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Review Article

Early mobilisation for prevention and treatment of delirium in critically ill patients: Systematic review and meta-analysis

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ABSTRACT

Objective: Does early mobilisation as standalone or part of a bundle intervention, compared to usual care, prevent and/or shorten delirium in adult patients in Intensive Care Units?
Background: Early mobilisation is recommended for the prevention and treatment of delirium in critically ill patients, but the evidence remains inconclusive.
Method: Systematic literature search in Pubmed, CINAHL, PEDRo, Cochrane from inception to March 2022, and hand search in previous *meta*-analysis. Included were randomized trials or quality-improvement projects. meta-analysis was performed for Odds Ratios or mean differences including 95% Confidence Intervals for presence/duration of delirium. Risk of bias was assessed by using Joanna Briggs Quality criteria. meta-regression was performed to analyse heterogeneity.
Results: The search led to 13 studies of low-moderate risk of bias including 2,164 patients. Early mobilisation reduced the risk of delirium by 47 % (13 studies, 2,164 patients, low to moderate risk of bias: Odds Ratio 0.53 (95 % Confidence Interval 0.34 till 0.83, $p = 0.01$), with significant heterogeneity ($I^2 = 78$ %, $p < 0.001$). Early mobilisation also reduced the duration of delirium by 1.8 days (3 studies, 296 patients, low-moderate risk of bias: Mean difference −1.78 days (95 % Confidence Interval −2.73 till −0.83 days, $p < 0.001$), heterogeneity 0 % ($p = 0.41$). Other analyses such as low risk of bias studies, randomised trials, studies published ≥ 2017, high intensity, and mobilisation as stand-alone intervention showed no significant results, with conflicting certainty of evidence and high heterogeneity. meta-regression could not explain heterogeneity.
Conclusion: There is an uncertain effect of mobilisation on delirium. Provision of early mobilisation to critical ill patients might prevent delirium. There is a possible effect of early mobilisation to shorten the duration of delirium. Due to the heterogeneity in the findings, further research to define the best method and dosage of early rehabilitation is required.

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Implications for clinical practice

- Early mobilisation, as stand-alone intervention or as part of a bundle approach, may prevent critically ill patients from delirium.
- Early mobilization may lower the burden of existing delirium in critically ill patients.
- It should be considered that extended periods of passive mobilisation, e.g. sitting in a chair for hours, may lead to exertion and may worsen delirium in some patients.
- The best dosage of mobilisation (duration, intensity, frequency) for prevention and treatment of delirium has to be found.

Introduction

Background

In adult patients in Intensive Care Units (ICU), delirium is a common complication with incidences between 20 % and 89 % (Berger et al., 2020, Devlin et al., 2018, DGAI, 2021, NICE, 2021). Delirium represents an acute encephalopathy and is characterised by altered consciousness, impaired attention, rapid onset and fluctuation, as well as impaired cognitive function (e.g. orientation, language, perception) (Wilson et al., 2020). It is a direct result of physical conditions, procedures or medications, and a combination of predisposing and triggering factors (Smith and Meyfroidt, 2017). The consequences of delirium are increased risks of prolonged mechanical ventilation and length of stay, persistent cognitive decline, prolonged rehabilitation, and institutionalisation (Krewulak et al., 2020, Oh et al., 2017, Stollings et al., 2021).

For the prevention and treatment of delirium, non-pharmacological treatments such as early mobilisation are recommended (Devlin et al., 2018, NICE, 2021). Early mobilisation is defined as an activity that consumes energy and has the goal of maintaining or supporting patient mobility through passive or active movement exercises (Amidei, 2012, Bein et al., 2015, Clarissa et al., 2019). Herein, we define early mobilisation as a range of activities from active exercises in bed (active range of motion, cycling, sitting up in bed, chair position in bed, or similar), to out-of-bed activities (sitting on the edge of bed, standing, active/passive transfer into a chair, walking, or similar); we excluded from this definition interventions such as turning in bed, change of positions, when done to prevent pressure sores, or sole use of Neuromuscular Electrical Stimulation or robotics. Early mobilisation can be delivered by nurses, physiotherapists, and other professionals as a stand-alone intervention or as part of a wider bundle such as the ABCDEF approach including protocols and interventions for analgesia and sedation, delirium, mobilisation and family integration (Frade-Mera et al., 2022, Liu et al., 2021, Pun et al., 2019). Some studies have found positive results in preventing and treating delirium in critically ill patients (Needham et al., 2010, Schaller et al., 2016, Schweickert et al., 2009, Wang et al., 2020), while others have shown conflicting results (Brummel et al., 2014, Morris et al., 2016, Nydahl et al., 2019).

Given other studies in patients after stroke, in which prolonged mobilisation led to a worse neurological outcome (Bernhardt et al., 2016), it seems to be reasonable that early mobilisation has advantages and disadvantages in terms of cerebral perfusion and likely the development and resolution of delirium (Ista and Nydahl, 2021). Hence, our research examined whether early mobilisation either as a stand-alone intervention or as part of a bundle, compared to usual care, prevents or shortens the duration of delirium in critically ill patients.

Methods

A systematic literature review and *meta*-analysis were conducted. The protocol of this research was registered in PROSPERO prospectively (blinded for review). This report is written in concordance with the PRISMA Statement for reporting systematic reviews and *meta*-analysis (Page et al., 2021) (Supplement Table E6).

Eligibility criteria

Criteria for inclusion of studies were a) randomised controlled trials (RCT); b) quasi-experimental studies; c) quality-improvement projects (QI projects); or d) before/after studies. Excluded were a) paediatric studies, or studies with majority of patients <18 years old; b) assessment of delirium was not performed with validated instruments or unclear; or c) no data of interest: i) no report of data in comparing delirium prevalence in intervention/control or before/after (e.g. "ICU days in delirium", or "days in delirium and coma"); or ii) without providing data in duration of delirium in mean (standard deviation) days; d) other reasons (e.g. conference abstracts, case reports with n < 10 patients, duplicated publications). Inclusion and exclusion of articles are reported in the PRISMA flowchart (Fig. 1).

Information sources

Several information sources were surveyed. Databases were Medline via Pubmed, Cochrane, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Physiotherapy Evidence Database (PEDro), since these are relevant for interventions delivered by mainly nurses and physiotherapists. Identified systematic reviews and reference lists of included studies were used for reference screening (Table E1). The search was completed manually. The search was performed from inception until 15 March 2022.

Search strategy

The search had no limits in time or language. The main search terms were "delirium, confusion, mobilisation, rehabilitation, Critical Care, Intensive Care Unit", combined with Boolean operators (full strategy in Table E2). Identified titles were imported into EndNote, and duplicates were removed.

Selection process

All researchers were trained in identification and selection of titles. All titles and abstracts were screened by two researchers independently for eligibility, followed by a review of the full texts by two researchers independently. Results were discussed and conflicts were resolved by discussion with other researchers. No automation tools were used.

Data collection

Data of included full texts were screened for relevant data by two researchers independently who used pre-defined Excel tables for data extraction. Results were compared and discussed, and conflicts were resolved by discussion with other researchers, without any automation tools.

Data items

Collected data items were predefined. The data items are shown in Table 1 *Study Characteristics* with the following included: author (name), publication year (year), country (name of country), study type (RCT, QI-Project, Quasi Randomized Trial, Before/After Trial), type of intervention (Out-of-bed mobilisation, passive transfers into chair, active in-bed-

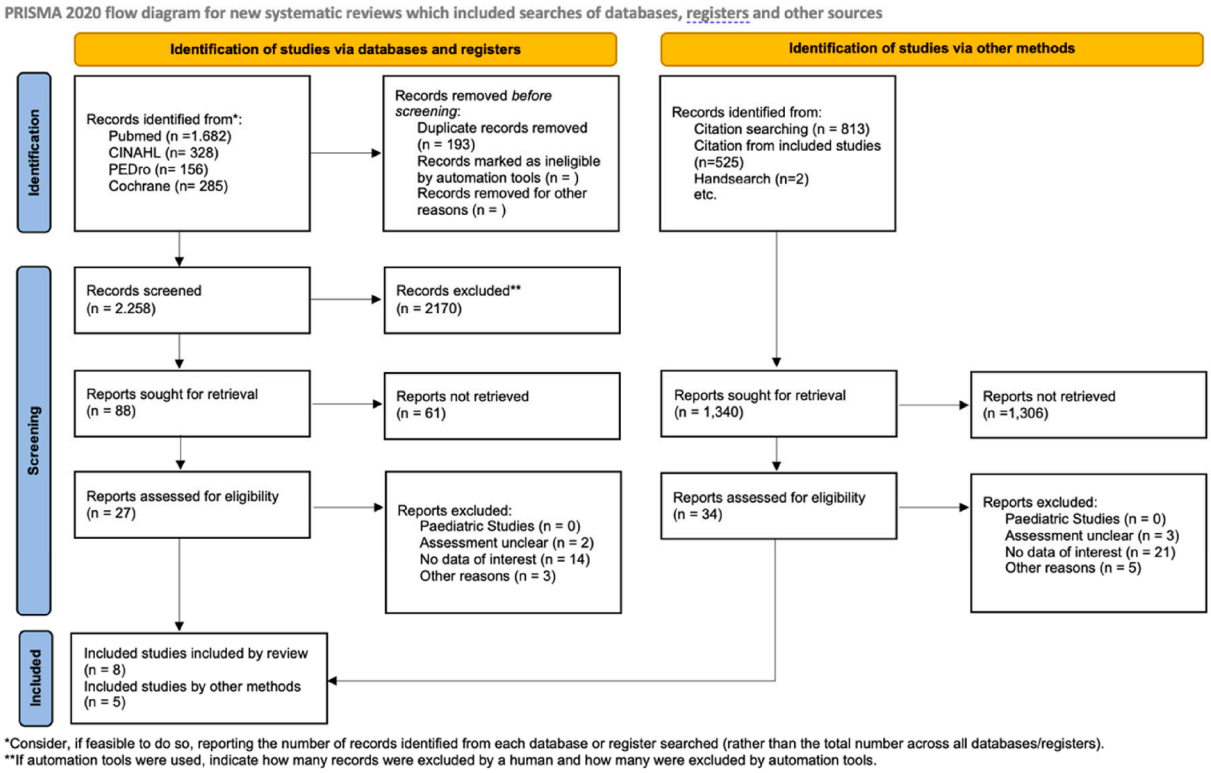

Fig. 1. PRISMA Flowchart.

Table 1
Characteristics of included studies.

Autor, Year, Country	Study type	Intervention	Usual care	Type of ICU population/ MV	Delirium Assessment	Professions
Alvarez 2017, Chile	RCT	Prevention bundle + OT bundle	Prevention bundle	Mixed ICU patients/Without MV	CAM, DRS	Occupational Therapist
Balas 2014, USA	Before/After Trial	Part of ABCDE/F bundle	Usual Care	Mixed ICU patients/Mixed with/out MV	CAM-ICU	Mixed Team
Berney 2020, Australia, USA	RCT	Usual Rehab + FES-Cycling	Usual Rehab	Medical ICU patients/Only ≥ 48 h MV	CAM-ICU	Mixed Team
Bounds 2016, USA	Before/After Trial	Part of ABCDE/F bundle	Usual Care	Mixed ICU patients/Only ≥ 24 h MV	ICDSC	Mixed Team
Chai 2017, USA	QI-Project	Part of ABCDE/F bundle	Usual Care	Mixed ICU patients/Mixed with/out MV	CAM-ICU	Mixed Team
Karadas 2016, Turkey	RCT	Assisted-active ROM	Usual Care	Mixed ICU patients/Without MV	CAM-ICU	Not reported
Lee 2020[a], Korea	Before/After Trial	Modified ABCDE bundle	ABCDE bundle	Mixed ICU patients/Mixed with/out MV	CAM-ICU	Mixed Team
Martínez 2017, Chile	Before/After Trial	Prevention bundle	Usual Care	Mixed ICU patients/Mixed with/out MV	CAM-ICU	Physiotherapist
Matsuki 2020, Japan	QI-Project	Rehab protocol + PT	Usual Care	Mixed ICU patients/Mixed with/out MV	ICDSC	Physiotherapist
Moon 2015, Korea	RCT	Part of ABCDE/F bundle	Usual Care	Mixed ICU patients/Mixed with/out MV	CAM-ICU	Mixed Team
Nydahl 2020, Germany	RCT	Out-of-bed mobilisation	Usual Care	Mixed ICU patients/Mixed with/out MV	CAM-ICU, ICDSC	Mixed Team
Nydahl 2021, Germany, UK	RCT	Out-of-bed mobilisation	Usual Care	Mixed ICU patients/Mixed with/out MV	CAM-ICU	Mixed Team
Winkelman 2016, USA	RCT	Twice daily mobilisation	Once daily mobilisation	Mixed ICU patients/Mixed with/out MV	CAM-ICU	Registered Nurse

Abbreviations: CAM-ICU Confusion Assessment Method for the Intensive Care Unit; DRS Delirium Rating Scale; FES Functional electrical stimulation; ICDSC Intensive Care Delirium Screening Checklist; ICU Intensive Care Unit; MV Mechanical Ventilation; RCT Randomized controlled trial; ROM Range of motion exercises; QI-Project Quality Improvement Project; UK United Kingdom; USA United States of America.

[a] Modification of ABCDE bundle included better interprofessional cooperation for medications, lower inclusion criteria for exercises, and improved performance of mobilisation.

mobilisation, cycling, mixed, part of ABCDE/F bundle, other), type of control (usual care, other), selected population (general/mixed ICU patients, surgical ICU patients, medical ICU patients, Neuro ICU patients), duration of mechanical ventilation (MV) (≥24 h, ≥48 h, ≥72 h, other, without MV), delirium assessment (Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), Intensive Care Delirium Screening Checklist (ICDSC), Nursing Delirium Screening Checklist (Nu-DESC), Diagnostic Statistical Manual (DSM IV/V), 4AT, other), and profession (Registered Nurse, Physiotherapist, Physician, Occupational Therapist, Respiratory Therapists, mixed team, other). Table E4 *patient* data for

intervention- and control groups included: age (years Mean (Standard deviation (SD)) or Median (Interquartile Range [IQR]), male gender (percentage), APACHE II score (Mean (SD) or Median [IQR]), patients with mechanical ventilation (percentage), dosage of intervention (eg. mobilisation 2 times/day), and duration of mobilisation (hours).

After data extraction, a standardised assessment of the dosage of the intervention in terms of frequency, intensity, or duration was not feasible. Hence, the dosage was dichotomised into low vs high intensity mobility (low intensity: <20 % of patients with MV and/or <50 % of patients without MV experienced out-bed-activities such as sitting on the edge of bed, standing, sitting in a chair, ambulation, or else vs high intensity mobility with ≥ 20 % of patients with MV and/or ≥ 50 % of patients without MV experienced these activities)(Brock et al., 2018, Liu et al., 2021, Pun et al., 2019, Sibilla et al., 2020). Early mobilisation can be seen as safe procedure with a low rate of unwanted safety events, but nevertheless, studies were screened for unwanted safety events (Hodgson et al., 2014, Nydahl et al., 2017, Devlin et al., 2018, Katsukawa et al., 2021).

Risk of bias

Risk of bias was assessed by two researchers (blinded for review) independently, using the method by the Joanna Briggs Institute. Results were discussed and conflicts were resolved by discussion with the other researchers. This risk of bias assessment included 9 criteria; criteria were ranked as "yes" if reported and fulfilled. The number of reported criteria led to an estimation: ≤4: high risk of bias, 5–6: moderate risk of bias, 7–9: low risk of bias (Porritt et al., 2014). Certainty of evidence is based on risk of bias and reported methods and results in included studies.

Effect measures

For estimating the effect of mobilisation on prevention of delirium, the Odds Ratios (OR) with 95 % Confidence Intervals (CI) were calculated with studies reporting the numbers of patients with and without delirium in intervention and control groups; for the effect of mobilisation on treatment of delirium, the mean difference (MD) in delirium duration between both groups was calculated as MD (95 %CI) with studies reporting this outcome. I^2 statistic was used to assess the degree of heterogeneity. I^2 values of 25 % indicate low, 50 % moderate, and 75 % high heterogeneity. Substantial between-study heterogeneity was considered present when I^2 was ≥ 50 %. In this case a random effects model was used to calculate the OR of delirium prevalence, and MD of delirium duration including 95 %CI; otherwise, a fixed effects model was used. Review Manager 5.3 was used for analysis. Furthermore, an unplanned *meta*-regression was performed for analysing heterogeneity within sub-analyses by calculation of logOR including regression coefficient, standard error (SE), and 95 %CI, using Stata 17 (StataCorp, California). Consistent with guidance in the Cochrane Handbook to detect potential publication bias, funnel plots were generated for *meta*-analyses with greater than 10 studies (Higgins et al., 2022). meta-analyses were performed for prevention and treatment as primary outcome, and sub-analyses for RCT vs QI projects and before/after studies, younger vs older studies, and high vs low intensity mobilisation, and studies with low vs moderate risk of bias.

Results

The search yielded in 3,598 titles, 2,258 from database search and 1,340 from other sources (Fig. 1: PRISMA Flowchart). After excluding duplicate titles and assessment for eligibility, 13 studies including 2,164 patients could be analysed. One study from China could not be assessed for inclusion, despite support from Chinese speaking researchers (Wu et al., 2021).

The 13 studies include 7 RCT (Álvarez et al., 2017, Berney et al., 2021, Karadas and Ozdemir, 2016, Moon and Lee, 2015, Nydahl et al., 2020, Nydahl et al., 2022a, Winkelman et al., 2012), 4 before/after trials (Balas et al., 2014, Bounds et al., 2016, Lee et al., 2020, Martínez et al., 2017), and 2 QI-Projects (Chai, 2017, Matsuki et al., 2020)(Table 1: Included studies). All were mixed ICUs, except one which was a medical ICU (Berney et al., 2021). In general, patient data were similar in intervention and control groups (Table E4: patient data). The risk of bias was low in 7 studies (Álvarez et al., 2017, Chai, 2017, Karadas and Ozdemir, 2016, Lee et al., 2020, Moon and Lee, 2015, Nydahl et al., 2020, Nydahl et al., 2022a), moderate in 5 studies (Balas et al., 2014, Berney et al., 2021, Bounds et al., 2016, Martínez et al., 2017, Matsuki et al., 2020), and high in 1 study (Winkelman et al., 2018)(Table E5).

Delirium prevention

For delirium prevention, 13 studies could be included (Álvarez et al., 2017, Balas et al., 2014, Berney et al., 2021, Bounds et al., 2016, Chai, 2017, Karadas and Ozdemir, 2016, Lee et al., 2020, Martínez et al., 2017, Matsuki et al., 2020, Moon and Lee, 2015, Nydahl et al., 2020, Nydahl et al., 2022a, Winkelman et al., 2018). Mobilisation reduced the risk for developing delirium in ICU patients by 47 % (13 studies, 2,164 patients, low to moderate risk of bias: OR 0.53 (95 %CI 0.34 to 0.83, p = 0.01), with significant heterogeneity (I^2 = 78 %, p < 0.001) (Fig. 2a). The certainty of evidence is moderate.

Delirium treatment

For reducing duration of delirium, 3 studies could be analysed (Bounds et al., 2016, Chai, 2017, Lee et al., 2020). Mobilisation reduced the duration of delirium in patients in ICU by 1.8 days (3 studies, 296 patients, low-moderate risk of bias: MD −1.78 days (95 %CI −2.73 till −0.83 days, p < 0.001), heterogeneity 0 % (p = 0.41)(Fig. 2b). The certainty of evidence is moderate.

Further analyses

Additional sub-analyses for prevention of delirium showed significant results including none to moderate or no heterogeneity for: low-intensity interventions, studies published ≤ 2016, and for studies with moderate risk of bias. Significant risk reduction for developing delirium including significant heterogeneity was found in: studies focusing on out-of-bed mobilisation, QI projects and before/after studies, and mobilisation as part of bundles. Other analyses such as low risk of bias studies, RCTs, studies published ≥ 2017, high intensity, and mobilisation as stand-alone intervention showed no significant results, with conflicting certainty of evidence (Table 2). The rate of unwanted safety events was reported in five studies, and compared in three studies, with no significant differences in safety events between intervention and control group (Table E6).

Meta-regression found no significant differences in log OR between the analysis study design (RCT vs non-RCT, coefficient = −0.073 (SE = 0.454), p = 0.872, 95 %CI −0.962 to 0.816), year of publication (≥2016 vs ≥ 2017, coefficient = 0.238 (SE = 0.462), p = 0.607, 95 %CI −0.669 to 1.144), risk of bias (low vs moderate, coefficient = 0.233 (SE = 0.483), p = 0.535, 95 %CI −0.646 to 1.246), intensity (low vs high, coefficient = 0.454 (SE = 0.659), p = 0.490, 95 %CI −0.838 to 1.747), intervention (single interventions vs bundle, coefficient = 0.431 (SE = 0.439), p = 0.326, 95 %CI −0.429 to 1.293).

Interpretation of the funnel plot for publication bias (Fig. E1) does not exclude a risk for non-published trials with results favouring usual care, instead of early mobilisation.

Discussion

This systematic literature review yielded 13 studies with low-moderate risk of bias including 2,164 ICU patients. Analysis of all 13 studies showed that provision of early mobilisation reduces the risk of developing delirium in ICU by 47 %, albeit with meaningful heterogeneity. Additionally, mobilisation reduces the duration of existing delirium by nearly-two days. Sub-analyses showed that studies

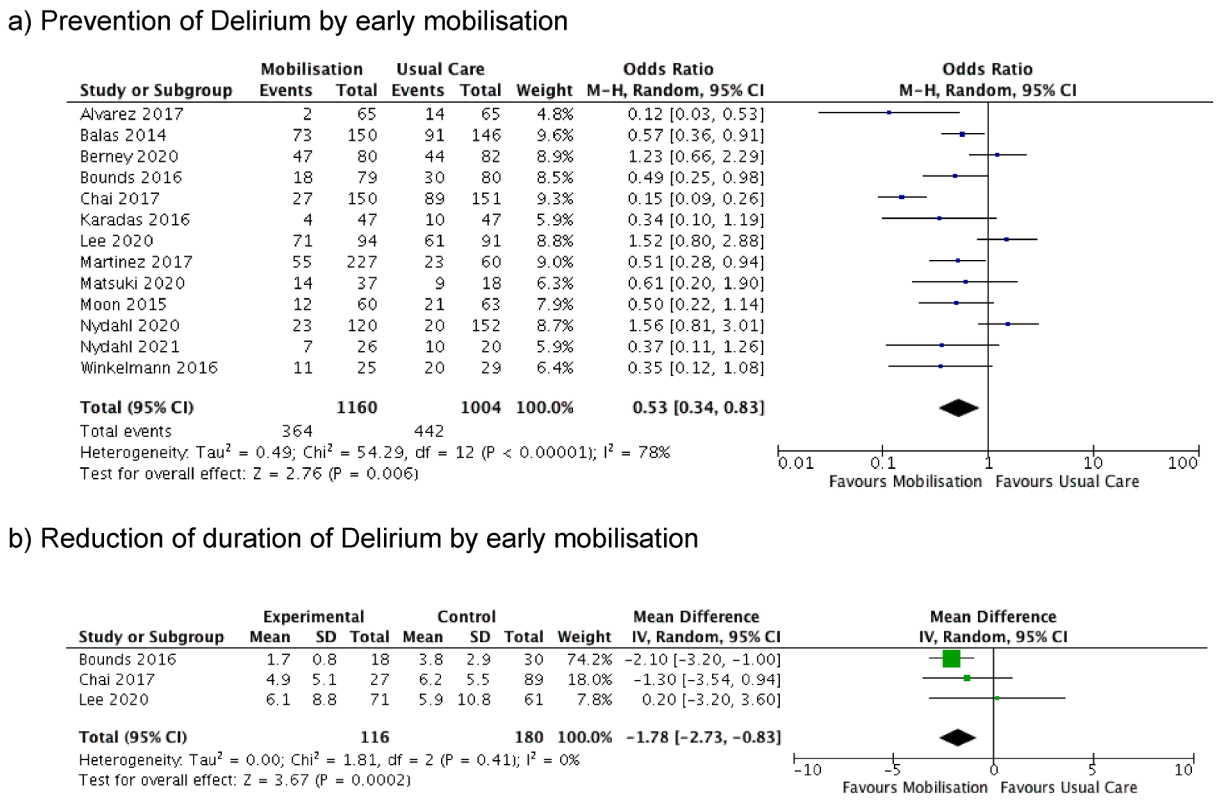

Fig. 2. Forest plots.

Table 2
Sub analyses for mobilisation as delirium prevention.

Analyses	Trials	Patients	Odds Ratio (95 % CI) for delirium	Significance	Heterogeneity (Significance)
Significant results and none till moderate heterogeneity					
Low intensity mobilisation	2	253	0.49 (0.25 till 0.83)	0.01	0 % (0.62)
Studies ≤ 2016	5	726	0.50 (0.37 till 0.70)	<0.001	0 % (0.900)
Moderate risk of bias	5	959	0.64 (0.46 till 0.90)	0.01	28 % (0.24)
Significant results and significant heterogeneity					
QI-Projects, before/after	6	1,283	0.51 (0.27 till 0.98)	0.04	84 % (<0.001)
Out-of-bed mobilisation	11	1,908	0.50 (0.31 till 0.82)	0.006	79 % (<0.001)
Mobilisation as part of bundles	7	1,481	0.44 (0.24 till 0.81)	0.008	82 % (<0.001)
Nonsignificant results and significant heterogeneity					
Low risk of bias	7	1,151	0.46 (0.19 till 1.10)	0.08	87 % (<0.001)
RCT	7	881	0.55 (0.30 till 1.04)	0.07	68 % (0.005)
Studies ≥ 2017	8	1,438	0.57 (0.27 till 1.17)	0.13	87 % (<0.001)
High intensity mobilisation	5	906	0.67 (0.34 till 1.33)	0.25	74 % (0.004)
Mobilisation as stand-alone intervention	6	683	0.71 (0.40 till 1.27)	0.25	55 % (0.05)

Abbreviations: CI Confidence Interval; RCT randomized controlled trials; QI-Projects Quality improvement projects.

published before 2017, studies with moderate risk of bias, and low-intensity studies had significant effects and no heterogeneity. There might be a risk for unpublished studies with negative results.

Heterogeneity

The overall analysis of the included studies showed significant heterogeneity. meta-regression could not explain the heterogeneity between the sub-groups. In this *meta*-analysis, assessment of heterogeneity is based on I^2 statistics, an estimation of the percentage of the variability in the results across the studies which is probably due to the true treatment effect, or by chance. Higher heterogeneity, in general ≥ 50 %, may indicate hidden effects, such as competing populations, interventions, treatment effects, or methods (Hatala et al., 2005). Interpretation of the results is challenging: on one hand, all but one study were on mixed ICUs with mixed populations, but the extent of single patient groups with special conditions such as sepsis, heart failure, cardiac surgery, and others might have differed between the studies, explaining heterogeneity to some extent. Furthermore, different mobilisation interventions from range-of-motion exercises in bed using cycle ergometry, up to out-of-bed mobilisation were included, likely explaining different intervention effects and leading to increased heterogeneity. On the other hand, studies with low-intensity mobilisation showed similar effects on delirium prevention compared to studies with high intensity or studies using out-of-bed mobilisations, but had differences in heterogeneity. Finally, analysis of RCTs, which usually have the best chance to identify true effects, showed no significant results and high heterogeneity. Considering these aspects of *meta*-analysing the included studies, mobilisation might have a true effect on preventing delirium in patients in ICU, but the best population and interventions, especially performed by nurses, have yet to be found.

Prevention

Most studies, but not all, could achieve a preventable effect on

delirium. Early mobilisation is a multifaceted physical, cognitive and psychosocial activity including coordinated movements, increased proprioception, gravity effects, sympathetic activation of neurotransmitters, cognitive activation and participation, and also interaction with the environment and nurses, physiotherapists and other clinicians, leading to improved orientation (Bein et al., 2015) and hence, represents a complex intervention (Möhler et al., 2015, Moore et al., 2015). This may explain why QI-projects led to better results than RCTs, as barriers, structures and processes can be adapted and improved during the multifaceted QI process (Ogrinc et al., 2016). On the contrary, RCTs are attributed with lower risk of bias, raising the question of the true effects in the included studies. Furthermore, mobilisation as part of the ABCDEF bundle showed better effects than mobilisation alone; this seems to be reasonable, giving the effects of medications, analgesia- and sedation management and the contributions of nurses and other profession on delirium, contrary the heterogeneity is considerable high and the effect of the intensity of mobilisation as stand-alone intervention on delirium requires further research (Devlin et al., 2018, Eggmann et al., 2022).

Some studies showed better effects from usual care instead of the intervention (Berney et al., 2021, Lee et al., 2020, Nydahl et al., 2020), and in such cases, where intervention effects are in 95 %CI above 1, there might be non-responders or advantages in usual care (Murad et al., 2014). This raises the question: is mobilisation always beneficial? In patients with severe stroke, extended early mobilisation within the first 24 h after stroke onset led to a worsened outcome (AVERT Trial Collaboration group, 2015). It seems to be plausible that long durations of sitting decreases cerebral perfusion and this might be harmful in patients with neurological or cardiovascular diseases. Delirium is a syndrome with different triggers and causes, therefore the one-size-fits-all of "mobilisation for all patients" approach might be misleading in some cases (Collet et al., 2018, Girard et al., 2018a). As Girard pointed out, 80 % of delirious episodes in patients in ICU can be related to shock, infection, hypoxia, or metabolic disbalances (Girard et al., 2018b). It is well known that older patients in ICU are at higher risk of delirium and that this is associated with increased morbidity. Therefore, recognition of the complexity and increased risk of elderly related adverse events should be included in prevention. Bloomer et al. and van den Boogaard et al. point out that family involvement has a crucial impact on delirium (Bloomer et al., 2022, van den Boogaard and Zegers, 2021). For ICU patients who are particularly likely to suffer from delirium, adherence to preventive measures, such as those of the ABCDEF bundle, should be a priority. It seems to be reasonable that mobilisation might be beneficial in patients with delirium, which is caused by hypoxia or metabolic disturbances, but might be less effective or potentially harmful in patients with shock, possibly leading to reduced cerebral perfusion and even increasing cerebral dysfunction (Girard et al., 2018b, Smith and Meyfroidt, 2017). Whilst we identified specific studies of early mobilisation in patients with septic shock, the authors, unfortunately, did not assess for delirium (Hickmann et al., 2014, Kayambu et al., 2015). Future studies should include the rate of unwanted safety events such as restraints or worsening delirium as well. In summary, different prevention effects might be explained by possible benefits, or harms in specific sub-groups. At the present time, authors have not differentiated between these groups and so we were unable to complete a more specific analysis of these populations. In future studies, delirium researchers should consider the different causes of delirium and focus on the specific impact of single bundle components, especially early mobilisation. In general, it seems to be plausible that provision of early mobilisation prevents patients in ICU from developing delirium, but the dosage in terms of duration, frequency, and intensity has to be adapted to the patients' conditions, favouring more frequent and shorter sessions (Eggmann et al., 2022).

Treatment

Early mobilisation seems to have beneficial effects on patients with existing delirium, decreasing the duration of delirium. Analysing the duration of delirium is challenging due to the heterogeneity in reporting the duration of delirium as 28-days-free-of-delirium, 28-days-free-of-delirium-and-coma, percentages-of-ICU-days-in-delirium, and others (Nydahl et al., 2021), and hence, only three studies could be included. There were excellent studies published about mobilisation of patients in ICU, but delirium data were not included or reported in a way that could not be used for *meta*-analysis (Hodgson et al., 2016, McWilliams et al., 2015, Needham et al., 2010, Schaller et al., 2016, Schweickert et al., 2009). Since there seems to be a strong relationship between mobilisation and physical therapy, we would like to encourage all physio- and occupational therapists to learn, use, and report delirium assessments and management in future trials. An important point that deserves more attention is the different delirium triggers that influence treatment. Mattiussi et al. report fixations because of the delirium in order to prevent self-harm. The lack of staff is another problem, which is why coercive measures such as fixations are justified in the affected patients (Mattiussi et al., 2022). It should be emphasized that nurse staffing levels are not associated with appearance, duration, or solution of delirium in patients (Nydahl et al., 2022b).

Beside multi-professional assessment, it is questionable whether duration of delirium is the best outcome parameter for the evaluation of interprofessional delirium bundles. A substantial percentage of patients with existing delirium are discharged from ICU, and the discharge is often counted as end of delirium, biasing the results (Nydahl et al., 2018). We were not able to assess the impact of mobilisation on the burden of delirium, including frightening hallucinations, anxiety, or shame (Kuusisto-Gussmann et al., 2021), and this requires further research. Using assessments with estimation of delirium burden such as ICDSC or CAM-ICU-7, and others is recommended in future trials (Lindroth et al., 2020).

Furthermore, during the last decade delirium prevention has become more routine in ICU practice, likely reducing the difference between effects sizes in intervention and control groups. If control groups are already a receiving strategies for delirium management, it requires very strong effect sizes or large numbers of populations to show significant results (Patil et al., 2016). Consequently, in later studies it has likely become more difficult to demonstrate effect sizes than in earlier studies (Denehy et al., 2017). Similarly, the pharmacological treatment of patients with delirium improved and became more symptom-specific, resulting in improved outcomes (Rood et al., 2021, Shaw et al., 2019).

However, it seems to be likely that early mobilisation reduces delirium duration in most cases. From a patient- and family-centred approach, severity of delirium should be a central outcome parameter, and considered in future research (Rose et al., 2021).

Limitations

A strength of the study was that studies with large sample sizes were included, even if the intervention and control groups differed minimally in intervention or usual care. Other strengths are the performed subanalyses and the detailed consideration and discussion of heterogeneity. There are several limitations. During the literature search, one Chinese study could not be assessed as full-text (Wu et al., 2021); however, it was a smaller study and it is unlikely that an inclusion would have changed major results. Interpretation of the funnel-plot for publication bias is a hypothetical indication signalling missing publications, but also other contributing factors, such as reporting bias, poor methodological quality, or true heterogeneity, can be considered (Sterne et al., 2011). Due to the heterogeneity, it was not possible to identify the most effective mobilisation for prevention and treatment of delirium. On the contrary, mobilisation can be seen as a multifactorial and complex intervention and it may be likely that this complexity is the main effect. A further limitation can be the use of various assessments and the diagnosis of delirium. Not all authors described who or whether the people who used the assessments were trained in assessing delirium.

There could be a difference in the use of the assessments, hence the diagnosis of delirium could also vary. Furthermore, different forms of delirium or other influencing factors such as multimorbidity were not considered.

Conclusions

There is a high level of uncertainty because multiple sensitivity analyses do not follow the overall result when all studies were pooled. The wide heterogeneity in terms of populations and interventions included makes it difficult to identify those patients most likely to benefit. Early mobilisation for patients in ICU may be effective in preventing delirium. There might be also a likely effect of mobilisation shortening the duration of ICU acquired delirium. Additionally, future work should investigate the impact of early mobilisation for specific populations admitted to ICU. In addition, as the provision of early and structured rehabilitation becomes more standard care in ICUs, severity of delirium should be a central outcome parameter and considered in future research.

Due to the heterogeneity in ICU populations and early mobilisation interventions, we are unable to draw specific conclusions regarding the appropriate method, frequency, duration or intensity of mobilisation. However, the avoidance of bed rest is paramount. Early mobilisation in ICU should be considered on an individual patient basis within an interprofessional approach, adapting to the patients' conditions for improving cerebral perfusion. This complex intervention, therefore, poses challenges for future research; striking a balance between rigorous trial methodology and the variability and practicalities of individualised patient care. From a patient- and family-centred approach, severity and long-term impacts of delirium beyond the ICU should also be considered as a central outcome parameter and considered in future research.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.iccn.2022.103334.

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