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

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Manuscripts

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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31 **Declaration of interests:** None.

32

33 **Word count:** 2950 words

34

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).

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

79 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**

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

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

120

121 **Materials and methods**

122 ***Compliance with reporting guidelines***

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

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

130 ***Research question and eligibility criteria***

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

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

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6 146 following ICU discharge improved clinically relevant outcomes, we excluded studies in
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9 147 which earlier and/or more intensive ICU physical rehabilitation (compared to the care
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12 148 received by the control group) was provided to patients in the intervention group. Any
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15 149 combination of one or more of the following activities was considered as a form of
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17 150 enhanced physical rehabilitation: neuromuscular stimulation, inspiratory or respiratory
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20 151 muscle training, passive range-of-motion exercise, cycle ergometer exercise,
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23 152 active-assisted exercises, active range-of-motion exercises, bed mobility activities (e.g.,
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26 153 bridging, rolling, lying-to-sitting exercise), ADL training, transfer training, pre-gait
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29 154 exercises (including marching in place), and walking exercise.

30 31 155 ***Outcomes of interest***

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34 156 The primary outcomes were QOL, ADL function, and mortality. Secondary
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37 157 outcomes included functional exercise capacity, pain, return-to-work rate, muscle
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40 158 strength, duration of delirium, and incidence of adverse events (defined by the trialists).

41 42 159 ***Search strategy and selection of studies***

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45 160 We searched the Cochrane Central Register of Controlled Trials (CENTRAL),
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48 161 MEDLINE via PubMed, Excerpta Medica Database (EMBASE) via Elsevier, the
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51 162 Physiotherapy Evidence Database (PEDro), and the World Health Organization
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54 163 International Clinical Trials Registry Platform (WHO ICTRP) via their dedicated search

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

Data abstraction and quality assessment

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

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6 182 Differences in opinion regarding the assessment of risk of bias were resolved through
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9 183 discussion between the two reviewers, occasionally with arbitration by a third reviewer
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12 184 (KY).

13 14 185 ***Data analysis***

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17 186 All analyses were conducted using the Cochrane Review Manager software
18
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20 187 (RevMan 5.3; Cochrane Collaboration, Copenhagen, Denmark). For the dichotomous
21
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23 188 variables of mortality and return-to-work rate, pooled risk ratios (RRs) with 95%
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26 189 confidence intervals (CIs) are provided. For continuous outcomes including QOL
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29 190 scores, ADL function scores, pain, muscle strength, and duration of delirium (expressed
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32 191 in days of ICU or hospital stay), the standardized mean differences, or the mean
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35 192 differences with 95% CIs were calculated, as recommended by the Cochrane
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38 193 Handbook.[17] Adverse events were narratively summarized because their definition
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41 194 likely varied across studies. We used the random-effects models for all analyses.

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43 195 We calculated I^2 as a measure of variation across studies that is due to
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46 196 heterogeneity rather than chance, and interpreted the values as follows: 0%–40%,
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49 197 negligible heterogeneity; 30%–60%, mild-to-moderate heterogeneity; 50%–90%,
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52 198 moderate-to-substantial heterogeneity; 75%–100%, considerable heterogeneity. If
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55 199 heterogeneity was identified for an outcome ($I^2 > 50\%$), we investigated the underlying

200 reasons and conducted the χ^2 test, with a *P*-value of <0.10 being considered to indicate
201 statistical significance. 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 protocolized physical rehabilitation in the ICU), timing of commencement of the
209 intervention (in-hospital or after hospital discharge), intervention duration (≤ 8 versus > 8
210 weeks), treatment frequency (< 5 versus ≥ 5 times/week), and type of control (no
211 intervention versus usual 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,
215 21]

216 ***Patient and public involvement***

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

218

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

236 following hospital discharge, while 4[12, 22–24] focused on rehabilitation started
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-
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*

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).

290

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

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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6 326 Trial (AVERT)[32] determined that intervention in such acute cases improved the odds
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8 327 of a favourable outcome with each episode of activity per day. Our present review did
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11 328 not include studies comparing high-dose rehabilitation and usual care, and thus the QOL
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14 329 effect of high-dose rehabilitation remains unclear. Additionally, we could not perform
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17 330 subgroup analysis for PICS symptoms with effect on QOL[3–5] or for sepsis, which is a
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20 331 risk factor for PICS.[37, 38] It remains unclear which population of critically ill patients
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23 332 may truly benefit from intensive physical rehabilitation.

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25 333 The studies included in our review did not cover all important outcomes
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28 334 included in the core outcome set of rehabilitation after critical illness,[7] including ADL
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31 335 function, functional exercise capacity, pain, return-to-work rate, muscle strength, or
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34 336 delirium incidence. Nonetheless, our findings regarding QOL and mortality suggest
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37 337 that, even if future studies report improvement in these other aspects, the amount of
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40 338 improvement would likely be too small to affect QOL.

41
42 339 The present review has several strengths. First, we employed rigorous
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45 340 methodology that followed a written, a priori protocol developed according to the
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48 341 PRISMA statement, including a comprehensive search for evidence. Second, we
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51 342 performed duplicate assessment of eligibility, risk of bias, and data abstraction. Third,
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54 343 we used the GRADE approach for assessing the certainty of evidence. In addition, we

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

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

363 mechanical ventilation.

364

For peer review only

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Author contributions

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

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Declaration of interests

None.

Data sharing statement

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

402 **Supplementary data**

403 Supplementary data to this article can be found online.

404

405 Online supplementary file 1: PRISMA 2009 checklist

406 Online supplementary file 2: Search strategies

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

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

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

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

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430 next? An expert consensus statement on physical rehabilitation after hospital
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- Figure legends**
- 532
- Fig 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)
- 533
- flow diagram
- 534
- Fig 2 Forest plot for quality of life and mortality

535 **Tables**

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

537

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

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SF-36: mental component summary score	(-3.18 to 1.73)				
Mortality	Study population		RR: 0.71	93	⊕⊕⊕⊖
Short term	43 per 1000	31 per 1000 (2 to 426)	(0.05 to 9.80)	(2 RCTs)	Low ^{b,c}
Mortality	Study population		RR: 1.05	907	⊕⊕⊕⊖
Long term	71 per 1000	75 per 1000 (47 to 119)	(0.66 to 1.66)	(5 RCTs)	Moderate ^d
Adverse events	Study population			153	⊕⊕⊕⊖
	Two studies reported no adverse events. One study reported 18 and 5 events in the intervention and control groups, respectively.			(3 RCTs)	Low ^{ef}
*The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect (and its 95% CI) estimated for the intervention group.					
GRADE Working Group grades of evidence					
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.					
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.					
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.					
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect					

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

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

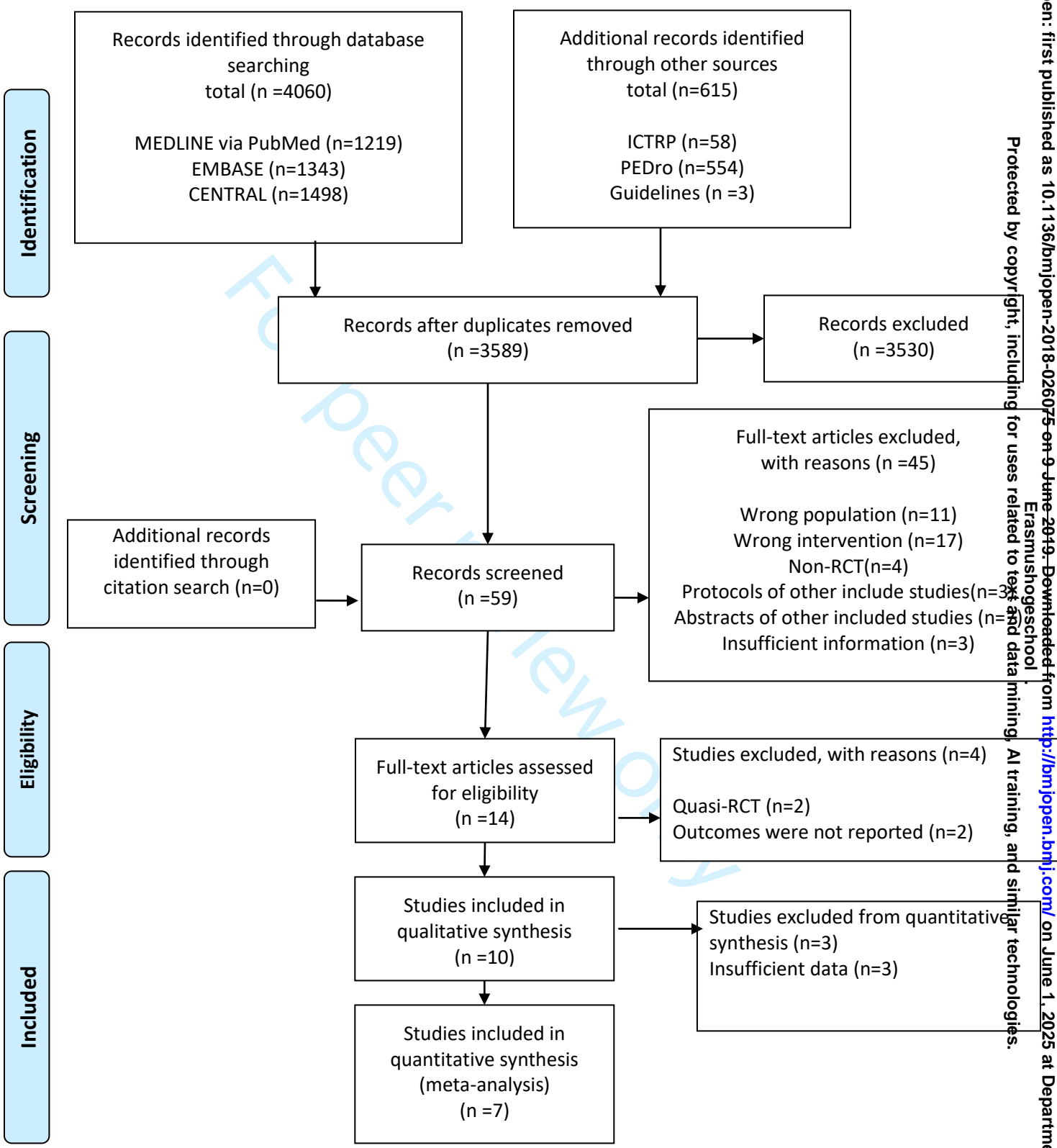
^bDowngraded one point because of high risk of bias associated with the fact that the intervention included nutritional therapy but the study provided very little detail regarding the therapy received in the control group (other bias).

^cDowngraded because of imprecision (only two small studies).

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

^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 control group, and the adherence in the intervention group was 70% (other bias).

^fDowngraded because of imprecision (only three small studies).

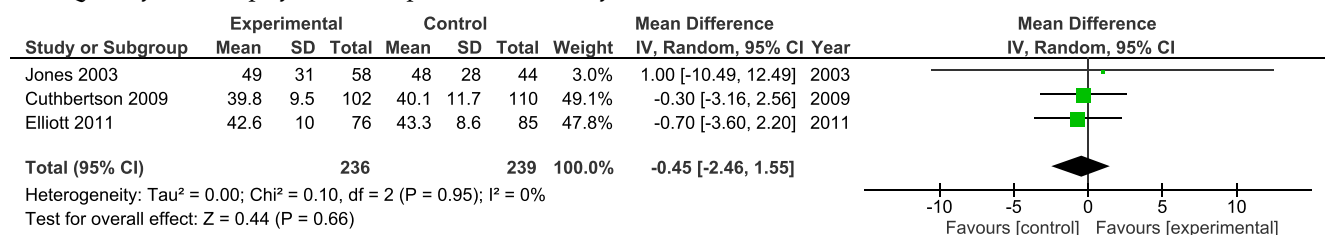


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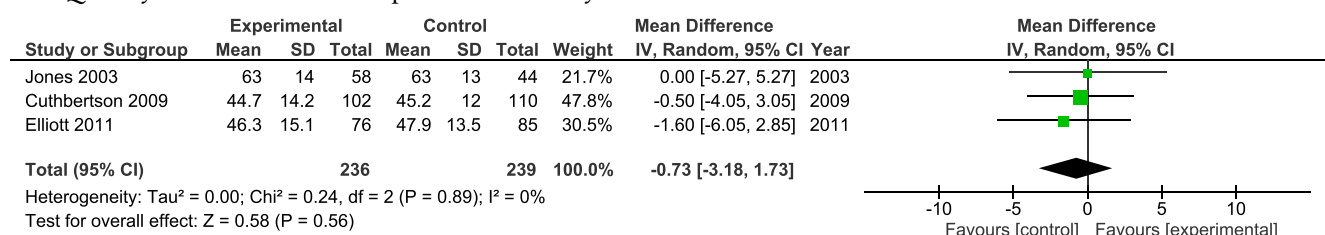
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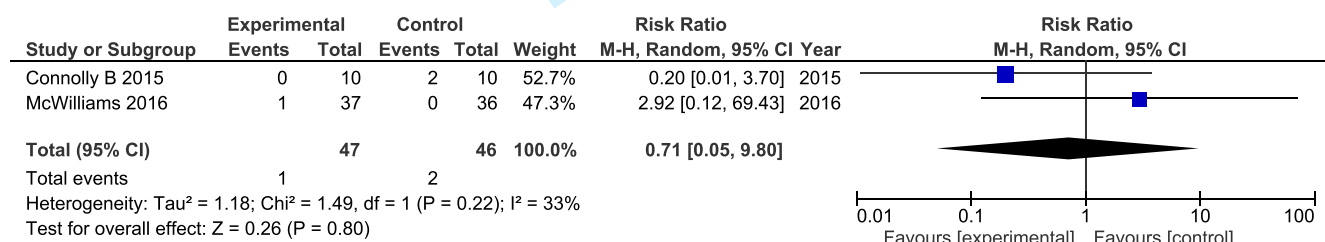
2-A Quality of life: physical component summary



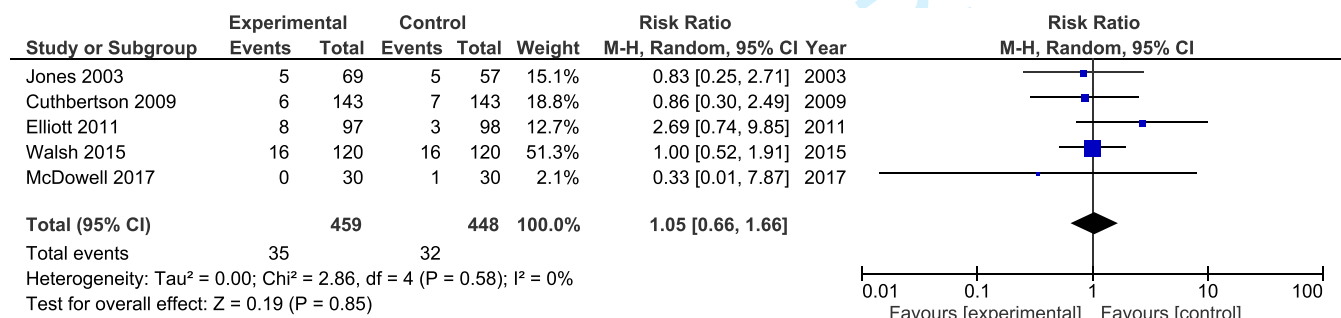
2-B Quality of life: mental component summary



2-C Short term mortality



2-D Long term mortality





PRISMA 2009 Checklist

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



PRISMA 2009 Checklist

Page 1 of 2

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

The cochrane central register of controlled trials (CENTRAL)

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

#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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OR #48 OR #49
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MEDLINE via PubMed

- #1 critical care[mh]
- #2 intensive care unit[mh]
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- #4 ventilator weaning[mh]
- #5 Respiratory Distress Syndrome, Adult[mh]
- #6 Sepsis[mh]
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#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]
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OR #48 OR #49
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#53 controlled clinical trial [pt]
#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

EMBASE

- #1 "critical care"/exp
- #2 "intensive care unit"/exp
- #3 "critical illness"/exp
- #4 "ventilator weaning"/exp
- #5 "Respiratory Distress Syndrome, Adult"/exp
- #6 Sepsis/exp
- #7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
- #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
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- #23 "Exercise therapy"/exp
- #24 Rehabilitation/exp
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- #26 "Physical Therapy Modalities"/exp
- #27 #22 OR #23 OR #24 OR #25 OR #26
- #28 exercise:ab,ti
- #29 rehabilitation:ab,ti
- #30 "physical fitness":ab,ti
- #31 training:ab,ti
- #32 mobilization:ab,ti
- #33 mobilisation:ab,ti

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

PEDro

Advance search

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

Method: clinical trial

For peer review 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
daily living OR ambulation OR walking)

#3 #1 AND #2

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

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

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

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

symptoms, Readiness to
exercise, Self-efficacy to
exercise

*Unpublished data

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

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

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

RCT, randomised controlled trial

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

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

^aUnpublished 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)

^bDose of physical rehabilitation was unknown

^cAdherence to the intervention was unknown

^dIntervention included nutritional therapy

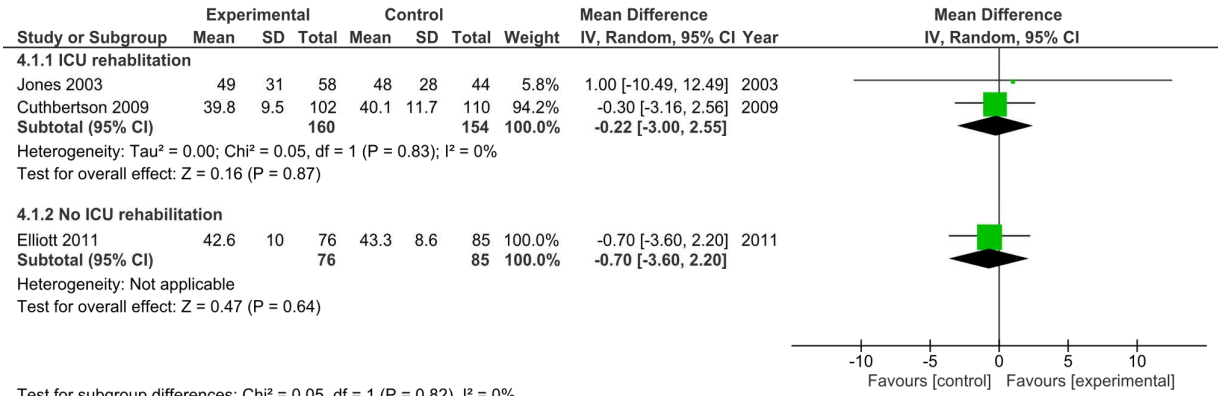
^eVery little detail given regarding the therapy received in the control group

^fAdherence to the intervention was 70%

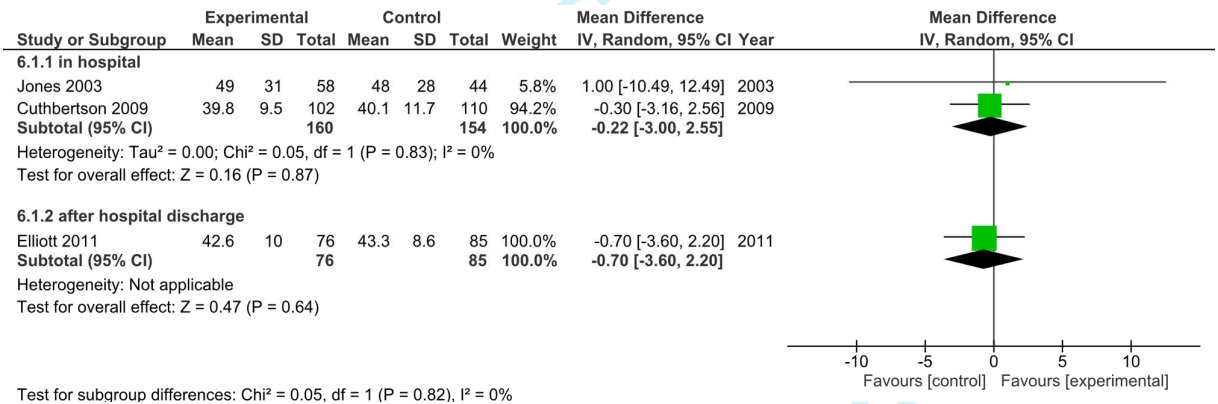
Online supplementary file 6: Subgroup analysis

A Quality of life: physical component summary

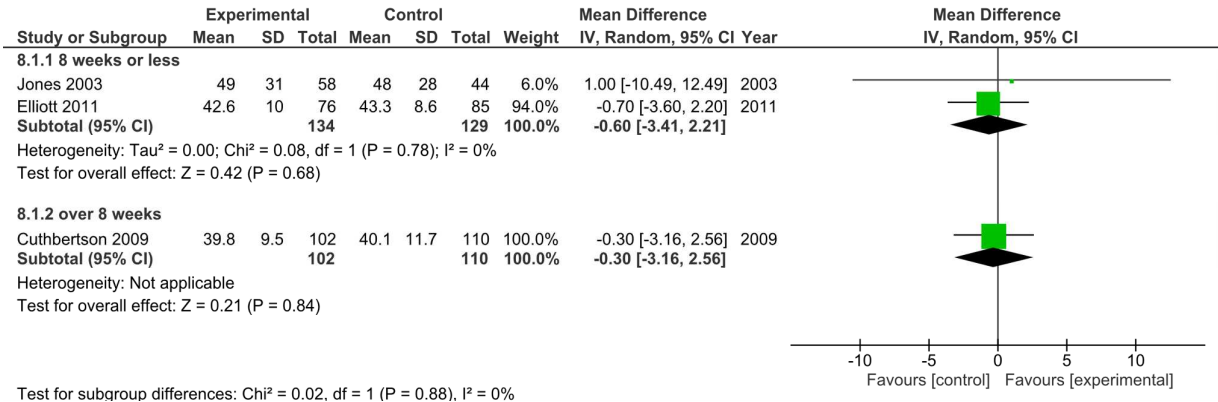
A-1 Rehabilitation practice in ICU (ICU rehabilitation before randomisation ve No ICU rehabilitation before randomisation)



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

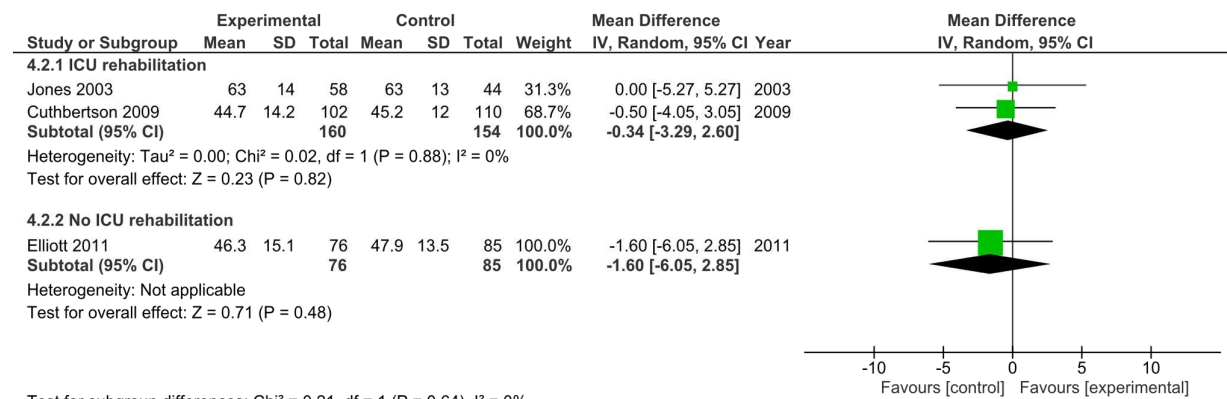


A-3. The intervention duration (8 weeks or less, and over 8 weeks)

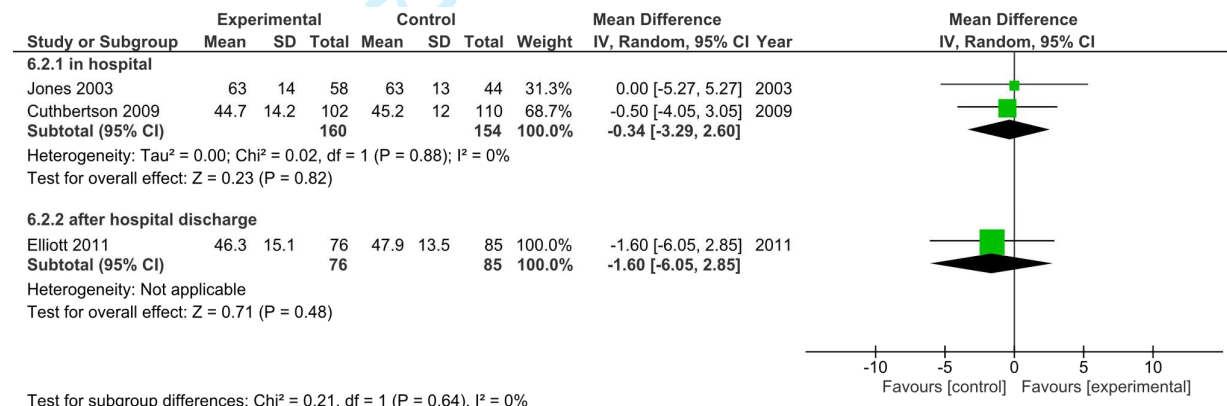


B Quality of life: mental component summary

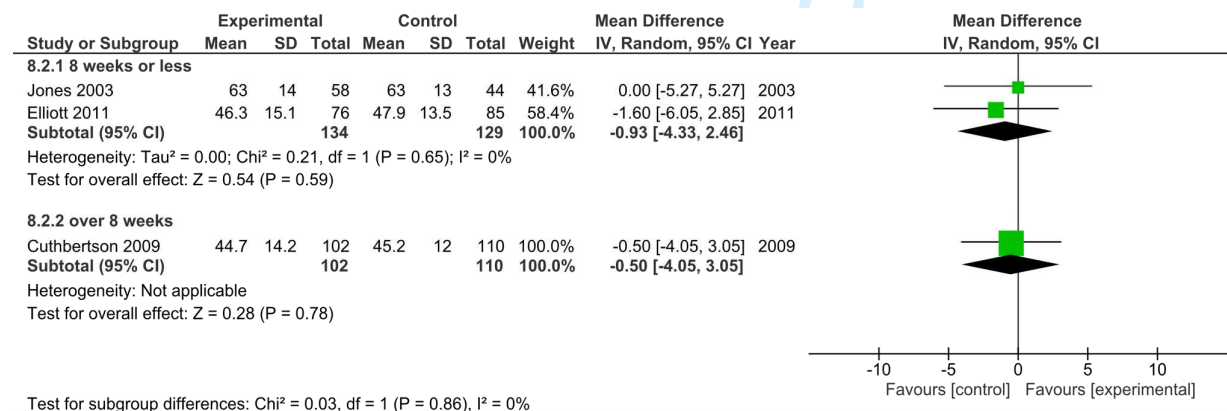
B-1. Rehabilitation practice in ICU (ICU rehabilitation before randomization ve No ICU rehabilitation before randomization)



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



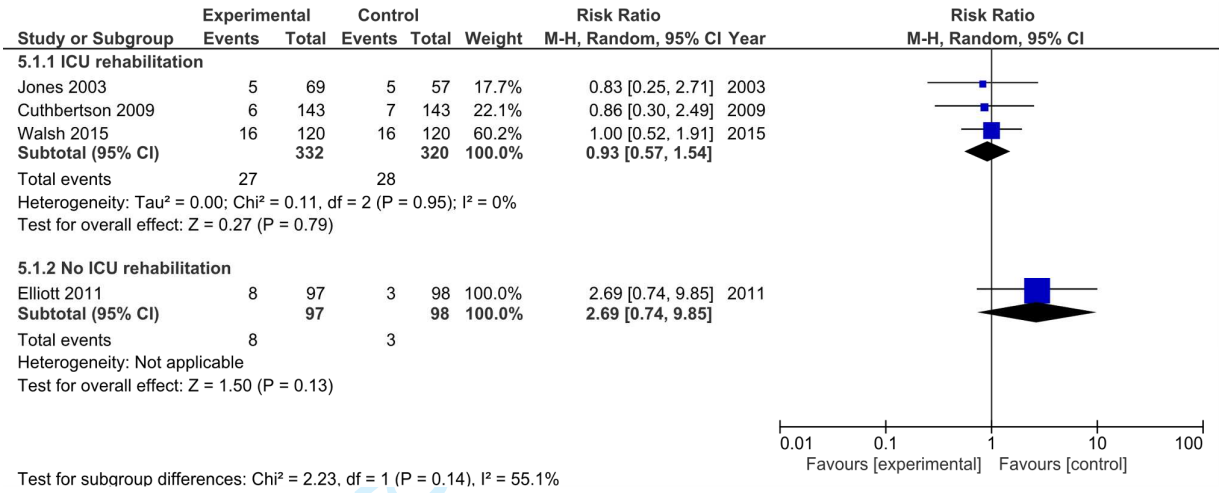
B-3. The intervention duration (8 weeks or less, and over 8 weeks)



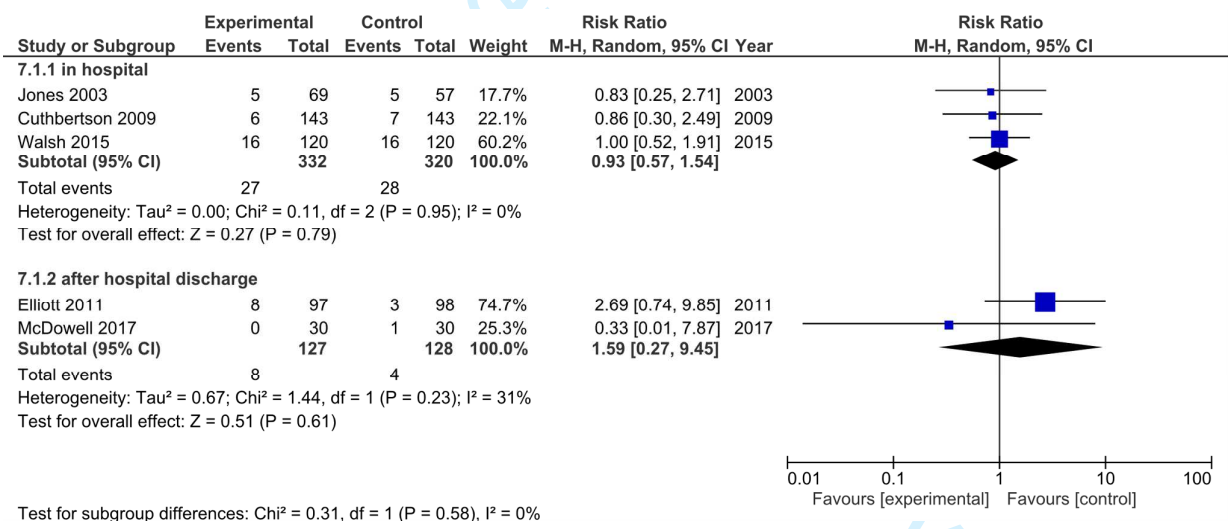
QOL: quality of life, PCS: physical component score, MCS: mental component score,

C Long term mortality

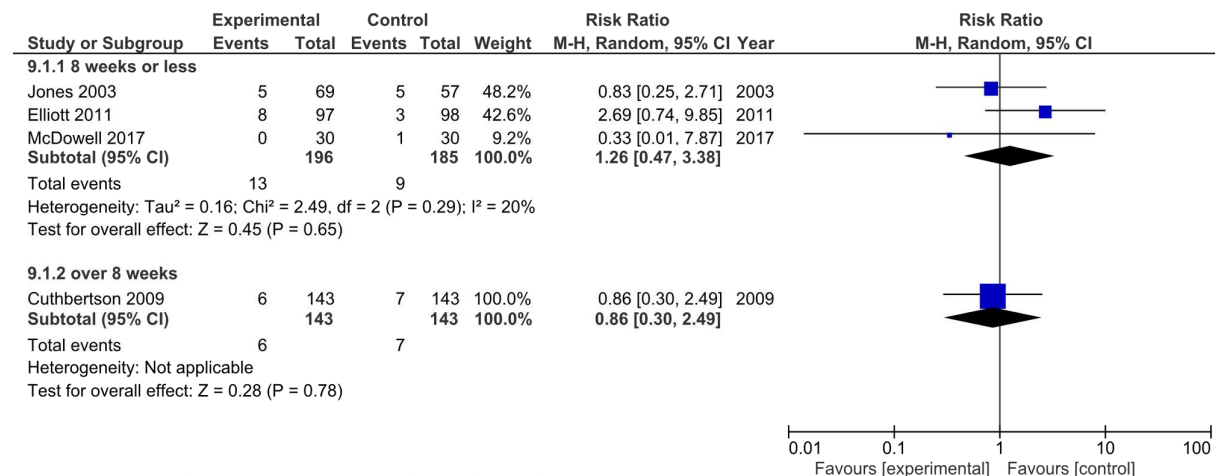
C-1. Rehabilitation practice in ICU (ICU rehabilitation before randomization ve No ICU rehabilitation before randomization)



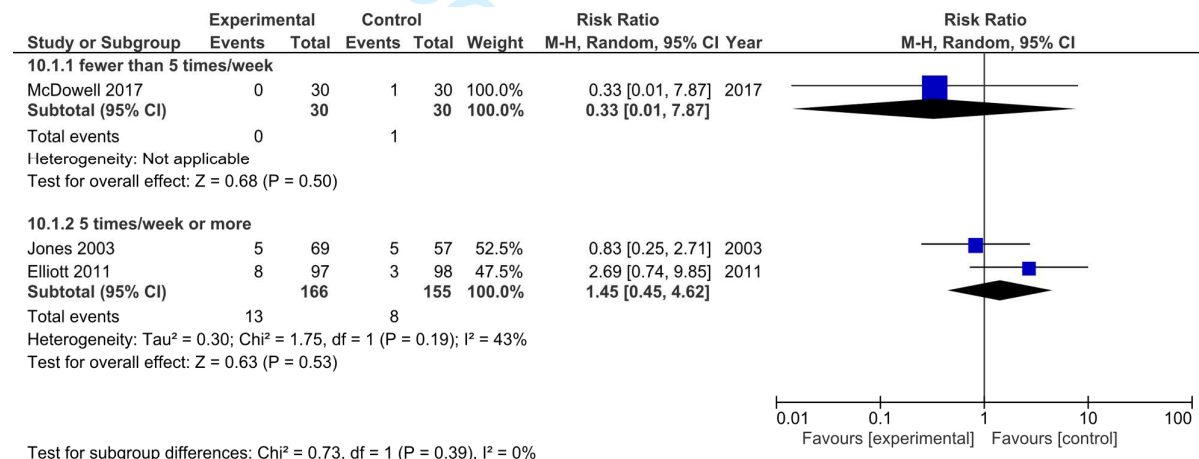
C-2 The timing of the commencement of the intervention (in hospital vs after hospital discharge)



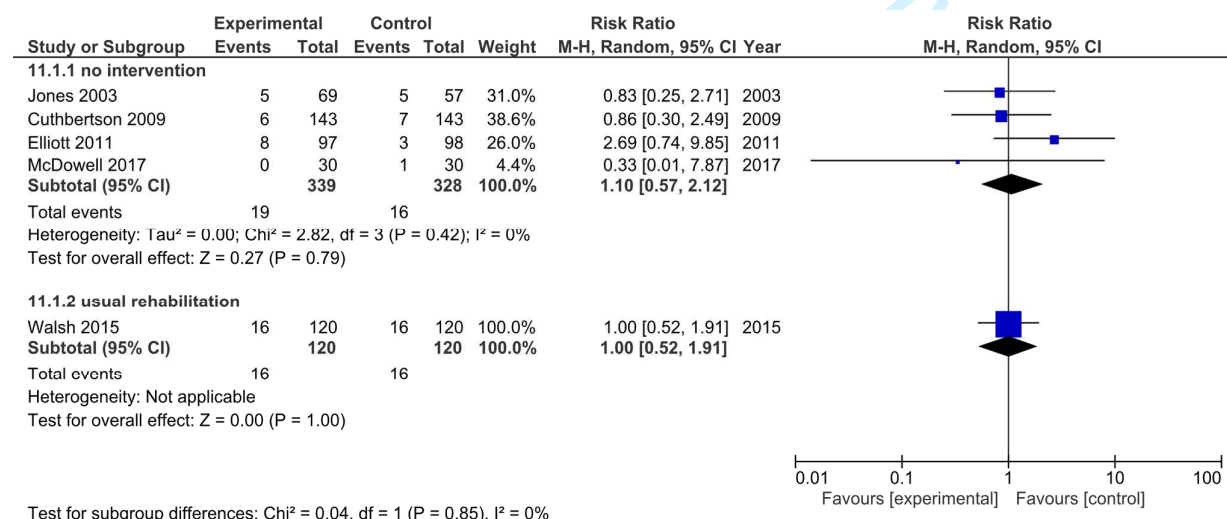
C -3. The intervention duration (8 weeks or less, and over 8 weeks)



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



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



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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Manuscript ID	bmjopen-2018-026075.R1
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
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Intensive care
Keywords:	critical illness, rehabilitation, post-intensive care syndrome, exercise, quality of life, mortality

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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 systematic**

4 **review and meta-analysis**

5

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31 **Declaration of interests:** None.

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33 **Word count: 3051 words**

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34 **Abbreviations**

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

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43 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 assessing the effect of rehabilitation following ICU discharge, designed to either
54 commence earlier and/or be more intensive for adult patients who received mechanical
55 ventilation.

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

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7 61 **Results:** Ten trials (enrolling 1110 patients) compared physical rehabilitation to usual
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9 62 care or no intervention after ICU discharge. Regarding QOL, the SMD [95% CI] between
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11 63 the intervention and control groups for the physical and mental component summary
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13 64 scores was 0.06 [-0.12 to 0.24] and -0.04 [-0.20 to 0.11], respectively. Rehabilitation did
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15 65 not significantly decrease long-term mortality (RR: 1.05 [0.66–1.66]). The analysed trials
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17 66 did not report on ADL. The certainty of the evidence was graded as moderate for QOL
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19 67 and mortality.
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27 68 **Conclusions:** Enhanced physical rehabilitation following ICU discharge may make little
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29 69 or no difference to QOL or mortality among patients who received mechanical ventilation.
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33 70 With regard to the wide CI, we believe further studies are needed to confirm the efficacy
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35 71 of rehabilitation.
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39 72 **Trial registration:** PROSPERO, CRD42017080532 (registered: 28 December 2017).
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45 74 **Keywords:** rehabilitation, critical illness, post-intensive care syndrome, exercise, quality
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47 75 of life, mortality
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76 Article Summary

77 Strengths and limitations of this study

78 • This is the first meta-analysis focused on enhanced physical rehabilitation to review
79 randomised controlled trials in which the study intervention was conducted only after
80 intensive care unit discharge.

81 • The findings are based on moderate certainty of evidence.

82 • 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.

85 • 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.

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Introduction

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

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

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

Materials and methods

Compliance with reporting guidelines

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

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125 consulting the PRISMA 2009 checklist[19] (details provided in online supplementary file
126 1).

127 ***Research question and eligibility criteria***

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

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

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

Outcomes of interest

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

Search strategy and selection of studies

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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***

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

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

Data analysis

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

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

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

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

215 21]

216 ***Patient and public involvement***

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

218

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
225 supplementary file 3). The 10 RCTs provided a pooled sample of 1110 critically ill
226 patients with an ICU stay of >48 hours during which mechanical ventilation was
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

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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.

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

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
 262 -0.04 (95% CI, -0.20 to 0.11), respectively (Fig. 2A and 2B, respectively). Rehabilitation
 263 did not significantly decrease short-term mortality (RR, 0.71; 95% CI, 0.05–9.80, I^2 =
 264 33%; n = 93) (Fig. 2C) or long-term mortality (RR, 1.05; 95% CI, 0.66–1.66, I^2 = 0%; n
 265 = 907) (Fig. 2D). The certainty of evidence for QOL and long-term mortality was
 266 moderate, while that for short-term mortality was low (Table 1). We performed additional
 267 analysis regarding follow-up at 12 months, and enhanced physical rehabilitation also did
 268 not increase QOL score or decrease mortality (see detail provided in online

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

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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
301 observed effect of the intervention. Furthermore, despite the large sample size in the
302 meta-analysis for QOL and long-term mortality, limited data for these outcomes were
303 available, and the certainty of evidence was only low or moderate.

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

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

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

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

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

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6 357 intervention. However, since studies included in this review compare rehabilitation
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9 358 intervention against standard care or no intervention, it is obvious that intensive
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15 360 Lastly, we could not consider psychological aspects in our review. However, effect of
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18 361 intervention for the general population is more clinically important than for that of
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21 362 highly self-motivated individuals, and we clarified that enhanced physical rehabilitation
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24 363 following ICU discharge may make little or no difference for the general population
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27 364 including highly self-motivated individuals.
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30 365 Taken together, the findings of the present meta-analysis indicate that enhanced
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33 366 physical rehabilitation following ICU discharge may make little or no difference to
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36 367 QOL or mortality among patients who received mechanical ventilation. With regards to
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39 368 the wide CI, we believe further studies are needed to confirm the efficacy of
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392 *Author contributions*

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
397 manuscript.

398

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401

402 *Declaration of interests*

403 None.

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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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408 **Supplementary data**

409 Supplementary data to this article can be found online.

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411 Online supplementary file 1: PRISMA 2009 checklist

412 Online supplementary file 2: Search strategies

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

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

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

417 Online supplementary file 6: Additional meta-analysis for quality of life and mortality at
418 12 months

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

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530 **Figure legends**

- 531 Fig 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)
- 532 flow diagram
- 533 Fig 2 Forest plot for quality of life and mortality

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534 **Tables**

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

536

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

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

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

GRADE Working Group grades of evidence

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

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

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

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

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

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

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

^cDowngraded because of imprecision (only two small studies).

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

^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 control group, and the adherence in the intervention group was 70% (other bias).

^fDowngraded because of imprecision (only three small studies).

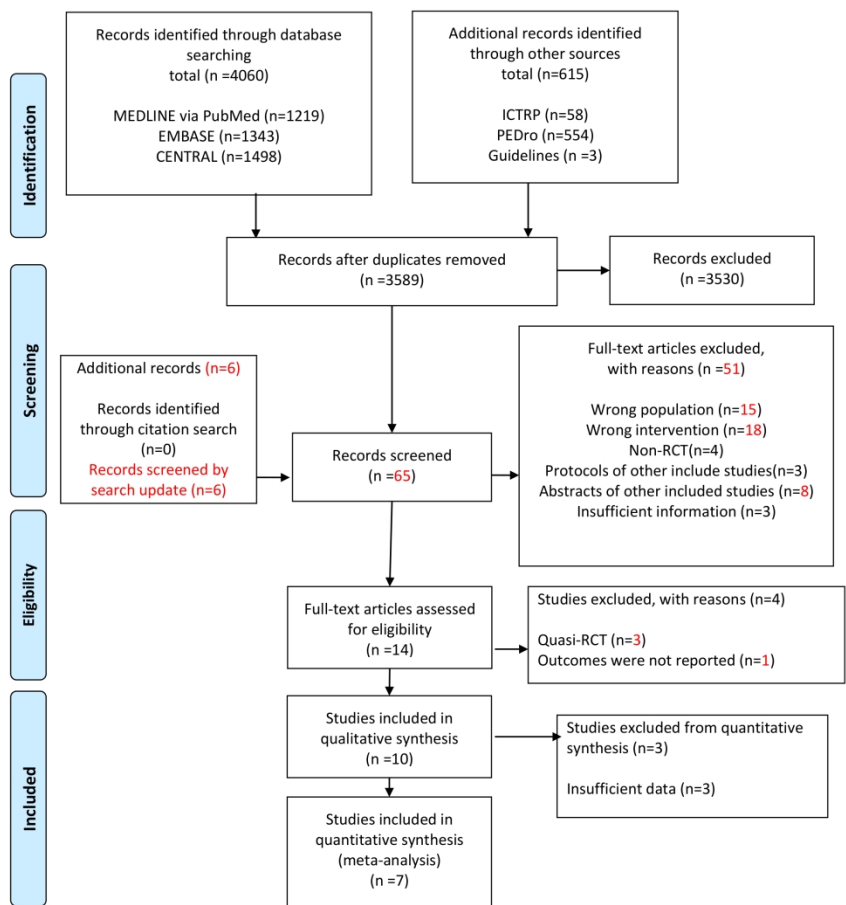
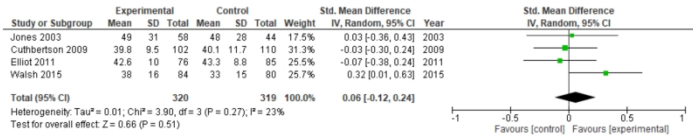


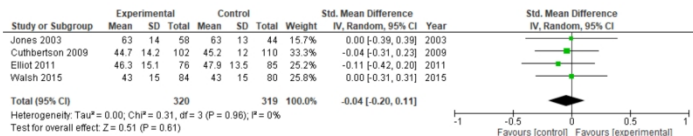
Fig 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram

215x279mm (300 x 300 DPI)

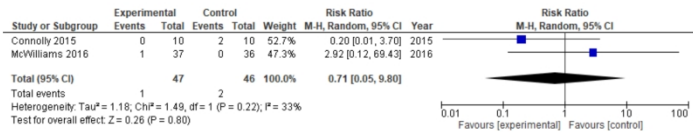
2-A Quality of life: physical component summary



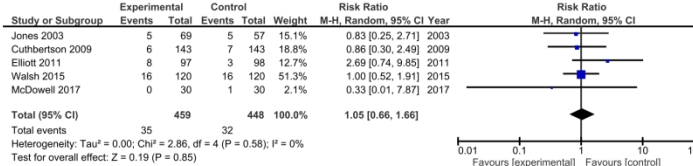
2-B Quality of life: mental component summary



2-C Short term mortality



2-D Long term mortality



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

Fig 2 Forest plot for quality of life and mortality

209x297mm (300 x 300 DPI)



PRISMA 2009 Checklist

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



PRISMA 2009 Checklist

Checklist item 9

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

Online supplementary file 2: Search strategies

The cochrane central register of controlled trials (CENTRAL)

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

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#32 mobilization:ti,ab,kw
#33 mobilisation:ti,ab,kw
#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
#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 #21 AND #51

MEDLINE via PubMed

- #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]
- #33 mobilisation[tiab]

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

- #1 "critical care"/exp
- #2 "intensive care unit"/exp
- #3 "critical illness"/exp
- #4 "ventilator weaning"/exp
- #5 "Respiratory Distress Syndrome, Adult"/exp
- #6 Sepsis/exp
- #7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
- #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
- #22 Exercise/exp
- #23 "Exercise therapy"/exp
- #24 Rehabilitation/exp
- #25 "Physical fitness"/exp
- #26 "Physical Therapy Modalities"/exp
- #27 #22 OR #23 OR #24 OR #25 OR #26
- #28 exercise:ab,ti
- #29 rehabilitation:ab,ti
- #30 "physical fitness":ab,ti
- #31 training:ab,ti
- #32 mobilization:ab,ti
- #33 mobilisation:ab,ti

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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

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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

For peer review only

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

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

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

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

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

exercise

*Unpublished data

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

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

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

RCT, randomised controlled trial

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

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

^aUnpublished 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)

^bDose of physical rehabilitation was unknown

^cAdherence to the intervention was unknown

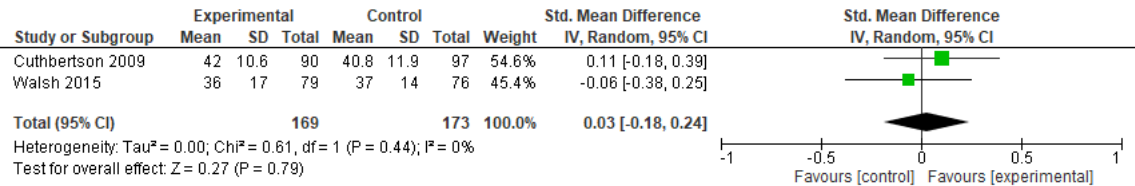
^dIntervention included nutritional therapy

^eVery little detail given regarding the therapy received in the control group

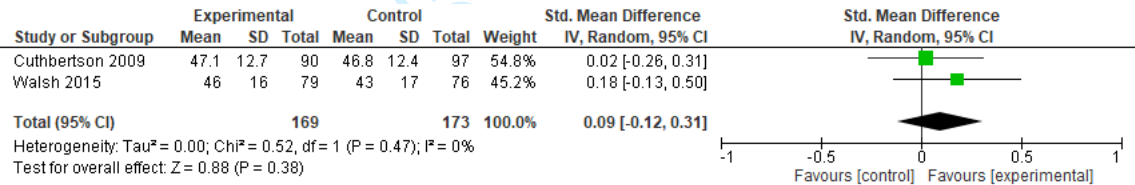
^fAdherence to the intervention was 70%

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

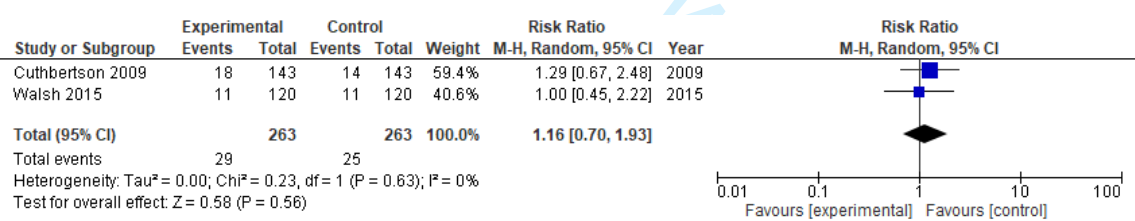
Quality of life: physical component summary



Quality of life: mental component summary



Mortality

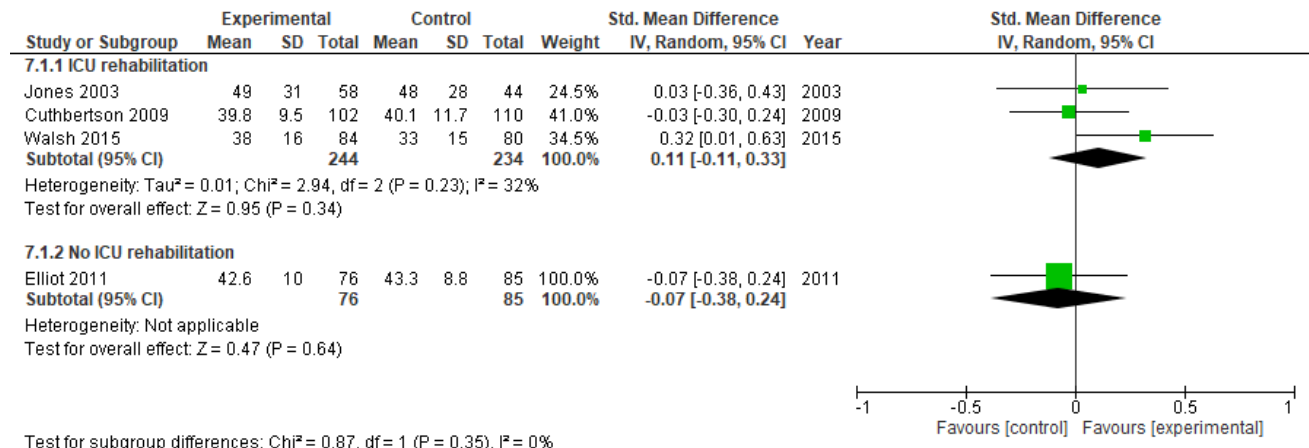


We converted median (inter quartile range) of QOL score in Walsh’s study to mean (standard deviation).

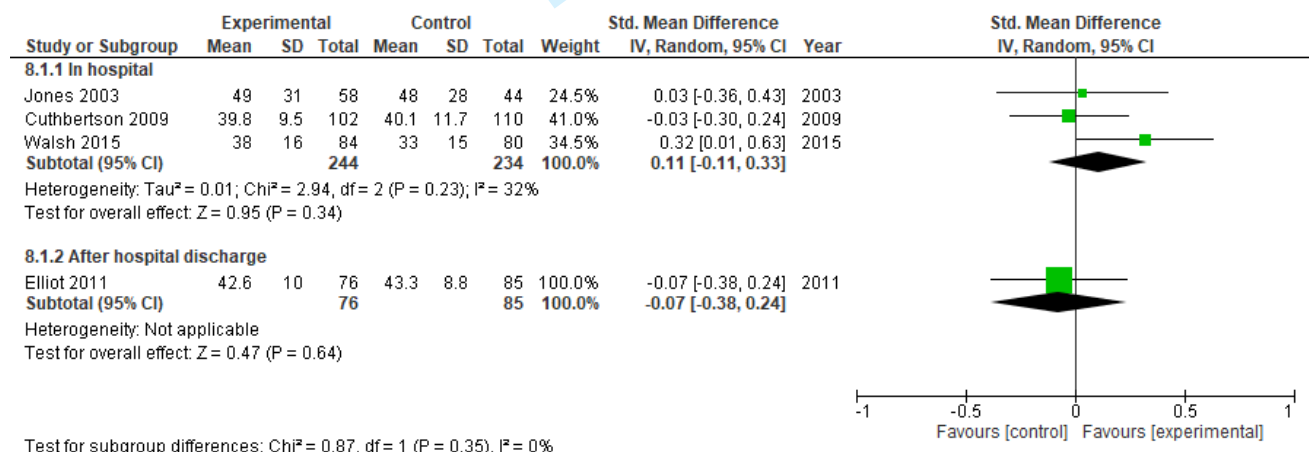
Online supplementary file 7: Subgroup analysis

A Quality of life: physical component summary

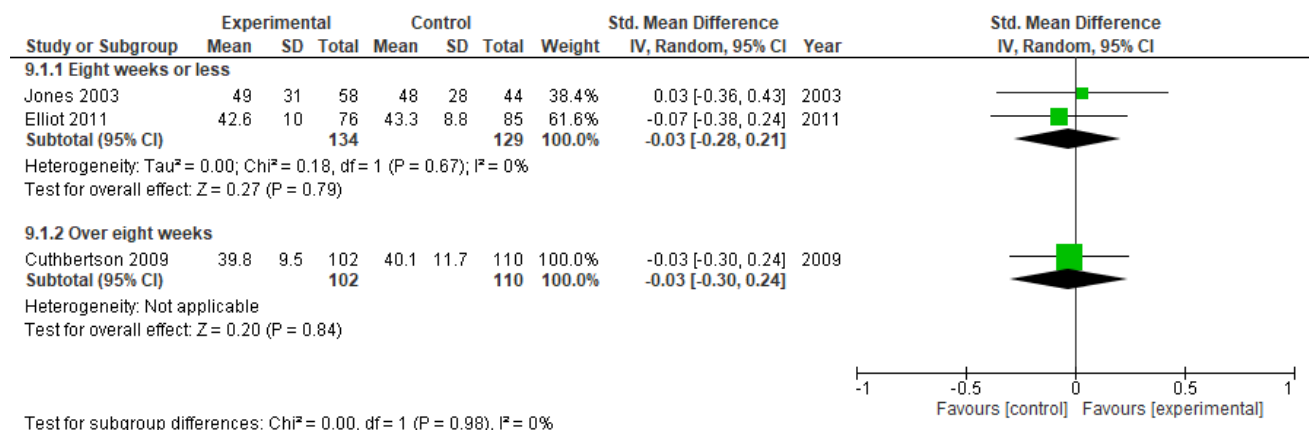
A-1 Rehabilitation practice in ICU (ICU rehabilitation before randomisation ve No ICU rehabilitation before randomisation)



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



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



1

2

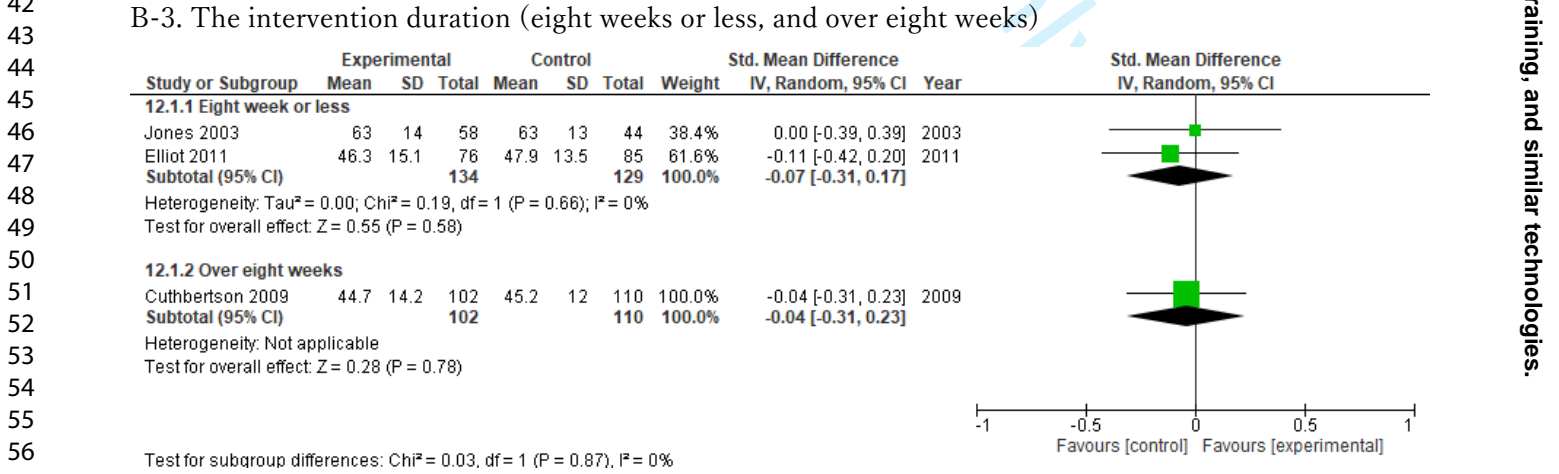
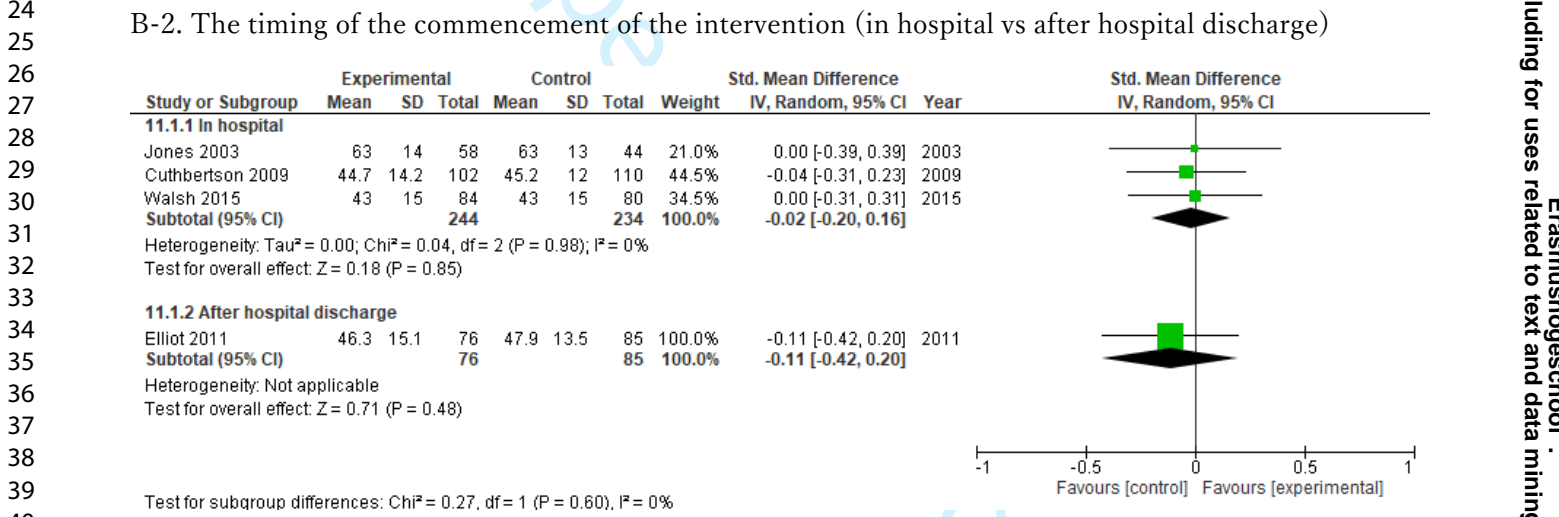
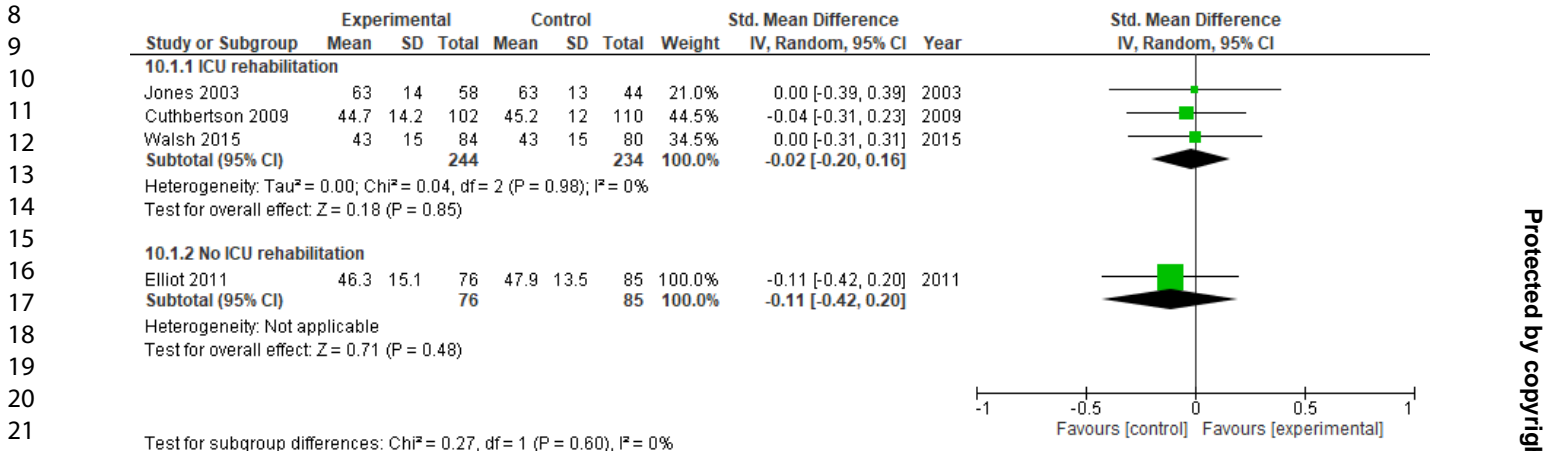
3

4 B Quality of life: mental component summary

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

6 before randomization)

7



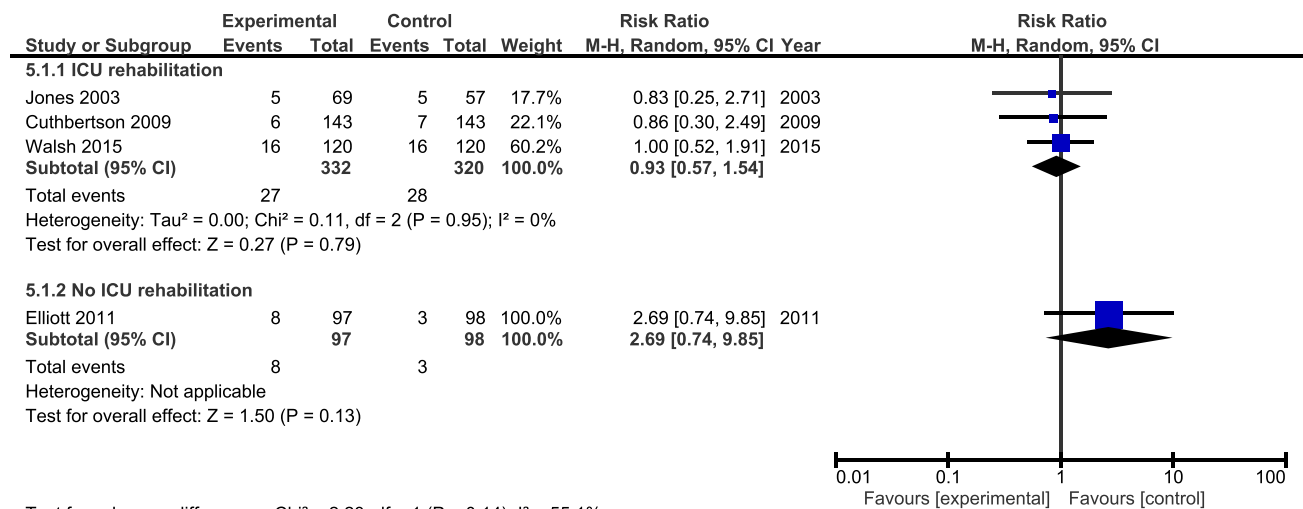
59 We converted median (inter quartile range) of QOL score in Walsh's study to mean (standard deviation).

60

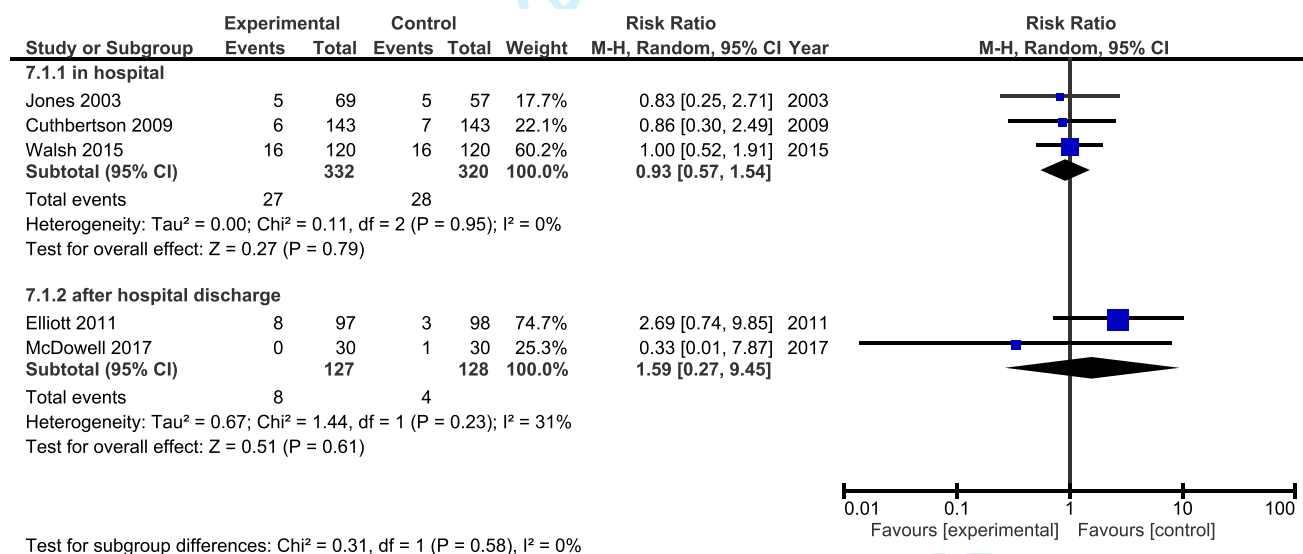
For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

C Long term mortality

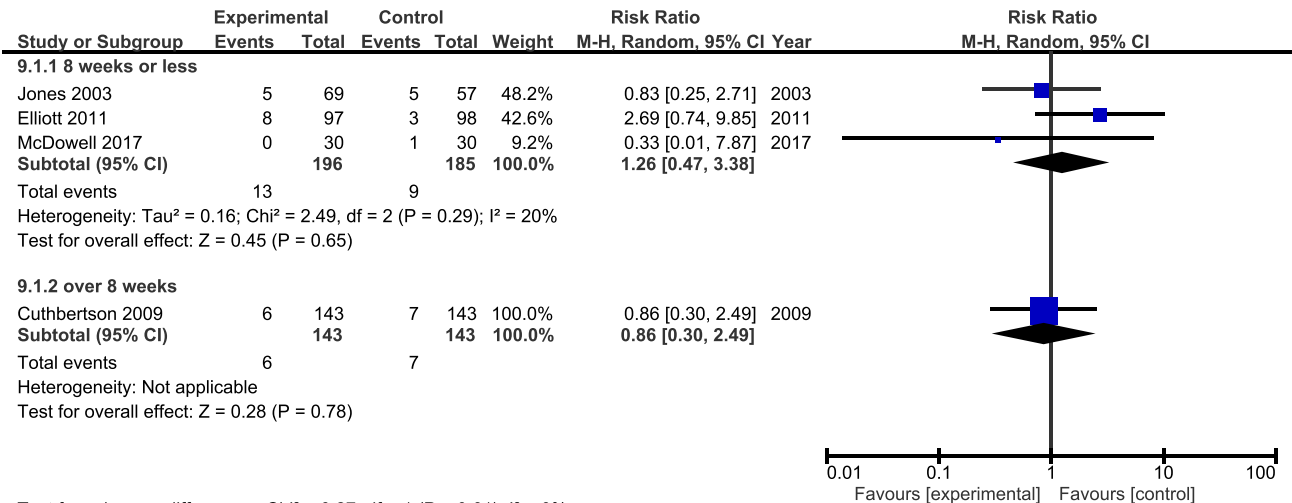
C-1. Rehabilitation practice in ICU (ICU rehabilitation before randomization ve No ICU rehabilitation before randomization)



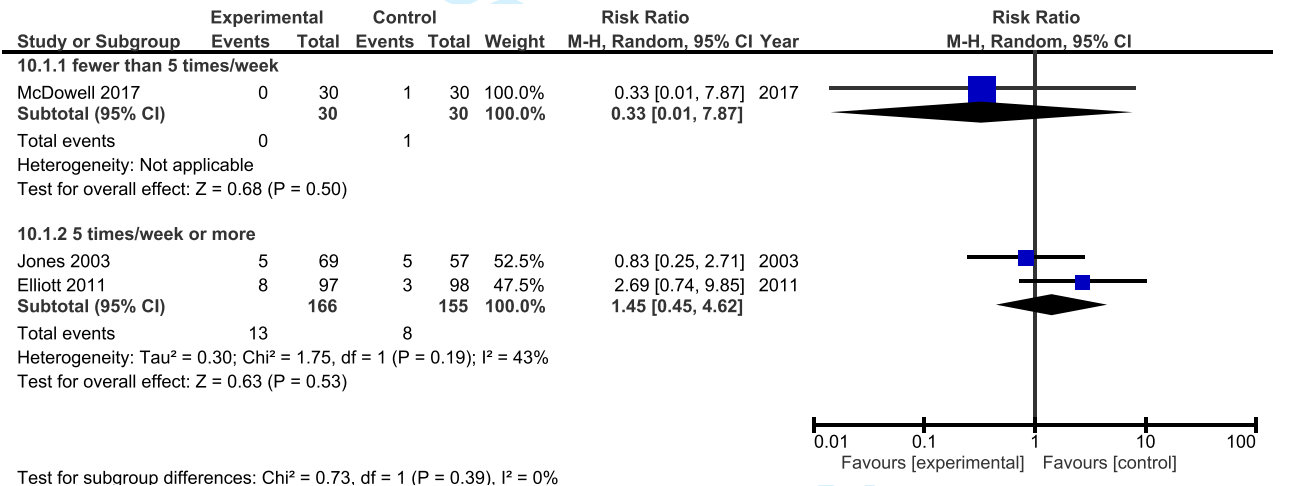
C-2 The timing of the commencement of the intervention (in hospital vs after hospital discharge)



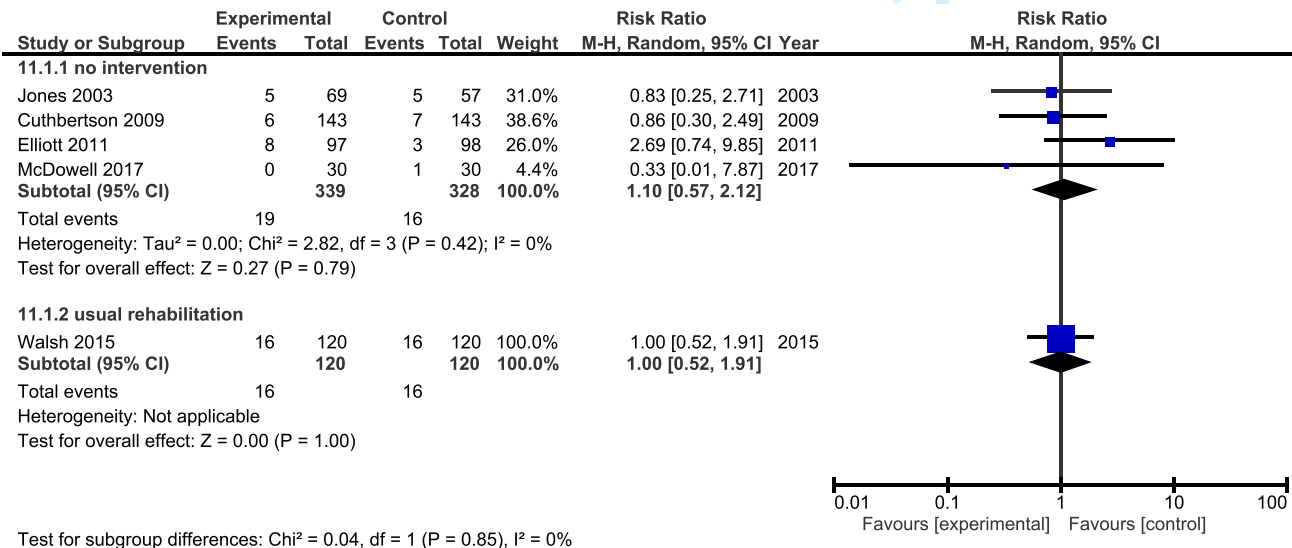
C -3. The intervention duration (8 weeks or less, and over 8 weeks)



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



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



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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- 1 Research – meta-analysis
- 2 **Does enhanced physical rehabilitation following intensive care unit discharge**
- 3 **improve outcomes in patients who received mechanical ventilation? A systematic**
- 4 **review and meta-analysis**
- 5
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31 **Declaration of interests:** None.

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34 **Abbreviations**

35 ADL, activities of daily living; APACHE, Acute Physiology And Chronic Health
36 Evaluation; CI, confidence interval; EMBASE, Excerpta Medica Database; GRADE,
37 Grading of Recommendations Assessment, Development, and Evaluation; ICU, intensive
38 care unit; PEDro, Physiotherapy Evidence Database; PICS, post-intensive care syndrome;
39 PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; QOL,
40 quality of life; RCT, randomised controlled trial; RR, risk ratio; WHO ICTRP, World
41 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
46 ICU.

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^2 and the certainty of evidence based on the GRADE
59 approach.

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

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

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

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

Article Summary

Strengths and limitations of this study

- This is the first meta-analysis focused on enhanced physical rehabilitation to review randomised controlled trials in which the study intervention was conducted only after intensive care unit discharge.

- The conclusions are based on moderate-certainty evidence.

- The main limitations of this meta-analysis are that (i) none of the included studies had a follow-up >6 months and (ii) medical resources and costs associated with each intervention were not considered.

- We employed rigorous methodology that followed a protocol developed *a priori* according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, and used the Grading of Recommendations Assessment, Development and Evaluation approach in the review process.

Introduction

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

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

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

115

116 **Materials and methods**

117 *Compliance with reporting guidelines*

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

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125 ***Research question and eligibility criteria***

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

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

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

Outcomes of interest

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

Search strategy and selection of studies

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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-

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

Data analysis

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

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

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

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

214 21]

215 *Patient and public involvement*

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

217

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
224 supplementary file 3). The 10 RCTs provided a pooled sample of 1,110 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, 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.

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

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250 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

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268 12 months post-intervention (see details provided in online supplementary file 6).

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

275 ***Secondary outcomes***

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

279 Adverse events were measured in 3 trials.[11, 13, 15] Two studies[11, 13]
280 reported no adverse events. One study[15] reported 18 events in the intervention group
281 and 5 events in the control group. Among the 18 adverse events reported in the
282 intervention group, 12 were mild or moderate (musculoskeletal pain higher than expected
283 or muscle soreness potentially indicating injury, 3 cases; any pain higher than expected,
284 1 case; cardiac symptoms or chest pain, 1 case; any other event considered by the
285 researcher to be of concern, 7 cases; 6 of 12 events were considered to be related or

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

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

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

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

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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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6 356 medical resources and costs associated with each intervention. However, since
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9 357 studies included in this review compare rehabilitation intervention against standard
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12 358 care or no intervention, it is obvious that intensive physical rehabilitation would be
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15 359 associated with increased medical resources and costs. Fourthly, the outcome measures
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18 360 might be not sufficiently sophisticated. For example, the RECOVER trial[15] did not
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21 361 demonstrate an improvement in the primary quantitative outcome, but showed evidence
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24 362 of benefit of the intervention in a parallel qualitative evaluation.[36] Fifthly, we could
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27 363 not consider the psychological aspects that are likely to affect the outcomes of
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30 364 rehabilitation. While our findings indicate a lack of benefit of enhanced post-ICU
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33 365 rehabilitation in the evaluated population, highly self-motivated individuals might have
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36 366 derived benefit from such therapies. Further studies should collect data on motivation
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39 367 and engagement, which are crucial in maximising the benefits of rehabilitation [37].
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42 368 Lastly, the patient characteristics, follow-up timing, and types of outcomes reported
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45 369 might exhibit substantial heterogeneity not only across trials but also within each
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48 370 individual trial, an aspect we did not examine in the present analysis. However, upon
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51 371 reviewing the best available evidence based on a standardised approach, we confirmed
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54 372 that the direction of the effect and the effect size of enhanced post-ICU physical
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373 rehabilitation were similar in pooled studies, as reflected in the Forest plots (see details
374 in online supplementary file 7).

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

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401

402 ***Author contributions***

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

408

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411

412 ***Declaration of interests***

413 None.

414

415 ***Data sharing statement***

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

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6 418 **Supplementary data**
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9 419 Supplementary data to this article can be found online.
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15 421 Online supplementary file 1: PRISMA 2009 checklist
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18 422 Online supplementary file 2: Search strategies
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21 423 Online supplementary file 3: Characteristics of the studies analysed in this review
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24 424 Online supplementary file 4: Characteristics of studies excluded from qualitative and
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26 425 quantitative synthesis
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29 426 Online supplementary file 5: Assessment of risk of bias in the trials analysed
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32 427 Online supplementary file 6: Additional meta-analysis for quality of life and mortality at
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34 428 12 months
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36 429 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

For peer review only

Tables

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

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

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

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

GRADE Working Group grades of evidence

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

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

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

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

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

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

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

^cDowngraded because of imprecision (only two small studies).

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

^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 control group, and the adherence in the intervention group was 70% (other bias).

^fDowngraded because of imprecision (only three small studies).

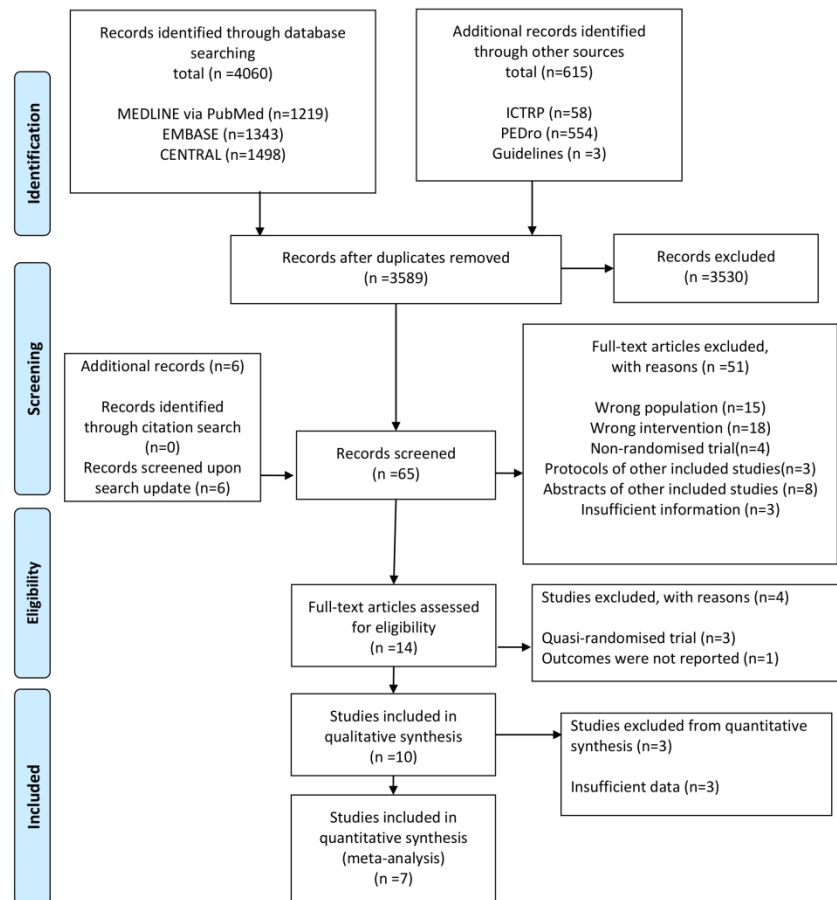
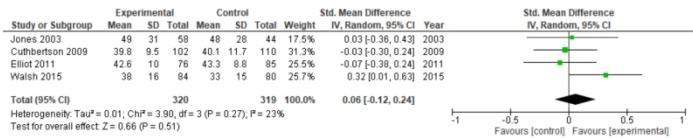


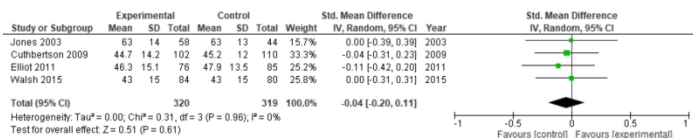
Fig 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram

215x279mm (300 x 300 DPI)

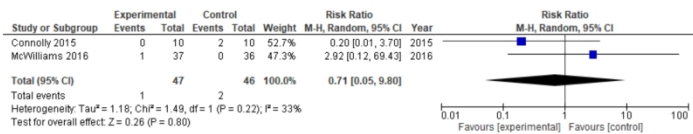
2-A Quality of life: physical component summary



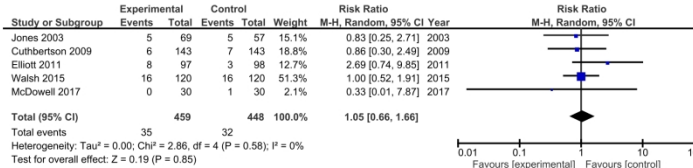
2-B Quality of life: mental component summary



2-C Short term mortality



2-D Long term mortality



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

Fig 2 Forest plot for quality of life and mortality

209x297mm (300 x 300 DPI)



PRISMA 2009 Checklist

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



PRISMA 2009 Checklist

Checklist item 9

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

Online supplementary file 2: Search strategies

The cochrane central register of controlled trials (CENTRAL)

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

#32 mobilization:ti,ab,kw
#33 mobilisation:ti,ab,kw
#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
#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 #21 AND #51

MEDLINE via PubMed

#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]
#33 mobilisation[tiab]

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

#1 "critical care"/exp
#2 "intensive care unit"/exp
#3 "critical illness"/exp
#4 "ventilator weaning"/exp
#5 "Respiratory Distress Syndrome, Adult"/exp
#6 Sepsis/exp
#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
#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
#22 Exercise/exp
#23 "Exercise therapy"/exp
#24 Rehabilitation/exp
#25 "Physical fitness"/exp
#26 "Physical Therapy Modalities"/exp
#27 #22 OR #23 OR #24 OR #25 OR #26
#28 exercise:ab,ti
#29 rehabilitation:ab,ti
#30 "physical fitness":ab,ti
#31 training:ab,ti
#32 mobilization:ab,ti
#33 mobilisation:ab,ti

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

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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

For peer review 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 daily living OR ambulation OR walking)
- #3 #1 AND #2

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

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

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

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

exercise

*Unpublished data

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

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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. 2017;195:A2337	Outcomes were not reported in the publication abstract. The full study will be considered when the review is updated.
Salisbury et al., Clin Rehabil. 2010;24:489-500	Insufficient outcome data for meta-analysis
Batterham et al., Br J Anaesth. 2014;113:130-7	Insufficient outcome data for meta-analysis
Shelly et al., Indian J Crit Care Med. 2017;21:89-93	Insufficient outcome data for meta-analysis

RCT, randomised controlled trial

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

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

^aUnpublished 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)

^bDose of physical rehabilitation was unknown

^cAdherence to the intervention was unknown

^dIntervention included nutritional therapy

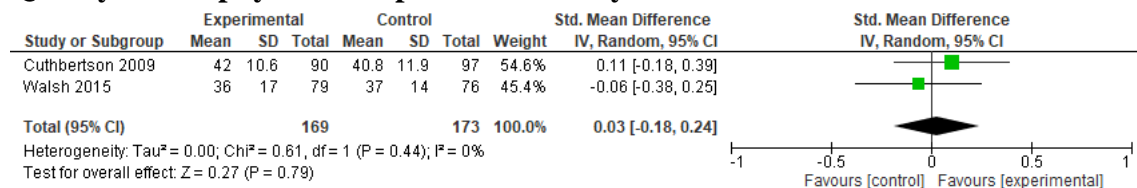
^eVery little detail given regarding the therapy received in the control group

^fAdherence to the intervention was 70%

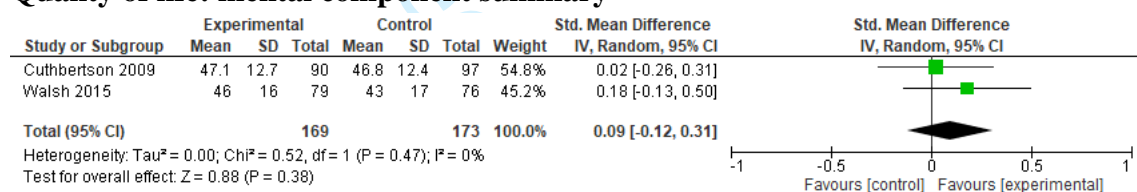
Online supplementary file 6: Additional meta-analysis for quality of life and mortality at

12 months

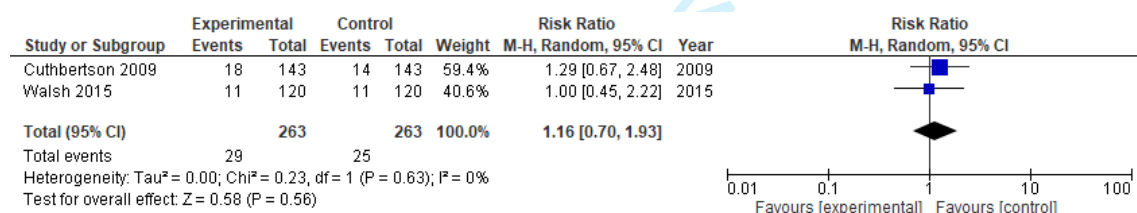
Quality of life: physical component summary



Quality of life: mental component summary



Mortality



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

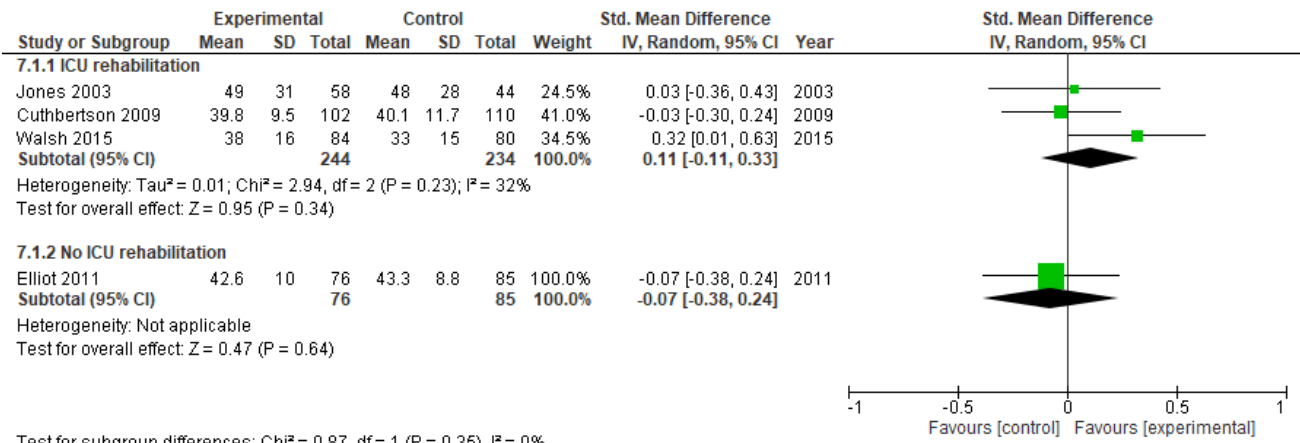
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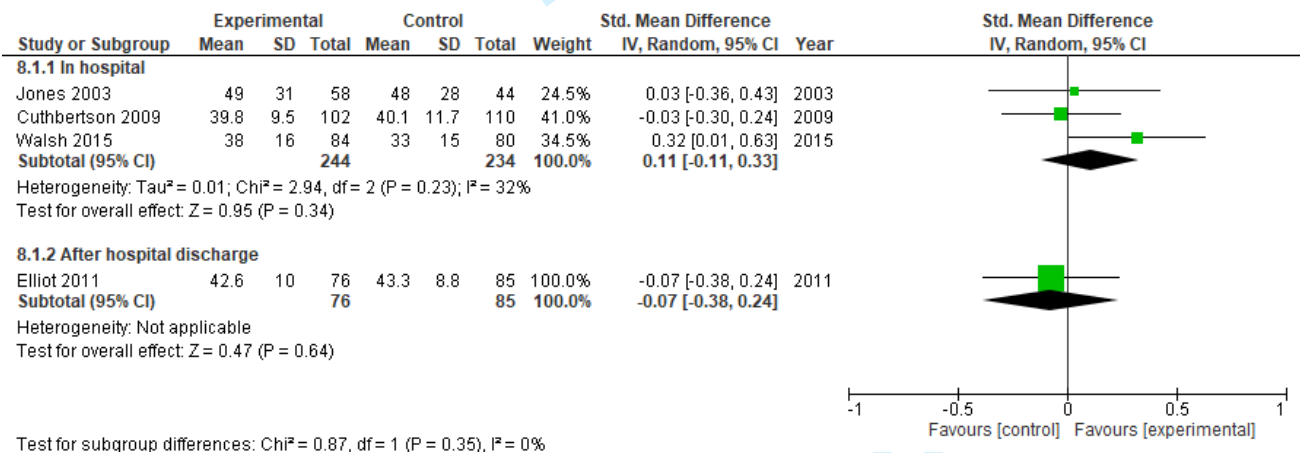
Online supplementary file 7: Subgroup analysis

A Quality of life: physical component summary

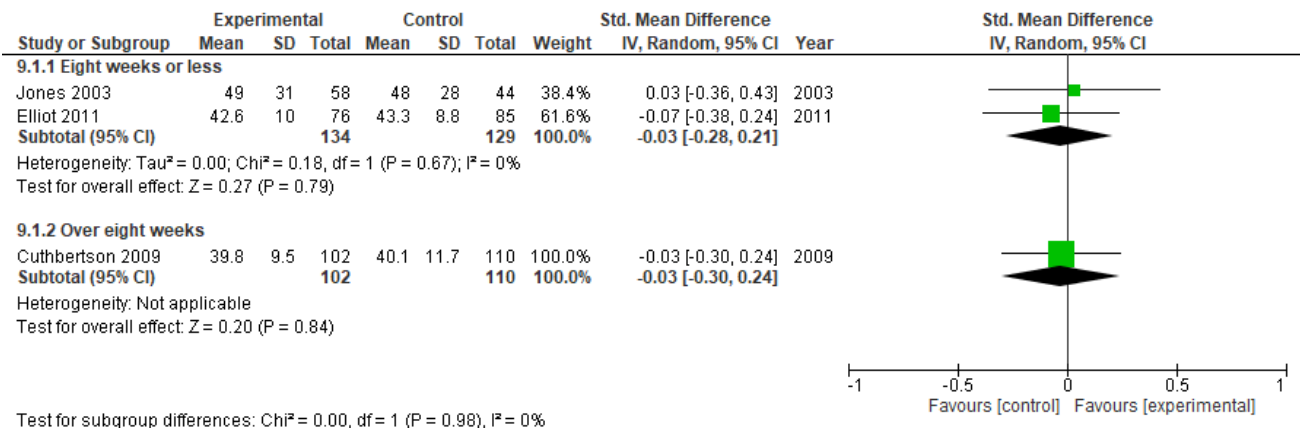
A-1 Rehabilitation practice in ICU (ICU rehabilitation before randomisation vs No ICU rehabilitation before randomisation)



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

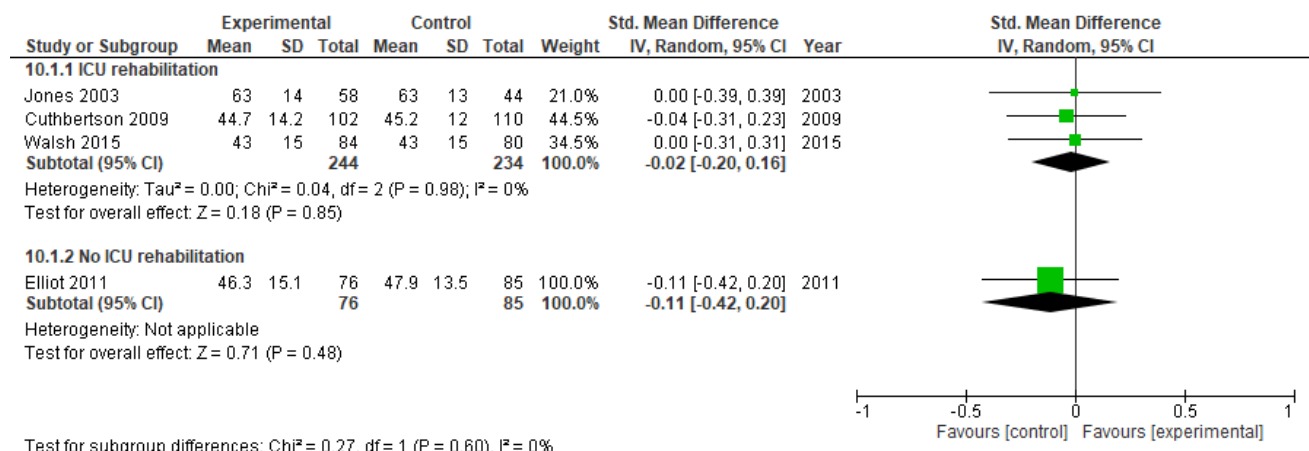


A-3. The intervention duration (eight weeks or less, and over eight weeks)

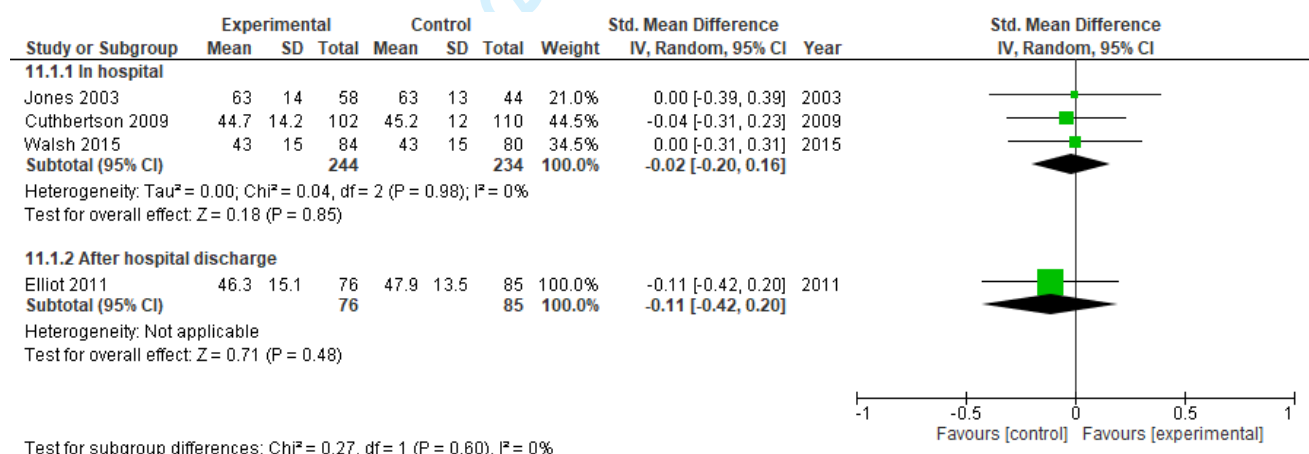


B Quality of life: mental component summary

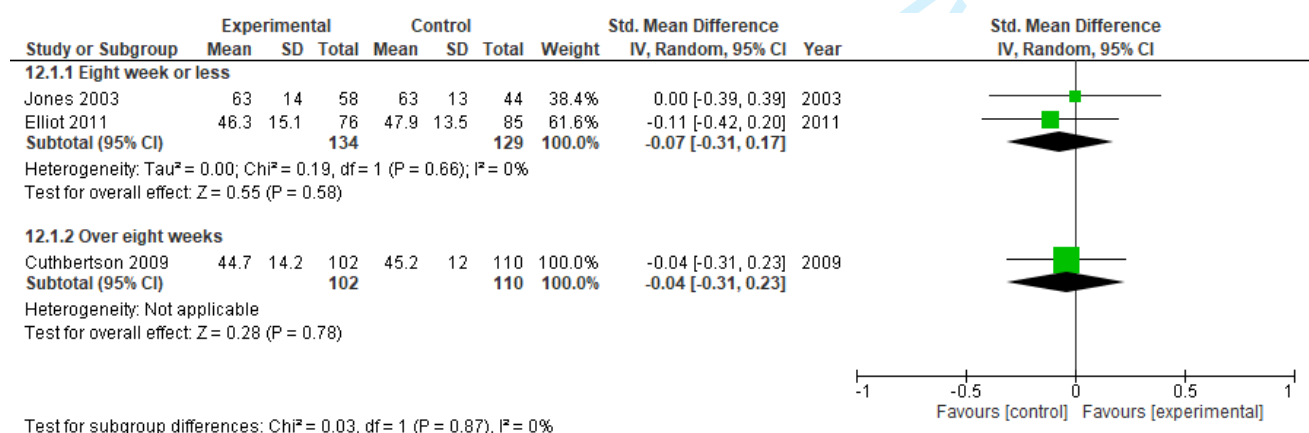
B-1. Rehabilitation practice in ICU (ICU rehabilitation before randomization vs No ICU rehabilitation before randomization)



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



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

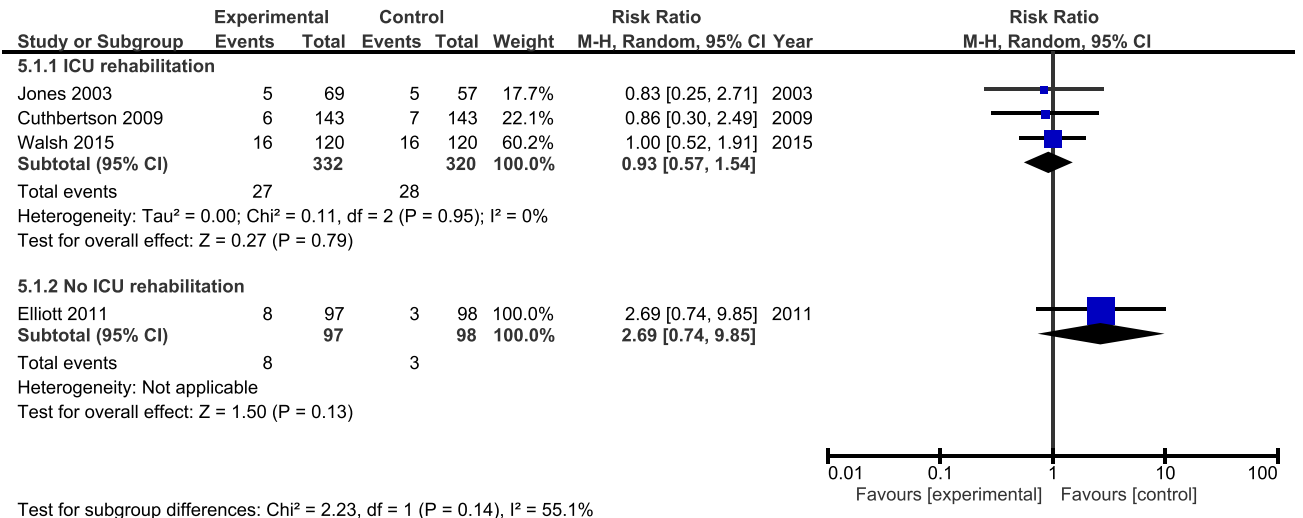


We converted median (inter quartile range) of QOL score in Walsh's study to mean (standard deviation).

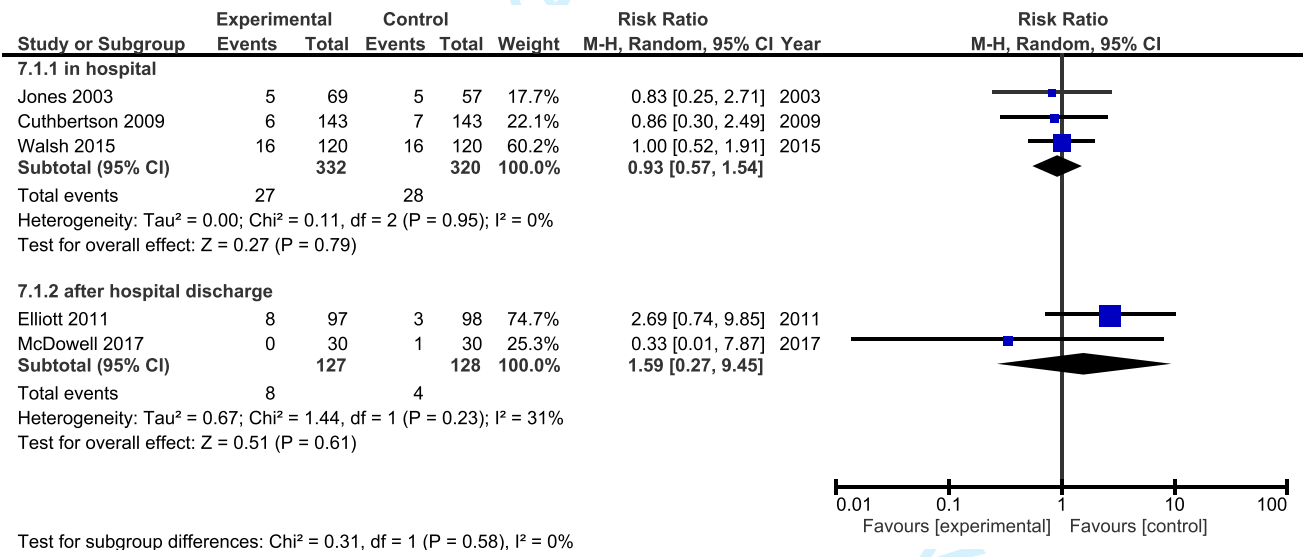
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C Long term mortality

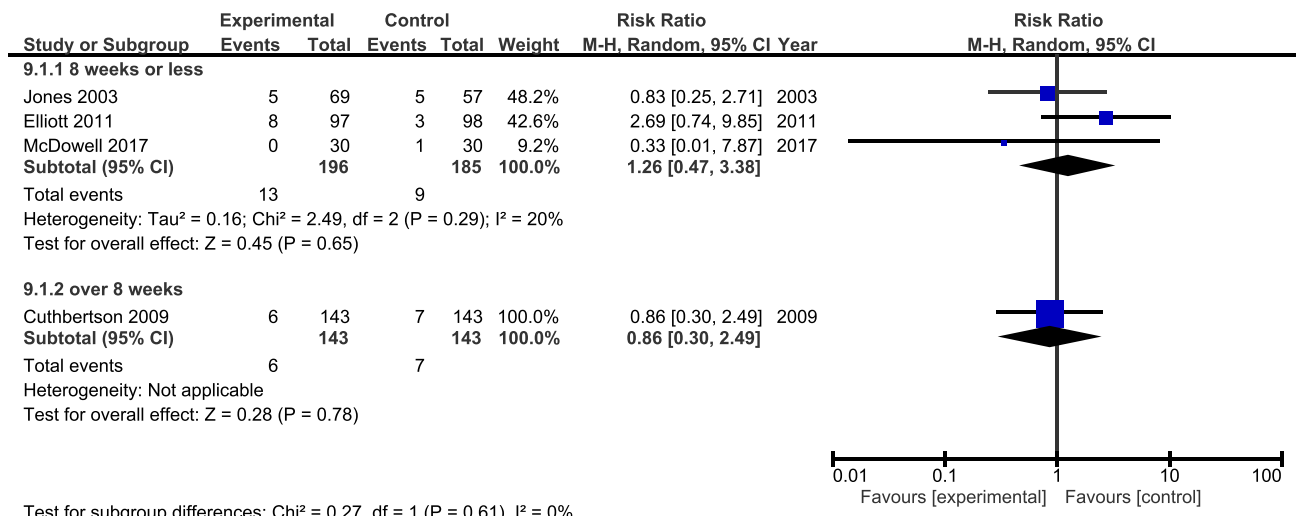
C-1. Rehabilitation practice in ICU (ICU rehabilitation before randomization vs No ICU rehabilitation before randomization)



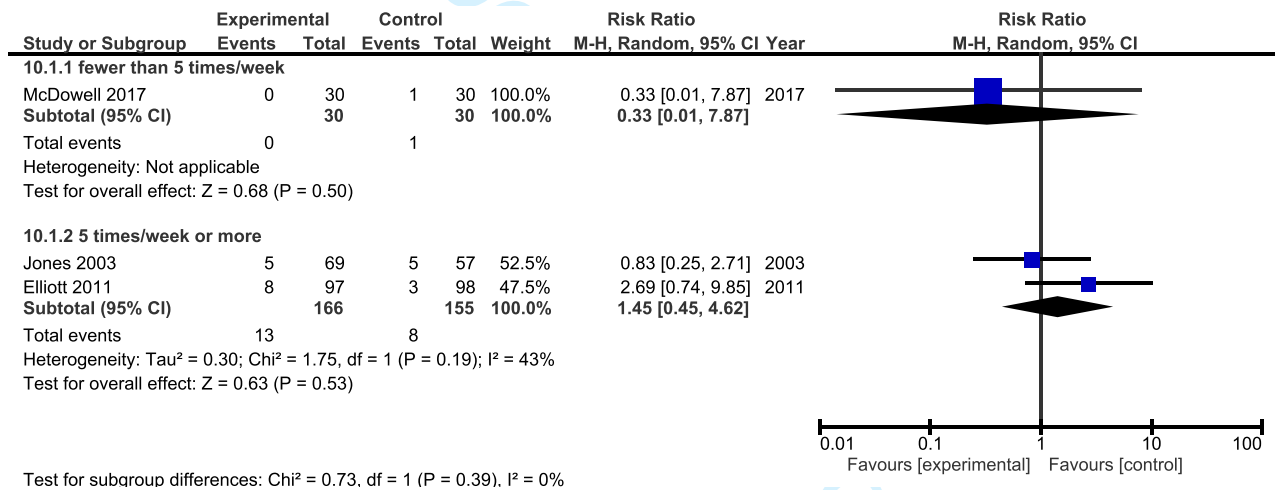
C-2 The timing of the commencement of the intervention (in hospital vs after hospital discharge)



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



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



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

