect of enhanced physical rehabilitation for a particular group, we selected studies including only participants with an ICU stay of >48 hours during which mechanical ventilation was provided for at least 24 hours.

This systematic review has several potential limitations. Firstly, few studies [12, 23] had a follow-up >6 months, and thus we could not consider longer follow-up data for primary analysis. The meta-analysis should be updated as the outcomes of further studies with follow-up beyond 6 months become available. Secondly, none of the studies included in our meta-analysis reported mortality outcomes as time-to-event data, which is the preferred approach for reporting mortality data. Future studies should report time-to-event data for mortality. Thirdly, we could not take into account the

medical resources and costs associated with each intervention. However, since studies included in this review compare rehabilitation intervention against standard care or no intervention, it is obvious that intensive physical rehabilitation would be associated with increased medical resources and costs. Fourthly, the outcome measures might be not sufficiently sophisticated. For example, the RECOVER trial[15] did not demonstrate an improvement in the primary quantitative outcome, but showed evidence of benefit of the intervention in a parallel qualitative evaluation.[36] Fifthly, we could not consider the psychological aspects that are likely to affect the outcomes of rehabilitation. While our findings indicate a lack of benefit of enhanced post-ICU rehabilitation in the evaluated population, highly self-motivated individuals might have derived benefit from such therapies. Further studies should collect data on motivation and engagement, which are crucial in maximising the benefits of rehabilitation [37]. Lastly, the patient characteristics, follow-up timing, and types of outcomes reported might exhibit substantial heterogeneity not only across trials but also within each individual trial, an aspect we did not examine in the present analysis. However, upon reviewing the best available evidence based on a standardised approach, we confirmed that the direction of the effect and the effect size of enhanced post-ICU physical

rehabilitation were similar in pooled studies, as reflected in the Forest plots (see details in online supplementary file 7).

Taken together, the findings of the present meta-analysis indicate that enhanced physical rehabilitation following ICU discharge may make little or no difference to QOL or mortality among patients who received mechanical ventilation in the ICU. Given the wide CIs, further studies are needed to determine the efficacy of enhanced rehabilitation in selected populations of ICU survivors.

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Author contributions

ST and KY designed the study, were involved in the systematic review process, analysed and interpreted the data, and drafted the manuscript. MB, HT, YK, and YT participated in the systematic review process, critically reviewed the initial manuscript, and approved the final manuscript as submitted. All authors read and approved the final manuscript.

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Declaration of interests

None.

Data sharing statement

All data associated with this manuscript are included in the main text and supplementary materials.

Supplementary data

Supplementary data to this article can be found online.

Online supplementary file 1: PRISMA 2009 checklist

Online supplementary file 2: Search strategies

Online supplementary file 3: Characteristics of the studies analysed in this review

Online supplementary file 4: Characteristics of studies excluded from qualitative and quantitative synthesis

Online supplementary file 5: Assessment of risk of bias in the trials analysed

Online supplementary file 6: Additional meta-analysis for quality of life and mortality at 12 months

Online supplementary file 7: Subgroup analysis for quality of life and mortality

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Figure legends

Fig 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram

Fig 2 Forest plot for quality of life and mortality

Tables

Table 1. Findings from ten trials focused on post-ICU rehabilitation of critically ill patients who received mechanical ventilation

Overview of study design						
Patients or study population: adult patients who have been discharged from an ICU or critical care environment during which mechanical ventilation was provided for at least 24 hours **Setting:** any **Intervention:** protocolised physical rehabilitation following ICU discharge, designed to be more intensive than the care received by the control group. **Comparison:** no intervention or usual care						
Outcome	**Illustrative comparative risks[*] (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Assumed risk Control	Corresponding risk Intervention				
Quality of life Physical component summary score (6 months)	**Study population**	**SMD: 0.06** (-0.12 to 0.24)		649 (4 RCTs)	⨁⨁⨁◯ **Moderate**[a]	
	Study population			639	⨁⨁⨁◯	

Quality of life Mental component summary score (6 months)		**SMD: -0.04** (-0.20 to 0.11)		(4 RCTs)	**Moderate**[a]
Mortality Short term (28–35 days)	**Study population** **43 per 1000**	**31 per 1000** (2 to 426)	**RR: 0.71** (0.05 to 9.80)	93 (2 RCTs)	⨁⨁⨁◯ **Low**[b]
Mortality Long term (6 months)	**Study population** **71 per 1000**	**75 per 1000** (47 to 119)	**RR: 1.05** (0.66 to 1.66)	907 (5 RCTs)	⨁⨁⨁◯ **Moderate**[d]
Adverse events	**Study population** Two studies reported no adverse events. One study reported 18 and 5 events in the intervention and control groups, respectively.			153 (3 RCTs)	⨁⨁◯⨁ **Low**[ef]

*The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect (and its 95% CI) estimated for the intervention group.

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

.136/bmjopen-2018-022075 on 9 June 2019

Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

CI, confidence interval; RR, risk ratio; ICU, intensive care unit; SF-36, Short Form 36; SMD, standardized mean difference; RCT, randomised controlled trial

[a]Downgraded one point because of high risk of bias associated with the lack of information regarding the dose of physical rehabilitation and adherence in the intervention group (other bias).

[b]Downgraded one point because of high risk of bias associated with the fact that the intervention included nutritional therapy but the study provided very little detail regarding the therapy received in the control group (other bias).

[c]Downgraded because of imprecision (only two small studies).

[d]Downgraded one point because of high risk of bias associated with incomplete outcome data and lack of information regarding the dose of physical rehabilitation and adherence in the intervention group, as well as with the fact that the intervention included nutritional therapy but the study provided very little detail regarding the therapy received in the control group (other bias).

[e]Downgraded one point because of high risk of bias associated with the fact that very little detail was given regarding the therapy received in the control group, and the adherence in the intervention group was 70% (other bias).

[f]Downgraded because of imprecision (only three small studies).

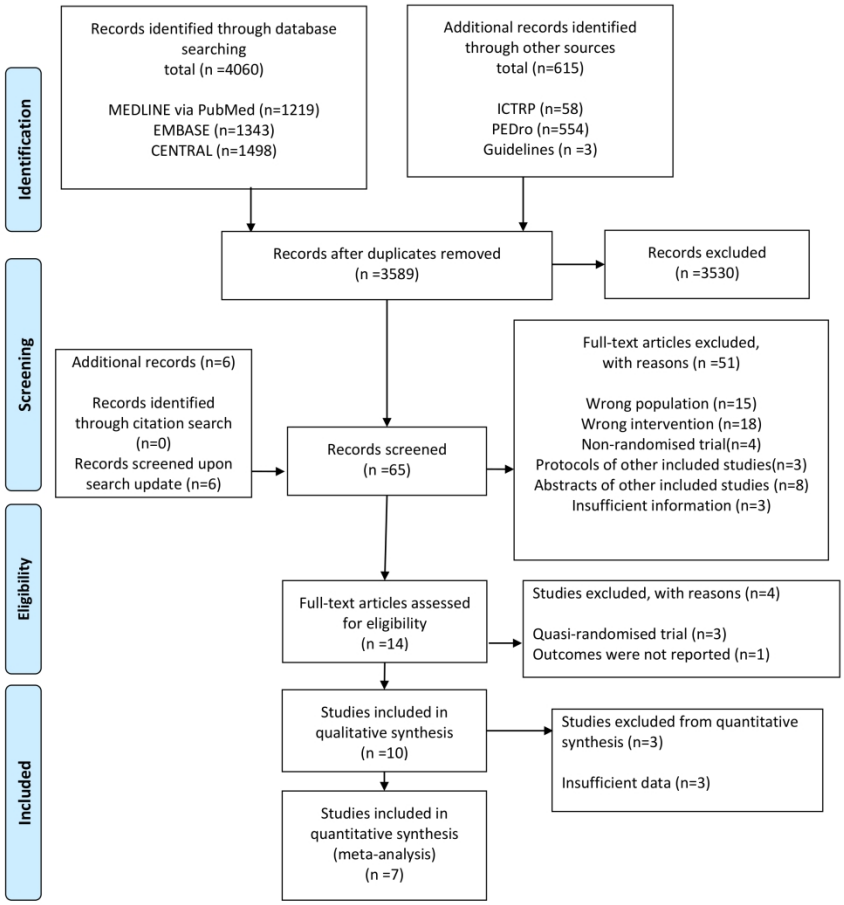
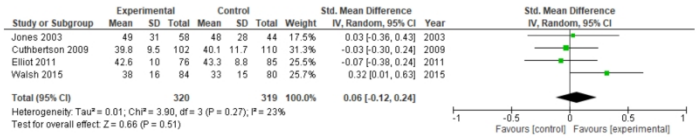


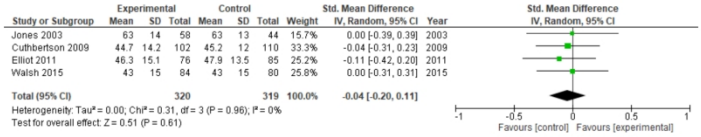
Fig 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram

215x279mm (300 x 300 DPI)

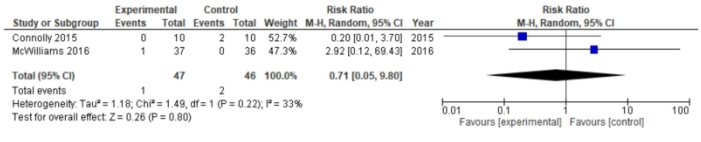
2-A Quality of life: physical component summary



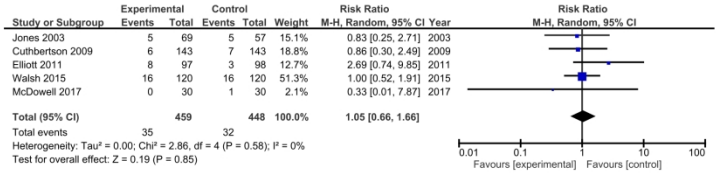
2-B Quality of life: mental component summary



2-C Short term mortality



2-D Long term mortality



We converted median (inter quartile range) of QOL score in Walsh's study to mean (standard deviation).

Fig 2 Forest plot for quality of life and mortality

209x297mm (300 x 300 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4, 5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	7, 8
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	8
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	8
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	9, 10
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	11
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	11
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	11
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	11, 12
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	10
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	11, 12
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	12
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	13

PRISMA 2009 Checklist

Checklist item 9			
Section/topic	**#**		**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	13
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicateng which were pre-specified.	13
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	14
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	14, 15
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	15, 16
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	16-18
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	16-18
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	15
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	17
DISCUSSION			
Summary of evidence	14	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	18, 19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21, 22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	24

Online supplementary file 2: Search strategies

The cochrane central register of controlled trials (CENTRAL)

#1 MeSH descriptor:[critical care]explode all trees
#2 MeSH descriptor:[intensive care unit]explode all trees
#3 MeSH descriptor:[critical illness]explode all trees
#4 MeSH descriptor:[ventilator weaning]explode all trees
#5 MeSH descriptor:[Respiratory Distress Syndrome, Adult]explode all trees
#6 MeSH descriptor:[Sepsis]explode all trees
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#9 "intensive care unit":ti,ab,kw
#10 ICU:ti,ab,kw
#11 "critical illness":ti,ab,kw
#12 ventilator:ti,ab,kw
#13 ARDS:ti,ab,kw
#14 "acute respiratory distress syndrome":ti,ab,kw
#15 sepsis:ti,ab,kw
#16 CIN:ti,ab,kw
#17 CIM:ti,ab,kw
#18 CIPN:ti,ab,kw
#19 CIPNM:ti,ab,kw
#20 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#21 #7 OR #20
#22 MeSH descriptor:[Exercise]explode all trees
#23 MeSH descriptor:[Exercise therapy]explode all trees
#24 MeSH descriptor:[Rehabilitation]explode all trees
#25 MeSH descriptor:[Physical fitness]explode all trees
#26 MeSH descriptor:[Physical Therapy Modalities]explode all trees
#27 #22 OR #23 OR #24 OR #25 OR #26
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#29 rehabilitation:ti,ab,kw
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#31 training:ti,ab,kw

#32 mobilization:ti,ab,kw
#33 mobilisation:ti,ab,kw
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#35 physiotherapy:ti,ab,kw
#36 "occupational therapy":ti,ab,kw
#37 "electrical muscle stimulation":ti,ab,kw
#38 "neuromuscular electrical stimulation":ti,ab,kw
#39 "respiratory muscle training":ti,ab,kw
#40 "inspiratory muscle training":ti,ab,kw
#41 "cycle ergometer":ti,ab,kw
#42 bridging:ti,ab,kw
#43 rolling:ti,ab,kw
#44 "lying to sitting":ti,ab,kw
#45 marching:ti,ab,kw
#46 ambulation:ti,ab,kw
#47 "activities of daily living":ti,ab,kw
#48 ADL:ti,ab,kw
#49 walking:ti,ab,kw
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#51 #27 OR #50
#52 #21 AND #51

MEDLINE via PubMed

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#3 critical illness[mh]
#4 ventilator weaning[mh]
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#6 Sepsis[mh]
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#62 #21 AND #51 AND #61

EMBASE

#1 "critical care"/exp
#2 "intensive care unit"/exp
#3 "critical illness"/exp
#4 "ventilator weaning"/exp
#5 "Respiratory Distress Syndrome, Adult"/exp
#6 Sepsis/exp
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#10 ICU:ab,ti
#11 "critical illness":ab,ti
#12 ventilator:ab,ti
#13 ARDS:ab,ti
#14 "acute respiratory distress syndrome":ab,ti
#15 sepsis:ab,ti
#16 CIN:ab,ti
#17 CIM:ab,ti
#18 CIPN:ab,ti
#19 CIPNM:ab,ti
#20 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#21 #7 OR #20
#22 Exercise/exp
#23 "Exercise therapy"/exp
#24 Rehabilitation/exp
#25 "Physical fitness"/exp
#26 "Physical Therapy Modalities"/exp
#27 #22 OR #23 OR #24 OR #25 OR #26
#28 exercise:ab,ti
#29 rehabilitation:ab,ti
#30 "physical fitness":ab,ti
#31 training:ab,ti
#32 mobilization:ab,ti
#33 mobilisation:ab,ti

#34 "physical therapy":ab,ti
#35 physiotherapy:ab,ti
#36 "occupational therapy":ab,ti
#37 "electrical muscle stimulation":ab,ti
#38 "neuromuscular electrical stimulation":ab,ti
#39 "respiratory muscle training":ab,ti
#40 "inspiratory muscle training":ab,ti
#41 "cycle ergometer":ab,ti
#42 bridging:ab,ti
#43 rolling:ab,ti
#44 "lying to sitting":ab,ti
#45 marching:ab,ti
#46 ambulation:ab,ti
#47 "activities of daily living":ab,ti
#48 ADL:ab,ti
#49 walking:ab,ti
#50 #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49
#51 #27 OR #50
#52 random*:ab,ti OR (clinical NEXT/1 trial*) OR 'health care quality'/exp
#53 #21 AND #51 AND #52

PEDro

Advance search

Abstract & Title: critical illness OR critical care OR intensive care unit OR acute respiratory distress syndrome OR ards OR sepsis OR septic OR ventilator

Method: clinical trial

The world health organization international clinical trials platform search portal (WHO ICTRP)

#1 Conditions: (critical illness OR critical care OR intensive care unit OR acute respiratory distress syndrome OR ARDS OR sepsis OR ventilator)

#2 Intervention: (rehabilitation OR exercise OR training OR mobilization OR mobilisation OR physical therapy OR physiotherapy OR occupational therapy OR neuromuscular electrical stimulation OR cycle ergometer OR ADL or activity of daily living OR ambulation OR walking)

#3 #1 AND #2

Online supplementary file 3. Characteristics of the studies analysed in this review

Author, year, country	No. of participants	Study type	Intervention (a, Timing of commencement; b, Contents; c, Duration; d, Frequency)	Control	Outcomes	Notes
Jones et al., 2003, UK	126	Multi-centre RCT	a: in-hospital b: routine follow-up plus rehabilitation package consisting of 93 pages of text c: 6 weeks d: every day*	No intervention	HRQoL, Mortality, Depression symptoms, PTSD-related symptoms	ICU rehabilitation before randomisation*
Cuthbertson et al., 2009, UK	286	Multi-centre RCT	a: in-hospital b: manual based, self-directed, physical rehabilitation program developed by physiotherapists and introduced by a study nurse c: continued for 3 months after discharge d: unknown	No intervention	HRQoL, Mortality, Quality-adjusted life years, Incidence and severity of PTSD, Anxiety and depression symptoms, Cost-effectiveness	ICU rehabilitation before randomisation*
Elliott et al., 2011, Australia	195	Multi-centre RCT	a: after hospital discharge b: home-based physical rehabilitation program focused on strength training and walking c: 8 weeks d: 5 times/week	No intervention	HRQoL, Mortality, Physical function	No ICU rehabilitation before randomisation*

Salisbury et al., 2010, UK	16	Single-centre pilot RCT	a: in-hospital b: enhanced physiotherapy and dietetic rehabilitation package c: unknown d: unknown	Standard care	Physical outcomes, Nutritional outcome, Breathlessness on the Visual analogue scale scores for breathlessness, fatigue, joint stiffness, pain, and appetite	
Batterham et al., 2014, UK	59	Multi-centre RCT	a: after hospital discharge b: hospital-based, physiotherapist-led, supervised exercise c: 8 weeks d: 2 times/week	No intervention	HRQoL, Oxygen uptake, Mood disorder	
Connolly et al., 2015, UK	20	Two-centre pilot RCT	a: after hospital discharge b: exercise-base rehabilitation session of 40 minutes c: 8 weeks d: 3 times/week (2 times supervised, 1 time unsupervised)	No intervention	HRQoL, ADL, Mortality, Physical function, Muscle strength, Adverse events, Anxiety and depression symptoms	ICU rehabilitation before randomisation*
Walsh et al., 2015, UK	240	Two-centre RCT	a: in-hospital b: mobilization exercise and relevant dietetic, occupational, and speech/language therapy c: from ICU discharge until hospital	Standard care	Mobility index, HRQoL, Anxiety and depression symptoms, Self-reported symptom scores (using visual analogue scales)	ICU rehabilitation before randomisation

			discharge but no longer than 3 months d: unknown		for fatigue, breathlessness, appetite, pain, and joint stiffness, Mortality	
McWilliams et al., 2016, UK	73	Single-centre RCT	a: after hospital discharge b: outpatient-based exercise and education program c: 7 weeks d: 3 times/week (1 supervised, 2 self-directed titrated)	No intervention	Exercise capacity, HRQoL, Mortality, Adverse events	ICU rehabilitation before randomisation*
Shelly et al., 2017, India	35	RCT	a: after hospital discharge b: home-based respiratory and mobility training c: 4 weeks d: 5 times/week	No intervention	HRQoL	
McDowell et al., 2017, UK	60	Multi-centre RCT	a: after hospital discharge b: standard care plus personalized exercise program c: 6 weeks d: 3 times/week (2 supervised and 1 unsupervised)	No intervention	HRQoL, Mortality, Adverse events, Mobility index, Hand function, Exercise capacity, Breathlessness, Anxiety and depression, symptoms, Readiness to exercise, Self-efficacy to	

	exercise

*Unpublished data

ICU, intensive care unit; RCT, randomised controlled trial; HRQoL, health-related quality of life; PTSD, post-traumatic stress disorder; ADL, activity of daily living

Online supplementary file 4: Characteristics of studies excluded from qualitative and quantitative synthesis

Study	Reason for exclusion
Chiang et al., Phys Ther. 2006;86:1271-81	Quasi-RCT
Patsaki et al., J Crit Care. 2017;40:76-82	Quasi-RCT
Verceles et al., J Crit Care. 2018; 47: 204-10	Quasi-RCT
Chen et al., Am J Respir Crit Care Med. 2017;195:A2337	Outcomes were not reported in the publication abstract. The full study will be considered when the review is updated.
Salisbury et al., Clin Rehabil. 2010;24:489-500	Insufficient outcome data for meta-analysis
Batterham et al., Br J Anaesth. 2014;113:130-7	Insufficient outcome data for meta-analysis
Shelly et al., Indian J Crit Care Med. 2017;21:89-93	Insufficient outcome data for meta-analysis

RCT, randomised controlled trial

Online supplementary file 5. Assessment of risk of bias in the analysed trials using the Cochrane risk-of-bias assessment tool

Trial	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Jones et al., 2003 (22)	Low[a]	Low[a]	High	Low	High	Unclear[a]	Unclear[b]
Cuthbertson et al., 2009 (23)	Low	Low	High	Low	High	Low	Unclear[b]
Elliott et al., 2011 (24)	Low	Low	High	Low	High	High	Unclear[c]
Salisbury et al., 2010 (25)	Low	Low	High	Low	Low	Unclear	High[d]
Batterham et al., 2014 (26)	Low	Low	High	Low	Low	High	Unclear[e]
Connolly et al., 2015 (11)	Low	Low	High	High	Low	High	Unclear[e]
Walsh et al., 2015 (12)	Low	Low	High	Low	High	High	High[d]
McWilliams et al., 2016 (13)	Low	Low	High	Low	Low	Low	Unclear[e]
Shelly et al., 2017 (27)	Low	Low	High	Unclear	Low	Low	Unclear[e]
McDowell et al., 2017 (15)	Low	Low	High	Low	High	Low	High[f]

[a]Unpublished data (reply from the authors: the randomization was undertaken the old-fashioned way, with 6 slips of paper, 3 marked interventions and 3 controls, put in 6 sequentially numbered opaque envelopes and sealed and shuffled to mix them, but protocol was not published)

[b]Dose of physical rehabilitation was unknown

[c]Adherence to the intervention was unknown

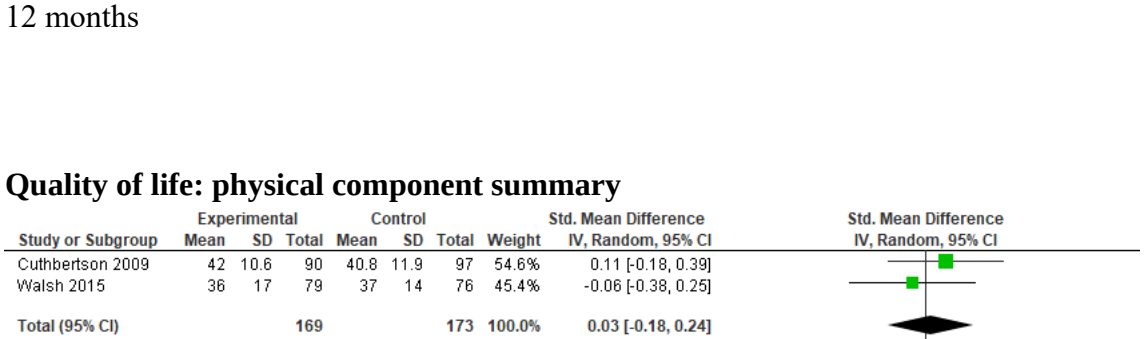
[d]Intervention included nutritional therapy

[e]Very little detail given regarding the therapy received in the control group

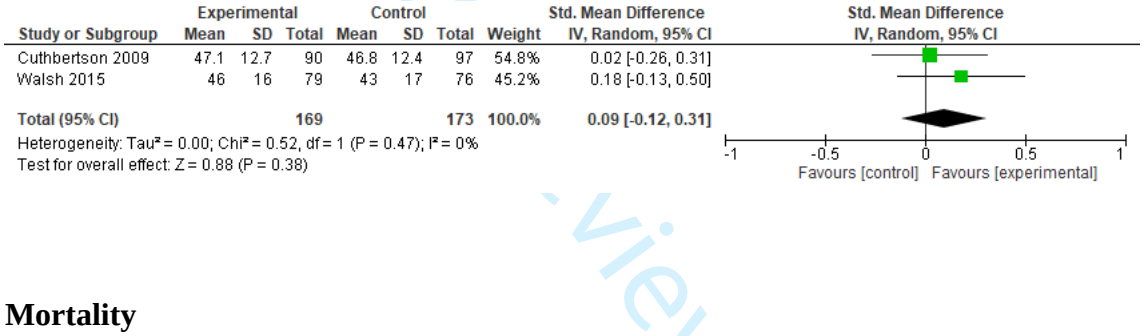
[f]Adherence to the intervention was 70%

Online supplementary file 6: Additional meta-analysis for quality of life and mortality at 12 months

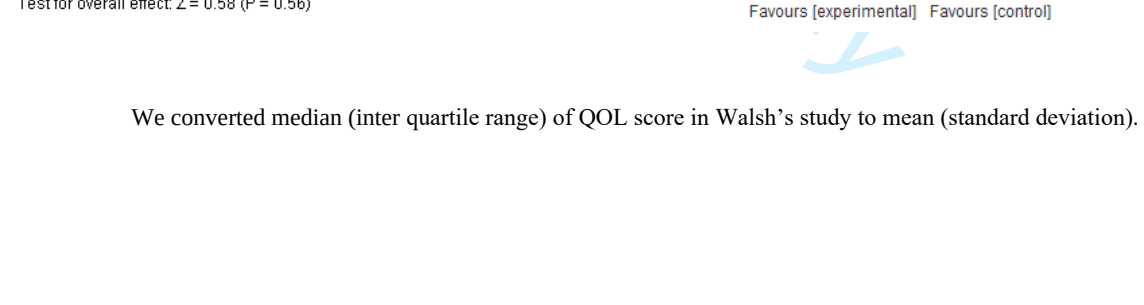
Quality of life: physical component summary



Quality of life: mental component summary



Mortality

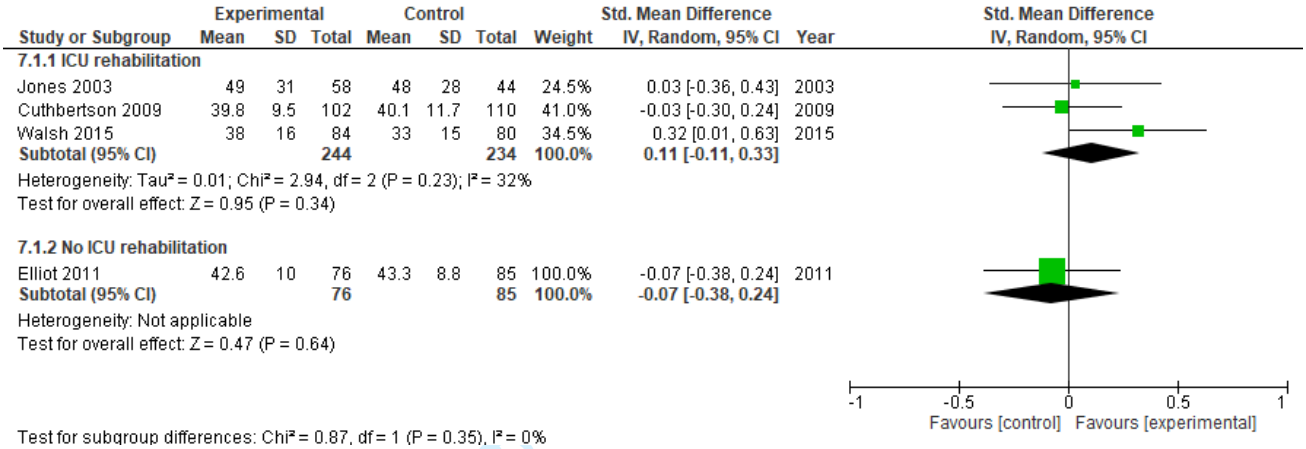


We converted median (inter quartile range) of QOL score in Walsh's study to mean (standard deviation).

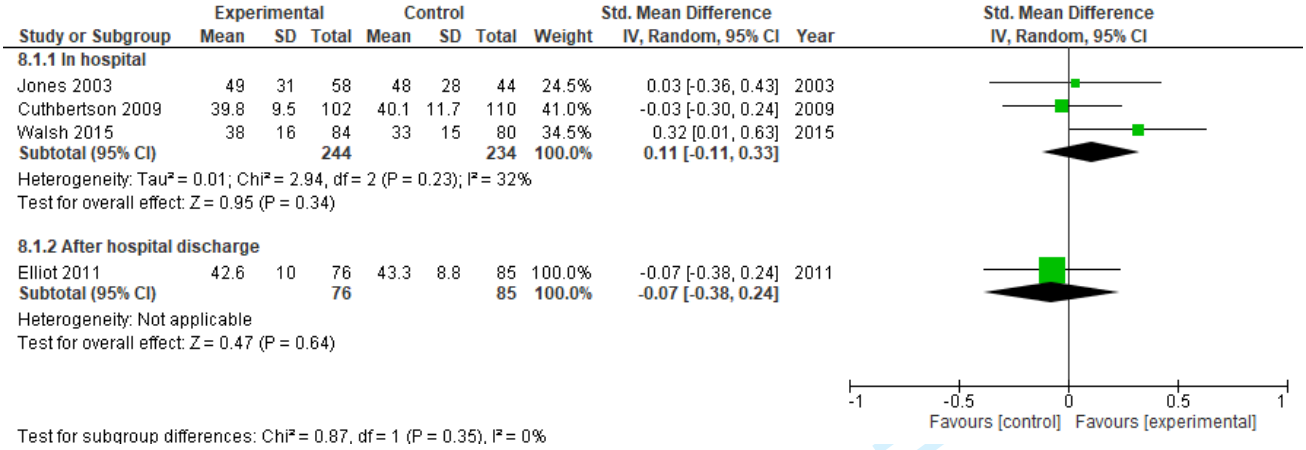
Online supplementary file 7: Subgroup analysis

A Quality of life: physical component summary

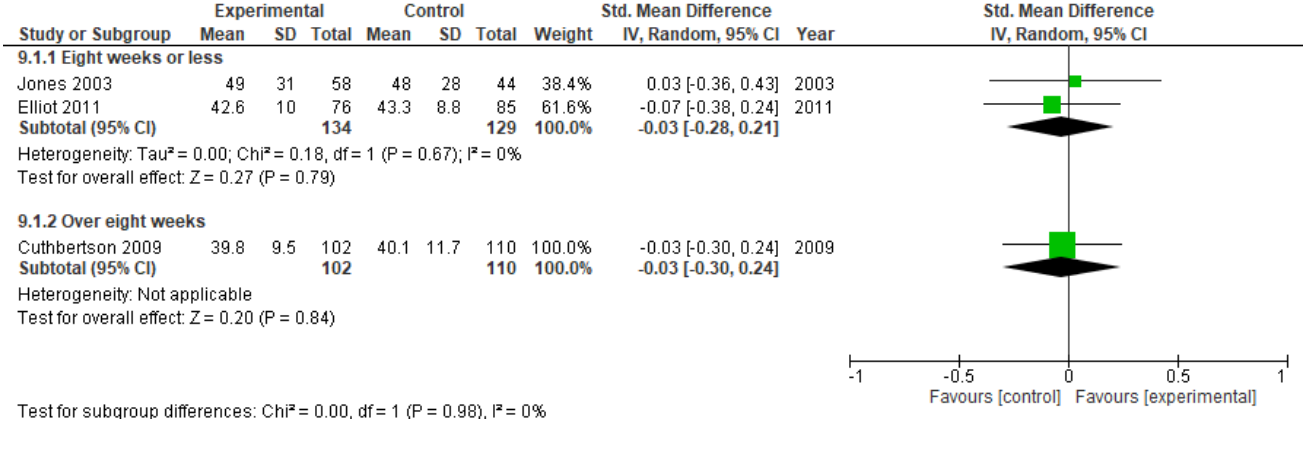
A-1 Rehabilitation practice in ICU (ICU rehabilitation before randomisation vs No ICU rehabilitation before randomisation)



A-2 The timing of the commencement of the intervention (in hospital vs after hospital discharge)

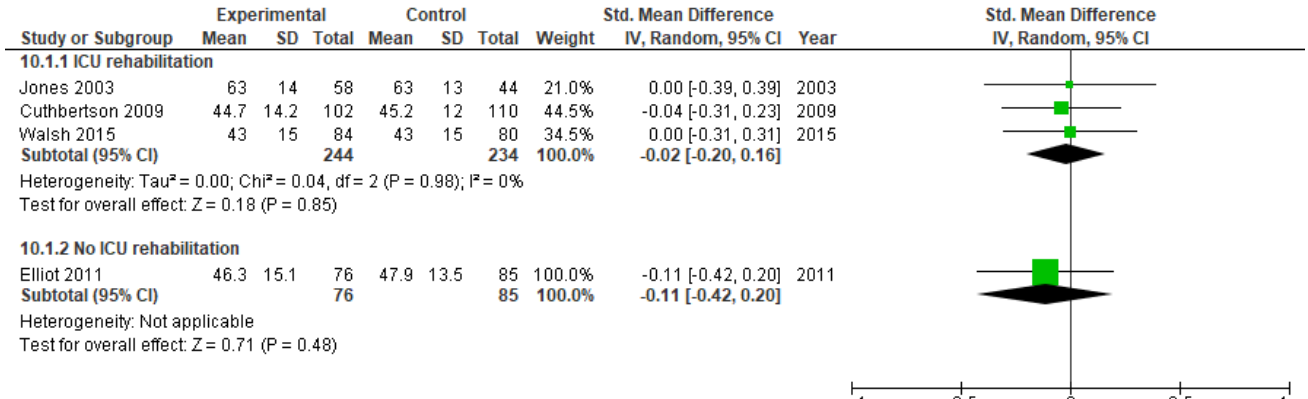


A-3. The intervention duration (eight weeks or less, and over eight weeks)

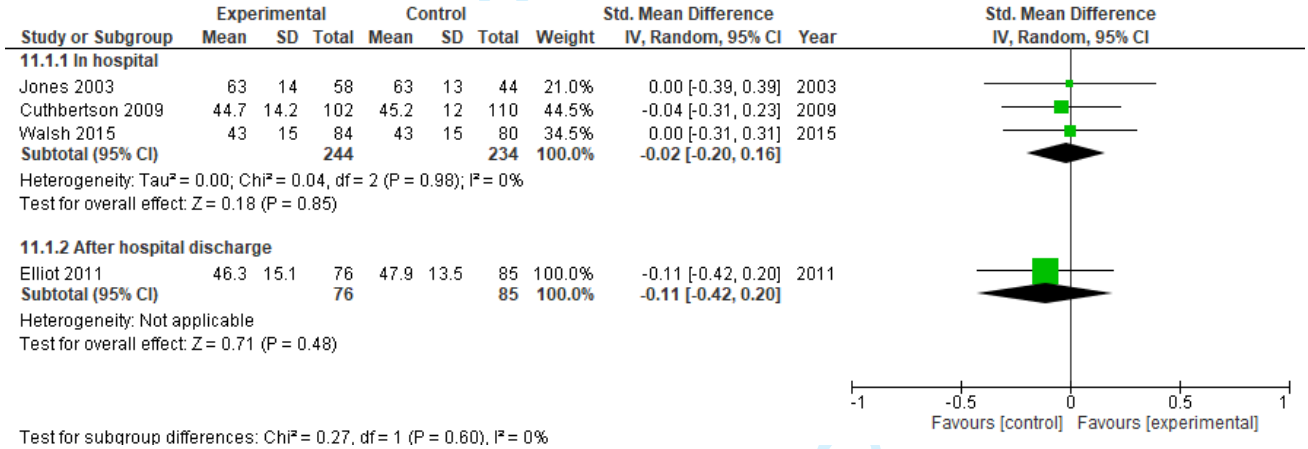


B Quality of life: mental component summary

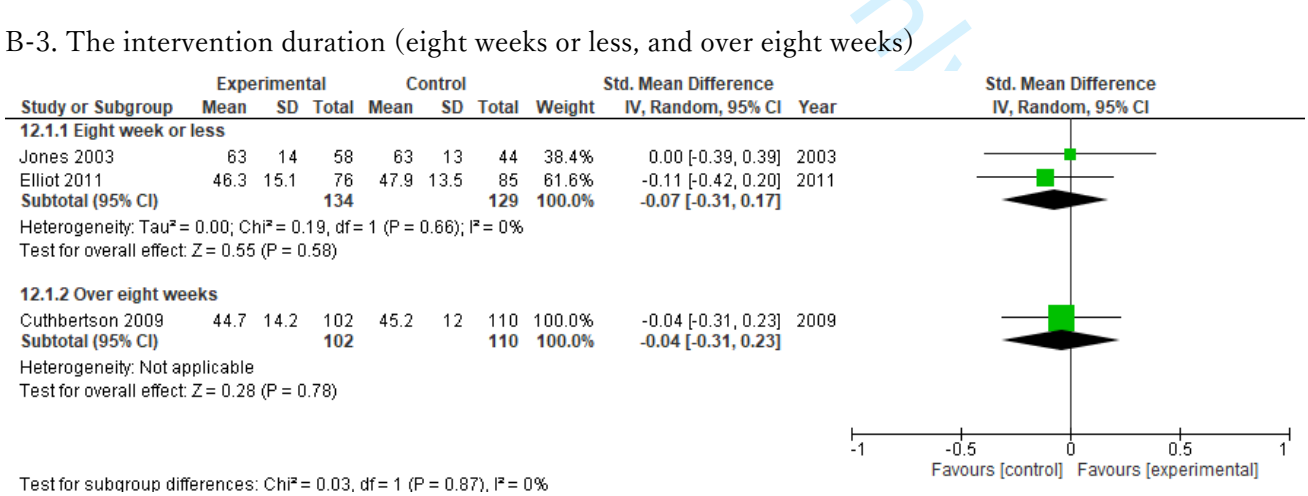
B-1. Rehabilitation practice in ICU (ICU rehabilitation before randomization vs No ICU rehabilitation before randomization)



B-2. The timing of the commencement of the intervention (in hospital vs after hospital discharge)



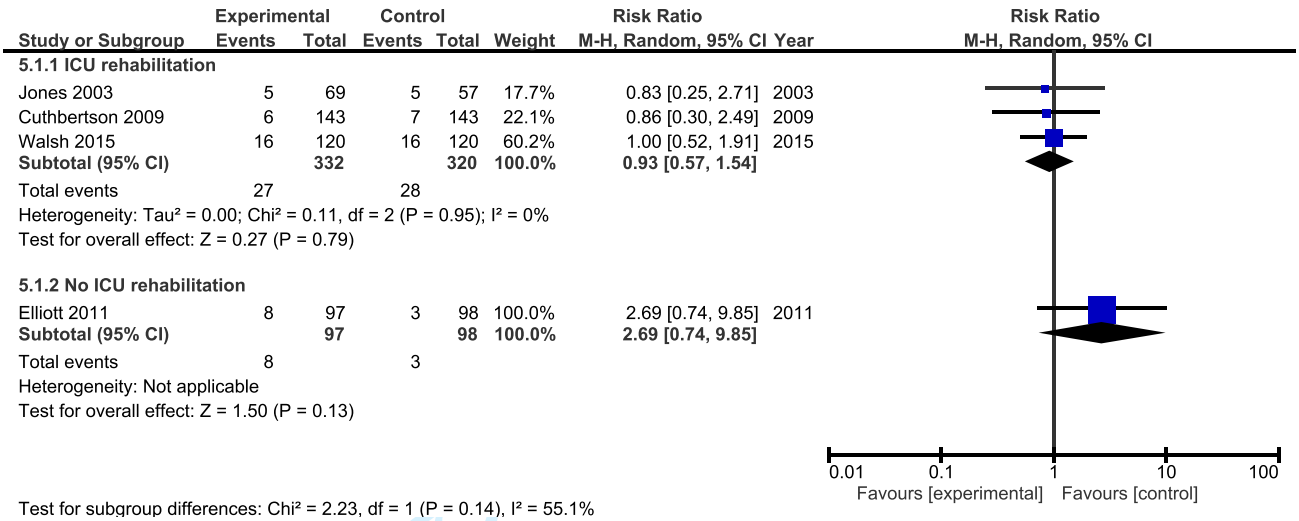
B-3. The intervention duration (eight weeks or less, and over eight weeks)



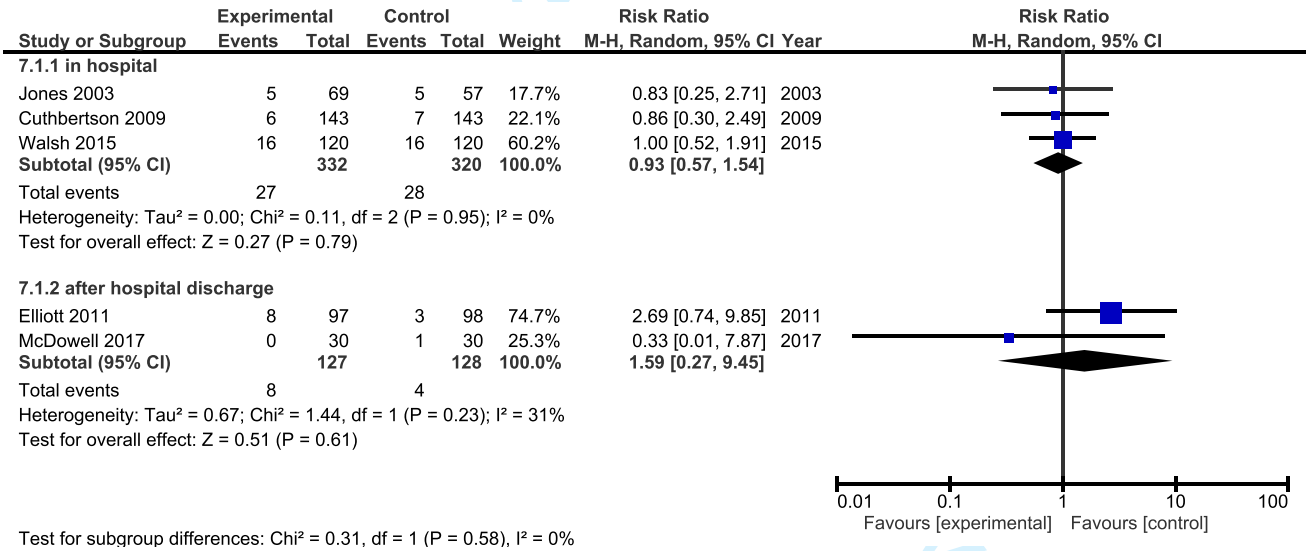
We converted median (inter quartile range) of QOL score in Walsh's study to mean (standard deviation).

C Long term mortality

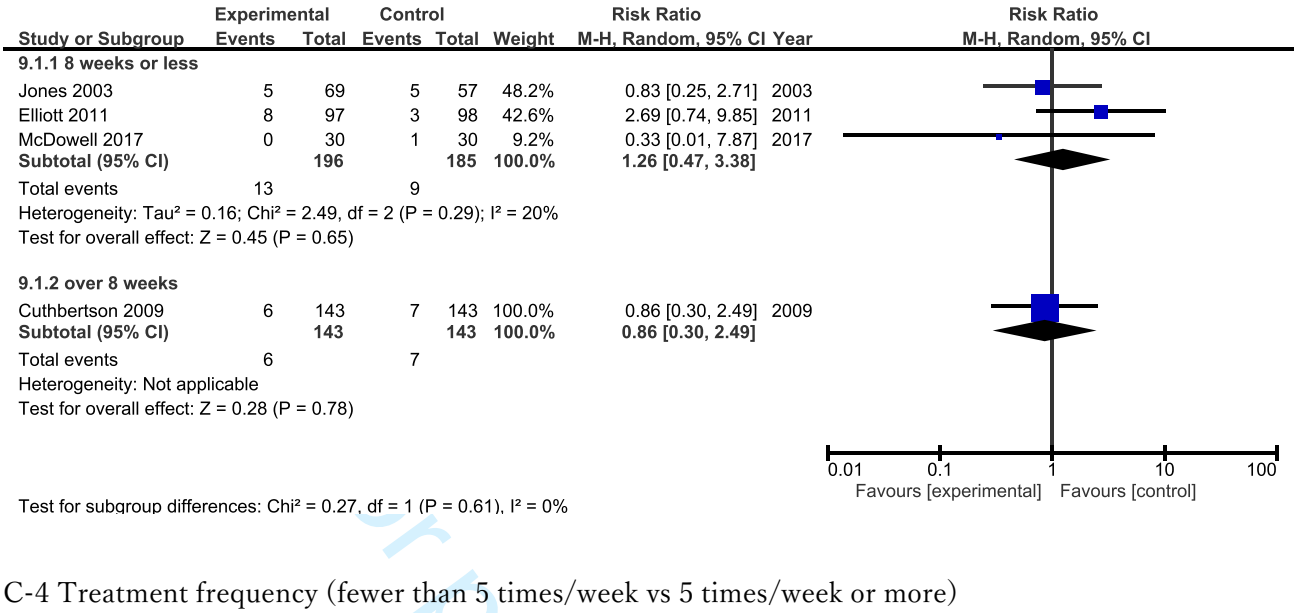
C-1. Rehabilitation practice in ICU (ICU rehabilitation before randomization vs No ICU rehabilitation before randomization)



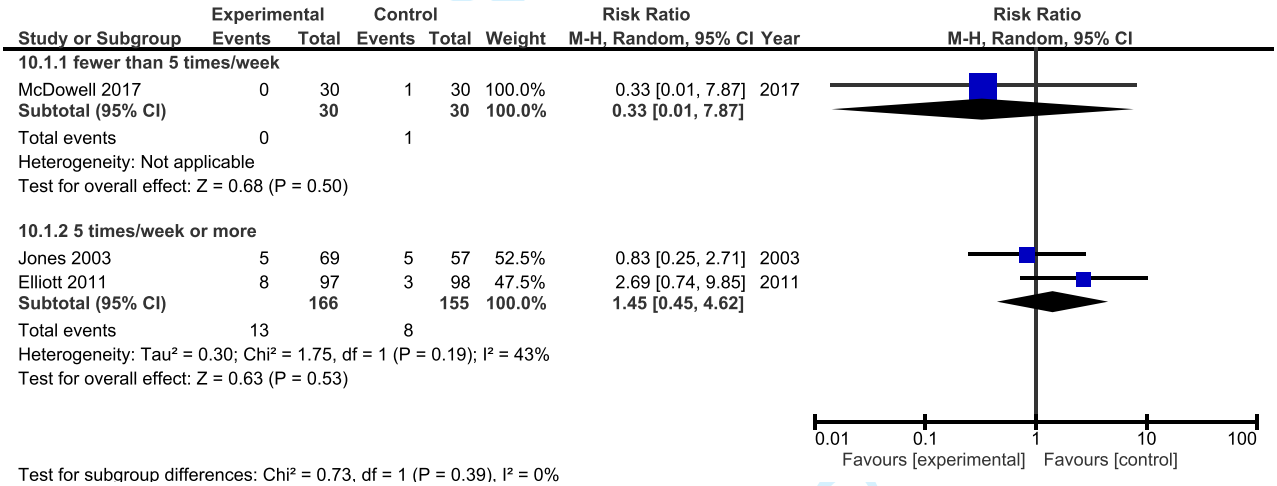
C-2 The timing of the commencement of the intervention (in hospital vs after hospital discharge)



C -3. The intervention duration (8 weeks or less, and over 8 weeks)



C-4 Treatment frequency (fewer than 5 times/week vs 5 times/week or more)



C-5 Type of control (no intervention and usual rehabilitation)