Investigating the impact of physical activity interventions on delirium outcomes in intensive care unit patients: A systematic review and meta-analysis

Authors:

Annika Jarman

Keeleigh Chapman

Sarah Vollam

Robyn Stiger

Mark Williams

Owen Gustafson

Author's accepted manuscript for an article published in:

Journal of the Intensive Care Society

DOI: https://doi.org/10.1177/175114372211036

Investigating the impact of physical activity interventions on delirium outcomes in intensive care unit patients: A systematic review and meta-analysis

Authors:

Annika Jarman

Keeleigh Chapman

Sarah Vollam

Robyn Stiger

Mark Williams

Owen Gustafson

Author's accepted manuscript for an article published in:

Journal of the Intensive Care Society

DOI: https://doi.org/10.1177/175114372211036

Abstract

Background: To investigate the impact of physical activity interventions, including early mobilisation, on delirium outcomes in critically ill patients.

Methods: Electronic database literature searches were conducted, and studies were selected based on pre-specified eligibility criteria. Cochrane Risk of Bias-2 and Risk Of Bias In Non-randomised Studies-of Interventions quality assessment tools were utilised. Grading of Recommendations, Assessment, Development and Evaluations was used to assess levels of evidence for delirium outcomes. The study was prospectively registered on PROSPERO (CRD42020210872).

Results: Twelve studies were included; ten randomised controlled trials one observational case-matched study and one before-after quality improvement study. Only five of the included randomised controlled trial studies were judged to be at low risk of bias, with all others, including both non-randomised controlled trials deemed to be at high or moderate risk. The pooled relative risk for incidence was 0.85 (0.62-1.17) which was not statistically significant in favour of physical activity interventions. Narrative synthesis for effect on duration of delirium found favour towards physical activity interventions reducing delirium duration with median differences ranging from 0 to 2 days in three comparative studies. Studies comparing varying intervention intensities showed positive outcomes in favour of greater intensity. Overall levels of evidence were low quality.

Conclusions: Currently there is insufficient evidence to recommend physical activity as a stand-alone intervention to reduce delirium in Intensive Care Units. Physical activity intervention intensity may impact on delirium outcomes, but a lack of high-quality studies limits the current evidence base.

1.Introduction

Delirium is a syndrome characterised by acute fluctuating changes in attention and cognition affecting up to 80% of patients undergoing mechanical ventilation [1]. Intensive Care Unit (ICU) delirium is independently associated with increased mortality, ICU and hospital length of stay [2,3]. ICU delirium results in long-term cognitive impairments in up to 70% of ICU survivors [1,4].

Delirium pathophysiology remains poorly understood, however both iatrogenic (drugs) and environmental factors (e.g. immobilisation) may contribute [5]. Numerous hypotheses including neuro-inflammation and neurotransmitter imbalance have been proposed to inform potential treatment strategies [6,7].

Delirium and physical activity (PA) are closely linked as immobility and functional decline have been identified as potential risk factors [5]. PA encompasses a variety of interventions such as exercise, rehabilitation and mobilisation that can improve functional outcomes and minimise critical illness morbidity [8]. In non-ICU patients, PA has been shown to provide neuroprotective effects by increasing neurotransmitter and anti-inflammatory mediator release and synaptic transmission facilitation [9]. In older adults' PA can also increase cerebral blood flow and oxygen extraction efficiency, resulting in improved cognition [10]. Alongside physical effects, it is hypothesised that the psychosocial aspects of mobility may also aid preserving cognitive function during critical illness [10].

Early mobilisation (EM) currently has no defined consensus but is thought to be the initiation of a form of PA within the first 2 to 5 days of critical illness [11]. PA encompassing EM is recommended in International guidelines to reduce negative critical illness outcomes by coordinating better ICU care [12,13]. Within these guidelines the ABCDE/F (A-E/F) bundle has been created to minimise negative consequences such as delirium during ICU stay [14]. In particular, the 'E' bundle aspect recommending EM to reduce delirium and improve physical outcomes.

The effectiveness of the A-E/F bundle has previously been evaluated but there are few reviews investigating the contribution of the individual bundle elements on delirium [15–17]. A 2020 systematic review investigated delirium outcome reporting in prevention or treatment studies but did not specifically focus on EM trials outside of an A-E/F bundle [18]. A

systematic review investigating multi-component non-pharmacologic strategies by Rossom and colleagues in 2011 highlighted the need to investigate individual bundle elements, to establish which components are most successful in delivering positive outcomes [19].This could enable more cost-effective treatment delivery [19]. While it is thought that all the A-E/F bundle components interlink to provide an effective treatment, evaluating individual components will also inform intervention prioritisation.

Within ICU literature numerous questions remain regarding the optimal type, timing, and intensity of PA interventions. The majority of A-E/F bundle recommendation papers tend to utilise only two studies as evidence for the impact PA has on delirium [20,21]. As awareness of long-term delirium consequences on ICU survivors has grown, further studies investigating ICU PA interventions on delirium have recently been published [22,23]. These studies have yet to be synthesised together to establish any correlation between PA and delirium. Evaluating PA interventions will also help inform the optimum type and delivery to positively impact delirium.

This systematic review aimed to investigate the impact of PA interventions, including EM, on delirium outcomes in ICU patients.

2.Methods

A protocol for this review was registered prospectively on PROSPERO in November 2020: CRD 42020210872 (https://www.crd.york.ac.uk/prospero/). The methodology is reported according to the updated 2020 PRISMA guidelines [24]. See Supplementary material for checklist.

2.1 Eligibility criteria

Studies that recruited participants aged over 18 admitted to ICU were eligible for inclusion. Studies including participants with pre-existing cognitive impairments prior to admission and non-ICU patients were excluded.

The target intervention was PA which could be delivered independently but not as part of an established A-E/F bundle or deemed, by the authors, to be part of a delirium prevention bundle. Studies including PA as part of interventions listed in Supplementary material were

excluded. For the comparator group, studies delivering no intervention or usual care as defined in the protocol were considered.

Eligible study designs included randomised controlled trials (RCT), cohort, retrospective and cross-sectional studies assessing PA for prevention or management of ICU delirium. Non-English studies were excluded. Studies with interventions beginning outside ICU were not included. Table 4 (Supplementary material) details further inclusion and exclusion information.

The primary outcome of interest was delirium incidence, defined as a positive measurement using a validated delirium screening tool such as Confusion Assessment Method for the ICU (CAM-ICU) or Intensive Care Delirium Screening Checklist (ICDSC) as recommended in the Pain, Agitation, Delirium, Immobility and Sleep disruption guidelines [12]. Studies using non-validated delirium assessment tools were excluded. Secondary outcomes included delirium duration, prevalence, severity, and number of delirium-coma free days.

2.2 Information sources

The following databases were searched through Healthcare Databases Advanced Search (AMED, BNI, CINAHL, EMBASE, MEDLINE, PSYCHinfo, PubMed). Other databases were searched through their respective individual platforms, Physiotherapy Evidence Database (PEDro) and Cochrane Library (CENTRAL). Searches included all study types published until 30th November 2020 and were updated in November 2021 with no limits placed.

2.3 Search strategy

Key terms and subject headings were used to search the above databases with assistance from a specialist healthcare librarian. The Boolean operators of 'AND' and 'OR' were employed to narrow and broaden the search, respectively. Asterisks were used where there could be multiple spellings or endings to a search term. Full search strategies are in Supplementary material. Included studies references were manually screened to identify studies not identified via the electronic database search. Other literature was identified via open grey (http://www.opengrey.eu). Relevant unpublished literature, ongoing studies or pre-print papers were identified from ClinicalTrials.gov, International Clinical Trials Registry and ResearchGate.

2.4 Selection process

Titles and abstracts of retrieved studies were exported into Rayyan where duplicates were automatically removed [25]. Rayyan is a free web tool designed to assist screening and selection processes [25] .Two independent reviewers screened study titles and abstracts of the retrieved studies (AJ+KC) prior to meeting, with each reviewer blinded to the other's decision. Any eligibility discrepancies were first discussed between the two reviewers, if no agreement was reached a third reviewer was consulted (OG). The full text of any citation considered potentially relevant by either reviewer was retrieved and screened to confirm eligibility.

2.5 Data extraction

Data extracted from eligible studies included study design, setting, intervention and control details, participant demographics, delirium measurements and results (Supplementary material).

2.6 Risk of bias

Tools specific to study design were used to assess risk of bias (ROB). To improve inter-rater reliability the two reviewers (AJ+KC) undertook calibration exercises of the tools before independently appraising each study then discussing discrepancies that arose. The third reviewer (OG) was available if no consensus could be achieved via discussion.

For RCTs both the Cochrane Risk of Bias 2 (ROB2) and Physiotherapy Evidence Database (PEDro) tools were used [26,27]. Due to its physiotherapy relevance and having demonstrated good reliability [28],the PEDro tool was initially utilised. However, whilst trialling the tool, the reviewers decided that it did not investigate each bias component as thoroughly as the ROB2. Therefore, ROB2 results were utilised for the main results and PEDro scores are available in Supplementary material.

For non-RCTs the Cochrane "Risk Of Bias In Non-randomised Studies-of Interventions" (ROBINS-I) was used [29]. The ROBINS-I tool allowed for some guidance on weighting of non-RCTs, in the overall results of a review, with those deemed as having a low ROB possibly being comparable to an RCT.

2.7 Synthesis methods

A meta-analysis was completed using Review Manager (RevMan 5.4, London, UK) for the dichotomous outcome of delirium incidence with a meta-analysis for delirium duration also being considered [30]. A random-effects model was used to calculate pooled estimates. Heterogeneity between studies was determined through the I^2 statistic. Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was used to assess the quality of evidence gained from the meta-analysis and classified into 4 possible ratings: very low, low, moderate or high [31]. Narrative synthesis was undertaken for other outcome variables of interest.

3.Results

3.1 Study selection and characteristics

Study selection is detailed in the PRISMA flow sheet (Figure 1). After excluding duplicates, 3014 papers were screened for eligibility. Subsequently 27 full texts were retrieved with 11 meeting the inclusion criteria. One further study was included after reference screening. The 12 included studies (Table 1) comprised of 10 RCTs [20,22,23,32–38] one observational case-matched control [39] and one before-after quality improvement study [21] . The two reviewers reached consensus regarding study inclusion, data extraction, quality, and ROB assessments (100% agreement), without recourse to a third reviewer.

Overall, 1460 patients were included across the studies (Table 1). Sample sizes varied from 16 [39] to 312 participants [32]. One study had an age requirement of 65 years and above [33]. All other studies included participants over 18 years with varying intervention start times from minimum of 24 hours [33,37] to maximum 96 hours post admission [22] (Supplementary material).

3.2 PA interventions

PA interventions differed between studies (Table 3), most commonly delivered as a progressive early mobility protocol [20–22,35–37,39] . Two studies investigated range of movement (ROM) exercises [21,37] , two studies used in-bed cycling [22,39] and two used functional electrical stimulation (FES)-cycling [32,38]. PA dosage was clearly stated in seven studies [21,23,32,33,37–39] ranging from three minutes to two hours. Control interventions were mainly reported as "usual care", although was not defined clearly by most studies and normally included some form of low-grade PA. Two studies did not involve PA in their control group [20,21].

Of the twelve included studies, six interventions were delivered specifically by Physiotherapists (PT) or Occupational Therapists (OT) (Table 3) [20–22,32,38,39]. In three studies, the interventions were delivered by either registered nurses (RN), physicians or a primary researcher whose primary role was undefined. Both in-bed cycling studies utilised a RN for the in-bed cycling and PT for the functional activity [22,39]. In one study, sessions delivered by PTs or OTs lasted twenty-three minutes on average compared to fifteen when the same intervention was delivered by physicians or nurses [36].

3.3 Delirium measurement

Most of the studies [20–22,32–34,36–39] used CAM-ICU to measure delirium (Table 1). One study [23] used the ICDSC, and one multi-centre study utilised both tools [35]. Delirium measurements varied in assessment frequency from once to three times daily, at differing times of the day.

3.4 ROB

Figure 2 presents the included RCTs ROB2 assessments. Five studies were judged to be at high ROB either through having high risk in one domain or some concerns in multiple domains [23,33–35,37].

Bias for non-RCTs using ROBINS-1 is reported in Table 2. Both studies were judged at moderate ROB and therefore were not comparable to the RCTs. [21,39].

3.5 Delirium Incidence

Nine studies investigated delirium incidence [20,21,29–31,35,36] with variation in how incidence was reported or categorised. Seven of the nine studies were included in a meta-analysis [21,29,30,32,34–36] (Figure 3). The other two papers were excluded as one totalled delirious days across patients meaning incidence was unable to be calculated [21]. The other study did not report actual delirium post intervention but rather sub-delirium or no-delirium incidence [23]. The pooled relative risk for incidence was 0.85 (0.62-1.17) which was not statistically significant in favour of physical activity interventions. Heterogeneity may have been moderate (I^2=51%, p0.06). This could be explained by the inconsistency in individual study effect estimates and validates the choice to use a random effects model.

3.6 Delirium duration, severity, prevalence, and delirium-coma free days

Six studies investigated delirium duration in days [20,22,23,37–39] with one study examining it in hours [33] (Table 1). Meta-analysis was not possible for this outcome due to insufficient summary statistics, so a narrative synthesis was performed. One study no longer assessed for delirium once a positive CAM-ICU score was detected meaning it wasn't possible to calculate duration or compare to other studies [32]. Three comparative studies found statistically significant improvements in favour of PA interventions for delirium duration ranging from a median difference of 0 to 2 days [19,22,32]. One study found no statistically significant difference [32]. Two studies reported their delirium outcome as the number of delirium-coma free days within the first 30 or 28 days of a patient's ICU stay [35,36]. None of the studies reported any outcomes on delirium severity or prevalence.

3.7 Quality of Evidence

Table 4 represents the GRADE summary of findings table with the meta-analysis quality of evidence downgraded to low due to risk of bias and inconsistency.

4. Discussion

This review has investigated PA intervention impact on delirium outcomes in ICU patients from 12 eligible studies. While the impact of PA on delirium outcomes was not the primary outcome of interest or focus for the majority of studies, when assessing the five highest quality papers only one demonstrated a significant benefit of PA on delirium duration ($p=0.03$) [20]. The other four high quality papers all had very small sample sizes limiting the certainty of effect of PA interventions on delirium outcomes in ICU patients [22,32,36]. There is weak evidence that PA may shorten delirium duration and lead to reduced risk of becoming delirious, but the quality of evidence is considered low with no statistical significance shown in meta-analysis.

Our review is the first to fully investigate the sole contribution of PA interventions on ICU delirium outcomes. This review demonstrates that there is insufficient evidence to recommend one type or dosage of PA over another. These results agree with a review by Haley and colleagues who investigated PA impact on delirium outcomes in hospitalised patients both in and out of ICU [40]. They also found extensive variation in intervention type, frequency, and intensity, concluding an inability to recommend PA as a sole intervention over a multi-component bundle. PA delivery differences and whether physiotherapy was

included in usual service delivery across the different services and countries may have affected the included studies results and generalisability.

One proposed hypothesis of the pathophysiology of delirium is of dysregulated cytokines causing a systemic inflammatory response [41]. Gleeson et al (2011) reported how moderately intense PA could produce an anti-inflammatory response in healthy individuals [42]. PA intensity has previously been studied in ICU and conclusions drawn that passive leg cycling is of an insufficient intensity to elicit systemic changes to produce an anti-inflammatory response [43]. In contrast FES-cycling can potentially produce sufficiently high intensity to elicit anti-inflammatory effects and therefore could impact delirium [43]. This is in agreement with the significant reduction in delirium duration reported by Parry and colleagues in their FES-based study ($p=0.042$) [39]. However, while duration was significantly reduced, no difference was found in delirium incidence and the study was judged at moderate ROB [39]. Usual care has evolved significantly since Schweickert et al (2009) demonstrated the impact early mobilisation can have on outcomes such as delirium. While usual care was often not elaborated on, most studies included some form of PA which may contribute to the lack of significant changes in incidence or duration that were found. Some studies specifically altering PA intensity between groups demonstrated reductions in both delirium duration [20] status [21] and incidence [34]. However further research into how PA intensity may impact delirium is required.

Intervention delivery time may be impacted by professions. Previous studies report greater perceived mobilisation barriers for ICU nurses with safety concerns classed as the main limitation [44,45]. Overall, PA delivery by non-PTs may be reduced compared to interventions conducted by PTs as seen in the 8-minute difference reported by Brummel and colleagues [33]. With ICU patients, who have a lower physiological reserve than healthy patients, such time differences could result in differing intensities being achieved emphasising this could be a potential factor in delirium prevention.

This review has several strengths, including methodology transparency by registering the study protocol prior to database searching [46]. It is one of few reviews not investigating the A-E/F bundle, but instead exploring the EM aspect as per recommendations from previous reviews [19]. The use of two reviewers independently searching and analysing the extracted data prior to discussion further improves this reviews rigour.

This review was limited by the exclusion of non-English language studies, potentially missing relevant studies in other languages. One of the papers included was identified and found in pre-print as part of the ROB assessments given its relevance to the question of interest [37]. Post ROB completion it has now been published with a change in methodological approach from an RCT to a pilot RCT therefore investigating evening mobilisation feasibility as its primary aim rather than proving the effect of mobilisation on delirium outcomes [47]. This means the primary outcomes also changed from delirium duration to feasibility measures. Therefore, results presented for this study should be interpreted with caution. Wide variation in delirium outcome reporting made data synthesis challenging, as also found in a recent systematic review by Rose et al (2020) [18]. Increased awareness of the variation in delirium assessment and documentation methods has led to the recent creation of an established delirium core outcome set (COS). This aims to improve comparisons regarding effective delirium interventions in future studies [48].

Current evidence is limited as delirium is generally only explored as a secondary outcome alongside poor intervention reporting and a lack of clarity about which PA intervention is most effective at impacting ICU delirium. Overall, there is insufficient high-quality evidence to suggest that PA is beneficial as a stand-alone treatment for delirium. In future, reviews may be better able to compare interventions given the recent focus on delirium and PA COS [48,49]. Future, well designed and powered studies should investigate altering PA type, frequency, and intensity. Adequate and transparent reporting of delivered interventions to enable study replication and synthesis to inform best practise is also recommended.

5. Conclusion

In summary there is limited evidence to support the use of PA as stand-alone intervention to impact delirium in ICU. Delirium is a highly complex condition with poorly understood pathophysiology, suggesting that A-E/F bundles are likely to benefit delirium outcomes in ICU. PA intensity shows promise regarding impact on delirium but requires further research. Future reviews should include papers using specified COS allowing for thorough meta-analyses to be conducted and firmer conclusions drawn to guide best practice.

Bibliography

1. Ouimet S, Kavanagh BP, Gottfried SB, Skrobik Y. Incidence, risk factors and consequences of ICU delirium. *Intensive Care Med* 2007; 33(1):66–73.
2. Pisani MA, Kong SYJ, Kasl S V., et al. Days of delirium are associated with 1-year mortality in an older intensive care unit population. *Am J Respir Crit Care Med* 2009; 180(11):1092–7.
3. Peres IT, Hamacher S, Oliveira FLC, et al. What factors predict length of stay in the intensive care unit? Systematic review and meta-analysis. *J Crit Care* 2020; 60:183–94.
4. Girard TD, Jackson JC, Pandharipande PP, et al. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. *Crit Care Med* 2010; 38(7):1513–20.
5. Wilson JE, Mart MF, Cunningham C, et al. Delirium. *Nat Rev Dis Prim* 2020; 6(1).
6. Cerejeira J, Firmino H, Vaz-Serra A, Mukaetova-Ladinska EB. The neuroinflammatory hypothesis of delirium. *Acta Neuropathol*. 2010;119(6):737–54.
7. Stagno D, Gibson C, Breitbart W. The delirium subtypes: a review of prevalence, phenomenology, pathophysiology, and treatment response. *Palliat Support Care* 2004; 2(2):171–9.
8. Reid JC, Unger J, McCaskell D, et al. Physical rehabilitation interventions in the intensive care unit: A scoping review of 117 studies. *J Intensive Care*. 2018; 6(1):1–12.
9. Hopkins RO, Suchyta MR, Farrer TJ, Needham D. Improving post-intensive care unit neuropsychiatric outcomes: Understanding cognitive effects of physical activity. *Am J Respir Crit Care Med* 2012; 186(12):1220–8.
10. Churchill JD, Galvez R, Colcombe S, Swain RA, et al. Exercise, experience and the aging brain. *Neurobiol Aging* 2002; 23(5):941–55.
11. Hodgson CL, Berney S, Harrold M, Saxena M, Bellomo R. Clinical review: Early patient mobilization in the ICU. *Crit Care.* 2012;17(1):1–7.
12. Devlin JW, Skrobik Y, Gélinas C, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. *Crit Care Med* 2018; 46(9).e825–73.
13. White C, Connolly B, Rowland MJ. Rehabilitation after critical illness. *BMJ* 2021;373
14. Marra. A, Ely. E., Pandharipande. P., Patel. M. The ABCDEF Bundle in Critical Care. *Crit Care Clin* 2017; 33(2):225–43.

15. Zhang S, Han Y, Xiao Q, et al. Effectiveness of Bundle Interventions on ICU Delirium: A Meta-Analysis∗. *Crit Care Med* 2021; 335–46.
16. Deng L-X, Cao L, Zhang L-N, et al. Non-pharmacological interventions to reduce the incidence and duration of delirium in critically ill patients: A systematic review and network meta-analysis. *J Crit Care* 2020; 60:241–8.
17. Kang J, Lee M, Ko H, et al. Effect of nonpharmacological interventions for the prevention of delirium in the intensive care unit: A systematic review and meta-analysis. *J Crit Care* 2018; 48:372–84.
18. Rose L, Agar M, Burry L, et al. Reporting of Outcomes and Outcome Measures in Studies of Interventions to Prevent and/or Treat Delirium in the Critically Ill: A Systematic Review. *Crit Care Med* 2020; 48(4).
19. Rossom R, Anderson P, Greer N. Evidence-based Synthesis Program Delirium : Screening , Prevention , and Diagnosis – A Systematic Review of the Evidence. Delirium Screening, Prev Diagnosis – A Syst Rev Evid 2011; 1–91.
20. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet* 2009; 1874-1882.
21. Needham DM, Korupolu R, Zanni JM, et al. Early physical medicine and rehabilitation for patients with acute respiratory failure: a quality improvement project. *Arch Phys Med Rehabil* 2010; 91(4):536–42.
22. Nickels MR, Aitken LM, Barnett AG, et al. Effect of in-bed cycling on acute muscle wasting in critically ill adults: A randomised clinical trial. *J Crit Care* 2020; 59:86–93.
23. Farzammanesh A, Jahani S, Rashidi M, et al. The effect of joints range of motion exercises on delirium prevention in patients admitted to intensive care units. *Int J Pharm Phytopharm Res* 2020;10(1):105-113.
24. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* 2021; 372.
25. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Syst Rev* 2016; 5(1):1–10.
26. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016; 355:4–10.
27. de Morton NA. The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. *Aust J Physiother* 2009; 55(2):129–33.
28. Maher CG, Sherrington C, Herbert RD, et al. Reliability of the PEDro scale for rating

quality of randomized controlled trials. *Phys Ther* 2003; 83(8):713–21.

29. Sterne JAC, Savović J, Page MJ, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; 366:1–8.
30. RevMan User guide. Welcome to RevMan 5 . 4. 2020;4(May). Available from: https://training.cochrane.org/system/files/uploads/protected_file/RevMan5.4_user_guide.pdf (2020 accessed 1 January 2020)
31. Granholm A, Alhazzani W, Møller MH. Use of the GRADE approach in systematic reviews and guidelines. *Br J Anaesth* 2019; 123(5):554–9.
32. Fossat G, Baudin F, Courtes L, et al. Effect of in-bed leg cycling and electrical stimulation of the quadriceps on global muscle strength in critically ill adults: A randomized clinical trial. *J Am Med Assoc* 2018; 320(4):368–78.
33. Karadas C, Ozdemir L. The effect of range of motion exercises on delirium prevention among patients aged 65 and over in intensive care units. *Geriatr Nurs* 2016; 37(3):180-185.
34. Winkelman C, Sattar A, Momotaz H, et al. Dose of Early Therapeutic Mobility: Does Frequency or Intensity Matter? *Biol Res Nurs* 2018; 20(5):522–30.
35. Nydahl P, Günther U, Diers A, et al. PROtocol-based MObilizaTION on intensive care units: stepped-wedge, cluster-randomized pilot study (Pro-Motion). *Nurs Crit Care* 2020; 25(6):368–75.
36. Brummel NE, Girard TD, Ely EW, et al. Feasibility and safety of early combined cognitive and physical therapy for critically ill medical and surgical patients: the Activity and Cognitive Therapy in ICU (ACT-ICU) trial. *Intensive Care Med* 2014 ; 40(3):370–9.
37. Nydahl P, McWilliams D, Weiler N, et al. Mobilization in the evening reduces delirium in critically ill patients: the MENTAL randomized, controlled trial. 2019; 1–22.
38. Berney S, Hopkins RO, Rose JW, et al. Functional electrical stimulation in-bed cycle ergometry in mechanically ventilated patients: A multicentre randomised controlled trial. *Thorax* 2021; 76(7):656–63.
39. Parry SM, Berney S, Warrillow S, et al. Functional electrical stimulation with cycling in the critically ill: A pilot case-matched control study. *J Crit Care* 2014; 29(4):695.
40. Haley MN, Casey P, Kane RY, et al. Delirium management: Let's get physical? A systematic review and meta-analysis. *Australas J Ageing* 2019; 38(4):231–41.
41. Simone MJ, Tan ZS. The Role of Inflammation in the Pathogenesis of Delirium and

Dementia in Older Adults: A Review. *CNS Neurosci Ther* 2011; 17(5):506–13.

42. Gleeson M, Bishop NC, Stensel DJ, et al. The anti-inflammatory effects of exercise: Mechanisms and implications for the prevention and treatment of disease. *Nat Rev Immunol* 2011; 11(9):607–10.
43. Medrinal C, Combret Y, Prieur G, et al. Comparison of exercise intensity during four early rehabilitation techniques in sedated and ventilated patients in ICU: A randomised cross-over trial. *Crit Care* 2018; 22(1):1–8.
44. Lewis M, Cumming L, Twose P. Comparison of perceptions and barriers to mobilization in critical care: A comparison of nursing staff and physiotherapists—A single-site service evaluation. *Nurs Crit Care* 2021; 1–8.
45. Garzon-Serrano J, Ryan C, Waak K, et al. Early mobilization in critically ill patients: Patients' mobilization level depends on health care provider's profession. *PM R* 2011; 3(4):307–13.
46. The PLoS Medicine Editors. Best practice in systematic reviews: The importance of protocols and registration. *PLoS Med* 2011; 8(2):1–2.
47. Nydahl P, McWilliams D, Weiler N, et al. Mobilization in the evening to prevent delirium: A pilot randomized trial. *Nurs Crit Care* 2021; 1–9.
48. Rose L, Burry L, Agar M, Campbell NL, et al. A Core Outcome Set for Research Evaluating Interventions to Prevent and/or Treat Delirium in Critically Ill Adults. *Crit Care Med* 2021; 1–12.
49. Connolly. B, Denehy. L, Hart N, et al. Physical Rehabilitation Core Outcomes In Critical illness (PRACTICE): Protocol for development of a core outcome set. *Trials* 2018; 19(1):1–8.

Tables and figures.

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flow diagram, n = number.

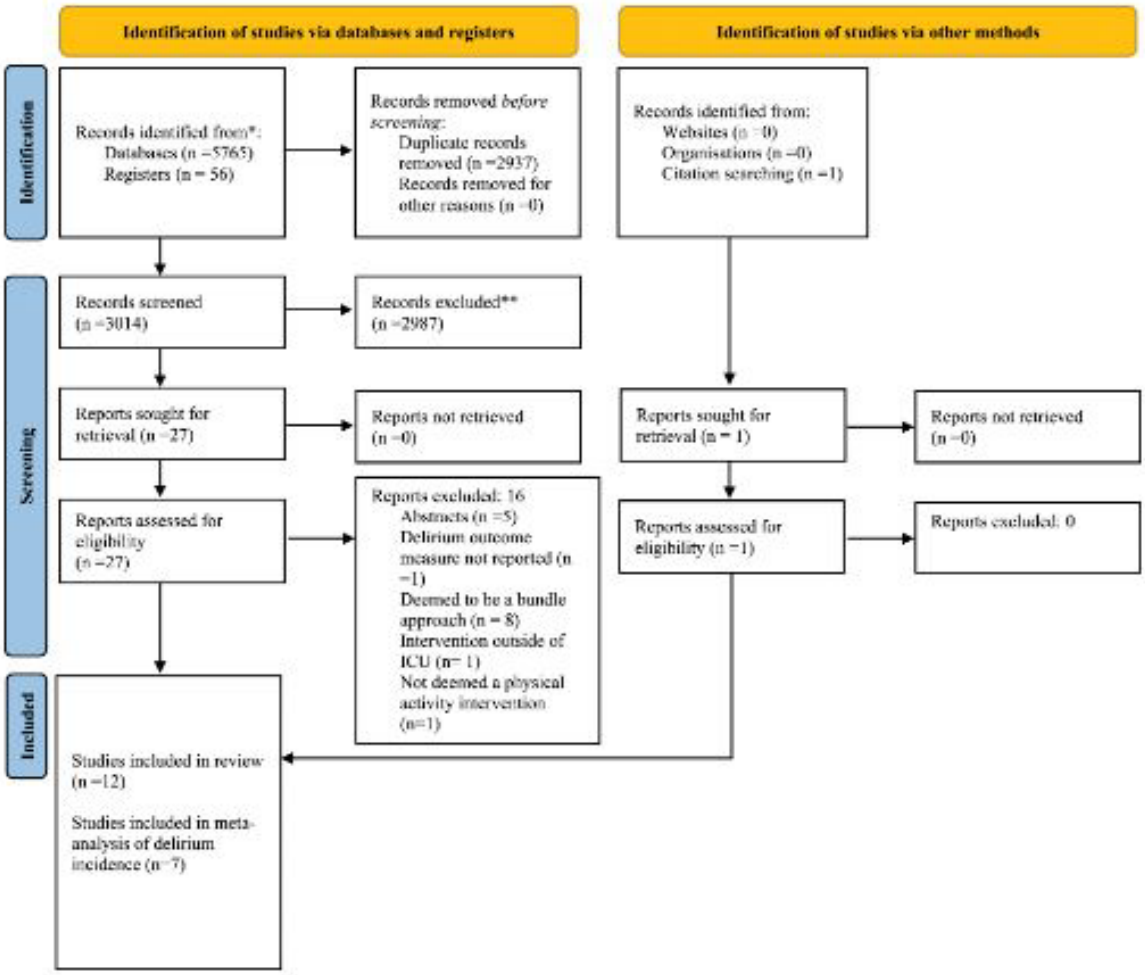


Figure 2. Cochrane Risk of Bias 2 judgements for included randomised control trials. Red= High risk of bias, Yellow = medium risk of bias, green =low risk of bias.

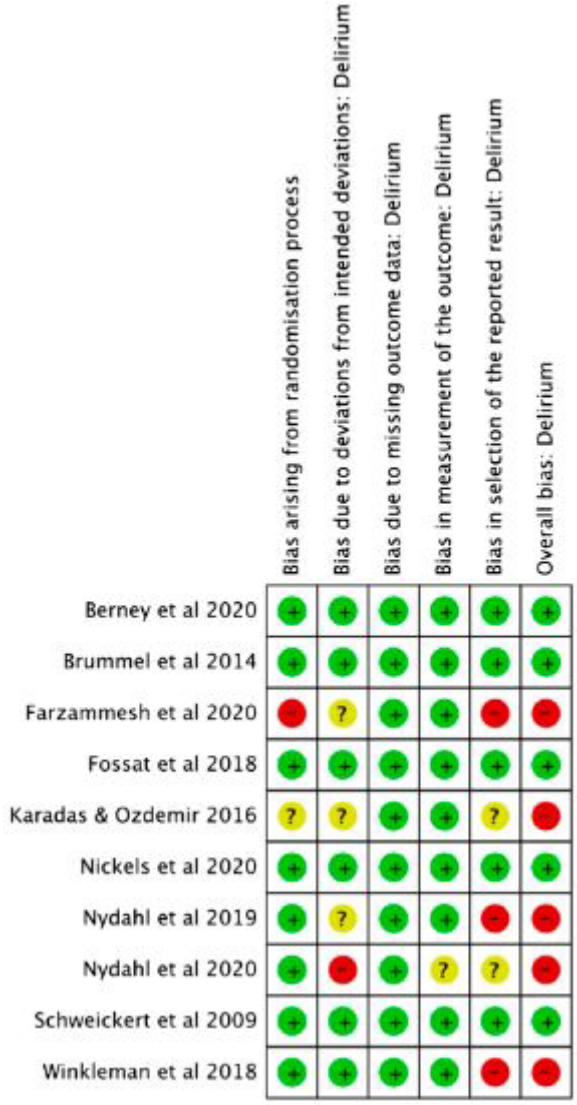
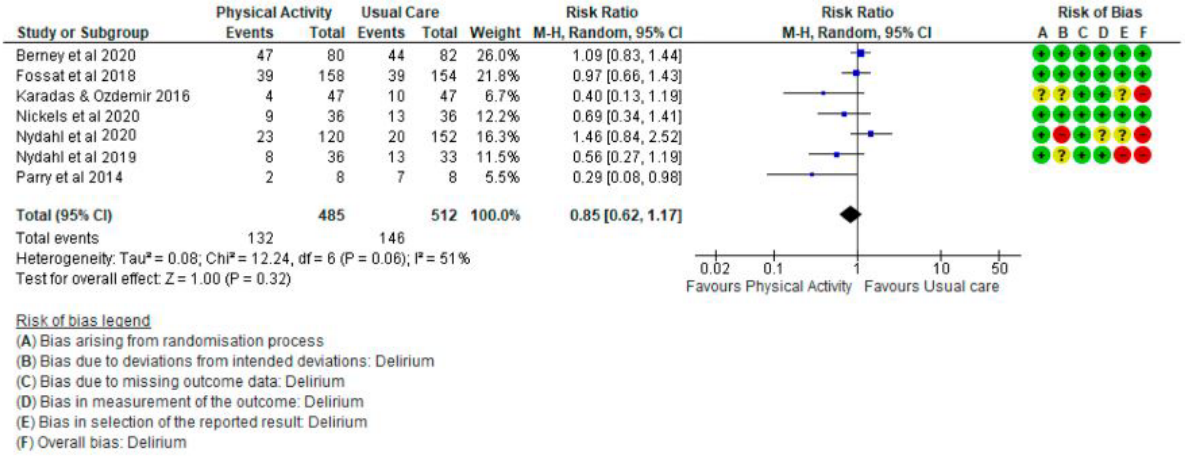


Figure 3. Meta-analysis for delirium incidence with physical activity versus usual care.



Risk of bias legend
(A) Bias arising from randomisation process
(B) Bias due to deviations from intended deviations: Delirium
(C) Bias due to missing outcome data: Delirium
(D) Bias in measurement of the outcome: Delirium
(E) Bias in selection of the reported result: Delirium
(F) Overall bias: Delirium

Table 1. The GRADE summary of findings.

Summary of findings for the main comparison. Physical activity versus usual care for critically ill adults

Physical activity compared to usual care for intensive care unit patients
Patients or population: Critically ill adults
Settings: Intensive care units
Intervention: Physical activity
Control: Usual care

Outcome	Anticipated absolute effect (95% CI)	Relative effect (95%)	No. of participants	Quality of evidence (GRADE)	Comments
Delirium incidence (presence) in ICU	2 studies that did not provide sufficient data reported no statistically significant difference between groups for delirium incidence	Relative risk of 0.85 [0.62,1.17]	997 (7 studies)	**[a]low	—
Delirium duration (days) in ICU	Data not sufficient to estimate absolute effect	—	678 (6 studies)	—	Only 1 study investigating duration reported means and SD.[b] The other 6 studies[c] reported medians and IQR so inappropriate to conduct a meta-analysis or GRADE summary

ICU: Intensive care unit, GRADE: Grading of Recommendations Assessment, Development and Evaluation.
GRADE working group grades of evidence
High quality: The authors have a lot of confidence that the true effect is similar to the estimated effect
Moderate quality: The authors believe that the true effect is probably close to the estimated effect
Low quality: The authors believe the true effect might be markedly different from the estimated effect
Very low quality: The authors believe the true effect is probably markedly different from the estimated effect
[a]Downgraded one point for risk of bias (selective reporting, deviations from intended deviations) and one point for inconsistency (clinical and statistically moderate).
[b]Farzammensh et al. 2020 study reported values in Mean and SD.
[c]Berney et al. (2020); Karadas and Ozdemir (2015); Nickels et al. (2020); Nydahl et al. (2019); Parry et al. (2014); Schweickert et al., 2009.

Table 2. Description of studies physical activity interventions in ICU (N=12).

Author /Year	Intervention details	Duration	Control /Comparator	Who carried out the intervention
Berney et al (2020)	Usual care plus FES-cycling with synchronised stimulation of four muscle groups One leg of participant randomised to FES-cycling and the other leg to cycling without FES.	Up to 1 h at least 5 × week for 28 days or ICU discharge If 20 sessions not occurred at this time intervention continued until 20 sessions were achieved	Usual care including rehabilitation with mobilisation such as sitting out of bed, marching on the spot and mobility training Aim was to maximise physical function	PT
Brummel et al (2014)	2 groups Once daily physical therapy only Twice daily cognitive therapy and once daily PT Progressed from PROM through to ambulation based on RASS score and ability	Mean of 15 min when delivered by physicians/RN Mean of 23 min when delivered by PT/OT Received intervention most days	Usual care Mobility commenced once ordered by treating clinicians PT sessions 1–2 x week Resulted in 1 session every 6 days	Physicians/RN PT/OT
Farzammenesh et al (2020)	Joint ROM performed twice daily until discharge (morning and evening) Passive, active-assisted and active ROM as able Began when vital signs stable and anaesthetist authorised commencement	Each movement was performed 10 times for 30 s in full range of major UL and LL joints	Usual care Joint ROM only performed with MV patients after 3–4 days in ICU with physician order Unclear amount as inconsistencies with protocol	Researcher
Fossat et al (2018)	Leg cycling, electrical muscle stimulation and usual care Leg cycling could be done in or out of bed Electrical stimulation of quadriceps Standardised early mobilisation progressing from PROM through to ambulation	Leg cycling 15 min Electrical stimulation 50 min Weekdays only	Usual care Standardised early mobilisation progressing from PROM through to ambulation Weekdays only	PT
Karadas and ozdemir (2015)	Joint ROM performed in supine daily until discharge Passive, active assisted, or active based on response to commands	10 reps for 30 min on UL and LL	Usual care Not specified beyond routine clinical practice	Researcher
Needham et al (2010)	Post 4-months QI period Functional based activities progressing from SOEOB to ambulation	N/A	3-months Pre-QI period Usual care "Bed rest" standard prescribed activity level RNs reposition every 2 h No routine PT/OT input but available if requested	PT/OT (specifically employed to implement intervention)

Table 2 (cont.) Description of studies physical activity interventions in ICU (N=12).

Nickels et al (2020)	In-bed cycling and usual care Once daily in bed cycling progressing from passive to resisted based on patient's ability and consciousness Plus, daily functional activities progressing from SOEOB through to ambulation	In bed cycling delivered for maximum of 30 min up to 6 days per week	Usual care Daily functional activities progressing from SOEOB through to ambulation	In bed cycling delivered by researcher (registered PT) Functional activities for both groups delivered by PTs
Nydahl et al (2019)	Early mobilisation in the evening Mobilised between 21:00 and 23:00 Progressed from PROM to ambulation alongside soothing activities	Minimum 3 min to maximum 2 h on up to 3 consecutive evenings	Usual care Mobilised during the day Progressed from PROM to ambulation Could also be mobilised in the evening on individual judgement of bedside nurse	Mobilisation team (trained ICU RN, PT and complemented by medical professionals
Nydahl et al (2020)	Protocol based mobilisation Progressed from SOEOB through to ambulation Based on traffic light safety system	N/A	Usual care Mobilisation based on clinician's decision	PT or RN
Parry et al (2014)	FES-cycling with routine PT FES cycling involved stimulating LL muscles at specific points during cycling phases Early functional activities from SOEOB to ambulation	FES-cycling 20–60 min daily 5 × week Functional activities. Up to 15 min daily	Usual care SOEOB through to ambulation 15 min daily	Researcher (registered PT) delivered FES-cycling Other PTs delivered functional activities
Schweickert et al (2009)	Early exercise and mobilisation Progression from PROM through to ambulation	Median delivery time 32 min	Usual care PT/OT only delivered once ordered by primary care team PT not routine for anyone MV for <2 weeks Median delivery time 0 min	PT/OT
Winkelman et al (2018)	Twice daily ETM Progressed from PROM through to ambulation Low intensity = in bed or passive transfer Moderate intensity = SOEOB to ambulation	N/A	Once daily ETM Progressed from PROM through to ambulation	Trained RN

ETM= Early Therapeutic Mobility; FES= Functional Electrical Stimulation; ICU=Intensive Care Unit; LL= Lower Limb; MV= Mechanical Ventilation; OT= Occupational therapist; PROM= Passive Range of Movement; PT= Physiotherapist; QI= Quality Improvement; RASS= Richmond Agitation Assessment Score; ROM= Range of Movement; RN= Registered Nurse; SOEOB= Sit on edge of bed; UL = Upper Limb

Table 3. Characteristics of included studies (N=12).

Author /Year/ Country	Study type	Setting and population	Outcome type, measure and frequency of assessment	Main results
Berney et al (2020) Australia/USA	RCT	*N* = 162 4 multicentre ICUs	Secondary Incidence (%) and duration of delirium (days) CAM-ICU daily	No significant difference in incidence or duration between groups
Brummel et al (2014) USA	RCT	*N* = 87 Single-centre MICU/ SICU	Secondary Presence of delirium as number of delirium-coma free days within first 30 days CAM-ICU 2 × daily	No significant difference between groups (p = 0.83)
Farzanmehesh et al (2020) Iran	RCT	N=161 2 multi-centre ICUs	Primary Delirium duration and sub type level (no delirium/sub-delirium/delirium as %) ICDSC daily	Sub-delirium was 4.54 times greater in control group (p = 0.006) Did not report actual delirium % post intervention only 'no delirium' and 'sub-delirium' % Duration was significantly lower in intervention group (p = 0.003)
Fossat et al (2018) France	RCT	*N* = 312 Single-centre MICU/ SICU	Secondary Frequency of delirium (*n*, %) CAM-ICU daily (stopped after first positive result for delirium)	No significant difference in duration between interventions (p = 0.94)
Karadas and Ozdemir (2015) Turkey	RCT	*N* = 94 Single centre MICU	Primary Delirium duration (hours) and incidence (*n*, %) Type of delirium (hypo/ hyperactive) CAM-ICU daily	No significant difference in incidence or duration (p > 0.05)
Nickels et al (2020) Australia	RCT	*N* = 72 Single centre MICU/ SICU/trauma ICU	Secondary Delirium duration (days) and incidence (*n*, %) CAM-ICU daily	No significant differences between incidence (p = 0.94) or duration (p = 0.27)
Needham et al (2010) USA	CBA QI	*N* = 57 Single centre MICU	Primary Delirium status of MICU days Delirium incidence (*n*,%) CAM-ICU daily	During post-QI phase the delirium status was significantly reduced (p = 0.003)
Nydahl et al (2019) Germany and UK	RCT	*N* = 69 5 multicentre ICUs (in 3 hospitals in 2 countries)	Primary Delirium duration (days) Secondary Delirium incidence (*n*,%) CAM-ICU 3 × daily	No significant difference in duration (p = 0.860) or incidence (p = 0.099) Unplanned post-hoc analysis showed significantly reduced incidence in intervention group in first 4 days after inclusion (p = 0.032)
Nydahl et al (2020) Germany	RCT	*N* = 272 5 multicentre MICU and SICUs	Secondary Delirium duration/presence (delirium free days within 28 days follow up) CAM-ICU or ICDSC daily	No significant difference in delirium free days or presence of delirium between groups
Parry et al (2014) Australia	Non-RCT Observational case-matched control	*N* = 16 Single centre quaternary ICU	Secondary Delirium duration (days) and incidence (*n*,%) CAM-ICU daily	No significant difference in incidence Duration significantly shorter in intervention group (p = 0.042)
Schweickert et al (2009) USA	RCT	*N* = 104 2 multicentre MICUs	Secondary Delirium duration (days) Time in ICU with delirium (%) CAM-ICU daily	Significant reduction in duration in intervention group (p = 0.03) Significant reduction in time delirious in ICU (p = 0.02)
Winkelman et al (2018) USA	RCT	*N* = 54 2 multicentre 4 MICUs	Secondary Delirium incidence on day 1 and 3 (*n*,%) CAM-ICU once daily in the afternoon	No significant difference between once daily versus twice daily (p > 0.1) Significant difference between low versus moderate intensity at day 1 (p = 0.003 and day 3 (p = 0.007)

CAM-ICU= Confusion Assessment Method for the Intensive Care Unit; CBA QI, = Controlled Before and After Quality Improvement study; ICDSC = Intensive Care Delirium Screening Checklist; ICU= Intensive Care Unit; MICU = Medical Intensive Care Unit; N= number, RCT= Randomised Controlled Trial; SICU= Surgical Intensive Care Unit; UK= United Kingdom; USA= United States of America

Table 4. Cochrane ROBINS-I analysis (N=2).

Study	Confounding	Participant selection	Classification of interventions	Deviations from intended interventions	Missing data	Measurement of outcomes	Selection of reported result	Overall risk of bias
Needham et al. 2010	Moderate Risk	Low Risk	Moderate Risk	Low Risk	Low Risk	Moderate Risk	Moderate Risk	Moderate Risk
Parry et al. 2017	Moderate Risk	Moderate Risk	Moderate Risk	Low Risk	Low Risk	Moderate risk	No Information	Moderate risk