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# **BMJ Open**

# 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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## 35 Abbreviations

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

#### 44 Abstract

45	Objective: We aimed to determine whether enhanced physical rehabilitation following
46	intensive care unit (ICU) discharge improves clinically relevant outcomes such as
47	activity-of-daily-living (ADL), quality of life (QOL), and mortality among patients who
48	received mechanical ventilation.
49	Design: Systematic review and meta-analysis.
50	Data sources: Randomised controlled trials published in the Cochrane Central Register
51	of Controlled Trials (CENTRAL), MEDLINE, Excerpta Medica Database (EMBASE),
52	Physiotherapy Evidence Database (PEDro), and World Health Organization
53	International Clinical Trials Registry Platform between inception and December 2017.
54	Outcomes: Primary outcomes included ADL, QOL, and mortality. Secondary outcomes
55	included functional exercise capacity, pain, return-to-work rate, muscle strength,
56	duration of delirium, and incidence of adverse events. The quality of evidence was
57	determined using the Grading of Recommendations Assessment, Development, and
58	Evaluation (GRADE) approach.
59	Results: Ten trials (enrolling 1110 patients) compared physical rehabilitation to usual
60	care or no intervention after ICU discharge (four studies) or hospital discharge (six
61	studies). Regarding QOL, the mean difference [95% confidence interval] between the

62	intervention and control groups regarding physical and mental component summary
63	scores of Short Form 36 was -0.45 [-2.46 to 1.55] and -0.73 [-3.18 to 1.73], respectively
64	(certainty of evidence: moderate). Rehabilitation did not significantly decrease
65	long-term mortality (relative risk: 1.05 [0.66–1.66]; $I^2 = 0\%$ ; 907 patients; certainty of
66	evidence, moderate). Adverse events were evaluated in three trials (153 patients), with
67	18 and 5 events reported for the intervention and control groups, respectively (certainty
68	of evidence: low). The analysed trials did not report short- or long-term data on ADL
69	function, functional exercise capacity, pain, return-to-work rate, muscle strength, or
70	delirium.
71	Conclusions: Enhanced physical rehabilitation following ICU discharge did not
72	improve QOL or mortality among patients who received mechanical ventilation.
73	Implementing an intensive physical rehabilitation program for all ICU survivors
74	requiring mechanical ventilation is unnecessary.
75	Trial registration: PROSPERO, CRD42017080532 (registered: 28 December 2017).
76	
77	Keywords: rehabilitation, critical illness, post-intensive care syndrome, exercise,
78	quality of life, mortality

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#### **Article Summary**

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

92	Introduction
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93	In critically ill patients, rehabilitation mainly aims to enhance quality of life
94	(QOL) by improving activities of daily living (ADL) function,[1, 2] which may be
95	severely impaired also due to post-intensive care syndrome (PICS).[3-5] According to
96	the guidelines issued by the National Institute for Health and Care Excellence, provision
97	of rehabilitation should be seamlessly integrated with the patient's transition from the
98	intensive care unit (ICU) to the ward and then to out-of-hospital care.[6] However, at
99	the time the guideline was issued, there was little evidence from clinical trials to support
100	the use of enhanced physical rehabilitation following ICU discharge. Some experts do
101	recommend physical rehabilitation following ICU discharge to improve ADL function
102	and QOL.[7] Regarding sepsis survivors, the findings of a large observational study
103	suggested that physical rehabilitation following ICU discharge improves long-term
104	mortality.[8, 9]
105	A recent meta-analysis by Connolly et al.[10] focused on randomised
106	controlled trials (RCTs) regarding the effectiveness of enhanced exercise rehabilitation
107	following ICU discharge in adult ICU survivors who had been mechanically ventilated
108	for longer than 24 hours. Despite the comprehensive search, only six RCTs with
109	conflicting results were included, and no clear effect of the intervention on clinically
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110	relevant outcomes such as QOL, mortality, functional exercise capacity, or incidence of
111	adverse events could be established at the time. Additionally, some clinically relevant
112	outcomes such as ADL, pain, return-to-work rate, muscle strength, and duration of
113	delirium were not considered in their review.[10] Several RCTs assessing the effect of
114	enhanced physical rehabilitation following ICU discharge on clinically relevant
115	outcomes[11-15] have been published since Connolly and colleagues conducted their
116	Cochrane review.[10] Therefore, in the present study, we aimed to re-evaluate the
117	available literature and determine whether enhanced physical rehabilitation following
118	ICU discharge improves clinically relevant outcomes among critically ill adults who
119	received mechanical ventilation.
120	
121	Materials and methods
122	Compliance with reporting guidelines
123	Using a pre-specified protocol (PROSPERO registry ID:
124	CRD42017080532),[16] we conducted a systematic review of the relevant literature in
125	agreement with the recommendations listed in the Cochrane Handbook[17] and the
126	Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)
127	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  $\geq$  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

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146	following ICU discharge improved clinically relevant outcomes, we excluded studies in
147	which earlier and/or more intensive ICU physical rehabilitation (compared to the care
148	received by the control group) was provided to patients in the intervention group. Any
149	combination of one or more of the following activities was considered as a form of
150	enhanced physical rehabilitation: neuromuscular stimulation, inspiratory or respiratory
151	muscle training, passive range-of-motion exercise, cycle ergometer exercise,
152	active-assisted exercises, active range-of-motion exercises, bed mobility activities (e.g.,
153	bridging, rolling, lying-to-sitting exercise), ADL training, transfer training, pre-gait
154	exercises (including marching in place), and walking exercise.
155	Outcomes of interest
156	The primary outcomes were QOL, ADL function, and mortality. Secondary
157	outcomes included functional exercise capacity, pain, return-to-work rate, muscle
158	strength, duration of delirium, and incidence of adverse events (defined by the trialists).
159	Search strategy and selection of studies
160	We searched the Cochrane Central Register of Controlled Trials (CENTRAL),
161	MEDLINE via PubMed, Excerpta Medica Database (EMBASE) via Elsevier, the
162	Physiotherapy Evidence Database (PEDro), and the World Health Organization
163	International Clinical Trials Registry Platform (WHO ICTRP) via their dedicated search

164	portal. The search was performed in December 2017 using a set of suitable search terms
165	(details provided in online supplementary file 2). We hand-searched reference lists for
166	the guideline for rehabilitation after critical illness.[6] We attempted to identify other
167	relevant research by hand-searching the reference lists of the studies returned by the
168	search and those of articles citing such studies (based on citation information from the
169	Web of Science). If the database entry for a candidate study did not contain the
170	necessary information, we contacted the study authors. Two reviewers (ST and KY)
171	independently screened the title and abstract of each study returned by the search to
172	determine whether the inclusion criteria were met. The two reviewers performed a
173	full-text review to assess the eligibility of each candidate study. Disagreement was
174	resolved by discussion between the two reviewers, occasionally with arbitration by a
175	third reviewer (YK).
176	Data abstraction and quality assessment
177	Two reviewers (ST and KY) independently abstracted trial-level data using
178	pre-specified forms. Disagreements regarding data extraction were resolved through
179	discussions. Where necessary, we contacted the authors of studies that did not provide
180	sufficient information. The risk of bias in each study was assessed independently by two
181	reviewers (ST and KY) using the Cochrane risk-of-bias assessment tool.[17]

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

185 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 OOL 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<sup>2</sup> 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 ( $l^2 > 50\%$ ), we investigated the underlying

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reasons and conducted the $\chi^2$ test, with a <i>P</i> -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 ( $\leq 8$ versus > 8
weeks), treatment frequency (<5 versus $\geq$ 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.

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

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following hospital discharge, while 4[12, 22-24] focused on

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237	during hospitalization. The duration of intervention ranged from 6 weeks to 3 months,
238	while the frequency of intervention ranged from 3 times per week to once daily. No
239	study considered intensive intervention (>30 minutes of active rehabilitation daily) or
240	intervention with neuromuscular stimulation.
241	Most studies were at high or unclear risk of bias (details provided in online
242	supplementary file 5). All 10 studies demonstrated adequate random sequence
243	generation and allocation concealment, but participants and personnel were not blinded
244	to the intervention. One study[11] demonstrated a high risk of detection bias for all
245	outcomes except mortality, and another study[27] did not report whether or not the
246	outcome assessor was aware of group allocation. Four studies had high risk of selective
247	reporting bias, and two studies had unclear risk of bias because the protocols were not
248	published. High or unclear risk of other bias was noted for all studies because of
249	insufficient information regarding the intervention and control protocols.
250	Primary outcomes
251	QOL was measured in 8 trials (see online supplementary file 3), but the short-

251 QOL was measured in 8 trials (see online supplementary file 3), but the short-252 and long-term physical component summary (PCS) scores and mental component 253 summary (MCS) scores in Short Form 36 were only available in 3 trials,[22–24]

254	whereas the other five trials measured these outcomes at a different time or did not
255	report PCS or MCS scores. ADL function was measured in 1 trial,[11] but the short-
256	and long-term data were not available. Short-term mortality was reported in 2 trials,[11,
257	13] while long-term mortality was reported in 5 trials.[12, 15, 22–24]
258	The mean differences between intervention and control regarding PCS and
259	MCS scores characterizing QOL were -0.45 (95% CI, -2.46 to 1.55) and -0.73 (95% CI,
260	-3.18 to 1.73), respectively (Fig. 2A and 2B, respectively). Rehabilitation did not
261	significantly decrease short-term mortality (RR, 0.71; 95% CI, 0.05–9.80, $I^2 = 33\%$ ; n =
262	93) (Fig. 2C) or long-term mortality (RR, 1.05; 95% CI, 0.66–1.66, $I^2 = 0\%$ ; n = 907)
263	(Fig. 2D). The certainty of evidence for QOL and long-term mortality was moderate,
264	while that for short-term mortality was low (Table 1).
265	We could not carry out all pre-specified sensitivity analyses because there was
266	no study using imputed statistics, and we judged that the risk of bias of all included
267	studies was similar in terms of random sequence generation, allocation concealment,
268	incomplete outcome data, and other bias. The pre-specified subgroup analyses for the
269	primary outcomes revealed no significant differences among sub-groups (see details
270	provided in online supplementary file 6).
271	Secondary outcomes

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272	Functional exercise capacity was measured in 2 trials,[11, 24] pain was
273	measured in 1 trial,[12] and muscle strength was measured in 1 trial,[11] but short- and
274	long-term data were not available. No trials evaluated return-to-work rate or incidence
275	of delirium.
276	Adverse events were measured in 3 trials.[11, 13, 15] Two studies[11, 13]
277	reported no adverse events. One study[15] reported 18 events in the intervention group
278	and 5 events in the control group. Among the 18 adverse events reported in the
279	intervention group, 12 were mild or moderate (musculoskeletal pain higher than
280	expected or muscle soreness potentially indicating injury, 3 cases; any pain higher than
281	expected, 1 case; cardiac symptoms or chest pain, 1 case; any other event considered by
282	the researcher to be of concern, 7 cases; 6 of 12 events were considered to be related or
283	possibly related to study participation), while 6 were serious (hospitalization or
284	prolonged hospitalization, with 1 event related/possibly related to study participation).
285	In the control group, there was 1 adverse event (musculoskeletal pain higher than
286	expected, muscle soreness potentially indicating injury, related/possibly related to study
287	participation) and 4 serious adverse events (hospitalization or prolonged hospitalization,
288	with 1 event related/possibly related to study participation). The certainty of evidence
289	for adverse events was low (Table 1).

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291	Discussion
292	The results of this up-to-date review covering 10 RCTs and 1110 patients
293	suggest that enhanced rehabilitation following ICU discharge could not improve QOL
294	or reduce short- or long-term mortality among patients who received mechanical
295	ventilation. We could not confirm the effect of enhanced physical rehabilitation even
296	though all included studies exhibited performance bias potentially increasing the
297	observed effect of the intervention. Furthermore, despite the large sample size in the
298	meta-analysis for QOL and long-term mortality, limited data for these outcomes were
299	available, and the certainty of evidence was only moderate.
300	Furthermore, subgroup meta-analyses revealed no differences among
301	subgroups defined according to the nature or timing of the intervention. The previous
302	review by Connolly et al.[10] did not conduct meta-analysis due to the limited number
303	of included studies. A recent systematic review of ICU rehabilitation[28, 29] also
304	reported no significant difference in QOL between the intervention and control groups.
305	Thus, neither enhanced rehabilitation in the ICU nor rehabilitation following ICU
306	discharge is likely to be superior to usual care in terms of QOL outcomes. In addition,
307	we found no benefit in terms of short- or long-term mortality regardless of timing of

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308	commencement, which is consistent with previous findings that ICU rehabilitation did
309	not decrease mortality at ICU discharge, at hospital discharge, or at 6 months after
310	discharge.[28, 30] On the other hand, rehabilitation may be detrimental in acute
311	conditions. Specifically, intensive physical rehabilitation started within 48 hours of
312	admission for exacerbations of chronic respiratory disease increased mortality at 12
313	months,[31] whereas higher-dose, physical rehabilitation very early after stroke
314	decreased the odds of a favourable outcomes at 3 months.[32] Thus, implementation of
315	an intensive rehabilitation program may not be indicated for all ICU survivors requiring
316	mechanical ventilation. Though physical rehabilitation is relatively safe, it is labour
317	intensive.[33] Our present findings do not support the allocation of additional resources
318	to ensure intensive rehabilitation following ICU discharge, and rather indicate that
319	physical rehabilitation staff resources might be better allocated to the management of
320	non-severe patients such as those undergoing elective surgery and not requiring ICU
321	admission.[34–36]
322	Subgroup analysis in a previous systematic review[28] indicated that,
323	compared with low-dose rehabilitation, high-dose active rehabilitation for >30 minutes
324	daily was associated with significantly higher QOL. Dose-response analysis of early
325	physical rehabilitation[35] in stroke patients enrolled in A Very Early Rehabilitation

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326	Trial (AVERT)[32] determined that intervention in such acute cases improved the odds
327	of a favourable outcome with each episode of activity per day. Our present review did
328	not include studies comparing high-dose rehabilitation and usual care, and thus the QOL
329	effect of high-dose rehabilitation remains unclear. Additionally, we could not perform
330	subgroup analysis for PICS symptoms with effect on QOL[3–5] or for sepsis, which is a
331	risk factor for PICS.[37, 38] It remains unclear which population of critically ill patients
332	may truly benefit from intensive physical rehabilitation.
333	The studies included in our review did not cover all important outcomes
334	included in the core outcome set of rehabilitation after critical illness,[7] including ADL
335	function, functional exercise capacity, pain, return-to-work rate, muscle strength, or
336	delirium incidence. Nonetheless, our findings regarding QOL and mortality suggest
337	that, even if future studies report improvement in these other aspects, the amount of
338	improvement would likely be too small to affect QOL.
339	The present review has several strengths. First, we employed rigorous
340	methodology that followed a written, a priori protocol developed according to the
341	PRISMA statement, including a comprehensive search for evidence. Second, we
342	performed duplicate assessment of eligibility, risk of bias, and data abstraction. Third,
343	we used the GRADE approach for assessing the certainty of evidence. In addition, we

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344	only included RCTs, most of which were multicentre studies. We could thus conduct
345	an intention-to-treat analysis to understand the effect of intensive physical
346	rehabilitation or usual care, which gives a pragmatic estimate of the benefit of a
347	change in treatment policy.
348	This systematic review has two potential limitations. Firstly, none of the
349	included studies had a follow-up >6 months, and thus we could not account for later
350	outcomes. A previous study reported that, in patients with exacerbations of chronic
351	respiratory disease, intensive physical rehabilitation increased mortality at 12
352	months.[31] Since we found no evidence of mortality benefit at 6 months, we believe
353	that the conclusions of this review would not change even if further data on harm
354	outcomes were available. Lastly, we could not take into account the medical
355	resources and costs associated with each intervention. However, since studies
356	included in this review compare rehabilitation intervention against usual care or no
357	intervention, it is obvious that intensive physical rehabilitation would be associated
358	with increased medical resources and costs.
359	Taken together, the findings of the present meta-analysis indicate that
360	enhanced physical rehabilitation following ICU discharge does not improve QOL or
361	mortality among patients who received mechanical ventilation. It is unnecessary to

implement an intensive physical rehabilitation program for all ICU survivors requiring

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2 3	
4 5 6 531 7	Figure legends
8 9 532 10	Fig 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)
11 12 13 533	flow diagram
14 534 15 16 17	Fig 2 Forest plot for quality of life and mortality
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6 7	535	Tables	
8 9 10 11	536 537	Table 1. Findings	s from te
12		Overview of study	y design
13 14 15 16 17 18 19 20		Patients or study ventilation was pro Setting: any Intervention: prot group. Comparison: no i	ovided for
21 22		Outcome	Illus
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24 25 26			Assu
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29 30		Quality of life	Stuc
31 32		SF-36: physical	
33		component	
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ndings from ten trials focused on post-ICU rehabilitation of critically ill patients who received mechanical ventilation

study population: adult patients who have been discharged from an ICU or critical care environment during which mechanical was provided for at least 24 hours n: protocolized physical rehabilitation following ICU discharge, designed to be more intensive than the care received by the control **n**: no intervention or usual care

Outcome	Illustrative comparative risks <sup>*</sup> (95%		<b>Relative effect</b>	No. of	Certainty of the	Comments
	CI)		(95% CI)	participants	evidence	
	Assumed risk	Corresponding	_	(studies)	(GRADE)	
		risk				
	Control	Intervention				
Quality of life	Study populatio	n		475	$\oplus \oplus \oplus \ominus$	
		MD: -0.45	-	(3 RCTs)	Moderate <sup>a</sup>	
SF-36: physical		(-2.46 to 1.55)				
component						
summary score						
Quality of life	Study populatio	n		475	$\oplus \oplus \oplus \ominus$	
		MD: -0.73	_	(3 RCTs)	<b>Moderate</b> <sup><i>a</i></sup>	

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BMJ Open: first published as 10.1136/bmjopen-2018-026075 on 9 June 2019. Downloaded from http://bmjopen.bmj.com/ on June 5, 2025 at Dep Erasmushogeschool . Protected by copyright,אופנוןקואפוראאפולאפואנפט לפוגנאל פוטפולמא, ומונועין אל ואפואנאסאבאטל פויחוואר technologies.

 BMJ Open

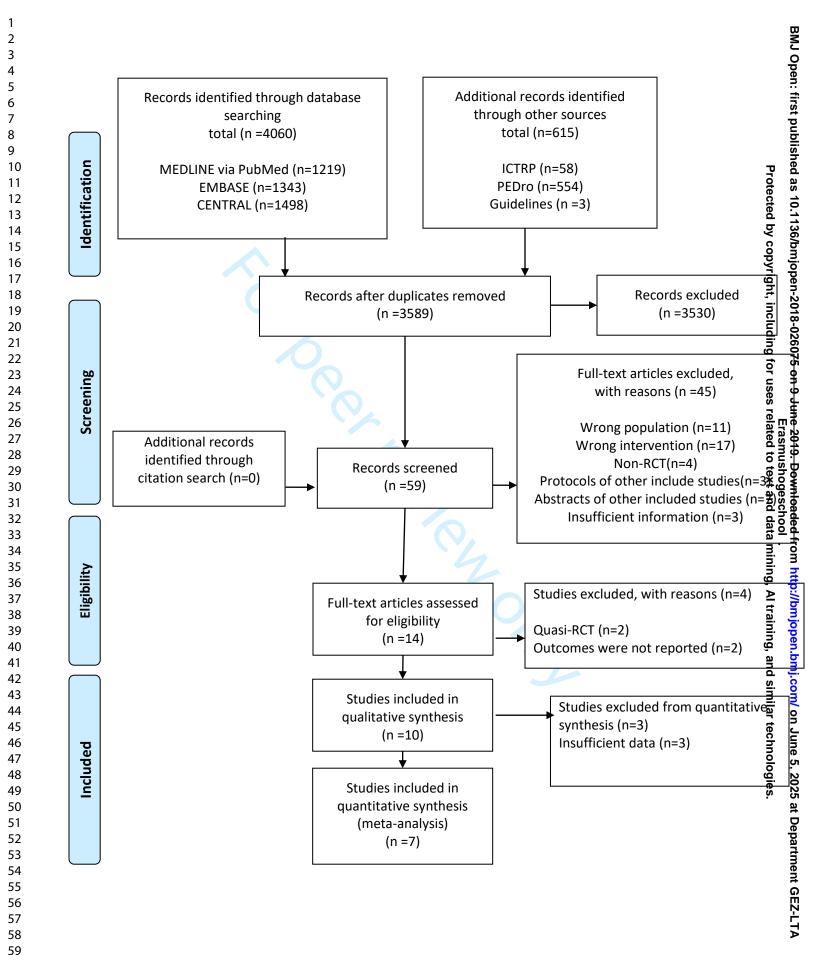
SF-36: mental component summary score		(-3.18 to 1.73)			
Mortality	Study populatio	n	RR: 0.71	93	$\oplus \oplus \Theta \Theta$
Short term	43 per 1000	<b>31 per 1000</b> (2 to 426)	(0.05 to 9.80)	(2 RCTs)	Low <sup>b,c</sup>
Mortality	Study populatio	n	RR: 1.05	907	$\oplus \oplus \oplus \Theta$
Long term	71 per 1000	<b>75 per 1000</b> (47 to 119)	(0.66 to 1.66)	(5 RCTs)	<b>Moderate</b> <sup>d</sup>
Adverse events	Study populatio	n		153	$\oplus \oplus \Theta \Theta$
	-	y reported 18 and 5 rvention and control	rer	(3 RCTs)	Low <sup>ef</sup>
*The corresponding	g risk (and its 95% C	I) is based on the assu	med risk in the comp	arison group and t	he relative effect (and its 95% CI) esti
for the intervention	group.				).
<b>GRADE</b> Working	Group grades of ev	idence			
	-	hat the true effect lies			
	y: We are moderately it is substantially diff		ct estimate; the true e	ffect is likely to be	e close to the estimate of the effect, bu
-			-		lifferent from the estimate of the effect
Very low certainty effect	: We have very little	confidence in the effe	ect estimate; the true	effect is likely to b	be substantially different from the estin

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- 538 CI, confidence interval; RR, risk ratio; ICU, intensive care unit; SF-36, Short Form 36; MD, mean difference; RCT, randomised controlled trial
- <sup>3</sup>Downgraded one point because of high risk of bias associated with the lack of information regarding the dose of physical rehabilitation and
- 540 adherence in the intervention group (other bias).
- 541 <sup>b</sup>Downgraded one point because of high risk of bias associated with the fact that the intervention included nutritional therapy but the study
- 542 provided very little detail regarding the therapy received in the control group (other bias).
- 543 <sup>c</sup>Downgraded because of imprecision (only two small studies).
- <sup>d</sup>Downgraded one point because of high risk of bias associated with the lack of information regarding the dose of physical rehabilitation and
- 545 adherence in the intervention group, as well as with the fact that the intervention included nutritional therapy but the study provided very little
- 546 detail regarding the therapy received in the control group (other bias).
- <sup>6</sup>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
- 548 control group, and the adherence in the intervention group was 70% (other bias).
- 549 <sup>f</sup>Downgraded because of imprecision (only three small studies).

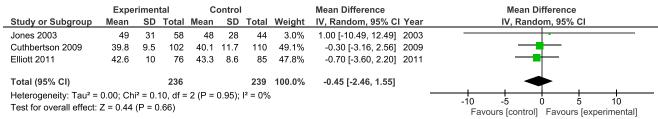
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# 2-A Quality of life: physical component summary



# 2-B Quality of life: mental component summary

							-		
	Expe	erimen	tal	Co	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI Year	IV, Random, 95% CI
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	<b></b>
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: Tau <sup>2</sup> =	0.00; Cł	ni² = 0.2	24, df =	= 2 (P = 0	0.89);	$I^2 = 0\%$	,	-	
Test for overall effect:	Z = 0.58	6 (P = 0	).56)						-10 -5 0 5 10 Favours [control] Favours [experimental]
-C Short term	morta	ality							
	Expe	erimen	tal	Cont	rol			Risk Ratio	Risk Ratio

# 2-C Short term mortality

	Experim	ental	Conti	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI Year	M-H, Random, 95% CI
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: Tau <sup>2</sup> =				= 0.22);	; I² = 33%		0.01 0.1 1 10 100
Test for overall effect:	Z = 0.26 (F	r = 0.80	)				Favours [experimental] Favours [control]

# 2-D Long term mortality

-		-								
	Experim	ental	Contr	rol		Risk Ratio		Risl	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI Yea	ar	M-H, Ran	dom, 95% Cl	
Jones 2003	5	69	5	57	15.1%	0.83 [0.25, 2.71] 200	)3		•	
Cuthbertson 2009	6	143	7	143	18.8%	0.86 [0.30, 2.49] 200	)9		•	
Elliott 2011	8	97	3	98	12.7%	2.69 [0.74, 9.85] 201	1	-		
Walsh 2015	16	120	16	120	51.3%	1.00 [0.52, 1.91] 201	15		<b>-</b>	
McDowell 2017	0	30	1	30	2.1%	0.33 [0.01, 7.87] 201	17			
Total (95% CI)		459		448	100.0%	1.05 [0.66, 1.66]		•	•	
Total events	35		32							
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>	= 2.86, (	df = 4 (P =	= 0.58)	; l² = 0%					100
Test for overall effect:	Z = 0.19 (F	<b>P</b> = 0.85	)				0.01 Fa	0.1 avours [experimental]	1 10 Favours [control]	100

# 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
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
7 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
2 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
3 Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., l <sup>2</sup> )for each meta-analysis. ງອບປອອງ ມອງເພເຮົາງິທີຂ້າຍທີ່ທີ່ເຫຼັງ ເປັນເຫຼັງ ເພິ່ງ ເປັນເຮັດ ແລະ ເປັນ ເປັນ ເປັນ ເປັນ ເປັນ ເປັນ ເປັນ ເປັນ	12
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# 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	<u> </u>		
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

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8	#1 MeSH descriptor:[critical care]explode all trees
9	#2 MeSH descriptor: [intensive care unit]explode all trees
10 11	#3 MeSH descriptor:[critical illness]explode all trees
12	#4 MeSH descriptor:[ventilator weaning]explode all trees
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14	#5 MeSH descriptor:[Respiratory Distress Syndrome, Adult]explode all trees
15 16	#6 MeSH descriptor:[Sepsis]explode all trees
17	#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
18	#8 "critical care":ti,ab,kw
19	#9 "intensive care unit":ti,ab,kw
20 21	#10 ICU:ti,ab,kw
22	#11 "critical illness":ti,ab,kw
23	#12 ventilator:ti,ab,kw
24	
25 26	#13 ARDS:ti,ab,kw
27	#14 "acute respiratory distress syndrome":ti,ab,kw
28	#15 sepsis:ti,ab,kw
29	#16 CIN:ti,ab,kw
30 31	#17 CIM:ti,ab,kw
32	#18 CIPN:ti,ab,kw
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39	#22 MeSH descriptor:[Exercise]explode all trees
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42	#24 MeSH descriptor:[Rehabilitation]explode all trees
43	#25 MeSH descriptor: [Physical fitness]explode all trees
44	#26 MeSH descriptor: [Physical Therapy Modalities]explode all trees
45 46	#27 #22 OR #23 OR #24 OR #25 OR #26
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50 51	#30 "physical fitness":ti,ab,kw
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#34 "physical therapy":ti,ab,kw

- #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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#2 intensive care unit[mh]         #3 critical illness[mh]         #4 ventilator weaning[mh]         #5 Respiratory Distress Syndrome, Adult[mh]         #6 Sepsis[mh]         #7 #1 OR #2 OR #3 OR #4 OR #5 OR #6         #8 "critical care"[tiab]         #9 "intensive care unit"[tiab]         #0 ICU[tiab]         #11 "critical illness"[tiab]         #22         #11 "critical illness"[tiab]         #23         #12 ventilator[tiab]         #14 "acute respiratory distress syndrome"[tiab]         #15 sepsis[tiab]         #16 CIN[tiab]         #17 CIM[tiab]         #18 OR #19         #18 OR #19         #18 OR #19         #22 Exercise[mh]         #23 Exercise[thrl]         #24 Rehabilitation[mh]         #25 Physical Threapy Modalities[mh]         #26 Physical Threapy Modalities[mh]         #27 #22 OR #23 OR #24 OR #25 OR #26         #28 exercise[tiab]         #29 rehabilitation[tiab]         #31         #32         #33         #41         #44         #44         #45         #46         #47         #47		
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13	11	#3 critical illness[mh]
14       #5 Respiratory Distress Syndrome, Adult[mh]         15       #6 Sepsis[mh]         16       #7 #1 OR #2 OR #3 OR #4 OR #5 OR #6         17       #7 #1 OR #2 OR #3 OR #4 OR #5 OR #6         18       #8 "critical care"[tiab]         19       #9 "intensive care unit"[tiab]         20       #9 "intensive care unit"[tiab]         21       #10 ICU[tiab]         22       #11 "critical illness"[tiab]         23       #12 ventilator[tiab]         24       #12 ventilator[tiab]         25       #13 ARDS[tiab]         26       #14 "acute respiratory distress syndrome"[tiab]         27       #15 Sepsis[tiab]         28       #15 Sepsis[tiab]         29       #16 CIN[tiab]         31       #17 CIM[tiab]         32       #18 CIPN[fiab]         33       #19 CIPNM[tiab]         34       #19 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR         36       #21 #7 OR #20         37       #21 #7 OR #20         38       #21 #7 OR #20         39       #22 Exercise[mh]         40       #23 Exercise therapy[mh]         41       #25 Physical fitness[mh]         42       #24 OR #23 OR #		#4 ventilator weaning[mh]
15       #6 Sepsis[mh]         16       #7 #1 OR #2 OR #3 OR #4 OR #5 OR #6         17       #7 #1 OR #2 OR #3 OR #4 OR #5 OR #6         18       #8 "critical care"[tiab]         19       #9 "intensive care unit [tiab]         20       #0 ICU[tiab]         21       #10 ICU[tiab]         22       #11 "critical illness"[tiab]         23       #12 ventilator[tiab]         24       #12 ventilator[tiab]         25       #13 ARDS[tiab]         26       #14 "acute respiratory distress syndrome"[tiab]         27       #16 CIN[tiab]         28       #15 sepsis[tiab]         29       #16 CIN[tiab]         30       #17 CIM[tiab]         31       #17 CIM[tiab]         32       #18 CIPN[tiab]         33       #19 CIPNM[tiab]         34       #20 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR         36       #21 #7 OR #20         37       #22 Exercise[nh]         40       #23 Exercise therapy[mh]         42       #24 Rehabilitation[mh]         43       #25 Physical fitness[mh]         44       #26 Physical Therapy Modalities[mh]         45       #26 Physical fitness"[tiab		#5 Respiratory Distress Syndrome, Adult[mh]
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22       #15 sepsis[tiab]         23       #16 CIN[tiab]         33       #17 CIM[tiab]         34       #18 CIPN[tiab]         35       #20 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR         36       #18 OR #19         37       #21 #7 OR #20         38       #21 #7 OR #20         39       #22 Exercise[mh]         40       #23 Exercise therapy[mh]         41       #23 Exercise therapy[mh]         42       #24 Rehabilitation[mh]         43       #25 Physical fitness[mh]         44       #26 Physical Therapy Modalities[mh]         45       #26 Physical Therapy Modalities[mh]         46       #27 #22 OR #23 OR #24 OR #25 OR #26         47       #28 exercise[tiab]         49       #29 rehabilitation[tiab]         50       #30 "physical fitness"[tiab]         51       #33 mobilisation[tiab]         52       #31 training[tiab]         53       #32 mobilisation[tiab]	26	#14 "acute respiratory distress syndrome"[tiab]
29       #16 CIN[tiab]         30       #17 CIM[tiab]         31       #17 CIM[tiab]         32       #18 CIPN[tiab]         33       #19 CIPNM[tiab]         34       #10 R #19 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR         35       #20 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR         36       #18 OR #19         37       #21 #7 OR #20         38       #21 #7 OR #20         39       #22 Exercise[mh]         40       #23 Exercise therapy[mh]         41       #23 Exercise therapy[mh]         42       #24 Rehabilitation[mh]         43       #25 Physical fitness[mh]         44       #26 Physical Therapy Modalities[mh]         45       #26 Physical Therapy Modalities[mh]         46       #27 #22 OR #23 OR #24 OR #25 OR #26         47       #28 exercise[tiab]         48       #29 rehabilitation[tiab]         50       #30 "physical fitness"[tiab]         51       #31 maining[tiab]         52       #31 training[tiab]         53       #32 mobilisation[tiab]         54       #33 mobilisation[tiab]		
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43       #25 Physical fitness[mh]         44       #26 Physical Therapy Modalities[mh]         45       #26 Physical Therapy Modalities[mh]         46       #27 #22 OR #23 OR #24 OR #25 OR #26         47       #28 exercise[tiab]         49       #29 rehabilitation[tiab]         50       #30 "physical fitness"[tiab]         51       #31 training[tiab]         53       #32 mobilization[tiab]         54       #33 mobilisation[tiab]         55       #33 mobilisation[tiab]	40	#23 Exercise therapy[mh]
43       #25 Physical fitness[mh]         44       #26 Physical Therapy Modalities[mh]         45       #26 Physical Therapy Modalities[mh]         46       #27 #22 OR #23 OR #24 OR #25 OR #26         47       #28 exercise[tiab]         49       #29 rehabilitation[tiab]         50       #30 "physical fitness"[tiab]         51       #31 training[tiab]         53       #32 mobilization[tiab]         54       #33 mobilisation[tiab]         55       #33 mobilisation[tiab]	41	#24 Pahabilitation[mb]
44       #25 Filystear filess[filit]         45       #26 Physical Therapy Modalities[mh]         46       #27 #22 OR #23 OR #24 OR #25 OR #26         47       #28 exercise[tiab]         49       #29 rehabilitation[tiab]         50       #30 "physical fitness"[tiab]         51       #31 training[tiab]         52       #31 training[tiab]         53       #32 mobilization[tiab]         54       #33 mobilisation[tiab]		
46       #27 #22 OR #23 OR #24 OR #25 OR #26         47       #28 exercise[tiab]         49       #29 rehabilitation[tiab]         50       #30 "physical fitness"[tiab]         51       #31 training[tiab]         52       #32 mobilization[tiab]         53       #32 mobilization[tiab]         54       #33 mobilisation[tiab]         55       #33 mobilisation[tiab]	44	
<ul> <li>47</li> <li>48</li> <li>49</li> <li>49</li> <li>40</li> <li>40</li> <li>410</li> <li>411</li> <li>41</li></ul>	45	
<ul> <li>#28 exercise[tiab]</li> <li>#29 rehabilitation[tiab]</li> <li>#30 "physical fitness"[tiab]</li> <li>#31 training[tiab]</li> <li>#32 mobilization[tiab]</li> <li>#33 mobilisation[tiab]</li> <li>#33 mobilisation[tiab]</li> </ul>		#27 #22 OR #23 OR #24 OR #25 OR #26
<ul> <li>#29 rehabilitation[tiab]</li> <li>#30 "physical fitness"[tiab]</li> <li>#31 training[tiab]</li> <li>#32 mobilization[tiab]</li> <li>#33 mobilisation[tiab]</li> <li>#33 mobilisation[tiab]</li> </ul>		#28 exercise[tiab]
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51       #31 training[tiab]         52       #31 training[tiab]         53       #32 mobilization[tiab]         54       #33 mobilisation[tiab]         55       #33 mobilisation[tiab]         56       56	50	#30 "physical fitness"[tiab]
<ul> <li>#32 mobilization[tiab]</li> <li>#33 mobilisation[tiab]</li> <li>#33 mobilisation[tiab]</li> </ul>		
54 #33 mobilisation[tiab] 56	52 53	
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#34 "physical therapy"[tiab] #35 physiotherapy[tiab] #36 "occupational therapy"[tiab] #37 "electrical muscle stimulation"[tiab] #38 "neuromuscular electrical stimulation"[tiab] #39 "respiratory muscle training"[tiab] #40 "inspiratory muscle training"[tiab] #41 "cycle ergometer"[tiab] #42 bridging[tiab] #43 rolling[tiab] #44 "lying to sitting"[tiab] #45 marching[tiab] #46 ambulation[tiab] #47 "activities of daily living"[tiab] #48 ADL[tiab] #49 walking[tiab] #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 randomized controlled trial [pt] #53 controlled clinical trial [pt] 071 #54 randomized [tiab] #55 placebo [tiab] #56 clinical trials as topic [mesh: noexp] #57 randomly [tiab] #58 trial [ti] #59 #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 #60 animals [mh] NOT humans [mh] #61 #59 NOT #60 #62 #21 AND #51 AND #61

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6	EMBASE
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8	#1 "critical care"/exp
9	#2 "intensive care unit"/exp
10 11	#3 "critical illness"/exp
12	#4 "ventilator weaning"/exp
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14	#5 "Respiratory Distress Syndrome, Adult"/exp
15 16	#6 Sepsis/exp
10	#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
18	#8 "critical care":ab,ti
19	#9 "intensive care unit":ab,ti
20 21	#10 ICU:ab,ti
21	#11 "critical illness":ab,ti
23	
24	#12 ventilator:ab,ti
25	#13 ARDS:ab,ti
26 27	#14 "acute respiratory distress syndrome":ab,ti
28	#15 sepsis:ab,ti
29	#16 CIN:ab,ti
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31 32	#18 CIPN:ab,ti
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39	#22 Exercise/exp
40	#22 Exercise/exp #23 "Exercise therapy"/exp #24 Rehabilitation/exp
41 42	#24 Rehabilitation/exp
43	#25 "Physical fitness"/exp
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45	#26 "Physical Therapy Modalities"/exp
46 47	#27 #22 OR #23 OR #24 OR #25 OR #26
48	#28 exercise:ab,ti
49	#29 rehabilitation:ab,ti
50	#30 "physical fitness":ab,ti
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#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

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# 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 ving OK a.... ) #2 daily living OR ambulation OR walking)
- #3 #1 AND #2

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	<ul> <li>a: in-hospital</li> <li>b: routine follow-up plus</li> <li>rehabilitation package consisting of</li> <li>93 pages of text</li> <li>c: 6 weeks</li> <li>d: every day*</li> </ul>	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	<ul> <li>a: after hospital discharge</li> <li>b: home-based physical rehabilitation</li> <li>program focused on strength training</li> <li>and walking</li> <li>c: 8 weeks</li> </ul>	No intervention	HRQoL, Mortality, Physical function	No ICU rehabilitation before randomisation*

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

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		7	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	73	Single-centre		No	Exercise capacity,	ICU rehabilitatio
et al., 2016, UK		RCT	<ul> <li>b: outpatient-based exercise and education program</li> <li>c: 7 weeks</li> <li>d: 3 times/week (1 supervised, 2 self-directed titrated)</li> </ul>	intervention	HRQoL, Mortality, Adverse events*	before randomisation*
Shelly et al., 2017, India	35	RCT	a: after hospital discharge b: homeE based respiratory and mobility training c: 4 weeks d: 5 times/week	No intervention	HRQoL	
McDowell et al., 2017, UK	60	Multi-centre RCT	<ul> <li>a: after hospital discharge</li> <li>b: standard care plus personalized</li> <li>exercise program</li> <li>c: 6 weeks</li> <li>d: 3 times/week (2 supervised and 1 unsupervised)</li> </ul>	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 activity of daily living	, randomised controlled trial; HRQoL, health-related	quality of life; PTSD, post-traumatic stress disorder; ADL,
	, randomised controlled trial; HRQoL, health-related	

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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.	Outcomes were not reported in the
2015;191:A6352	publication abstract. The full study will be
	considered when the review is updated.
Chen et al., Am J Respir Crit Care Med.	Outcomes were not reported in the
2017;195:A2337	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.	Insufficient outcome data for meta-analysis
2017;21:89-93	

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 <sup>a</sup>	Low <sup>a</sup>	High	Low	Low	Unclear <sup>a</sup>	Unclear <sup>b</sup>
Cuthbertson et al., 2009 (23)	Low	Low	High	Low	Low	Low	Unclear <sup>b</sup>
Elliott et al., 2011 (24)	Low	Low	High	Low	Low	High	Unclear <sup>c</sup>
Salisbury et al., 2010 (25)	Low	Low	High	Low	Low	Unclear	High <sup>d</sup>
Batterham et al., 2014 (26)	Low	Low	High	Low	Low	High	Unclear <sup>e</sup>
Connolly et al., 2015 (11)	Low	Low	High	High	Low	High	Unclear <sup>e</sup>
Walsh et al., 2015 (12)	Low	Low	High	Low	Low	High	High <sup>d</sup>
McWilliams et al., 2016 (13)	Low	Low	High	Low	Low	Low	Unclear <sup>e</sup>
Shelly et al., 2017 (27)	Low	Low	High	Unclear	Low	Low	Unclear <sup>e</sup>
McDowell et al., 2017 (15)	Low	Low	High	Low	Low	Low	High <sup>f</sup>

'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) trol group

<sup>b</sup>Dose of physical rehabilitation was unknown

<sup>c</sup>Adherence to the intervention was unknown

<sup>d</sup>Intervention included nutritional therapy

<sup>e</sup>Very little detail given regarding the therapy received in the control group

<sup>f</sup>Adherence to the intervention was 70%

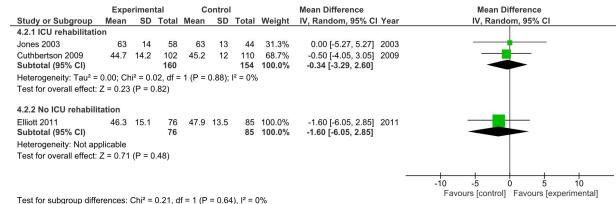
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6	A Quality of lif	fe: physical co	omponent summa	ry		
7	A-1 Rehabilitat	tion practice	in ICU (ICU	rehabilitation	before randomisation ve No	ICU
8	rehabilitation k	before randomis	sation)			
9 10			Control	Mean Difference	Mean Difference	
11		lean SD Total Mean	SD Total Weight	IV, Random, 95% CI Year	IV, Random, 95% CI	
12	4.1.1 ICU rehablitation Jones 2003	49 31 58 48	28 44 5.8%	1.00 [-10.49, 12.49] 2003		
13	Cuthbertson 2009 3 Subtotal (95% CI)	39.8 9.5 102 40.1 <b>160</b>	11.7 110 94.2% <b>154 100.0</b> %	-0.30 [-3.16, 2.56] 2009 -0.22 [-3.00, 2.55]		
14	Heterogeneity: Tau <sup>2</sup> = 0.00	0; Chi² = 0.05, df = 1 (P =		0.22 [ 0.00, 2.00]		
15	Test for overall effect: Z =	0.16 (P = 0.87)				
16	4.1.2 No ICU rehabilitatio			0.701.0.00.0.001.0044		
17	Elliott 2011 4 Subtotal (95% CI)	42.6 10 76 43.3 <b>76</b>	8.6 85 100.0% 85 100.0%	-0.70 [-3.60, 2.20] 2011 -0.70 [-3.60, 2.20]		
18 19	Heterogeneity: Not applica Test for overall effect: Z =					
20		0.47 (1 = 0.04)				
21					-10 -5 0 5 10 Favours [control] Favours [experimental]	
22	Test for subgroup differen	nces: Chi² = 0.05, df = 1 (F	P = 0.82), I <sup>2</sup> = 0%		Favours [control] Favours [experimental]	
23						
24						
25	A-2 The timing of	f the common con	ont of the int	orvention (in her	spital vs after hospital dischar	
26	N 2 The timing 0.	i the commenced	lent of the int		spital vs after nospital disenar	gC)
27						
28 29			Control SD Total Weight	Mean Difference IV, Random, 95% CI Year	Mean Difference IV, Random, 95% Cl	
30	6.1.1 in hospital					
31	Jones 2003 Cuthbertson 2009 3	49 31 58 48 39.8 9.5 102 40.1	28 44 5.8% 11.7 110 94.2%	1.00 [-10.49, 12.49] 2003 -0.30 [-3.16, 2.56] 2009		
32	Subtotal (95% CI)	160	154 100.0%	-0.22 [-3.00, 2.55]	-	
33	Heterogeneity: Tau <sup>2</sup> = 0.00 Test for overall effect: Z =		0.83); 1 <sup>2</sup> = 0%			
34	6.1.2 after hospital disch	arge				
35	Elliott 2011 4	42.6 10 76 43.3		-0.70 [-3.60, 2.20] 2011	— <u>—</u> —	
36	Subtotal (95% CI) Heterogeneity: Not applica	76 able	85 100.0%	-0.70 [-3.60, 2.20]		
37	Test for overall effect: Z =					
38 39						_
40	Test for subgroup differen	ices: Chi² = 0.05, df = 1.(F	$P = 0.82$ ) $I^2 = 0\%$		Favours [control] Favours [experimental]	
41			0.02,1 0,0			
42			(0 1	1 1 0		
43				less, and over 8		
44			Control SD Total Weight	Mean Difference IV, Random, 95% CI Year	Mean Difference IV, Random, 95% Cl	
45	8.1.1 8 weeks or less		-			
46	Jones 2003 Elliott 2011 4	49 31 58 48 42.6 10 76 43.3		1.00 [-10.49, 12.49] 2003 -0.70 [-3.60, 2.20] 2011		
47	Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = 0.00	134	129 100.0%	-0.60 [-3.41, 2.21]		
48 49	Test for overall effect: Z =		0.70), 1 = 078			
50	8.1.2 over 8 weeks					
51			11.7 110 100.0%	-0.30 [-3.16, 2.56] 2009		
52	Subtotal (95% CI) Heterogeneity: Not applica	102 able	110 100.0%	-0.30 [-3.16, 2.56]		
53	Test for overall effect: Z =	0.21 (P = 0.84)				
54					-10 -5 0 5 10	
55	Test for subgroup differen	ices: Chi² = 0.02 df = 1.04	P = 0.88), I <sup>2</sup> = 0%		Favours [control] Favours [experimental]	
56			5.007,1 - 070			
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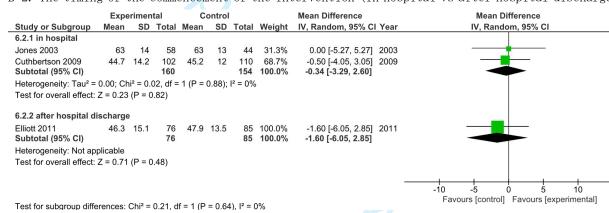


B-1. Rehabilitation practice in ICU (ICU rehabilitation before randomization ve No ICU

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)

Church and Carls and an		rimen			ontrol		14/-:	Mean Difference	Mean Difference
Study or Subgroup	Mean	50	Total	Mean	50	Total	Weight	IV, Random, 95% CI Year	IV, Random, 95% Cl
8.2.1 8 weeks or less									
Jones 2003	63	14	58	63	13	44	41.6%	0.00 [-5.27, 5.27] 2003	
Elliott 2011	46.3	15.1	76	47.9	13.5	85	58.4%	-1.60 [-6.05, 2.85] 2011	
Subtotal (95% CI)			134			129	100.0%	-0.93 [-4.33, 2.46]	
Heterogeneity: Tau <sup>2</sup> = (	0.00; Ch	i <sup>2</sup> = 0.2	21, df =	1 (P =	0.65);	l <sup>2</sup> = 0%			
Test for overall effect: 2	Z = 0.54	(P = 0	.59)						
		-							
8.2.2 over 8 weeks									
	44.7	14.2	102	45.2	12	110	100.0%	-0.50 [-4.05, 3.05] 2009	
8.2.2 over 8 weeks Cuthbertson 2009 Subtotal (95% CI)	44.7	14.2	102 <b>102</b>	45.2	12	110 <b>110</b>		-0.50 [-4.05, 3.05] 2009 -0.50 [-4.05, 3.05]	
		14.2		45.2	12				-
Cuthbertson 2009 Subtotal (95% CI) Heterogeneity: Not app	licable		102	45.2	12				-
Cuthbertson 2009 Subtotal (95% CI)	licable		102	45.2	12				
Cuthbertson 2009 Subtotal (95% CI) Heterogeneity: Not app	licable		102	45.2	12				

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

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C Long term mortality

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

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	ear M-H, Random, 95%	6 CI
5.1.1 ICU rehabilitatio	n							
Jones 2003	5	69	5	57	17.7%	0.83 [0.25, 2.71]	003	
Cuthbertson 2009	6	143	7	143	22.1%	0.86 [0.30, 2.49]	009	
Walsh 2015 Subtotal (95% Cl)	16	120 332	16	120 <b>320</b>	60.2% <b>100.0%</b>	1.00 [0.52, 1.91] <b>0.93 [0.57, 1.54</b> ]	015	
Total events	27		28					
Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: 2	Z = 0.27 (P			- 0.95),	1 - 076			
	Z = 0.27 (P			98		2.69 [0.74, 9.85]	011	
Test for overall effect: 2	Z = 0.27 (P ation 8 olicable	= 0.79) 97 <b>97</b>	3		100.0%	2.69 [0.74, 9.85] 2.69 [0.74, 9.85]	011	

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

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI Year	M-H, Random, 95% Cl
7.1.1 in hospital							
Jones 2003	5	69	5	57	17.7%	0.83 [0.25, 2.71] 2003	
Cuthbertson 2009	6	143	7	143	22.1%	0.86 [0.30, 2.49] 2009	
Walsh 2015 Subtotal (95% CI)	16	120 <b>332</b>	16	120 <b>320</b>	60.2% <b>100.0%</b>	1.00 [0.52, 1.91] 2015 0.93 [0.57, 1.54]	
Total events	27		28				
Heterogeneity: Tau <sup>2</sup> =	= 0.00; Chi <sup>2</sup> :	= 0.11, 0	df = 2 (P =	= 0.95);	l <sup>2</sup> = 0%		
Test for overall effect:	: Z = 0.27 (F	e = 0.79	i È	,			
7.1.2 after hospital d	lischarge						
Elliott 2011	8	97	3	98	74.7%	2.69 [0.74, 9.85] 2011	
McDowell 2017	0	30	1	30	25.3%	0.33 [0.01, 7.87] 2017	
Subtotal (95% CI)		127		128	100.0%	1.59 [0.27, 9.45]	
Total events	8		4				
Heterogeneity: Tau <sup>2</sup> =	= 0.67; Chi <sup>2</sup> :	= 1.44, d	df = 1 (P =	= 0.23);	l² = 31%		
Test for overall effect:	: Z = 0.51 (F	e = 0.61)	)				
	`						
							0.01 0.1 1 10 100 Favours [experimental] Favours [control]
Test for subgroup diff	erences: Ch	ni² = 0.3 <sup>2</sup>	1, df = 1 (	P = 0.5	8), l <sup>2</sup> = 0%	)	Favours [experimental] Favours [control]

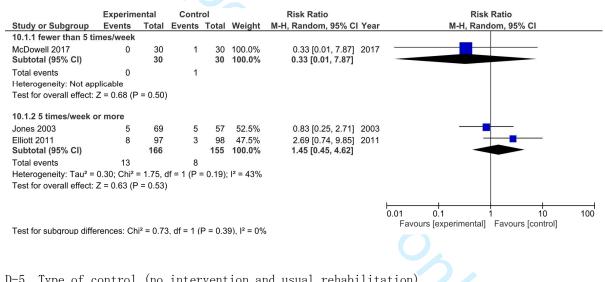
BMJ Open: first published as 10.1136/bmjopen-2018-026075 on 9 June 2019. Downloaded from http://bmjopen.bmj.com/ on June 5, 2025 at Department GEZ-LTA Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

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

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI Year	M-H, Random, 95% Cl
9.1.1 8 weeks or less							
Jones 2003	5	69	5	57	48.2%	0.83 [0.25, 2.71] 2003	
Elliott 2011	8	97	3	98	42.6%	2.69 [0.74, 9.85] 2011	
McDowell 2017 Subtotal (95% CI)	0	30 <b>196</b>	1	30 <b>185</b>	9.2% 100.0%	0.33 [0.01, 7.87] 2017 1.26 [0.47, 3.38]	
Total events Heterogeneity: Tau² = Test for overall effect:				= 0.29);	l² = 20%	. / .	
9.1.2 over 8 weeks							
Cuthbertson 2009 Subtotal (95% CI)	6	143 <b>143</b>	7	143 <b>143</b>	100.0% <b>100.0%</b>	0.86 [0.30, 2.49] 2009 <b>0.86 [0.30, 2.49]</b>	
Total events Heterogeneity: Not app	6 blicable		7				
Test for overall effect:	Z = 0.28 (F	<b>?</b> = 0.78)					
						ł	0.01 0.1 1 10 10

Test for subgroup differences: Chi<sup>2</sup> = 0.27, df = 1 (P = 0.61),  $I^2 = 0\%$ 

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)

	Experim	ental	Contr	ol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% Cl
11.1.1 no interventio	n							
Jones 2003	5	69	5	57	31.0%	0.83 [0.25, 2.71]	2003	
Cuthbertson 2009	6	143	7	143	38.6%	0.86 [0.30, 2.49]	2009	
Elliott 2011	8	97	3	98	26.0%	2.69 [0.74, 9.85]	2011	
McDowell 2017	0	30	1	30	4.4%	0.33 [0.01, 7.87]	2017	
Subtotal (95% CI)		339		328	100.0%	1.10 [0.57, 2.12]		<b>•</b>
Total events	19		16					
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>	= 2.82, (	df = 3 (P =	= 0.42);	$ ^2 = 0\%$			
Test for overall effect:	Z = 0.27 (F	P = 0.79	)					
11.1.2 usual rehabili	tation							
Walsh 2015	16	120	16	120	100.0%	1.00 [0.52, 1.91]	2015	
Subtotal (95% CI)		120		120	100.0%	1.00 [0.52, 1.91]		
Total events	16		16					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 0.00 (F	P = 1.00	)					
	·							
							F	.01 0.1 1 10 10
							0	.01 0.1 1 10 10 Favours [experimental] Favours [control]
Test for subgroup diff	erences: Ch	ni² = 0.04	4, df = 1 (I	P = 0.8	5), l <sup>2</sup> = 0%	0		

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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

Hospital Care Research Unit         Kataoka, Yuki; Hyogo Prefectural Amagasaki Hospital, Hospital Care <b>Primary Subject         Heading</b> :         Secondary Subject Heading:         Intensive care		
Article Type:       Research         Date Submitted by the Author:       13-Feb-2019         Complete List of Authors:       Taito, Shunsuke; Hiroshima University Hospital, Yamauchi, Kota; Steel Memorial Yawata Hospital, Department of Rehabilitation Tsujimoto, Yasushi ; School of Public Health in the Graduate School of Medicine, Kyoto University, Healthcare Epidemiology; Kyoritsu Hospital, Nephrology and Dialysis Banno, Masahiro; Seichiryo Hospital, Department of Psychiatry; Nagoya University, Graduate School of Medicine, Department of Psychiatry Tsujimoto, Hiraku; Hyogo Prefectural Amagasaki General Medical Center, Hospital Care Research Unit Kataoka, Yuki; Hyogo Prefectural Amagasaki Hospital, Hospital Care Research Unit; Hyogo Prefectural Amagasaki Hospital <b>Primary Subject Heading</b> :       Rehabilitation medicine         Secondary Subject Heading:       Intensive care	Journal:	BMJ Open
Date Submitted by the Author:13-Feb-2019Complete List of Authors:Taito, Shunsuke; Hiroshima University Hospital, Yamauchi, Kota; Steel Memorial Yawata Hospital, Department of Rehabilitation Tsujimoto, Yasushi ; School of Public Health in the Graduate School of Medicine, Kyoto University, Healthcare Epidemiology; Kyoritsu Hospital, Nephrology and Dialysis Banno, Masahiro; Seichiryo Hospital, Department of Psychiatry; Nagoya University, Graduate School of Medicine, Department of Psychiatry Tsujimoto, Hiraku; Hyogo Prefectural Amagasaki General Medical Center, Hospital Care Research Unit Kataoka, Yuki; Hyogo Prefectural Amagasaki Hospital, Hospital Care Research Unit; Hyogo Prefectural Amagasaki Hospital  Secondary Subject HeadingRehabilitation medicine	Manuscript ID	bmjopen-2018-026075.R1
Author:13-FeD-2019Complete List of Authors:Taito, Shunsuke; Hiroshima University Hospital, Yamauchi, Kota; Steel Memorial Yawata Hospital, Department of Rehabilitation Tsujimoto, Yasushi ; School of Public Health in the Graduate School of Medicine, Kyoto University, Healthcare Epidemiology; Kyoritsu Hospital, Nephrology and Dialysis Banno, Masahiro; Seichiryo Hospital, Department of Psychiatry; Nagoya University, Graduate School of Medicine, Department of Psychiatry Tsujimoto, Hiraku; Hyogo Prefectural Amagasaki General Medical Center, Hospital Care Research Unit Kataoka, Yuki; Hyogo Prefectural Amagasaki Hospital, Hospital Care Research Unit; Hyogo Prefectural Amagasaki Hospital Secondary Subject Heading:Intensive care	Article Type:	Research
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Heading:     Renabilitation medicine       Secondary Subject Heading:     Intensive care	Complete List of Authors:	Yamauchi, Kota; Steel Memorial Yawata Hospital, Department of Rehabilitation Tsujimoto, Yasushi ; School of Public Health in the Graduate School of Medicine, Kyoto University, Healthcare Epidemiology; Kyoritsu Hospital, Nephrology and Dialysis Banno, Masahiro; Seichiryo Hospital, Department of Psychiatry; Nagoya University, Graduate School of Medicine, Department of Psychiatry Tsujimoto, Hiraku; Hyogo Prefectural Amagasaki General Medical Center, Hospital Care Research Unit Kataoka, Yuki; Hyogo Prefectural Amagasaki Hospital, Hospital Care
		Rehabilitation medicine
	Secondary Subject Heading:	Intensive care
Keywords: critical liness, renabilitation, post-intensive care syndrome, exercise, quality of life, mortality	Keywords:	critical illness, rehabilitation, post-intensive care syndrome, exercise, quality of life, mortality

# SCHOLARONE<sup>™</sup> Manuscripts

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1	Research – meta-analysis
2	Does enhanced physical rehabilitation following intensive care unit discharge
3	improve outcomes in patients who received mechanical ventilation? A system
4	review and meta-analysis
5	
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improve outcomes in patients who received mechanical ventilation? A systematic
review and meta-analysis
Shunsuke Taito, PT, PhD <sup>1</sup> , Kota Yamauchi, PT <sup>2</sup> , Yasushi Tsujimoto, MD, MPH <sup>3,4</sup> ,
Masahiro Banno, MD, PhD <sup>5,6</sup> , Hiraku Tsujimoto, MD <sup>7</sup> , Yuki Kataoka, MD, MPH <sup>7,8</sup>
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Declaration of interests: None.

Word count: 3051 words

# 34 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

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Abstract

44	Objective: We aimed to determine whether enhanced physical rehabilitation following
45	intensive care unit (ICU) discharge improves clinically relevant outcomes, such as
46	activity-of-daily-living (ADL), quality of life (QOL), and mortality among patients who
47	received mechanical ventilation.
48	Design: Systematic review and meta-analysis using the Grading of Recommendations
49	Assessment, Development, and Evaluation (GRADE) approach.
50	Data sources: MEDLINE, Embase, CENTRAL, PEDro, and World Health Organization
51	International Clinical Trials Registry Platform searched through January 2019.
52	Eligibility criteria for selecting studies: We included randomised controlled trials
53	
55	assessing the effect of rehabilitation following ICU discharge, designed to either
54	assessing the effect of rehabilitation following ICU discharge, designed to either commence earlier and/or be more intensive for adult patients who received mechanical
54	commence earlier and/or be more intensive for adult patients who received mechanical
54 55	commence earlier and/or be more intensive for adult patients who received mechanical ventilation.
54 55 56	<ul> <li>commence earlier and/or be more intensive for adult patients who received mechanical ventilation.</li> <li>Data extraction and synthesis: Two independent reviewers extracted data and assessed</li> </ul>

60 evidence.

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 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

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# 76 Article Summary

# 77 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

- 80 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
- 83 a follow-up >6 months and (ii) medical resources and costs associated with each
- 84 intervention were not considered.
- We employed rigorous methodology that followed a written priori protocol developed
- 86 according to the Preferred Reporting Items for Systematic Reviews and Meta- (PRISMA)
- 87 statement, and used the Grading of Recommendations Assessment, Development and
- 88 Evaluation approach in the review process.

Introduction

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90	In critically ill patients, rehabilitation mainly aims to enhance quality of life
91	(QOL) by improving activities of daily living (ADL) function,[1, 2] which may be
92	severely impaired also due to post-intensive care syndrome (PICS).[3-5] According to
93	the guidelines issued by the National Institute for Health and Care Excellence, provision
94	of rehabilitation should be seamlessly integrated with the patient's transition from the
95	intensive care unit (ICU) to the ward and then to out-of-hospital care.[6] However, at
96	the time the guidelines were issued, there was little evidence from clinical trials to
97	support the use of enhanced physical rehabilitation following ICU discharge. Some
98	experts do recommend physical rehabilitation following ICU discharge to improve ADL
99	function and QOL.[7] With regards to sepsis survivors, the findings of a large
100	observational study suggested that physical rehabilitation following ICU discharge
101	improves long-term mortality.[8, 9]
102	A recent meta-analysis by Connolly et al.[10] focused on randomised
103	controlled trials (RCTs) regarding the effectiveness of enhanced exercise rehabilitation
104	following ICU discharge in adult ICU survivors who had been mechanically ventilated
105	for longer than 24 hours. Despite the comprehensive search, only 6 RCTs with
106	conflicting results were included, and no clear effect of the intervention on clinically

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107	relevant outcomes such as QOL, mortality, functional exercise capacity, or incidence of
108	adverse events could be established at the time. Additionally, some clinically relevant
109	outcomes such as ADL, pain, return-to-work rate, muscle strength, and duration of
110	delirium were not considered in their review.[10] Several RCTs assessing the effect of
111	enhanced physical rehabilitation following ICU discharge on clinically relevant
112	outcomes[11-15] have been published since Connolly and colleagues conducted their
113	Cochrane review.[10] Therefore, in the present study, we aimed to re-evaluate the
114	available literature and determine whether enhanced physical rehabilitation following
115	ICU discharge improves clinically relevant outcomes among critically ill adults who
116	received mechanical ventilation.
117	
118	Materials and methods
119	Compliance with reporting guidelines
120	Using a pre-specified protocol (PROSPERO registry ID:
121	CRD42017080532),[16] we conducted a systematic review of the relevant literature in
122	agreement with the recommendations listed in the Cochrane Handbook[17] and the
123	Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)
124	guidelines.[18] We confirmed that this systematic review was PRISMA-compliant by

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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  $\geq 18$  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

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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-tositting 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).

# 160 Search strategy and selection of studies

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161	We searched the Cochrane Central Register of Controlled Trials (CENTRAL),
162	MEDLINE via PubMed, Excerpta Medica Database (EMBASE) via Elsevier, the
163	Physiotherapy Evidence Database (PEDro), and the World Health Organization
164	International Clinical Trials Registry Platform (WHO ICTRP) via their dedicated search
165	portal. The search was performed in December 2017 and updated in January 2019 using
166	a set of suitable search terms (details provided in online supplementary file 2). We hand-
167	searched reference lists for the guidelines for rehabilitation after critical illness.[6] We
168	attempted to identify other relevant research by hand-searching the reference lists of the
169	studies returned by the search and those of articles citing such studies (based on citation
170	information from the Web of Science). If the database entry for a candidate study did not
171	contain the necessary information, we contacted the study authors. Two reviewers (ST
172	and KY) independently screened the title and abstract of each study returned by the search
173	to determine whether the inclusion criteria were met. The 2 reviewers performed a full-
174	text review to assess the eligibility of each candidate study. Disagreement was resolved
175	by discussion between the 2 reviewers, occasionally with arbitration by a third reviewer
176	(YK).
177	Data abstraction and quality assessment
170	

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> 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<sup>2</sup> as a measure of variation across studies that is due to heterogeneity rather than chance, and interpreted the values as follows: 0%-40%,

197	negligible heterogeneity; 30%-60%, mild-to-moderate heterogeneity; 50%-90%,
198	moderate-to-substantial heterogeneity; 75%-100%, considerable heterogeneity. If
199	heterogeneity was identified for an outcome ( $I^2 > 50\%$ ), we investigated the underlying
200	reasons and conducted the $\chi^2$ test, with a <i>P</i> -value of <0.10 being considered to be
201	statistically significant. We investigated reporting bias by checking the WHO ICTRP to
202	detect trials that had been completed but not published at the time of the review.
203	We planned the following pre-specified sensitivity analyses for the primary
204	outcomes: (i) exclusion of studies using imputed statistics, and (ii) exclusion of studies
205	with high or unclear risk of bias. We also carried out pre-specified subgroup analyses
206	according to the type of rehabilitation involved (neuromuscular stimulation versus other
207	types of rehabilitation), rehabilitation provision in the ICU (received versus did not
208	receive protocoled physical rehabilitation in the ICU), timing of commencement of the
209	intervention (in-hospital or after hospital discharge), intervention duration ( $\leq 8$ versus > 8
210	weeks), treatment frequency (<5 versus $\geq$ 5 times/week), and type of control (no
211	intervention versus standard rehabilitation). Statistical significance was set at $P < 0.05$ . We
212	created a summary-of-findings table that included an overall grading of the certainty of
213	evidence for each of the main outcomes, which was evaluated using the Grading of
214	Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[20,

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# 216 Patient and public involvement

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

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# 219 Results

# 220 Characteristics of trials on rehabilitation in ICU survivors

221 After removing duplicates, we identified 3,589 records during the search 222 conducted in December 2017 and updated the electronic searches in January 2019. We 223 identified 10 unique RCTs[11-13, 15, 22-27] that fulfilled all eligibility criteria and 224 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 225 patients with an ICU stay of >48 hours during which mechanical ventilation was 226 227 provided for at least 24 hours. Eight studies were performed in the United Kingdom, one 228 in Australia, and one in India. The mean or median age in the analysed studies ranged 229 from 40.5 to 68.5 years, while the mean or median Acute Physiology and Chronic Health 230 Evaluation (APACHE) II score ranged from 15.2 to 31. Only 1 study included 231 participants with PICS symptoms or ICU-acquired weakness.[11] Three RCTs[25-27] 232 did not have sufficient outcome data for meta-analysis (details provided in online

233	supplementary file 4), leaving a total pooled sample of 1000 patients (506 patients in the
234	intervention groups; 494 controls) represented across 7 studies to be included in the
235	quantitative synthesis. Of the 10 trials analysed, 6 evaluated the effect of physical
236	rehabilitation including self-directed exercise and/or supervised exercise following
237	hospital discharge, while 4[12, 22-24] focused on rehabilitation started during
238	hospitalisation. The duration of intervention ranged from 6 weeks to 3 months, while the
239	frequency of intervention ranged from 3 times per week to once daily. No study
240	considered intensive intervention (>30 minutes of active rehabilitation daily) or
241	intervention with neuromuscular stimulation. Two studies [12, 23] had a follow-up >6
242	months. We did not identify any ongoing studies.
242 243	months. We did not identify any ongoing studies. Most studies were at high or had an unclear risk of bias, as determined using the
243	Most studies were at high or had an unclear risk of bias, as determined using the
243 244	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
243 244 245	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
<ul><li>243</li><li>244</li><li>245</li><li>246</li></ul>	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
<ul> <li>243</li> <li>244</li> <li>245</li> <li>246</li> <li>247</li> </ul>	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,
<ul> <li>243</li> <li>244</li> <li>245</li> <li>246</li> <li>247</li> <li>248</li> </ul>	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

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251	protocols were not published. High or unclear risk of other bias was noted for all studies
252	because of insufficient information regarding the intervention and control protocols.
253	Primary outcomes
254	QOL was measured in 9 trials (see online supplementary file 3), but the short-
255	and long-term QOL score were only available in four trials,[12, 22–24] whereas the
256	other 5 trials measured these outcomes at a different time or had insufficient outcome
257	data for meta-analysis. ADL function was measured in 1 trial,[11] but the short- and
258	long-term data were not available. Short-term mortality was reported in 2 trials,[11, 13]
259	while long-term mortality was reported in 5 trials.[12, 15, 22–24]
260	The SMD between intervention and control regarding PCS and MCS scores
261	measured by SF-36 or SF-12 characterising QOL were 0.06 (95% CI, -0.12 to 0.24) and
261 262	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
262	-0.04 (95% CI, -0.20 to 0.11), respectively (Fig. 2A and 2B, respectively). Rehabilitation
262 263	-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, $I^2 =$
262 263 264	-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
262 263 264 265	-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

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

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287	possibly related to study participation), while 6 were serious (hospitalisation or prolonged
288	hospitalisation, with 1 event related/possibly related to study participation). In the control
289	group, there was 1 adverse event (musculoskeletal pain higher than expected, muscle
290	soreness potentially indicating injury, related/possibly related to study participation) and
291	4 serious adverse events (hospitalisation or prolonged hospitalisation, with 1 event
292	related/possibly related to study participation). The certainty of evidence for adverse
293	events was low (Table 1).
294	
295	Discussion
296	The results of this up-to-date review covering 10 RCTs and 1110 patients
297	suggest that enhanced rehabilitation following ICU discharge might not improve QOL
298	or reduce mortality among patients who received mechanical ventilation at the 6 or 12
299	month follow-ups. We could not confirm the effect of enhanced physical rehabilitation
300	even though all included studies exhibited performance bias potentially increasing the
	even though an included statics exhibited performance ones potentiarly including the
301	observed effect of the intervention. Furthermore, despite the large sample size in the
301 302	
	observed effect of the intervention. Furthermore, despite the large sample size in the
302	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

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

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321	Subgroup analysis in a previous systematic review[28] indicated that,
322	compared with low-dose rehabilitation, high-dose active rehabilitation for >30 minutes
323	daily was associated with significantly higher QOL. Dose-response analysis of early
324	physical rehabilitation[33] in stroke patients enrolled in A Very Early Rehabilitation
325	Trial (AVERT)[32] determined that intervention in such acute cases improved the odds
326	of a favourable outcome with each episode of activity per day. This review did not
327	include studies comparing high-dose rehabilitation and usual care, and thus the QOL
328	effect of high-dose rehabilitation remains unclear. Additionally, we could not perform
329	subgroup analysis for PICS symptoms with effect on QOL[3–5] or for sepsis, which is a
330	risk factor for PICS.[34, 35] It remains unclear which population of critically ill patients
331	may truly benefit from intensive physical rehabilitation.
332	The studies included in our review did not cover all important outcomes included
333	in the core outcome set of rehabilitation after critical illness,[7] including ADL function,
334	functional exercise capacity, pain, return-to-work rate, muscle strength, or delirium
335	incidence. Nonetheless, our findings regarding QOL and mortality suggest that, even if
336	future studies report improvement in these other aspects, the amount of improvement
337	would likely be too small to affect QOL.
338	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

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357	intervention. However, since studies included in this review compare rehabilitation
358	intervention against standard care or no intervention, it is obvious that intensive
359	physical rehabilitation would be associated with increased medical resources and costs.
360	Lastly, we could not consider psychological aspects in our review. However, effect of
361	intervention for the general population is more clinically important than for that of
362	highly self-motivated individuals, and we clarified that enhanced physical rehabilitation
363	following ICU discharge may make little or no difference for the general population
364	including highly self-motivated individuals.
365	Taken together, the findings of the present meta-analysis indicate that enhanced
366	physical rehabilitation following ICU discharge may make little or no difference to
367	QOL or mortality among patients who received mechanical ventilation. With regards to
368	the wide CI, we believe further studies are needed to confirm the efficacy of
369	rehabilitation.

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393	ST and KY designed the study, were involved in the systematic review process,
394	analysed and interpreted the data, and drafted the manuscript. MB, HT, YK, and YT
395	participated in the systematic review process, critically reviewed the initial manuscript,
396	and approved the final manuscript as submitted. All authors read and approved the final
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401	
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403	None.
404	
405	Data sharing statement
406	All data associated with this manuscript are included in the main text and supplementary
407	materials.

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9	409	Supplementary data to this article can be found online.
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16	411	Online supplementary file 1: PRISMA 2009 checklist
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56 57 58 59 60	527	35.	Iwashyna TJ, Ely EW, Smith DM, et al. Long-term cognitive impairment and

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528 functional disability among survivors of severe sepsis. *JAMA* 2010;304:1787–

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) Figure legends
Fig 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)
2 flow diagram
Fig 2 Forest plot for quality of life and mortality
Fig 2 Forest plot for quality of life and mortality
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Table 1. Findings fro	m ten trials tocuse	ed on post-ICU rehat	bilitation of critical	ly ill patients who		nanical ventilat	ion		
	lesign 🗼				une 20 Eras relatec				
Overview of study de Patients or study pop	pulation: adult pati	ents who have been di	ischarged from an IC	U or critical care er	nvironmente durin	ng which mechai	nical		
ventilation was provid	ded for at least 24 he	ours	-		ownload hogesche ext and c	-			
Setting: any					oade schoo nd d <i>a</i>				
	Intervention: protocolized physical rehabilitation following ICU discharge, designed to be more intensive that the care received by the control								
group.	group. Comparison: no intervention or usual care								
Outcome		oarative risks <sup>*</sup> (95%	Relative effect	No. of	Certainty o	of the Comm			
Guttome	CI)		(95% CI)	participants	evigence				
	Assumed risk	Corresponding	_ ` _ (	(studies)	(GEADE)				
		risk			nj.com/ c nd simila				
	Control	Intervention		U					
Quality of life	Study population		_	649					
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summary score		(-0.12 10 0.24)			5, 2025 a logies.				
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	Study population	<u>.</u>		039	2				
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Page 35 of 59				BMJ Open		136/bmjopen 1 by copyrigh	
1 2 3						-201: t, inc	
4 5	Quality of life		SMD: -0.04		(4 RCTs)	<u> </u>	
6			(-0.20 to 0.11)			75 or	
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10 11	(6 months)						
12	Mortality	Study population		RR: 0.71	93	I⊕texx Lox	
13 14	Short term	43 per 1000	31 per 1000	(0.05 to 9.80)	(2 RCTs)		
15	(28-35 days)		(2 to 426)	(0.00 00 9.000)		nload gescho	
16 17	Mortality	Study population	NO	RR: 1.05	907	$\oplus \oplus \oplus \oplus$	
18	Long term	71 per 1000	75 per 1000	(0.66 to 1.66)	(5 RCTs)	Moglerated	
19 20	(6 months)		(47 to 119)			http://	
21	Adverse events	Study population		- 191.	153	⊕∰aing,	
22 23		Two studies report	ed no adverse		(3 RCTs)	Long g	
24		events. One study i	reported 18 and 5			g, ar	
25 26		events in the interv	rention and control			bmj.com/ o and simila	
27		groups, respectivel	у.				
28 29	*The corresponding	g risk (and its 95% CI)	is based on the assun	ned risk in the comp	arison group and t	he relative effect (and its 95%	CI) estimated
30	for the intervention	group.				hno <mark>-</mark>	
31 32	GRADE Working	Group grades of evid	ence			5, 2025 logies.	
33	High certainty: W	e are very confident the	at the true effect lies	close to that of the e	stimate of the effe	ct. 95 at	
34 35	Moderate certaint	y: We are moderately of	confident in the effec	t estimate; the true e	ffect is likely to be	e close to the stimate of the e	ffect, but there
36	is a possibility that	it is substantially differ	rent.			oartn	
37 38	Low certainty: Ou	r confidence in the effe	ect estimate is limited	l; the true effect may	be substantially d	lifferent from the estimate of t	he effect.
39						GEZ	
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	ight,
	Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substant different from the estimate of
	effect of o
537	CI, confidence interval; RR, risk ratio; ICU, intensive care unit; SF-36, Short Form 36; SMD, standardized meak difference; RCT, randomised
538	controlled trial
539	$\mathbb{R}$
540	adherence in the intervention group (other bias). <sup>b</sup> Downgraded one point because of high risk of bias associated with the fact that the intervention included nutriting as therapy but the study provided
541	<sup>b</sup> Downgraded one point because of high risk of bias associated with the fact that the intervention included nutrit the attempt but the study provided
42	very little detail regarding the therapy received in the control group (other bias).
43	<sup>c</sup> Downgraded because of imprecision (only two small studies).
44	<sup>d</sup> Downgraded one point because of high risk of bias associated with the incomplete outcome and data the lact $\vec{E}$ of $\vec{E}$ formation regarding the dose of
45	physical rehabilitation and adherence in the intervention group, as well as with the fact that the intervention included nutritional therapy but the
46	study provided very little detail regarding the therapy received in the control group (other bias).
47	eDowngraded one point because of high risk of bias associated with the fact that very little detail was given regarding the therapy received in the
48	control group, and the adherence in the intervention group was 70% (other bias).
549	control group, and the adherence in the intervention group was 70% (other bias). <sup>1</sup> Downgraded because of imprecision (only three small studies). <sup>1</sup> Downgraded because of imprecision (only three small studies). <sup>1</sup> Downgraded because of imprecision (only three small studies).
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Additional records identified

through other sources

total (n=615)

ICTRP (n=58)

PEDro (n=554)

Guidelines (n =3)

Records excluded (n =3530)

Full-text articles excluded,

with reasons (n =51)

Wrong population (n=15)

Wrong intervention (n=18)

Non-RCT(n=4)

Protocols of other include studies(n=3)

Abstracts of other included studies (n=8)

Insufficient information (n=3)

Studies excluded, with reasons (n=4)

Outcomes were not reported (n=1)

Studies excluded from quantitative

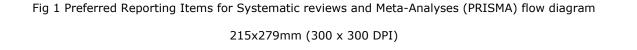
Ouasi-RCT (n=3)

synthesis (n=3)

Insufficient data (n=3)

Records identified through database searching total (n =4060) MEDLINE via PubMed (n=1219) Identification EMBASE (n=1343) CENTRAL (n=1498) Records after duplicates removed (n =3589) Screening Additional records (n=6) Records identified through citation search (n=0) Records screened Records screened by search update (n=6) Eligibility Full-text articles assessed for eligibility Studies included in

Included



(n =65)

(n =14)

qualitative synthesis

(n =10)

Studies included in

quantitative synthesis

(meta-analysis) (n =7)

#### 2-A Quality of life: physical component summary

	Expe	rimen	tal	C	ontrol			Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% Cl
Jones 2003	49	31	58	48	28	44	17.5%	0.03 [-0.36, 0.43]	2003	
Cuthbertson 2009	39.8	9.5	102	40.1	11.7	110	31.3%	-0.03 [-0.30, 0.24]	2009	
Elliot 2011	42.6	10	76	43.3	8.8	85	25.5%	-0.07 [-0.38, 0.24]	2011	
Walsh 2015	38	16	84	33	15	80	25.7%	0.32 [0.01, 0.63]	2015	
Total (95% CI)			320			319	100.0%	0.06 [-0.12, 0.24]		-
Heterogeneity: Tau <sup>2</sup> =	= 0.01; Ch	i <sup>2</sup> = 3.	90, df=	= 3 (P =	0.27);	P = 239	6		H	1 .05 0 05 1
Test for overall effect Z = 0.66 (P = 0.51)										Favours [control] Favours [experimental]

#### 2-B Quality of life: mental component summary

	Expe	rimen	tal	C	ontrol			Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% Cl
Jones 2003	63	14	58	63	13	44	15.7%	0.00 [-0.39, 0.39]	2003	
Cuthbertson 2009	44.7	14.2	102	45.2	12	110	33.3%	-0.04 [-0.31, 0.23]	2009	
Elliot 2011	46.3	15.1	76	47.9	13.5	85	25.2%	-0.11 [-0.42, 0.20]	2011	
Walsh 2015	43	15	84	43	15	80	25.8%	0.00 [-0.31, 0.31]	2015	<b>_</b>
Total (95% CI)			320			319	100.0%	-0.04 [-0.20, 0.11]		-
Heterogeneity: Tau <sup>2</sup> =	0.00; C	hi² = 0.	31, df=	= 3 (P =	0.96);	1 <sup>2</sup> = 0%				-1 -0.5 0 0.5 1
Test for overall effect:	Z = 0.51	(P = 0	1.61)							Favours [control] Favours [experimental]

#### 2-C Short term mortality

	Experime	ental	Contr	ol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI
Connolly 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: Tau <sup>2</sup> = Test for overall effect:				= 0.22)	; I² = 33%	•		0.01 0.1 1 10 100 Favours [experimental] Favours [control]

#### 2-D Long term mortality

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI Yea	ar M-H, Random, 95% Cl
Jones 2003	5	69	5	57	15.1%	0.83 [0.25, 2.71] 200	3
Cuthbertson 2009	6	143	7	143	18.8%	0.86 [0.30, 2.49] 200	9
Elliott 2011	8	97	3	98	12.7%	2.69 [0.74, 9.85] 201	1
Walsh 2015	16	120	16	120	51.3%	1.00 [0.52, 1.91] 201	5 —
McDowell 2017	0	30	1	30	2.1%	0.33 [0.01, 7.87] 201	7
Total (95% CI)		459		448	100.0%	1.05 [0.66, 1.66]	+
Total events	35		32				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup> :	= 2.86, c	if = 4 (P =	= 0.58);	$I^2 = 0\%$		0.01 0.1 1 10 100
Test for overall effect:	Z = 0.19 (P	= 0.85)					0.01 0.1 1 10 100 Favours [experimental] Favours [control]

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

P	age 39 of 59		BMJ Open BMJ Open										
1 2	PRISMA 20	009	Checklist <sup>36/bmj</sup> open										
3 4 5	Section/topic	#	Checklist item	Reported on page #									
6 7	TITLE		ng f										
8	Title	1	Identify the report as a systematic review, meta-analysis, or both.	1									
9 1			es r Lu										
1 1 1 1	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; limitation because and because and synthesis methods; results; limitation because and bec	4, 5									
1													
1	6 Rationale	3	Describe the rationale for the review in the context of what is already known.	7, 8									
1 1 1	Objectives	4	Provide an explicit statement of questions being addressed with reference to participant being addressed with reference to participant being be rventions, comparisons, outcomes, and study design (PICOS).	8									
2			ning htt										
2	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									
2	0,00	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									
2	Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with stady authors to identify additional studies) in the search and date last searched.	11									
2 2 3	9 Search	8	Present full electronic search strategy for at least one database, including any limits use to that it could be repeated.	11									
3	Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic studies, and, if applicable, included in the meta-analysis).	11									
3	Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in disclosed by and any processes for obtaining and confirming data from investigators.	11, 12									
3	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									
3 3 4		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									
4	Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	12									
4 4 4	Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including masures of consistency (e.g., l <sup>2</sup> ) for each meta-analysis.	13									
4 4 4	5 6		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml Page 1 of 2										



		BMJ Open dd H 10,11	Page 40 of 59
PRISMA 20	009	Checklist by copyright	
Checklist item 9		2018-0260	
7 8 9 9	#	g for use	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
3 Additional analyses 4	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regezion), if done, indicateng which were pre-specified.	13
	<u> </u>		
7 Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, where 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, PCOS, 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 sum 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-	17
DISCUSSION			
22 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
7 Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implication for future research.	22
	<u> </u>		
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
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9	The cochrane central register of controlled trials (CENTRAL)
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13	#2 MeSH descriptor: [intensive care unit]explode all trees
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15	#3 MeSH descriptor:[critical illness]explode all trees
16	#4 MeSH descriptor:[ventilator weaning]explode all trees
17 18	#5 MeSH descriptor:[Respiratory Distress Syndrome, Adult]explode all trees
19	#6 MeSH descriptor: [Sepsis] explode all trees
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22 23	#8 "critical care":ti,ab,kw
24	#9 "intensive care unit":ti,ab,kw
25	#10 ICU:ti,ab,kw
26	#11 "critical illness":ti,ab,kw
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29	#12 ventilator:ti,ab,kw
30	#13 ARDS:ti,ab,kw
31 32	#14 "acute respiratory distress syndrome":ti,ab,kw
33	#15 sepsis:ti,ab,kw
34	#16 CIN:ti,ab,kw
35 36	#17 CIM:ti,ab,kw
37	#18 CIPN:ti,ab,kw
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40 41	#20 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR
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47	#24 MeSH descriptor:[Rehabilitation]explode all trees
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50	#25 MeSH descriptor:[Physical fitness]explode all trees
51	#26 MeSH descriptor: [Physical Therapy Modalities]explode all trees
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55	#29 rehabilitation:ti,ab,kw
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#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
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17 18	#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
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57	#32 mobilization[tiab]
58	#33 mobilisation[tiab]

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#35 physiotherapy[tiab]
#36 "occupational therapy"[tiab]
#37 "electrical muscle stimulation"[tiab]
#38 "neuromuscular electrical stimulation"[tiab]
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15	#5 "Respiratory Distress Syndrome, Adult"/exp
16	#6 Sepsis/exp
17 18	#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
19	#8 "critical care":ab,ti
20 21	#9 "intensive care unit":ab,ti
21	#10 ICU:ab,ti
23	#11 "critical illness":ab,ti
24 25	
26	#12 ventilator:ab,ti
27 28	#13 ARDS:ab,ti
28 29	#14 "acute respiratory distress syndrome":ab,ti
30	#15 sepsis:ab,ti
31 32	#16 CIN:ab,ti
33	#17 CIM:ab,ti
34 35	#18 CIPN:ab,ti
36	#19 CIPNM:ab,ti
37	#20 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR
38 39	#18 OR #19
40	#21 #7 OR #20
41 42	#21 #/ OR #20 #22 Exercise/exp #23 "Exercise therapy"/exp #24 Bababilitation/own
42	#23 "Exercise therapy"/exp
44	#24 Rehabilitation/exp
45 46	#25 "Physical fitness"/exp
47	
48 49	#26 "Physical Therapy Modalities"/exp
50	#27 #22 OR #23 OR #24 OR #25 OR #26
51	#28 exercise:ab,ti
52 53	#29 rehabilitation:ab,ti
54	#30 "physical fitness":ab,ti
55 56	#31 training:ab,ti
57	#32 mobilization:ab,ti
58 50	#33 mobilisation:ab,ti
59 60	

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- #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

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

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# 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 R amu. daily living OR ambulation OR walking)
- #3 #1 AND #2

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11	ementary file	3. Characteri	stics of the studies analysed in this rev	view	136/bmjopen-2018-0260 1 by copyright, including	
Author, year, country	No. of participants	Study type	Intervention (a, Timing of commencement; b, Contents; c, Duration; d, Frequency)	Control	G D75 on 9 June Outcomes res rela	Notes
Jones et al., 2003, UK	126	Multi- centre RCT	<ul> <li>a: in-hospital</li> <li>b: routine follow-up plus rehabilitation</li> <li>package consisting of 93 pages of text</li> <li>c: 6 weeks</li> <li>d: every day*</li> </ul>	No intervention	TTT A T T ST ON N	ICU rehabilitatio 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 TSD, Anxiety and depression symptoms, Cost effectivences of	ICU rehabilitatio before randomisation*
Elliott et al., 2011, Australia	195	Multi- centre RCT	<ul> <li>a: after hospital discharge</li> <li>b: home-based physical rehabilitation</li> <li>program focused on strength training</li> <li>and walking</li> <li>c: 8 weeks</li> <li>d: 5 times/week</li> </ul>	No intervention	HRQoL, Mortanity, Physical function s at Department	No ICU rehabilitation before randomisation*
	Country fones et al., 2003, UK Cuthbertson et al., 2009, UK Elliott et al., 2011,	Cuthbertson 286 et al., 2009, UK Elliott et al., 195 2011, 195	country       Iones et al., 126       Multi-         2003, UK       centre RCT         Cuthbertson 286       Multi-         Cuthbertson 286       Multi- </td <td>country       Duration; d, Frequency)         Jones et al., 126       Multi-       a: in-hospital         2003, UK       centre RCT       b: routine follow-up plus rehabilitation package consisting of 93 pages of text         c: 6 weeks       d: every day*         Cuthbertson 286       Multi-       a: in-hospital         ctubertson 286       Multi-       a: after hospital discharge         ci unknown       a: after hospital discharge       discharge         continued for 3 months after       b: home-based physical rehabilitation         Australia       RCT       program focused on strength training         and walking</td> <td>country       Duration; d, Frequency)         Jones et al., 126       Multi-       a: in-hospital       No         2003, UK       centre RCT       b: routine follow-up plus rehabilitation       intervention         package consisting of 93 pages of text       c: 6 weeks       d: every day*         Cuthbertson 286       Multi-       a: in-hospital       No         tal., 2009,       centre       b: manual based, self-directed,       intervention         JK       RCT       physical rehabilitation program       intervention         JK       RCT       physical rehabilitation program       e: c: continued for 3 months after         discharge       d: unknown       d: unknown       No         Elliott et al., 195       Multi-       a: after hospital discharge       No         Australia       RCT       program focused on strength training and walking       intervention         Cutharentalia       RCT       program focused on strength training       intervention</td> <td>Iones et al.,126Multi- centre RCTa: in-hospitalNoHRQoL, Merrisity, intervention2003, UKcentre RCTb: routine follow-up plus rehabilitation package consisting of 93 pages of text c: 6 weeks d: every day*interventionDepression of pression of pres</td>	country       Duration; d, Frequency)         Jones et al., 126       Multi-       a: in-hospital         2003, UK       centre RCT       b: routine follow-up plus rehabilitation package consisting of 93 pages of text         c: 6 weeks       d: every day*         Cuthbertson 286       Multi-       a: in-hospital         ctubertson 286       Multi-       a: after hospital discharge         ci unknown       a: after hospital discharge       discharge         continued for 3 months after       b: home-based physical rehabilitation         Australia       RCT       program focused on strength training         and walking	country       Duration; d, Frequency)         Jones et al., 126       Multi-       a: in-hospital       No         2003, UK       centre RCT       b: routine follow-up plus rehabilitation       intervention         package consisting of 93 pages of text       c: 6 weeks       d: every day*         Cuthbertson 286       Multi-       a: in-hospital       No         tal., 2009,       centre       b: manual based, self-directed,       intervention         JK       RCT       physical rehabilitation program       intervention         JK       RCT       physical rehabilitation program       e: c: continued for 3 months after         discharge       d: unknown       d: unknown       No         Elliott et al., 195       Multi-       a: after hospital discharge       No         Australia       RCT       program focused on strength training and walking       intervention         Cutharentalia       RCT       program focused on strength training       intervention	Iones et al.,126Multi- centre RCTa: in-hospitalNoHRQoL, Merrisity, intervention2003, UKcentre RCTb: routine follow-up plus rehabilitation package consisting of 93 pages of text c: 6 weeks d: every day*interventionDepression of pression of pres

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Salisbury et	16	Single-	a: in-hospital	Standard	Physical out conserved.	
al., 2010,		centre	b: enhanced physiotherapy and	care	Nutritional out come,	
UK		pilot RCT	dietetic rehabilitation package		Breathlessiess on the	
			c: unknown		Visual analogue scale	
			d: unknown		scores for the side lessness,	
					fatigue, joint at finess,	
			Jr.		pain, and a protection	
Batterham	59	Multi-	a: after hospital discharge	No	HRQoL, O	
et al., 2014,		centre	b: hospital-based, physiotherapist-led,	intervention	Mood diso	
UK		RCT	supervised exercise		vinin h	
			c: 8 weeks		g, A	
			d: 2 times/week	•	'bmj	
Connolly et	20	Two-centre	a: after hospital discharge	No	HRQoL, ABL, Mortality,	ICU rehabilitation
al., 2015,		pilot RCT	b: exercise-base rehabilitation session	intervention	Physical function,	before
UK			of 40 minutes		Muscle strongth, Adverse	randomisation*
			c: 8 weeks		events, Anstiety and	
			d: 3 times/week (2 times supervised, 1		depression symptoms	
			time unsupervised)		ne 5	
Walsh et al.,	240	Two-centre	a: in-hospital	Standard	Mobility in the North Real And Stranger	ICU rehabilitation
2015, UK		RCT	b: mobilization exercise and relevant	care	Anxiety and depression	before
			dietetic, occupational, and		symptoms, Sel	randomisation
			speech/language therapy		symptom score	
			c: from ICU discharge until hospital		visual analogu	

Page 51 of 59				BMJ Open		136/bmjopen-2018 J by copyright, incl	
1 2 3 4 5 5 7				discharge but no longer than 3 months d: unknown		for fatigues breathlessness, or ppetite,	
, 8 9 10						pain, and juint stiffness, Mortality	
11 12 13 14 15 16 17 18	McWilliams et al., 2016, UK	73	Single- centre RCT	<ul> <li>a: after hospital discharge</li> <li>b: outpatient-based exercise and</li> <li>education program</li> <li>c: 7 weeks</li> <li>d: 3 times/week (1 supervised, 2 self- directed titrated)</li> </ul>	No intervention	Exercise can be a constructed of the construction of the construct	ICU rehabilitation before randomisation*
19 20 21 22 23 24 25 26	Shelly et al., 2017, India	35	RCT	<ul> <li>a: after hospital discharge</li> <li>b: home-based respiratory and</li> <li>mobility training</li> <li>c: 4 weeks</li> <li>d: 5 times/week</li> </ul>	No intervention	HRQoL Al training, and si	
20 27 28 29 30 31 32 33 34 35 36 37 38	McDowell et al., 2017, UK	60	Multi- centre RCT	<ul> <li>a: after hospital discharge</li> <li>b: standard care plus personalized</li> <li>exercise program</li> <li>c: 6 weeks</li> <li>d: 3 times/week (2 supervised and 1 unsupervised)</li> </ul>	No intervention	HRQoL, Mortarity, Adverse events, Mobility index, Hand function, Exercise capacity, Breathlessness Anxiety and depression symptoms, Readiness to exercise, Self-efficacy to	
<ol> <li>39</li> <li>40</li> <li>41</li> <li>42</li> <li>43</li> <li>44</li> <li>45</li> </ol>			For	r peer review only - http://bmjopen.bmj.con	n/site/about/gui	GEZ-LTA	

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py rigi	
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exercise $\vec{a}$ $\vec{b}$	
*Unpublished data	
*Unpublished data ICU, intensive care unit; RCT, randomised controlled trial; HRQoL, health-related quality of life; PTSD, post-trougung tic stress disorder; ADL,	
activity of daily living	
For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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.	Outcomes were not reported in the
2017;195:A2337	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.	Insufficient outcome data for meta-analysis
2017;21:89-93	
	RCT, randomised controlled tri

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Al training, and similar technologies

		В	SMJ Open			10.1136/bmjoper cted by copyrigh	
Online supplementary file 5. Ass		of bias in the a	-	_	ane risk-of-	-Laszassessmer	nt tool
Trial	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomple outcome data	= selective	Other bias
Jones et al., 2003 (22)	Low <sup>a</sup>	Low <sup>a</sup>	High	Low	High	G Unclear <sup>a</sup>	Unclear <sup>b</sup>
Cuthbertson et al., 2009 (23)	Low	Low	High	Low	High	u Hunclear <sup>a</sup> S Low	Unclear <sup>b</sup>
Elliott et al., 2011 (24)	Low	Low	High	Low	High	a High	Unclear <sup>c</sup>
Salisbury et al., 2010 (25)	Low	Low	High	Low	Low	at a Unclear	High <sup>d</sup>
Batterham et al., 2014 (26)	Low	Low	High	Low	Low	related to High	Unclear <sup>e</sup>
Connolly et al., 2015 (11)	Low	Low	High	High	Low		Unclear <sup>e</sup>
Walsh et al., 2015 (12)	Low	Low	High	Low	High	<b>≚,2 ∄</b> High	High <sup>d</sup>
McWilliams et al., 2016 (13)	Low	Low	High	Low	Low	an solution	Unclear <sup>e</sup>
Shelly et al., 2017 (27)	Low	Low	High	Unclear	Low	and data	Unclear <sup>e</sup>
McDowell et al., 2017 (15)	Low	Low	High	Low	High		High <sup>f</sup>

<sup>a</sup>Unpublished data (reply from the authors: the randomization was undertaken the old-fashioned way, with 6 slips of pager, 3 marked interventions

and 3 controls, put in 6 sequentially numbered opaque envelopes and sealed and shuffled to mix them, but protocolewas not published)

<sup>b</sup>Dose of physical rehabilitation was unknown

<sup>c</sup>Adherence to the intervention was unknown

<sup>d</sup>Intervention included nutritional therapy

l group <sup>e</sup>Very little detail given regarding the therapy received in the control group

<sup>f</sup>Adherence to the intervention was 70%

12 months

## **Quality of life: physical component summary**

	Expe	erimen	tal	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Cuthbertson 2009	42	10.6	90	40.8	11.9	97	54.6%	0.11 [-0.18, 0.39]	
Walsh 2015	36	17	79	37	14	76	45.4%	-0.06 [-0.38, 0.25]	
Total (95% CI)			169			173	100.0%	0.03 [-0.18, 0.24]	-
Heterogeneity: Tau <sup>2</sup> =	= 0.00; Cl	hi <b>=</b> 0.	61, df=	= 1 (P =	0.44);	I <sup>2</sup> = 0%			
Test for overall effect	Z = 0.27	(P=0	.79)						Favours [control] Favours [experimental]

#### Quality of life: mental component summary

	Expe	erimen	tal	C	ontrol		:	Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	<b>SD</b>	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Cuthbertson 2009	47.1	12.7	90	46.8	12.4	97	54.8%	0.02 [-0.26, 0.31]	
Walsh 2015	46	16	79	43	17	76	45.2%	0.18 [-0.13, 0.50]	
Total (95% CI)			169			173	100.0%	0.09 [-0.12, 0.31]	
Heterogeneity: Tau <sup>2</sup> =	= 0.00; Cl	hi² = 0.	52, df=	= 1 (P =	0.47);	<b>r</b> = 0%		⊢	-0.5 0 0.5
Test for overall effect	: Z = 0.88	(P = 0	.38)					-1	Favours [control] Favours [experimental]
Mortality									

#### Mortality

	Experim	ental	Contr	ol		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl	
Cuthbertson 2009	18	143	14	143	59.4%	1.29 [0.67, 2.48]	2009		
Walsh 2015	11	120	11	120	40.6%	1.00 [0.45, 2.22]	2015		
Total (95% CI)		263		263	100.0%	1.16 [0.70, 1.93]		+	
Total events	29		25						
Heterogeneity: Tau <sup>2</sup> =	= 0.00; Chi <sup>2</sup>	= 0.23,	df = 1 (P	= 0.63)	); I² = 0%				100
Test for overall effect	Z = 0.58 (F	P = 0.56	)					Favours [experimental] Favours [control]	100

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

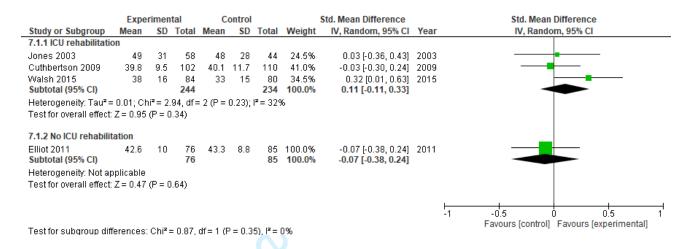
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## Online supplementary file 7: Subgroup analysis

#### A Quality of life: physical component summary

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

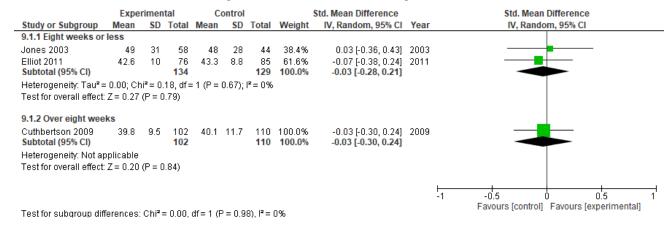
#### before randomisation)



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

	Exper	rimen	tal	C	ontrol			Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
8.1.1 In hospital										
Jones 2003	49	31	58	48	28	44	24.5%	0.03 [-0.36, 0.43]	2003	
Cuthbertson 2009	39.8	9.5	102	40.1	11.7	110	41.0%	-0.03 [-0.30, 0.24]	2009	
/Valsh 2015	38	16	84	33	15	80	34.5%	0.32 [0.01, 0.63]	2015	
Subtotal (95% CI)			244			234	100.0%	0.11 [-0.11, 0.33]		
Heterogeneity: Tau <sup>2</sup> : Test for overall effect				- 2 (1 -	0.20),	1 - 52				
8.1.2 After hospital of	lischarge	3								
Elliot 2011	42.6	10	76	43.3	8.8	85	100.0%	-0.07 [-0.38, 0.24]	2011	
Subtotal (95% CI)			76			85	100.0%	-0.07 [-0.38, 0.24]		
Heterogeneity: Not a	pplicable									
Test for overall effect	: Z = 0.47	(P = 0)	).64)							
									-1	-0.5 0 0.5
										Favours [control] Favours [experimental]
Test for subaroup dif	ferences:	Chi <sup>2</sup> =	= 0.87,	df = 1 (F	P = 0.3	5), I <sup>2</sup> =	0%			

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



B Quality of life: mental component summary

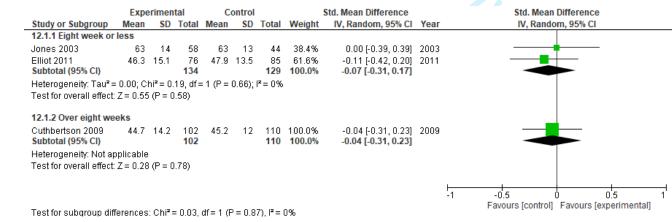
B-1. Rehabilitation practice in ICU (ICU rehabilitation before randomization ve No ICU rehabilitation

before randomization)

	Expe	erimen	tai		ontrol			Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% CI
10.1.1 ICU rehabilitat	tion									
Jones 2003	63	14	58	63	13	44	21.0%	0.00 [-0.39, 0.39]	2003	
Cuthbertson 2009	44.7	14.2	102	45.2	12	110	44.5%	-0.04 [-0.31, 0.23]	2009	<b></b>
Walsh 2015	43	15	84	43	15	80	34.5%	0.00 [-0.31, 0.31]	2015	<b>_</b>
Subtotal (95% CI)			244			234	100.0%	-0.02 [-0.20, 0.16]		
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:				- 0	,,					
Test for overall effect	Z = 0.18			- •	,1					
Test for overall effect 10.1.2 No ICU rehabi Elliot 2011	Z = 0.18	(P = 0	1.85) 76	47.9		85	100.0%	-0.11 [-0.42, 0.20]	2011	
Test for overall effect 10.1.2 No ICU rehabi Elliot 2011 Subtotal (95% CI)	Z = 0.18 litation 46.3	(P = 0	1.85)					-0.11 [-0.42, 0.20] - <b>0.11 [-0.42, 0.20]</b>	2011	-
Test for overall effect <b>10.1.2 No ICU rehabi</b> Elliot 2011 <b>Subtotal (95% CI)</b> Heterogeneity: Not ap	Z = 0.18 litation 46.3 oplicable	(P = 0	1.85) 76 <b>76</b>			85	100.0%		2011	-
Test for overall effect 10.1.2 No ICU rehabi Elliot 2011 Subtotal (95% CI)	Z = 0.18 litation 46.3 oplicable	(P = 0	1.85) 76 <b>76</b>			85	100.0%		2011	-
Test for overall effect <b>10.1.2 No ICU rehabi</b> Elliot 2011 <b>Subtotal (95% CI)</b> Heterogeneity: Not ap	Z = 0.18 litation 46.3 oplicable	(P = 0	1.85) 76 <b>76</b>			85	100.0%		2011	
Test for overall effect <b>10.1.2 No ICU rehabi</b> Elliot 2011 <b>Subtotal (95% CI)</b> Heterogeneity: Not ap	Z = 0.18 litation 46.3 oplicable	(P = 0	1.85) 76 <b>76</b>			85	100.0%		2011 -1	-0.5 0 0.5

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

	Expe	rimen	tal	Co	ontrol		:	Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% Cl
11.1.1 In hospital										
Jones 2003	63	14	58	63	13	44	21.0%	0.00 [-0.39, 0.39]	2003	
Cuthbertson 2009	44.7	14.2	102	45.2	12	110	44.5%	-0.04 [-0.31, 0.23]	2009	
Walsh 2015	43	15	84	43	15	80	34.5%	0.00 [-0.31, 0.31]	2015	<b>_</b>
Subtotal (95% CI)			244			234	100.0%	-0.02 [-0.20, 0.16]		-
Heterogeneity: Tau <sup>2</sup> =	0.00; CI	hi² = 0.	.04, df=	= 2 (P = 0	0.98);	l² = 0%				
Test for overall effect:	Z = 0.18	(P = 0	).85)							
11.1.2 After hospital	dischar	ge								
Elliot 2011	46.3	15.1	76	47.9	13.5	85	100.0%	-0.11 [-0.42, 0.20]	2011	
Subtotal (95% CI)			76			85	100.0%	-0.11 [-0.42, 0.20]		
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z=0.71	(P = 0	).48)							
									-1	-0.5 0 0.5
									-1	Favours [control] Favours [experiment
Test for subgroup diff	ferences	∶Chi <mark>²</mark> ∶	= 0.27,	df = 1 (P	9 = 0.6	0), I² =	0%			Tavours [control] Tavours [experiment
	· •	1		( .	1.		1 1	ess, and over eig	1. 1	



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

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# C Long term mortality

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

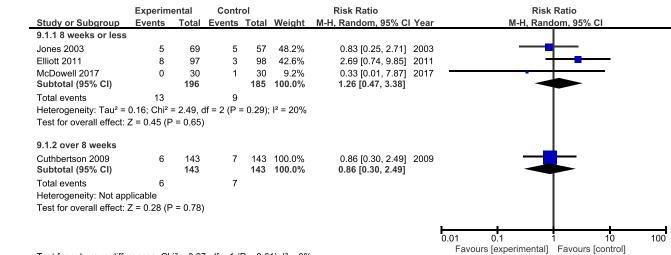
before randomization)

	Experime	ental	Contr	ol		Risk Ratio			Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year		M-H, Rano	dom, 95% Cl	
5.1.1 ICU rehabilitation	on										
Jones 2003	5	69	5	57	17.7%	0.83 [0.25, 2.71]	2003			<b></b>	
Cuthbertson 2009	6	143	7	143	22.1%	0.86 [0.30, 2.49]	2009			<b></b>	
Walsh 2015	16	120	16	120	60.2%	1.00 [0.52, 1.91]	2015		—	<b>—</b>	
Subtotal (95% CI)		332		320	100.0%	0.93 [0.57, 1.54]					
Total events	27		28								
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup> :	= 0.11, d	df = 2 (P =	= 0.95);	l² = 0%						
Test for overall effect:	Z = 0.27 (P	= 0.79)									
5.1.2 No ICU rehabili Elliott 2011 Subtotal (95% CI)	tation 8	97 <b>97</b>	3	98 <b>98</b>	100.0% <b>100.0%</b>	2.69 [0.74, 9.85] <b>2.69 [0.74, 9.85]</b>	2011		-		
Total events	8		3								
Heterogeneity: Not ap	plicable										
<b>o</b> , ,		- 0 13								1	
Test for overall effect:	Z = 1.50 (F	- 0.13									
Test for overall effect:	Z = 1.50 (F	- 0.15						L			
Test for overall effect:	Z = 1.50 (F	- 0.13,						0.01	0.1	1 10	
Test for overall effect:	,								0.1 rs [experimental]		

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

	Experim		Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI Year	M-H, Random, 95% Cl
7.1.1 in hospital							
Jones 2003	5	69	5	57	17.7%	0.83 [0.25, 2.71] 2003	
Cuthbertson 2009	6	143	7	143	22.1%	0.86 [0.30, 2.49] 2009	
Walsh 2015 Subtotal (95% CI)	16	120 <b>332</b>	16	120 <b>320</b>	60.2% <b>100.0%</b>	1.00 [0.52, 1.91] 2015 <b>0.93 [0.57, 1.54</b> ]	<b>‡</b>
Total events	27		28				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>	= 0.11. d	df = 2 (P =	= 0.95);	l² = 0%		
Test for overall effect:	Z = 0.27 (P	P = 0.79	,	,.			
	(	,					
7.1.2 after hospital d	ischarge						
Elliott 2011	8	97	3	98	74.7%	2.69 [0.74, 9.85] 2011	+
•	•	97 30	3 1	98 30		2.69 [0.74, 9.85] 2011 0.33 [0.01, 7.87] 2017	
Elliott 2011	8		3 1				
Elliott 2011 McDowell 2017	8	30	3 1 4	30	25.3%	0.33 [0.01, 7.87] 2017	
Elliott 2011 McDowell 2017 Subtotal (95% CI) Total events	8 0 8	30 127	1	30 128	25.3% <b>100.0%</b>	0.33 [0.01, 7.87] 2017	
Elliott 2011 McDowell 2017 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> =	8 0 8 : 0.67; Chi <sup>2</sup> :	30 <b>127</b> = 1.44, o	1 4 df = 1 (P =	30 128	25.3% <b>100.0%</b>	0.33 [0.01, 7.87] 2017	
Elliott 2011 McDowell 2017 Subtotal (95% CI) Total events	8 0 8 : 0.67; Chi <sup>2</sup> :	30 <b>127</b> = 1.44, o	1 4 df = 1 (P =	30 128	25.3% <b>100.0%</b>	0.33 [0.01, 7.87] 2017	
Elliott 2011 McDowell 2017 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> =	8 0 8 : 0.67; Chi <sup>2</sup> :	30 <b>127</b> = 1.44, o	1 4 df = 1 (P =	30 128	25.3% <b>100.0%</b>	0.33 [0.01, 7.87] 2017 1.59 [0.27, 9.45]	

C -3. The interv	vention duration	n (8 weeks or less	s, and over 8 weeks)
------------------	------------------	--------------------	----------------------



Test for subgroup differences:  $Chi^2 = 0.27$ , df = 1 (P = 0.61),  $I^2 = 0\%$ 

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

Study or Subarrow	Experime Events		Contr		Waicht	Risk Ratio	Risk Ratio
Study or Subgroup 10.1.1 fewer than 5 ti		lotal	Events	lotal	weight	M-H, Random, 95% CI Year	M-H, Random, 95% Cl
	nnes/week 0	20		20	400.00/	0 00 10 04 7 071 0047	
McDowell 2017 Subtotal (95% CI)	U	30 <b>30</b>	1		100.0% <b>100.0%</b>	0.33 [0.01, 7.87] 2017 <b>0.33 [0.01, 7.87]</b>	
Total events	0		1				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.68 (P	= 0.50)					
10.1.2 5 times/week	or more						
Jones 2003	5	69	5	57	52.5%	0.83 [0.25, 2.71] 2003	
Elliott 2011	8	97	3	98	47.5%	2.69 [0.74, 9.85] 2011	+- <b>-</b>
Subtotal (95% CI)		166		155	100.0%	1.45 [0.45, 4.62]	
Total events	13		8				
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:			lf = 1 (P :	= 0.19);	l² = 43%		
							<b>0.01 0.1 1 10</b>
							Favours [experimental] Favours [control]
Test for subgroup diffe	erences: Chi	² = 0.73	, df = 1 (	P = 0.3	9), l² = 0%		
	1 (				1	1 1 1 1 1 1	
C-5 Type of c	ontrol (	no in	terver	ntion	and us	ual rehabilitation)	
C-5 Type of c	ontrol (	no in	terver	ntion	and us	ual rehabilitation)	
C-5 Type of c	ontrol ( Experim		terver Con		and us	ual rehabilitation) Risk Ratio	Risk Ratio
C-5 Type of c		ental	Con	trol			
	Experim Events	ental	Con	trol		Risk Ratio	
Study or Subgroup	Experim Events	ental	Con	trol s Tota	l Weight	Risk Ratio	r M-H, Random, 95% Cl
Study or Subgroup 11.1.1 no interventio	Experim Events	ental Total	Con Events	trol <u>s Tota</u> 5 57	I Weight 31.0%	Risk Ratio M-H, Random, 95% CI Yea	r M-H, Random, 95% Cl
Study or Subgroup 11.1.1 no interventio Jones 2003	Experim Events on 5	ental <u>Total</u> 69	Con Events	trol <u>s Tota</u> 5 57 7 143	I Weight 31.0% 38.6%	Risk Ratio M-H, Random, 95% CI Yea 0.83 [0.25, 2.71] 2003 0.86 [0.30, 2.49] 2009	r M-H, Random, 95% Cl
Study or Subgroup 11.1.1 no interventic Jones 2003 Cuthbertson 2009 Elliott 2011	Experim Events on 5 6	ental Total 69 143 97	Con Events	trol <u>s Tota</u> 5 57 7 143 8 98	Weight           31.0%           38.6%           26.0%	Risk Ratio M-H, Random, 95% Cl Yea 0.83 [0.25, 2.71] 2003 0.86 [0.30, 2.49] 2009 2.69 [0.74, 9.85] 201	r M-H, Random, 95% Cl
Study or Subgroup 11.1.1 no interventic Jones 2003 Cuthbertson 2009	Experim Events on 5 6 8	ental <u>Total</u> 69 143	Con Events	trol <u>5 Tota</u> 5 57 7 143 8 98 1 30	Weight           31.0%           38.6%           26.0%	Risk Ratio M-H, Random, 95% CI Yea 0.83 [0.25, 2.71] 2003 0.86 [0.30, 2.49] 2009	r M-H, Random, 95% Cl
Study or Subgroup 11.1.1 no interventic Jones 2003 Cuthbertson 2009 Elliott 2011 McDowell 2017 Subtotal (95% CI)	Experim Events on 5 6 8 0	ental Total 69 143 97 30	Con Events	trol <u>5 Tota</u> 5 57 7 143 3 98 1 30 <b>328</b>	Weight           31.0%           38.6%           26.0%           4.4%	Risk Ratio M-H, Random, 95% Cl Yea 0.83 [0.25, 2.71] 2003 0.86 [0.30, 2.49] 2009 2.69 [0.74, 9.85] 2011 0.33 [0.01, 7.87] 2013	r M-H, Random, 95% Cl
Study or Subgroup 11.1.1 no interventic Jones 2003 Cuthbertson 2009 Elliott 2011 McDowell 2017 Subtotal (95% CI) Total events	Experim Events 5 6 8 0 19	ental Total 69 143 97 30 <b>339</b>	Con <u>Events</u> 7 3 1	trol <u>s Tota</u> 5 57 7 143 3 98 1 30 <b>328</b> 5	Weight           31.0%           38.6%           26.0%           4.4%           100.0%	Risk Ratio M-H, Random, 95% Cl Yea 0.83 [0.25, 2.71] 2003 0.86 [0.30, 2.49] 2009 2.69 [0.74, 9.85] 2011 0.33 [0.01, 7.87] 2013	r M-H, Random, 95% Cl
Study or Subgroup 11.1.1 no interventic Jones 2003 Cuthbertson 2009 Elliott 2011 McDowell 2017 Subtotal (95% CI)	Experim Events 5 6 8 0 19 = 0.00; Chi <sup>2</sup>	ental Total 69 143 97 30 339 = 2.82,	Con Events 7 3 16 df = 3 (P	trol <u>s Tota</u> 5 57 7 143 3 98 1 30 <b>328</b> 5	Weight           31.0%           38.6%           26.0%           4.4%           100.0%	Risk Ratio M-H, Random, 95% Cl Yea 0.83 [0.25, 2.71] 2003 0.86 [0.30, 2.49] 2009 2.69 [0.74, 9.85] 2011 0.33 [0.01, 7.87] 2013	r M-H, Random, 95% Cl
Study or Subgroup 11.1.1 no interventic Jones 2003 Cuthbertson 2009 Elliott 2011 McDowell 2017 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect	Experim Events 5 6 8 0 19 = 0.00; Chi <sup>2</sup> : Z = 0.27 (F	ental Total 69 143 97 30 339 = 2.82,	Con Events 7 3 16 df = 3 (P	trol <u>s Tota</u> 5 57 7 143 3 98 1 30 <b>328</b> 5	Weight           31.0%           38.6%           26.0%           4.4%           100.0%	Risk Ratio M-H, Random, 95% Cl Yea 0.83 [0.25, 2.71] 2003 0.86 [0.30, 2.49] 2009 2.69 [0.74, 9.85] 2011 0.33 [0.01, 7.87] 2013	r M-H, Random, 95% Cl
Study or Subgroup 11.1.1 no interventic Jones 2003 Cuthbertson 2009 Elliott 2011 McDowell 2017 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect 11.1.2 usual rehabili	Experim Events 5 6 8 0 19 = 0.00; Chi <sup>2</sup> : Z = 0.27 (F itation	ental Total 69 143 97 30 339 = 2.82, 2 = 0.79	Con Events 7 3 1 1 df = 3 (P )	trol 5 Tota 5 57 7 143 8 98 1 30 328 5 9 = 0.42	Weight           31.0%         38.6%           326.0%         4.4%           100.0%         100.0%	Risk Ratio M-H, Random, 95% Cl Yea 0.83 [0.25, 2.71] 2000 0.86 [0.30, 2.49] 2000 2.69 [0.74, 9.85] 2011 0.33 [0.01, 7.87] 2013 1.10 [0.57, 2.12]	r M-H, Random, 95% Cl
Study or Subgroup 11.1.1 no interventic Jones 2003 Cuthbertson 2009 Elliott 2011 McDowell 2017 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect 11.1.2 usual rehabili Walsh 2015	Experim Events 5 6 8 0 19 = 0.00; Chi <sup>2</sup> : Z = 0.27 (F	ental <u>Total</u> 69 143 97 30 <b>339</b> = 2.82, = 0.79 120	Con Events 7 3 16 df = 3 (P	trol 5 Tota 5 57 7 143 8 98 1 30 328 5 = 0.42 6 120	I         Weight           31.0%         38.6%           26.0%         4.4%           100.0%         100.0%	Risk Ratio M-H, Random, 95% CI Yea 0.83 [0.25, 2.71] 2003 0.86 [0.30, 2.49] 2009 2.69 [0.74, 9.85] 2013 0.33 [0.01, 7.87] 2013 1.10 [0.57, 2.12] 1.00 [0.52, 1.91] 2013	r M-H, Random, 95% Cl
Study or Subgroup 11.1.1 no interventic Jones 2003 Cuthbertson 2009 Elliott 2011 McDowell 2017 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect 11.1.2 usual rehabili Walsh 2015 Subtotal (95% Cl)	Experim Events 5 6 8 0 19 = 0.00; Chi <sup>2</sup> : Z = 0.27 (F itation 16	ental Total 69 143 97 30 339 = 2.82, 2 = 0.79	Con <u>Events</u> 7 3 1 1 6 df = 3 (P )	trol         5       Tota         5       57         7       143         8       98         1       30         3       98         3       98         3       98         3       98         5       120	Weight           31.0%         38.6%           326.0%         4.4%           100.0%         100.0%	Risk Ratio M-H, Random, 95% Cl Yea 0.83 [0.25, 2.71] 2000 0.86 [0.30, 2.49] 2000 2.69 [0.74, 9.85] 2011 0.33 [0.01, 7.87] 2013 1.10 [0.57, 2.12]	r M-H, Random, 95% Cl
Study or Subgroup 11.1.1 no interventic Jones 2003 Cuthbertson 2009 Elliott 2011 McDowell 2017 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect 11.1.2 usual rehabili Walsh 2015 Subtotal (95% Cl) Total events	Experim Events 5 6 8 0 19 = 0.00; Chi <sup>2</sup> : Z = 0.27 (F itation 16 16	ental <u>Total</u> 69 143 97 30 <b>339</b> = 2.82, = 0.79 120	Con Events 7 3 1 1 df = 3 (P )	trol         5       Tota         5       57         7       143         8       98         1       30         3       98         3       98         3       98         5       120         6       120	I         Weight           31.0%         38.6%           26.0%         4.4%           100.0%         100.0%	<b>Risk Ratio</b> <u>M-H, Random, 95% CI Yea</u> 0.83 [0.25, 2.71] 2003 0.86 [0.30, 2.49] 2009 2.69 [0.74, 9.85] 2011 0.33 [0.01, 7.87] 2013 1.10 [0.57, 2.12] 1.00 [0.52, 1.91] 2013	r M-H, Random, 95% Cl
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# **BMJ Open**

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

Hospital Care Research Unit Kataoka, Yuki; Hyogo Prefectural Amagasaki Hospital, Hospital Care Research Unit; Hyogo Prefectural Amagasaki Hospital <b>Primary Subject Heading</b> :       Rehabilitation medicine         Secondary Subject Heading:       Intensive care		
Article Type:ResearchDate Submitted by the Author:22-Mar-2019Complete List of Authors:Taito, Shunsuke; Hiroshima University Hospital, Yamauchi, Kota; Steel Memorial Yawata Hospital, Department of Rehabilitation Tsujimoto, Yasushi ; School of Public Health in the Graduate School of Medicine, Kyoto University, Healthcare Epidemiology; Kyoritsu Hospital, Nephrology and Dialysis Banno, Masahiro; Seichiryo Hospital, Department of Psychiatry Tsujimoto, Hiraku; Hyogo Prefectural Amagasaki General Medical Center, Hospital Care Research Unit 	Journal:	BMJ Open
Date Submitted by the Author:22-Mar-2019Complete List of Authors:Taito, Shunsuke; Hiroshima University Hospital, Yamauchi, Kota; Steel Memorial Yawata Hospital, Department of Rehabilitation Tsujimoto, Yasushi ; School of Public Health in the Graduate School of Medicine, Kyoto University, Healthcare Epidemiology; Kyoritsu Hospital, Nephrology and Dialysis Banno, Masahiro; Seichiryo Hospital, Department of Psychiatry; Nagoya University, Graduate School of Medicine, Department of Psychiatry Tsujimoto, Hiraku; Hyogo Prefectural Amagasaki General Medical Center, Hospital Care Research Unit Kataoka, Yuki; Hyogo Prefectural Amagasaki Hospital, Hospital Care Research Unit; Hyogo Prefectural Amagasaki Hospital <b>Primary Subject HeadingRehabilitation medicineSecondary Subject Heading:Intensive care</b>	Manuscript ID	bmjopen-2018-026075.R2
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Yamauchi, Kota; Steel Memorial Yawata Hospital, Department of Rehabilitation Tsujimoto, Yasushi ; School of Public Health in the Graduate School of Medicine, Kyoto University, Healthcare Epidemiology; Kyoritsu Hospital, Nephrology and Dialysis Banno, Masahiro; Seichiryo Hospital, Department of Psychiatry; Nagoya University, Graduate School of Medicine, Department of Psychiatry Tsujimoto, Hiraku; Hyogo Prefectural Amagasaki General Medical Center, Hospital Care Research Unit Kataoka, Yuki; Hyogo Prefectural Amagasaki Hospital, Hospital Care Research Unit; Hyogo Prefectural Amagasaki Hospital <b>Primary Subject Heading</b> Rehabilitation medicineSecondary Subject Heading:Intensive care	,	22-Mar-2019
Heading:     Renabilitation medicine       Secondary Subject Heading:     Intensive care	Complete List of Authors:	Yamauchi, Kota; Steel Memorial Yawata Hospital, Department of Rehabilitation Tsujimoto, Yasushi ; School of Public Health in the Graduate School of Medicine, Kyoto University, Healthcare Epidemiology; Kyoritsu Hospital, Nephrology and Dialysis Banno, Masahiro; Seichiryo Hospital, Department of Psychiatry; Nagoya University, Graduate School of Medicine, Department of Psychiatry Tsujimoto, Hiraku; Hyogo Prefectural Amagasaki General Medical Center, Hospital Care Research Unit Kataoka, Yuki; Hyogo Prefectural Amagasaki Hospital, Hospital Care
		Rehabilitation medicine
	Secondary Subject Heading:	Intensive care
Keywords: critical illness, rehabilitation, post-intensive care syndrome, exercise, quality of life, mortality	Keywords:	critical illness, rehabilitation, post-intensive care syndrome, exercise, quality of life, mortality

# SCHOLARONE<sup>™</sup> Manuscripts

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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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# 34 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

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## 42 Abstract

43 **Objective:** We aimed to determine whether enhanced physical rehabilitation following 44 intensive care unit (ICU) discharge improves activities-of-daily-living function, quality 45 of life (QOL), and mortality among patients who received mechanical ventilation in the ICU. 46 47 **Design:** Systematic review and meta-analysis using the Grading of Recommendations 48 Assessment, Development, and Evaluation (GRADE) approach. 49 Data sources: MEDLINE, Embase, CENTRAL, PEDro, and World Health Organization 50 International Clinical Trials Registry Platform searched through January 2019. 51 Eligibility criteria for selecting studies: We included randomised controlled trials 52 assessing the effect of post-ICU rehabilitation designed to either commence earlier and/or 53 be more intensive than the protocol employed in the control group. Only adults who 54 received mechanical ventilation for >24 hours were included. 55 Data extraction and synthesis: Two independent reviewers extracted data and assessed 56 risk of bias. Standard mean differences (SMDs) with 95% confidence intervals (CIs) were 57 calculated for QOL, and pooled risk ratios (RRs) with 95% CIs are provided for mortality. 58 We assessed heterogeneity based on I<sup>2</sup> and the certainty of evidence based on the GRADE

59 approach.

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60	Results: Ten trials (enrolling 1,110 patients) compared physical rehabilitation to usual
61	care or no intervention after ICU discharge. Regarding QOL, the SMD [95% CI] between
62	the intervention and control groups for the physical and mental component summary
63	scores was 0.06 [-0.12 to 0.24] and -0.04 [-0.20 to 0.11], respectively. Rehabilitation did
64	not significantly decrease long-term mortality (RR: 1.05 [0.66–1.66]). The analysed trials
65	did not report activities-of-daily-living data. The certainty of the evidence for QOL and
66	mortality was moderate.
67	Conclusions: Enhanced physical rehabilitation following ICU discharge may make little
68	or no difference to QOL or mortality among patients who received mechanical ventilation
69	in the ICU. Given the wide CIs, further studies are needed to confirm the efficacy of
70	intensive post-ICU rehabilitation in selected populations.
71	Trial registration: PROSPERO, CRD42017080532 (registered: 28 December 2017).
72	
73	Keywords: rehabilitation, critical illness, post-intensive care syndrome, exercise, quality
74	of life, mortality

# 75 Article Summary

# 76 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

- 79 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
- 82 a follow-up >6 months and (ii) medical resources and costs associated with each
- 83 intervention were not considered.
- We employed rigorous methodology that followed a protocol developed a priori
- 85 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses
- 86 (PRISMA) statement, and used the Grading of Recommendations Assessment,
- 87 Development and Evaluation approach in the review process.

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88 Introduction

89	In critically ill patients, rehabilitation mainly aims to enhance quality of life
90	(QOL) by improving activities-of-daily-living (ADL) function,[1, 2] which may be
91	severely impaired also due to post-intensive care syndrome (PICS).[3-5] According to
92	the guidelines issued by the National Institute for Health and Care Excellence, provision
93	of rehabilitation should be seamlessly integrated with the patient's transition from the
94	intensive care unit (ICU) to the ward and then to out-of-hospital care.[6] However, at
95	the time the guidelines were issued, there was little evidence from clinical trials to
96	support the use of enhanced physical rehabilitation following ICU discharge. Some
97	experts do recommend physical rehabilitation following ICU discharge to improve ADL
98	function and QOL.[7] With regards to sepsis survivors, the findings of a large
99	observational study suggested that physical rehabilitation following ICU discharge
100	improves long-term mortality.[8, 9]
101	A recent systematic review by Connolly et al.[10] focused on randomised
102	controlled trials (RCTs) regarding the effectiveness of enhanced exercise rehabilitation
103	following ICU discharge in adult ICU survivors who had been mechanically ventilated
104	for longer than 24 hours in the ICU. Despite the comprehensive search, this previous
105	systematic review included only 6 RCTs with conflicting results, and no clear effect of

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106	the intervention on QOL, mortality, functional exercise capacity, or incidence of
107	adverse events could be established at the time. Additionally, ADL, pain, return-to-work
108	rate, muscle strength, and duration of delirium were not considered in that review.[10]
109	Several RCTs assessing the effect of enhanced physical rehabilitation following ICU
110	discharge on clinically relevant outcomes[11-15] have been published since Connolly
111	and colleagues conducted their Cochrane review.[10] Therefore, in the present study,
112	we aimed to re-evaluate the available literature and determine whether enhanced
113	physical rehabilitation following ICU discharge improves clinically relevant outcomes
114	among critically ill adults who received mechanical ventilation.
115	
115 116	Materials and methods
	Materials and methods Compliance with reporting guidelines
116	
116 117	Compliance with reporting guidelines
116 117 118	Compliance with reporting guidelines Using a pre-specified protocol (PROSPERO registry ID:
116 117 118 119	Compliance with reporting guidelines Using a pre-specified protocol (PROSPERO registry ID: CRD42017080532),[16] we conducted a systematic review of the relevant literature in
116 117 118 119 120	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

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  $\geq 18$  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

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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

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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 postintervention, as short-term (evaluated at 28–35 days) or long-term (evaluated at 6 months). *Search strategy and selection of studies* 

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160	We searched the Cochrane Central Register of Controlled Trials (CENTRAL),
161	MEDLINE via PubMed, Excerpta Medica Database (EMBASE) via Elsevier, the
162	Physiotherapy Evidence Database (PEDro), and the World Health Organization
163	International Clinical Trials Registry Platform (WHO ICTRP) via their dedicated search
164	portal. The search, which employed a set of suitable search terms (details provided in
165	online supplementary file 2), was performed in December 2017 and updated in January
166	2019. We hand-searched reference lists for the guidelines for rehabilitation after critical
167	illness.[6] We attempted to identify other relevant research by hand-searching the
168	reference lists of the studies returned by the search and those of articles citing such studies
169	(based on citation information from the Web of Science). If the database entry for a
170	candidate study did not contain the necessary information, we contacted the study authors.
171	Two reviewers (ST and KY) independently screened the title and abstract of each study
172	returned by the search to determine whether the inclusion criteria were met. The two
173	reviewers performed a full-text review to assess the eligibility of each candidate study.
174	Disagreement was resolved by discussion between the two reviewers, occasionally with
175	arbitration by a third reviewer (YK).
176	Data abstraction and quality assessment
177	Two reviewers (ST and KY) independently abstracted trial-level data using pre-

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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<sup>2</sup> as a measure of variation across studies that is due to heterogeneity rather than chance, and interpreted the values as follows: 0%-40%,

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196	negligible heterogeneity; 30%-60%, mild-to-moderate heterogeneity; 50%-90%,
197	moderate-to-substantial heterogeneity; 75%-100%, considerable heterogeneity. If
198	heterogeneity was identified for an outcome ( $I^2 > 50\%$ ), we investigated the underlying
199	reasons and conducted the $\chi^2$ test, with a <i>P</i> -value of <0.10 being considered to indicate
200	statistical significance. We investigated reporting bias by checking the WHO ICTRP to
201	detect trials that had been completed but not published at the time of the review.
202	We planned the following pre-specified sensitivity analyses for the primary
203	outcomes: (i) exclusion of studies using imputed statistics, and (ii) exclusion of studies
204	with high or unclear risk of bias. We also carried out pre-specified subgroup analyses
205	according to the type of rehabilitation involved (neuromuscular stimulation versus other
206	types of rehabilitation), rehabilitation provision in the ICU (received versus did not
207	receive protocolised physical rehabilitation in the ICU), timing of commencement of the
208	intervention (in-hospital or after hospital discharge), intervention duration ( $\leq 8$ versus > 8
209	weeks), treatment frequency (<5 versus $\geq$ 5 times/week), and type of control (no
210	intervention versus standard rehabilitation). Statistical significance was also set at $P < 0.05$ .
211	We created a summary-of-findings table that included an overall grading of the certainty
212	of evidence for each of the main outcomes, which was evaluated using the Grading of
213	Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[20,

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# 215 Patient and public involvement

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

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# 218 Results

# 219 Characteristics of trials on rehabilitation in ICU survivors

220 After removing duplicates, we identified 3,589 records during the search 221 conducted in December 2017 and updated the electronic searches in January 2019. We 222 identified 10 unique RCTs[11-13, 15, 22-27] that fulfilled all eligibility criteria and 223 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 224 225 patients with an ICU stay of >48 hours during which mechanical ventilation was 226 provided for at least 24 hours. Eight studies were performed in the United Kingdom, one 227 in Australia, and one in India. The mean or median age in the analysed studies ranged 228 from 40.5 to 68.5 years, while the mean or median Acute Physiology and Chronic Health 229 Evaluation (APACHE) II score ranged from 15.2 to 31. Only 1 RCT included 230 participants with PICS symptoms or ICU-acquired weakness.[11] Three RCTs[25-27] 231 did not have sufficient outcome data for meta-analysis (details provided in online

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232	supplementary file 4), leaving a total pooled sample of 1,000 patients (506 patients in
233	the intervention groups; 494 controls) represented across 7 studies to be included in the
234	quantitative synthesis. Of the 10 trials analysed, 6 evaluated the effect of physical
235	rehabilitation including self-directed exercise and/or supervised exercise following
236	hospital discharge, while 4[12, 22-24] focused on rehabilitation started during
237	hospitalisation. The duration of intervention ranged from 6 weeks to 3 months, while the
238	frequency of intervention ranged from 3 times per week to once daily. No study
239	considered intensive intervention (>30 minutes of active rehabilitation daily) or
240	intervention with neuromuscular stimulation. Two studies [12, 23] had a follow-up >6
241	months. We did not identify any ongoing studies.
241 242	months. We did not identify any ongoing studies. Most studies were at high or unclear risk of bias, as determined using the
242	Most studies were at high or unclear risk of bias, as determined using the
242 243	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
242 243 244	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
<ul><li>242</li><li>243</li><li>244</li><li>245</li></ul>	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
<ul> <li>242</li> <li>243</li> <li>244</li> <li>245</li> <li>246</li> </ul>	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,
<ul> <li>242</li> <li>243</li> <li>244</li> <li>245</li> <li>246</li> <li>247</li> </ul>	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

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protocols were not published. High or unclear risk of other bias was noted for all studies

251	because of insufficient information regarding the intervention and control protocols.
252	Primary outcomes
253	QOL was measured in 9 trials (see online supplementary file 3), but the short-
254	and long-term QOL scores were only available in four trials,[12, 22–24] whereas the
255	other 5 trials measured these outcomes at a different time or had insufficient outcome
256	data for meta-analysis. ADL function was measured in 1 trial,[11] but the short- and
257	long-term data were not available. Short-term mortality was reported in 2 trials,[11, 13]
258	while long-term mortality was reported in 5 trials.[12, 15, 22–24]
259	The standard mean deviation between intervention and control regarding the
260	physical and mental component summary scores measured using QOL questionnaires
261	(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),
262	respectively (Fig. 2A and 2B, respectively). Rehabilitation did not significantly decrease
263	short-term mortality (RR, 0.71; 95% CI, 0.05–9.80, $I^2 = 33\%$ ; n = 93) (Fig. 2C) or long-
264	term mortality (RR, 1.05; 95% CI, 0.66–1.66, $I^2 = 0\%$ ; n = 907) (Fig. 2D). The certainty
265	of evidence for QOL and long-term mortality was moderate, while that for short-term
266	mortality was low (Table 1). The lack of benefit of enhanced physical rehabilitation after
267	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

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286	possibly related to study participation), while 6 were serious (hospitalisation or prolonged
287	hospitalisation, with 1 event related/possibly related to study participation). In the control
288	group, there was 1 adverse event (musculoskeletal pain higher than expected, muscle
289	soreness potentially indicating injury, related/possibly related to study participation) and
290	4 serious adverse events (hospitalisation or prolonged hospitalisation, with 1 event
291	related/possibly related to study participation). The certainty of evidence for adverse
292	events was low (Table 1).
293	
294	Discussion
295	The results of this up-to-date review covering 10 RCTs and 1,110 patients
296	suggest that enhanced rehabilitation following ICU discharge might not improve QOL
297	or reduce mortality at 6 or 12 months post-intervention among patients who received
298	mechanical ventilation in the ICU. We could not confirm the effect of enhanced
299	physical rehabilitation even though all included studies exhibited performance bias
300	potentially increasing the observed effect of the intervention. Furthermore, despite the
301	large sample size in the meta-analysis for QOL and long-term mortality, limited data for
302	these outcomes were available, and the certainty of evidence was only low or moderate.

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

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320	Subgroup analysis in a previous systematic review[28] indicated that,
321	compared with low-dose rehabilitation, high-dose active rehabilitation for >30 minutes
322	daily was associated with significantly higher QOL. Dose-response analysis of early
323	physical rehabilitation[33] in stroke patients enrolled in A Very Early Rehabilitation
324	Trial (AVERT)[32] determined that intervention in such acute cases improved the odds
325	of a favourable outcome with each episode of activity per day. Our present review did
326	not include studies comparing high-dose rehabilitation and usual care, and thus the QOL
327	effect of high-dose rehabilitation remains unclear. Additionally, we could not perform
328	subgroup analysis for PICS symptoms with effect on QOL[3–5] or for sepsis, which is a
329	risk factor for PICS.[34, 35] It remains unclear which population of critically ill patients
330	may truly benefit from intensive physical rehabilitation.
331	The studies included in our review did not cover all important outcomes included
332	in the core outcome set of rehabilitation after critical illness,[7] including ADL function,
333	functional exercise capacity, pain, return-to-work rate, muscle strength, or delirium
334	incidence. Nonetheless, our findings regarding QOL and mortality suggest that, even if
335	future studies report improvement in these other aspects, the amount of improvement
336	would likely be too small to affect QOL.
337	The present review has several strengths. First, we employed rigorous

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338	methodology that followed a written protocol developed a priori according to the
339	PRISMA statement, including a comprehensive search for evidence. Second, we
340	performed duplicate assessment of eligibility, risk of bias, and data abstraction. Third, we
341	used the GRADE approach for assessing the certainty of evidence. In addition, we only
342	included RCTs, most of which were multicentre studies. We could thus conduct an
343	intention-to-treat analysis to understand the effect of intensive physical rehabilitation
344	or standard care, which gives a pragmatic estimate of the benefit of a change in
345	treatment policy. Fourth, the cohorts of ICU survivors are heterogeneous in terms of
346	demographics and pathologies. To confirm the effect of enhanced physical rehabilitation
347	for a particular group, we selected studies including only participants with an ICU stay of
348	>48 hours during which mechanical ventilation was provided for at least 24 hours.
349	This systematic review has several potential limitations. Firstly, few studies
350	[12, 23] had a follow-up >6 months, and thus we could not consider longer follow-up
351	data for primary analysis. The meta-analysis should be updated as the outcomes of
352	further studies with follow-up beyond 6 months become available. Secondly, none of
353	the studies included in our meta-analysis reported mortality outcomes as time-to-event
354	data, which is the preferred approach for reporting mortality data. Future studies should
355	report time-to-event data for mortality. Thirdly, we could not take into account the

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

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6 7	373	rehabilitation were similar in pooled studies, as reflected in the Forest plots (see details
8 9 10	374	in online supplementary file 7).
11 12 13	375	Taken together, the findings of the present meta-analysis indicate that enhanced
14 15 16	376	physical rehabilitation following ICU discharge may make little or no difference to
17 18 19	377	QOL or mortality among patients who received mechanical ventilation in the ICU.
20 21 22	378	Given the wide CIs, further studies are needed to determine the efficacy of enhanced
23 24 25	379	rehabilitation in selected populations of ICU survivors.
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6 7 8	399	regarding their studies. We would like to thank Editage (http://www.editage.jp) for
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11 12 13	401	
14 15	402	Author contributions
16 17 18	403	ST and KY designed the study, were involved in the systematic review process,
19 20	404	analysed and interpreted the data, and drafted the manuscript. MB, HT, YK, and YT
21 22 23	405	participated in the systematic review process, critically reviewed the initial manuscript,
23 24 25	406	and approved the final manuscript as submitted. All authors read and approved the final
26 27 28	407	manuscript.
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37 38 39	411	
40 41 42 43	412	Declaration of interests None.
44 45	413	None.
46 47 48	414	
49 50 51 52	415	Data sharing statement
53 54 55	416	All data associated with this manuscript are included in the main text and supplementary
56 57 58 59 60	417	materials.

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# 418 Supplementary data

419 Supplementary data to this article can be found online.

- 421 Online supplementary file 1: PRISMA 2009 checklist
- 422 Online supplementary file 2: Search strategies
- 423 Online supplementary file 3: Characteristics of the studies analysed in this review
- 424 Online supplementary file 4: Characteristics of studies excluded from qualitative and

425 quantitative synthesis

- 426 Online supplementary file 5: Assessment of risk of bias in the trials analysed
  - 427 Online supplementary file 6: Additional meta-analysis for quality of life and mortality at

428 12 months

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

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# 546 Figure legends

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

## 548 flow diagram

549 Fig 2 Forest plot for quality of life and mortality

Page 35 of 60		BMJ Open BMJ Open								
1 2 3 4 5 6 7 8 9 10 11 12 13	550 551 552	BMJ Open       BMJ Open         Tables       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 environmentation         ventilation was provided for at least 24 hours								
14 15		Setting: any					nload Jeschd and d			
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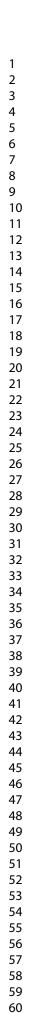
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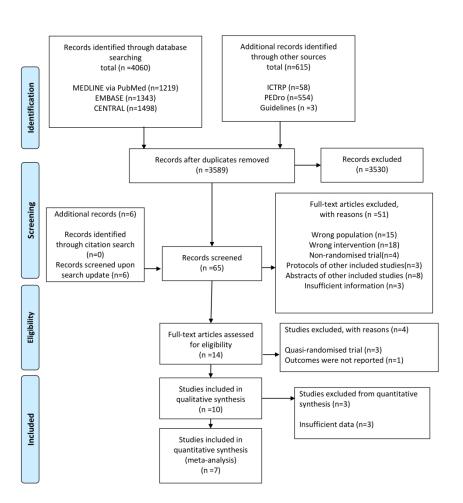
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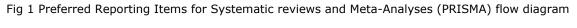
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Page 3	7 of 60	BMJ Open Sp m							
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8	553	CI, confidence interval; RR, risk ratio; ICU, intensive care unit; SF-36, Short Form 36; SMD, standardized mea 🖁 digerence; RCT, randomised							
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12	556	adherence in the intervention group (other bias).							
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18	560	<sup>d</sup> Downgraded one point because of high risk of bias associated with incomplete outcome data and lack of information regarding the dose of physical							
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2-A Quality of life: physical component summary

	Expe	rimen	tal	C	ontrol			Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	\$D	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% Cl
Jones 2003	49	31	58	48	28	44	17.5%	0.03 [-0.36, 0.43]	2003	
Cuthbertson 2009	39.8	9.5	102	40.1	11.7	110	31.3%	-0.03 [-0.30, 0.24]	2009	
Elliot 2011	42.6	10	76	43.3	8.8	85	25.5%	-0.07 [-0.38, 0.24]	2011	
Walsh 2015	38	16	84	33	15	80	25.7%	0.32 [0.01, 0.63]	2015	
Total (95% CI)			320			319	100.0%	0.06 [-0.12, 0.24]		-
Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 3.90, df = 3 (P = 0.27					0.27);	P = 239	6			1 .0.5 0 0.5 1
Test for overall effect	Z = 0.66	(P = 0	1.51)							Favours [control] Favours [experimental]

2-B Quality of life: mental component summary

	Expe	erimen	tal	с	ontrol			Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Jones 2003	63	14	58	63	13	44	15.7%	0.00 [-0.39, 0.39]	2003	
Cuthbertson 2009	44.7	14.2	102	45.2	12	110	33.3%	-0.04 [-0.31, 0.23]	2009	
Elliot 2011	46.3	15.1	76	47.9	13.5	85	25.2%	-0.11 [-0.42, 0.20]	2011	
Walsh 2015	43	15	84	43	15	80	25.8%	0.00 [-0.31, 0.31]	2015	
Total (95% CI)			320			319	100.0%	-0.04 [-0.20, 0.11]		-
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:				= 3 (P =	0.96);	I <sup>#</sup> = 0%				-1 -0.5 0 0.5 1 Favours [control] Favours [experimental]

#### 2-C Short term mortality

	Experim	ental	Cont	rol		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI	
Connolly 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: Tau <sup>2</sup> =	1.18; Chi*	= 1.49,	df = 1 (P	= 0.22	); I <sup>#</sup> = 33%			0.01 0.1 1 10	100
Test for overall effect:	Z=0.26 (F	P = 0.80	)					Favours [experimental] Favours [control]	100

#### 2-D Long term mortality

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI Ye	ar M-H, Random, 95% Cl
Jones 2003	5	69	5	57	15.1%	0.83 [0.25, 2.71] 200	03
Cuthbertson 2009	6	143	7	143	18.8%	0.86 [0.30, 2.49] 200	09
Elliott 2011	8	97	3	98	12.7%	2.69 [0.74, 9.85] 201	11
Walsh 2015	16	120	16	120	51.3%	1.00 [0.52, 1.91] 201	15
McDowell 2017	0	30	1	30	2.1%	0.33 [0.01, 7.87] 201	17
Total (95% CI)		459		448	100.0%	1.05 [0.66, 1.66]	+
Total events	35		32				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi2	= 2.86, c	if = 4 (P =	= 0.58);	$I^2 = 0\%$		0.01 0.1 1 10 100
Test for overall effect:	Z = 0.19 (F	= 0.85)					Favours [experimental] Favours [control]

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

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# PRISMA 2009 Checklist

		BMJ Open dd d 10,11	Page 40 of 60
	2009	Checklist	
Section/topic	#	Checklist item	Reported on page #
TITLE		6075 ing f	
8 Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
	<u> </u>	See	
1 Structured summary 12 13	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitation with the study appraisal and synthesis methods; results; limitation of key findings; systematic review registration number.	4, 5
6 Rationale	3	Describe the rationale for the review in the context of what is already known.	7, 8
8 Objectives	4	Provide an explicit statement of questions being addressed with reference to participant 🖉 🖗 Erventions, comparisons, outcomes, and study design (PICOS).	8
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
4 Eligibility criteria 5	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
f Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with stady authors to identify additional studies) in the search and date last searched.	11
9 Search ∮	8	Present full electronic search strategy for at least one database, including any limits use at such that it could be repeated.	11
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic evider, and, if applicable, included in the meta-analysis).	11
4 Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in diplicity in diplicity) 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
o G Risk of bias in individual of 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
3 Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including masures of consistency (e.g., I <sup>2</sup> ) for each meta-analysis.	13
45 46 47	_ • !	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml Page 1 of 2	

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46 47

# **PRISMA 2009 Checklist**

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Checklist item 9		, includir	
Section/topic	#	6075 on 9	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-reget seion), 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 a flow diagram.	14
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PCOS, 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 sum had data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plote	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-يَقْتِهْ والمعالية (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., in complete retrieval of identified research, reporting bias).	21, 22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implication between the research.	22
FUNDING	1		
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
		T A	
L 5		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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OR #17 OR

2 3	
4	
5 6 7	Online supplementary file 2: Search strategies
7 8 9	The cochrane central register of controlled trials (CENTRAL)
10	
11	#1 MeSH descriptor:[critical care]explode all trees
12 13	
14	#2 MeSH descriptor:[intensive care unit]explode all trees
15	#3 MeSH descriptor:[critical illness]explode all trees
16 17	#4 MeSH descriptor:[ventilator weaning]explode all trees
18	#5 MeSH descriptor:[Respiratory Distress Syndrome, Adult]explode all trees
19	#6 MeSH descriptor: [Sepsis] explode all trees
20 21	#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
22	#8 "critical care":ti,ab,kw
23	#9 "intensive care unit":ti,ab,kw
24 25	#10 ICU:ti,ab,kw
26	
27 28	#11 "critical illness":ti,ab,kw
28 29	#12 ventilator:ti,ab,kw
30	#13 ARDS:ti,ab,kw
31 32	#14 "acute respiratory distress syndrome":ti,ab,kw
33	#15 sepsis:ti,ab,kw
34	#16 CIN:ti,ab,kw
35 36	#17 CIM:ti,ab,kw
37	#18 CIPN:ti,ab,kw
38	
39 40	#19 CIPNM:ti,ab,kw
40	#20 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR
42	#18 OR #19
43 44	#21 #7 OR #20
45	#22 MeSH descriptor:[Exercise]explode all trees
46	#23 MeSH descriptor:[Exercise therapy]explode all trees
47 48	#24 MeSH descriptor:[Rehabilitation]explode all trees
49	#25 MeSH descriptor: [Physical fitness]explode all trees
50	#26 MeSH descriptor:[Physical Therapy Modalities]explode all trees
51 52	
53	#27 #22 OR #23 OR #24 OR #25 OR #26
54	#28 exercise:ti,ab,kw
55 56	#29 rehabilitation:ti,ab,kw
57	#30 "physical fitness":ti,ab,kw
58	#31 training:ti,ab,kw
59 60	

1	
2	
3	
4	
5 6	#32 mobilization:ti,ab,kw
7	#33 mobilisation:ti,ab,kw
8	#34 "physical therapy":ti,ab,kw
9 10	
11	#35 physiotherapy:ti,ab,kw
12	#36 "occupational therapy":ti,ab,kw
13 14	#37 "electrical muscle stimulation":ti,ab,kw
15	#38 "neuromuscular electrical stimulation":ti,ab,kw
16	#39 "respiratory muscle training":ti,ab,kw
17 18	#40 "inspiratory muscle training":ti,ab,kw
19	#41 "cycle ergometer":ti,ab,kw
20	
21	#42 bridging:ti,ab,kw
22 23	#43 rolling:ti,ab,kw
24	#44 "lying to sitting":ti,ab,kw
25	#45 marching:ti,ab,kw
26 27	#46 ambulation:ti,ab,kw
27	#47 "activities of daily living":ti,ab,kw
29	
30	#48 ADL:ti,ab,kw
31 32	#49 walking:ti,ab,kw
33	#50 #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37
34	#38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47
35 36	OR #48 OR #49
37	#51 #27 OR #50
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39	#52 #21 AND #51
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OR

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

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2 3	
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5	#34 "physical therapy"[tiab]
6 7	
8	#35 physiotherapy[tiab]
9	#36 "occupational therapy"[tiab]
10 11	#37 "electrical muscle stimulation"[tiab]
12	#38 "neuromuscular electrical stimulation"[tiab]
13	#39 "respiratory muscle training"[tiab]
14 15	#40 "inspiratory muscle training"[tiab]
16	#41 "cycle ergometer"[tiab]
17	
18 19	#42 bridging[tiab]
20	#43 rolling[tiab]
21	#44 "lying to sitting"[tiab]
22	#45 marching[tiab]
23 24	#46 ambulation[tiab]
25	#47 "activities of daily living"[tiab]
26	#48 ADL[tiab]
27 28	#49 walking[tiab]
29	
30	#50 #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR
31 32	#38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR
33	#48 OR #49
34	#51 #27 OR #50
35 36	#52 randomized controlled trial [pt]
37	#53 controlled clinical trial [pt]
38	#54 randomized [tiab]
39 40	
41	#55 placebo [tiab]
42	#56 clinical trials as topic [mesh: noexp] #57 randomly [tiab]
43 44	#57 randomly [tiab]
45	#58 trial [ti]
46	#59 #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58
47 48	#60 animals [mh] NOT humans [mh]
49	#61 #59 NOT #60
50	#62 #21 AND #51 AND #61
51 52	$\pi 02 \pi 21 \operatorname{AIND} \pi 31 \operatorname{AIND} \pi 01$
53	
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# **EMBASE**

#1 "critical care"/exp

#3 "critical illness"/exp

#2 "intensive care unit"/exp

#4 "ventilator weaning"/exp

#32 mobilization:ab,ti

#33 mobilisation:ab,ti

5 "Respiratory Distress Syndrome, Adult"/exp	
6 Sepsis/exp	
7 #1 OR #2 OR #3 OR #4 OR #5 OR #6	
8 "critical care":ab,ti	
9 "intensive care unit":ab,ti	
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	
21 #7 OR #20 22 Exercise/exp 23 "Exercise therapy"/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	

1	
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4 5	
6	#34 "physical therapy":ab,ti
7	#35 physiotherapy:ab,ti
8 9	#36 "occupational therapy":ab,ti
10	#37 "electrical muscle stimulation":ab,ti
11	#38 "neuromuscular electrical stimulation":ab,ti
12 13	
14	#39 "respiratory muscle training":ab,ti
15	#40 "inspiratory muscle training":ab,ti
16 17	#41 "cycle ergometer":ab,ti
17 18	#42 bridging:ab,ti
19	#43 rolling:ab,ti
20	#44 "lying to sitting":ab,ti
21 22	
23	#45 marching:ab,ti
24	#46 ambulation:ab,ti
25 26	#47 "activities of daily living":ab,ti
27	#48 ADL:ab,ti
28	#49 walking:ab,ti
29 30	#50 #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR
30 31	#38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR
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33	#48 OR #49
34 35	#51 #27 OR #50
36	#52 random*:ab,ti OR (clinical NEXT/1 trial*) OR 'health care quality'/exp
37	#53 #21 AND #51 AND #52
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### **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

to occure with only

# 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 R amou. daily living OR ambulation OR walking)
- #3 #1 AND #2

Online supple	ementary file	3 Characteri	stics of the studies analysed in this rev	view	136/bmjopen-2018-0260 4 by copyright, including	
Author,	No. of	Study type	Intervention (a, Timing of	Control	Outcomes of o	Notes
year,	participants		commencement; b, Contents; c,	uncomes of on use of o		
country			Duration; d, Frequency)	Outcomes relation		
Jones et al.,	126	Multi-	a: in-hospital	No	HRQoL, Mana HRQOL,	ICU rehabilitatio
2003, UK		centre RCT	b: routine follow-up plus rehabilitation	intervention	Depression signer toms,	before
			package consisting of 93 pages of text		HRQoL, Month and the second se	randomisation*
			c: 6 weeks		ind c	
			d: every day*		baded fr school . nd data i	
Cuthbertson	286	Multi-	a: in-hospital	No	HRQoL, Mortality,	ICU rehabilitatio
et al., 2009,		centre	b: manual based, self-directed,	intervention	Quality-adjusted life	before
UK		RCT	physical rehabilitation program		years, Incidence and	randomisation*
			developed by physiotherapists and		severity of TSD,	
			introduced by a study nurse		Anxiety and depression	
			c: continued for 3 months after		symptoms, Cost	
			discharge		effectivenes	
			d: unknown		n Ju r tec	
Elliott et al.,	195	Multi-	a: after hospital discharge	No	HRQoL, Mortanity,	No ICU
2011,		centre	b: home-based physical rehabilitation	intervention	Physical function	rehabilitation
Australia		RCT	program focused on strength training		25 at 95.	before
			and walking		t Department GEZ-LTA	randomisation*
			c: 8 weeks		artm	
			d: 5 times/week		nent	

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a 11 1		<u> </u>	· · · ·	a. 1.1	136/bmjopen-2018-02 J by copyright, includi	
Salisbury et	16	Single-	a: in-hospital	Standard	Physical outcomes,	
al., 2010,		centre	b: enhanced physiotherapy and	care	Nutritional out come,	
UK		pilot RCT	dietetic rehabilitation package		Breathless fess on the	
			c: unknown		Visual analogue scale	
			d: unknown		scores for the scores,	
					fatigue, joint stiffness,	
			Jr.		pain, and a	
Batterham	59	Multi-	a: after hospital discharge	No	HRQoL, Oz gen uptake,	
et al., 2014,		centre	b: hospital-based, physiotherapist-led,	intervention	Mood diso	
UK		RCT	supervised exercise		ini m ini b	
			c: 8 weeks		g, A	
			d: 2 times/week	•	<sup>1</sup> bmj	
Connolly et	20	Two-centre	a: after hospital discharge	No	HRQoL, ABL, Mortality,	ICU rehabilitation
al., 2015,		pilot RCT	b: exercise-base rehabilitation session	intervention	Physical function,	before
UK			of 40 minutes		Muscle strong gt, Adverse	randomisation*
			c: 8 weeks		events, Angiety and	
			d: 3 times/week (2 times supervised, 1		depression gymptoms	
			time unsupervised)		ne 5 nnol	
Walsh et al.,	240	Two-centre	a: in-hospital	Standard	Mobility in the NHRQoL,	ICU rehabilitation
2015, UK		RCT	b: mobilization exercise and relevant	care	Anxiety and depression	before
			dietetic, occupational, and		symptoms, Sel	randomisation
			speech/language therapy		symptom score	
			c: from ICU discharge until hospital		visual analogu	

Page 51

			discharge but no longer than 3 months		136/bmjopen-2018-0260 4 by copyright, including for fatigue	
			d: unknown		breathlessness, Sppetite,	
					pain, and jرقی nt جراز fifness, Mortality آور الم	
McWilliams '	73	Single-	a: after hospital discharge	No	Exercise capacity,	ICU rehabilitation
et al., 2016,		centre RCT	b: outpatient-based exercise and	intervention	HRQoL, Monthead ty,	before
UK			education program		Adverse events from the Adverse events and data mini	randomisation*
			c: 7 weeks		bade id da	
			d: 3 times/week (1 supervised, 2 self-		ded from hool . data mini	
			directed titrated)			
Shelly et .	35	RCT	a: after hospital discharge	No	HRQoL Al training,	
al., 2017,			b: home-based respiratory and	intervention	bmjc traii	
India			mobility training		ning	
			c: 4 weeks		and si	
			d: 5 times/week			
	60	Multi-	a: after hospital discharge	No	HRQoL, Mertadity,	
et al., 2017,		centre RCT	b: standard care plus personalized	intervention	Adverse events Mobility	
UK			exercise program		index, Hand function,	
			c: 6 weeks		Exercise control actory,	
			d: 3 times/week (2 supervised and 1		Breathlessness Anxiety	
			unsupervised)		and depression	
					symptoms, Realiness to	
					exercise, Self-efficacy to	

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Page 53 of 60	BMJ Open 6 by 6
1 2	BMJ Open BMJ Open-2018
3 4	
5	exercise ji 6
6	*Unpublished data
7	ICU, intensive care unit; RCT, randomised controlled trial; HRQoL, health-related quality of life; PTSD, post-traumeric stress disorder; ADL,
9 10 11 12 13	exercise *Unpublished data ICU, intensive care unit; RCT, randomised controlled trial; HRQoL, health-related quality of life; PTSD, post-diges related to using activity of daily living *Unpublished data ICU, intensive care unit; RCT, randomised controlled trial; HRQoL, health-related quality of life; PTSD, post-diges related to using activity of daily living *Unpublished data CU, intensive care unit; RCT, randomised controlled trial; HRQoL, health-related quality of life; PTSD, post-diges related to using activity of daily living
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43 44	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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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.	Outcomes were not reported in the
2017;195:A2337	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.	Insufficient outcome data for meta-analysis
2017;21:89-93	
	RCT, randomised controlled tria

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplet outcome in data fo	Selective Seporting	Other b
Jones et al., 2003 (22)	Low <sup>a</sup>	Low <sup>a</sup>	High	Low	High uses	<b>S</b> Unclear <sup>a</sup>	Unclea
Cuthbertson et al., 2009 (23)	Low	Low	High	Low		<b>ျိ</b> _ow	Unclea
Elliott et al., 2011 (24)	Low	Low	High	Low	High 🛃	<b>High</b>	Unclea
Salisbury et al., 2010 (25)	Low	Low	High	Low	Low 👼	<b>N</b> nclear	High <sup>d</sup>
Batterham et al., 2014 (26)	Low	Low	High	Low			Unclea
Connolly et al., 2015 (11)	Low	Low	High	High	Low 6	High	Unclea
Walsh et al., 2015 (12)	Low	Low	High	Low	High High	A shift of the shi	High <sup>d</sup>
McWilliams et al., 2016 (13)	Low	Low	High	Low	Low and	a Low	Unclea
Shelly et al., 2017 (27)	Low	Low	High	Unclear	Low a	<b>d</b> _ow	Unclea
McDowell et al., 2017 (15) <sup>a</sup> Unpublished data (reply from the au	Low	Low	High	Low	High 🚮		High <sup>f</sup>
<sup>c</sup> Adherence to the intervention was u <sup>d</sup> Intervention included nutritional the	erapy		roup		Al training, and	//bmjopen.bmj.com/ on June	
<sup>e</sup> Very little detail given regarding the	e therapy received	d in the control g	roup		simi	com	
<sup>f</sup> Adherence to the intervention was 7	0%				lar tecl	on Ju	
					hnolo	្រុ	
					logie	5, 20	
					hnologies.	្រុ	

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

12 months

## **Quality of life: physical component summary**

	Expe	erimen	tal	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	<b>SD</b>	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Cuthbertson 2009	42	10.6	90	40.8	11.9	97	54.6%	0.11 [-0.18, 0.39]	
Valsh 2015	36	17	79	37	14	76	45.4%	-0.06 [-0.38, 0.25]	
fotal (95% CI)			169			173	100.0%	0.03 [-0.18, 0.24]	
-leterogeneity: Tau <sup>2</sup> =	: 0.00; Cl	hi <b>²</b> = 0.	61, df=	= 1 (P =	0.44);	l² = 0%			
est for overall effect	Z = 0.27	(P = 0	.79)						Favours [control] Favours [experimental]

## Quality of life: mental component summary

	Expe	erimen	tal	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	<b>SD</b>	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Cuthbertson 2009	47.1	12.7	90	46.8	12.4	97	54.8%	0.02 [-0.26, 0.31]	
Walsh 2015	46	16	79	43	17	76	45.2%	0.18 [-0.13, 0.50]	
Total (95% CI)			169			173	100.0%	0.09 [-0.12, 0.31]	
Heterogeneity: Tau <sup>2</sup> =	0.00; C	hi² = 0.	52, df=	= 1 (P =	0.47);	l² = 0%		⊢ -1	-0.5 0 0.5
Test for overall effect:	Z = 0.88	8 (P = 0	.38)					-1	Favours [control] Favours [experimental]
Mortality									
•									

#### Mortality

	Experim	ental	Contr	ol		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl	
Cuthbertson 2009	18	143	14	143	59.4%	1.29 [0.67, 2.48]	2009		
Walsh 2015	11	120	11	120	40.6%	1.00 [0.45, 2.22]	2015	-+	
Total (95% CI)		263		263	100.0%	1.16 [0.70, 1.93]		+	
Total events	29		25						
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>a</sup>	= 0.23,	df = 1 (P	= 0.63)	); I² = 0%			0.01 0.1 1 10	100
Test for overall effect:	Z = 0.58 (F	° = 0.56	)					Favours [experimental] Favours [control]	100

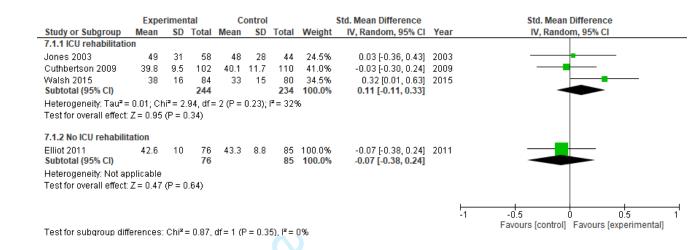
We converted median (inter quartile range) of QOL score in Walsh's study to mean (standard deviation).

## 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

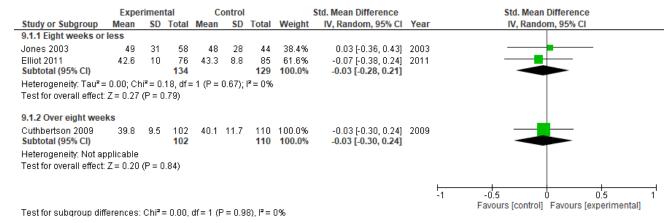
#### before randomisation)



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

	Expe	rimen	tal	C	ontrol			Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
8.1.1 In hospital										
Jones 2003	49	31	58	48	28	44	24.5%	0.03 [-0.36, 0.43]	2003	<b>_</b>
Cuthbertson 2009	39.8	9.5	102	40.1	11.7	110	41.0%	-0.03 [-0.30, 0.24]	2009	
Walsh 2015	38	16	84	33	15	80	34.5%	0.32 [0.01, 0.63]	2015	
Subtotal (95% CI)			244			234	100.0%	0.11 [-0.11, 0.33]		-
Heterogeneity: Tau <sup>2</sup> =	= 0.01; Ch	)i² = 2.	.94, df=	= 2 (P =	0.23);	I <sup>2</sup> = 329	Хо			
Test for overall effect	Z = 0.95	(P = 0)	).34)							
0.4.0.46										
8.1.2 After hospital d	-									
Elliot 2011	42.6	10	76	43.3	8.8		100.0%	-0.07 [-0.38, 0.24]	2011	
Subtotal (95% CI)			76			85	100.0%	-0.07 [-0.38, 0.24]		
Heterogeneity: Not a	oplicable									
Test for overall effect	Z=0.47	(P = 0	).64)							
										-1 -0.5 0 0.5 1
										Favours [control] Favours [experimental]
Test for subgroup dif	ferences:	Chi <b>²</b> :	= 0.87,	df = 1 (F	° = 0.3	5), I² =	0%			

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



# B Quality of life: mental component summary

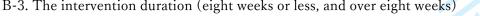
B-1. Rehabilitation practice in ICU (ICU rehabilitation before randomization vs No ICU rehabilitation

before randomization)

	Expe	erimen	tal	C	ontrol		1	Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% CI
10.1.1 ICU rehabilitat	ion									
Jones 2003	63	14	58	63	13	44	21.0%	0.00 [-0.39, 0.39]	2003	
Cuthbertson 2009	44.7	14.2	102	45.2	12	110	44.5%	-0.04 [-0.31, 0.23]	2009	<b>B</b>
Walsh 2015	43	15	84	43	15	80	34.5%	0.00 [-0.31, 0.31]	2015	<b>+</b>
Subtotal (95% CI)			244			234	100.0%	-0.02 [-0.20, 0.16]		
Heterogeneity: Tau <sup>2</sup> =	: 0.00; Cl	hi² = 0.1	04, df=	2 (P = I	0.98);	l² = 0%				
Test for overall effect:	7 = 0.18	(P = 0)	85)							
restion overall ender.	2-0.10									
restion overall ellect.	2-0.10	, - 0	,							
10.1.2 No ICU rehabil			,							
			76	47.9	13.5	85	100.0%	-0.11 [-0.42, 0.20]	2011	
10.1.2 No ICU rehabil	itation			47.9	13.5	85 <b>85</b>	100.0% <b>100.0%</b>	-0.11 [-0.42, 0.20] - <b>0.11 [-0.42, 0.20]</b>	2011	
<b>10.1.2 No ICU rehabil</b> Elliot 2011	l <b>itation</b> 46.3	15.1	76	47.9	13.5				2011	
10.1.2 No ICU rehabil Elliot 2011 Subtotal (95% CI)	i <b>tation</b> 46.3 oplicable	15.1	76 <b>76</b>	47.9	13.5				2011	
<b>10.1.2 No ICU rehabil</b> Elliot 2011 <b>Subtotal (95% CI)</b> Heterogeneity: Not ap	i <b>tation</b> 46.3 oplicable	15.1	76 <b>76</b>	47.9	13.5				2011	
<b>10.1.2 No ICU rehabil</b> Elliot 2011 <b>Subtotal (95% CI)</b> Heterogeneity: Not ap	i <b>tation</b> 46.3 oplicable	15.1	76 <b>76</b>	47.9	13.5				2011	
<b>10.1.2 No ICU rehabil</b> Elliot 2011 <b>Subtotal (95% CI)</b> Heterogeneity: Not ap	i <b>tation</b> 46.3 oplicable	15.1	76 <b>76</b>	47.9	13.5				2011 -1	-0.5 0 0.5 Favours [control] Favours [experimental]

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

	Expe	erimen	tal	Co	ontrol		:	Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% CI
11.1.1 In hospital										
Jones 2003	63	14	58	63	13	44	21.0%	0.00 [-0.39, 0.39]	2003	
Outhbertson 2009	44.7	14.2	102	45.2	12	110	44.5%	-0.04 [-0.31, 0.23]	2009	
Walsh 2015	43	15	84	43	15	80	34.5%	0.00 [-0.31, 0.31]	2015	
Subtotal (95% CI)			244			234	100.0%	-0.02 [-0.20, 0.16]		-
Heterogeneity: Tau <sup>2</sup> =	= 0.00; C	hi² = 0.	.04, df=	= 2 (P = 0	), (89.0	l² = 0%				
Test for overall effect	Z = 0.18	8 (P = 0	).85)							
11.1.2 After hospital	dischar	ge								
Elliot 2011	46.3	15.1	76	47.9	13.5	85	100.0%	-0.11 [-0.42, 0.20]	2011	
Subtotal (95% CI)			76			85	100.0%	-0.11 [-0.42, 0.20]		
Heterogeneity: Not a	pplicable	)								
Test for overall effect	: Z = 0.71	(P = 0	).48)							
									1	
									-1	-0.5 0 0.5 1
	~					o) 17	~~			Favours [control] Favours [experimental]
Test for subgroup dif	terences	: Chi <del>r</del> :	= 0.27,	at = 1 (P	= 0.6	U), I* =	0%			
0 171		1		(	1.		1 1	1 .	1. 1	
-3. The inter	ventic	on di	irati	on (ei	ight	wee	ks or le	ess, and over eig	gnt weeks)	



	Expe	erimer	ntal	C	ontrol			Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
12.1.1 Eight week or	less									
Jones 2003	63	14	58	63	13	44	38.4%	0.00 [-0.39, 0.39]	2003	<b>+</b>
Elliot 2011 Subtotal (95% CI)	46.3	15.1	76 <b>134</b>	47.9	13.5	85 <b>129</b>	61.6% <b>100.0%</b>	-0.11 [-0.42, 0.20] - <b>0.07 [-0.31, 0.17]</b>	2011	
Heterogeneity: Tau <sup>2</sup> =	= 0.00; CI	hi² = 0	.19, df=	= 1 (P =	0.66);	I <sup>2</sup> = 0%				
Test for overall effect:	Z = 0.55	5 (P = (	J.58)	,	~					
12.1.2 Over eight we	eks									
Cuthbertson 2009 Subtotal (95% CI)	44.7	14.2	102 <b>102</b>	45.2	12	110 <b>110</b>	100.0% <b>100.0%</b>	-0.04 [-0.31, 0.23] - <b>0.04 [-0.31, 0.23]</b>	2009	
Heterogeneity: Not ap	oplicable	9								
Test for overall effect:	Z = 0.28	8 (P = 0	0.78)							
									⊢ -1	-0.5 0 0.5 1
Toot for oubgroup dif	foronooo	- Chia	- 0 0 2	df = 1 /F		7) 12 - 1	002			Favours [control] Favours [experimental]
Test for subgroup dif	rerences	s. Onit	= 0.03,	ui = 1 (F	r = 0.8	(I, C = )	070			

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)

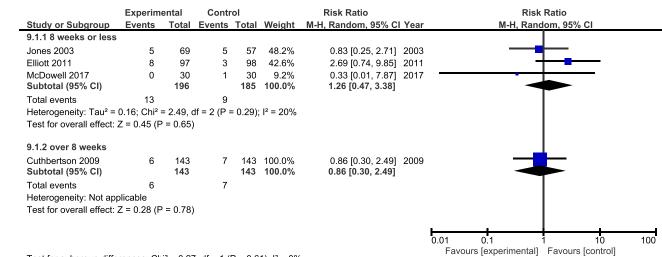
	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI Ye	ear M-H, Random, 95% Cl
5.1.1 ICU rehabilitati	on						
Jones 2003	5	69	5	57	17.7%	0.83 [0.25, 2.71] 20	03
Cuthbertson 2009	6	143	7	143	22.1%	0.86 [0.30, 2.49] 20	09
Walsh 2015	16	120	16	120	60.2%	1.00 [0.52, 1.91] 20	15
Subtotal (95% CI)		332		320	100.0%	0.93 [0.57, 1.54]	<b>•</b>
Total events	27		28				
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:				,,			
Test for overall effect: 5.1.2 No ICU rehabili Elliott 2011	Z = 0.27 (P	= 0.79) 97		98	100.0%	2.69 [0.74, 9.85] 20 2.69 [0.74, 9.85]	11
Test for overall effect: 5.1.2 No ICU rehabili Elliott 2011 Subtotal (95% CI)	Z = 0.27 (P tation 8	= 0.79)	3	98		2.69 [0.74, 9.85] 20 2.69 [0.74, 9.85]	11
Test for overall effect: 5.1.2 No ICU rehabili Elliott 2011 Subtotal (95% CI) Total events	Z = 0.27 (P tation 8 8	= 0.79) 97		98	100.0%		11
Test for overall effect: 5.1.2 No ICU rehabili Elliott 2011 Subtotal (95% CI) Total events Heterogeneity: Not ap	Z = 0.27 (P tation 8 plicable	97 97	3	98	100.0%		11
Test for overall effect: 5.1.2 No ICU rehabili Elliott 2011 Subtotal (95% CI) Total events	Z = 0.27 (P tation 8 plicable	97 97	3	98	100.0%		11
Test for overall effect: 5.1.2 No ICU rehabili Elliott 2011 Subtotal (95% CI) Total events Heterogeneity: Not ap	Z = 0.27 (P tation 8 plicable	97 97	3	98	100.0%		

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

Study or Subgroup	Events	Total	Lvento	Total	Weight	M-H, Random, 95% CI Yea	r M-H, Random, 95% Cl
7.1.1 in hospital							
Jones 2003	5	69	5	57	17.7%	0.83 [0.25, 2.71] 2003	
Cuthbertson 2009	6	143	7	143	22.1%	0.86 [0.30, 2.49] 2009	)
Walsh 2015	16	120	16	120	60.2%	1.00 [0.52, 1.91] 201	5
Subtotal (95% CI)		332		320	100.0%	0.93 [0.57, 1.54]	<b>•</b>
Total events	27		28				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup> :	= 0.11, d	df = 2 (P =	= 0.95);	l² = 0%		
Test for overall effect:	Z = 0.27 (P	= 0.79)	)				
7.1.2 after hospital d	ischarge						
Elliott 2011	8	97	3	98	74.7%	2.69 [0.74, 9.85] 201	
McDowell 2017	0	30	1	30	25.3%	0.33 [0.01, 7.87] 201	
Subtotal (95% CI)		127		128	100.0%	1.59 [0.27, 9.45]	
Total events	8		4				
	0.67; Chi <sup>2</sup> :	= 1.44, 0	df = 1 (P =	= 0.23);	l² = 31%		
Heterogeneity: Tau <sup>2</sup> =							
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	Z = 0.51 (P	- 0.01					
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	Z = 0.51 (F	- 0.61;					

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



Test for subgroup differences:  $Chi^2 = 0.27$ , df = 1 (P = 0.61),  $I^2 = 0\%$ 

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

Study or Subgroup	Experime Events		Contro		Weight	Risk Ratio M-H, Random, 95% CI Ye	Risk Ratio ear M-H, Random, 95% Cl	
10.1.1 fewer than 5 t		Total	Lvents	TULAI	weight	M-11, Randolli, 5576 CF 1		
McDowell 2017	0	30	1	30	100.0%	0.33 [0.01, 7.87] 20	17	
Subtotal (95% CI)	Ŭ	30	•		100.0%	0.33 [0.01, 7.87]		
Total events	0		1					
Heterogeneity: Not ap	oplicable							
Test for overall effect	: Z = 0.68 (P	= 0.50)						
10.1.2 5 times/week	or more							
Jones 2003	5	69	5	57	52.5%	0.83 [0.25, 2.71] 20	003 <b>— —</b>	
Elliott 2011	8	97	3	98	47.5%	2.69 0.74, 9.85 20		
Subtotal (95% CI)		166		155	100.0%	1.45 [0.45, 4.62]		
Total events	13		8					
Heterogeneity: Tau <sup>2</sup> =			f = 1 (P =	0.19);	l² = 43%			
Test for overall effect	: Z = 0.63 (P	= 0.53)						
							0.01 0.1 1 10	1
Test for subgroup diff	ierences: Chi	<sup>2</sup> = 0 73	df = 1 (F)	P = 0.39	$P_{1}^{2} = 0\%$		Favours [experimental] Favours [control]	
		0.10	, ar i (i	0.00	57.1 070			
C-5 Type of a	control (1	no in	terven	tion	and us	ual rehabilitation	)	
C-5 Type of c	control (	no in	terven	tion	and us	ual rehabilitation	)	
C-5 Type of c	control (1 Experim		terven Cont		and us	ual rehabilitation	) Risk Ratio	
C-5 Type of a Study or Subgroup	Experim	ental	Cont	rol			Risk Ratio	
~ 1	Experim Events	ental	Cont	rol		Risk Ratio	Risk Ratio	
Study or Subgroup	Experim Events	ental	Cont	rol	l Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio Year M-H, Random, 95% Cl	
Study or Subgroup 11.1.1 no intervention	Experim Events on	ental Total	Cont Events	rol Tota	I Weight 31.0%	Risk Ratio M-H, Random, 95% CI 0.83 [0.25, 2.71]	Risk Ratio Year M-H, Random, 95% Cl 2003	
Study or Subgroup 11.1.1 no interventio Jones 2003	Experim Events on 5	ental <u>Total</u> 69	Cont Events 5	rol <u>Tota</u> 57 143	I Weight 31.0% 38.6%	<b>Risk Ratio</b> <u>M-H, Random, 95% CI</u> 0.83 [0.25, 2.71] 0.86 [0.30, 2.49]	Risk Ratio Year M-H, Random, 95% Cl	
Study or Subgroup 11.1.1 no interventi Jones 2003 Cuthbertson 2009	Experim Events on 5 6	ental Total 69 143	Cont Events 5 7	rol <u>Tota</u> 57 143	I Weight 31.0% 38.6% 326.0%	<b>Risk Ratio</b> <b>M-H, Random, 95% CI</b> 0.83 [0.25, 2.71] 0.86 [0.30, 2.49] 2.69 [0.74, 9.85]	Risk Ratio           Year         M-H, Random, 95% CI           2003	
Study or Subgroup 11.1.1 no interventi Jones 2003 Cuthbertson 2009 Elliott 2011	Experime Events on 5 6 8	ental Total 69 143 97	Cont Events 5 7 3	rol <u>Tota</u> 57 143 98 30	I Weight 31.0% 38.6% 326.0%	<b>Risk Ratio</b> <u>M-H, Random, 95% CI</u> 0.83 [0.25, 2.71] 0.86 [0.30, 2.49] 2.69 [0.74, 9.85] 0.33 [0.01, 7.87]	Risk Ratio           Year         M-H, Random, 95% CI           2003	
Study or Subgroup 11.1.1 no interventi Jones 2003 Cuthbertson 2009 Elliott 2011 McDowell 2017	Experime Events on 5 6 8	ental Total 69 143 97 30	Cont Events 5 7 3	rol <u>Tota</u> 57 143 98 30	Weight           31.0%           38.6%           26.0%           4.4%	<b>Risk Ratio</b> <u>M-H, Random, 95% CI</u> 0.83 [0.25, 2.71] 0.86 [0.30, 2.49] 2.69 [0.74, 9.85] 0.33 [0.01, 7.87]	Risk Ratio           Year         M-H, Random, 95% CI           2003	
Study or Subgroup 11.1.1 no interventio Jones 2003 Cuthbertson 2009 Elliott 2011 McDowell 2017 Subtotal (95% CI)	Experim Events on 5 6 8 0 19	ental Total 69 143 97 30 <b>339</b>	Cont Events 5 7 3 1 16	rol <u>Tota</u> 57 143 98 30 <b>328</b>	Weight           31.0%           38.6%           26.0%           4.4%           100.0%	<b>Risk Ratio</b> <u>M-H, Random, 95% CI</u> 0.83 [0.25, 2.71] 0.86 [0.30, 2.49] 2.69 [0.74, 9.85] 0.33 [0.01, 7.87]	Risk Ratio           Year         M-H, Random, 95% CI           2003	
Study or Subgroup 11.1.1 no interventio Jones 2003 Cuthbertson 2009 Elliott 2011 McDowell 2017 Subtotal (95% CI) Total events	Experim Events on 5 6 8 0 19 = 0.00; Chi <sup>2</sup> :	ental Total 69 143 97 30 <b>339</b> = 2.82, 0	Cont Events 5 7 3 1 16 df = 3 (P	rol <u>Tota</u> 57 143 98 30 <b>328</b>	Weight           31.0%           38.6%           26.0%           4.4%           100.0%	<b>Risk Ratio</b> <u>M-H, Random, 95% CI</u> 0.83 [0.25, 2.71] 0.86 [0.30, 2.49] 2.69 [0.74, 9.85] 0.33 [0.01, 7.87]	Risk Ratio           Year         M-H, Random, 95% CI           2003	
Study or Subgroup 11.1.1 no interventi Jones 2003 Cuthbertson 2009 Elliott 2011 McDowell 2017 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> Test for overall effect	Experim Events on 5 6 8 0 19 = 0.00; Chi <sup>2</sup> : t: Z = 0.27 (P	ental Total 69 143 97 30 <b>339</b> = 2.82, 0	Cont Events 5 7 3 1 16 df = 3 (P	rol <u>Tota</u> 57 143 98 30 <b>328</b>	Weight           31.0%           38.6%           26.0%           4.4%           100.0%	<b>Risk Ratio</b> <u>M-H, Random, 95% CI</u> 0.83 [0.25, 2.71] 0.86 [0.30, 2.49] 2.69 [0.74, 9.85] 0.33 [0.01, 7.87]	Risk Ratio           Year         M-H, Random, 95% CI           2003	
Study or Subgroup 11.1.1 no interventi Jones 2003 Cuthbertson 2009 Elliott 2011 McDowell 2017 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> Test for overall effect 11.1.2 usual rehabil	Experim Events on 5 6 8 0 19 = 0.00; Chi <sup>2</sup> t: Z = 0.27 (P	ental <u>Total</u> 69 143 97 30 <b>339</b> = 2.82, 0 2 = 0.79	Cont Events 5 7 3 1 1 6 df = 3 (P	rol <u>Tota</u> 57 143 98 30 <b>328</b> = 0.42	I         Weight           31.0%         38.6%           326.0%         4.4%           100.0%         100.0%	<b>Risk Ratio</b> <b>M-H, Random, 95% CI</b> 0.83 [0.25, 2.71] 0.86 [0.30, 2.49] 2.69 [0.74, 9.85] 0.33 [0.01, 7.87] 1.10 [0.57, 2.12]	Risk Ratio Year M-H, Random, 95% Cl 2003 2009 2011 2017	
Study or Subgroup 11.1.1 no interventi- Jones 2003 Cuthbertson 2009 Elliott 2011 McDowell 2017 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> Test for overall effect 11.1.2 usual rehabil Walsh 2015	Experim Events on 5 6 8 0 19 = 0.00; Chi <sup>2</sup> : t: Z = 0.27 (P	ental <u>Total</u> 69 143 97 30 339 = 2.82, 6 = 0.79 120	Cont Events 5 7 3 1 16 df = 3 (P	rol <u>Tota</u> 57 143 98 30 <b>328</b> = 0.42	I         Weight           31.0%         38.6%           26.0%         4.4%           100.0%         100.0%	Risk Ratio M-H, Random, 95% CI 0.83 [0.25, 2.71] 0.86 [0.30, 2.49] 2.69 [0.74, 9.85] 0.33 [0.01, 7.87] 1.10 [0.57, 2.12]	Risk Ratio Year M-H, Random, 95% Cl 2003 2009 2011 2017	
Study or Subgroup 11.1.1 no interventi- Jones 2003 Cuthbertson 2009 Elliott 2011 McDowell 2017 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> Test for overall effect 11.1.2 usual rehabil Walsh 2015 Subtotal (95% Cl)	Experime Events on 5 6 8 0 19 = 0.00; Chi <sup>2</sup> : t: Z = 0.27 (P litation 16	ental <u>Total</u> 69 143 97 30 <b>339</b> = 2.82, 0 2 = 0.79	Cont Events 5 7 3 1 16 df = 3 (P ) 16	rol <u>Tota</u> 57 143 98 30 <b>328</b> = 0.42	I         Weight           31.0%         38.6%           326.0%         4.4%           100.0%         100.0%	<b>Risk Ratio</b> <b>M-H, Random, 95% CI</b> 0.83 [0.25, 2.71] 0.86 [0.30, 2.49] 2.69 [0.74, 9.85] 0.33 [0.01, 7.87] 1.10 [0.57, 2.12] 1.00 [0.52, 1.91]	Risk Ratio Year M-H, Random, 95% Cl 2003 2009 2011 2017	
Study or Subgroup 11.1.1 no interventi- Jones 2003 Cuthbertson 2009 Elliott 2011 McDowell 2017 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> Test for overall effect 11.1.2 usual rehabil Walsh 2015 Subtotal (95% Cl) Total events	Experime Events on 5 6 8 0 19 = 0.00; Chi <sup>2</sup> t: Z = 0.27 (P litation 16 16	ental <u>Total</u> 69 143 97 30 339 = 2.82, 6 = 0.79 120	Cont Events 5 7 3 1 1 6 df = 3 (P	rol <u>Tota</u> 57 143 98 30 <b>328</b> = 0.42	I         Weight           31.0%         38.6%           26.0%         4.4%           100.0%         100.0%	Risk Ratio M-H, Random, 95% CI 0.83 [0.25, 2.71] 0.86 [0.30, 2.49] 2.69 [0.74, 9.85] 0.33 [0.01, 7.87] 1.10 [0.57, 2.12]	Risk Ratio Year M-H, Random, 95% Cl 2003 2009 2011 2017	
Study or Subgroup 11.1.1 no interventi- Jones 2003 Cuthbertson 2009 Elliott 2011 McDowell 2017 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> Test for overall effect 11.1.2 usual rehabil Walsh 2015 Subtotal (95% Cl) Total events Heterogeneity: Not a	Experime Events on 5 6 8 0 19 = 0.00; Chi <sup>2</sup> : t: Z = 0.27 (P litation 16 16 pplicable	ental <u>Total</u> 69 143 97 30 <b>339</b> = 2.82, ( 2 = 0.79) 120 120	Cont Events 5 7 3 1 16 df = 3 (P ) 16 16	rol <u>Tota</u> 57 143 98 30 <b>328</b> = 0.42	I         Weight           31.0%         38.6%           26.0%         4.4%           100.0%         100.0%	Risk Ratio M-H, Random, 95% CI 0.83 [0.25, 2.71] 0.86 [0.30, 2.49] 2.69 [0.74, 9.85] 0.33 [0.01, 7.87] 1.10 [0.57, 2.12]	Risk Ratio Year M-H, Random, 95% Cl 2003 2009 2011 2017	
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