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Review paper

# Effects of nonpharmacological delirium-prevention interventions on critically ill patients' clinical, psychological, and family outcomes: A systematic review and meta-analysis

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ABSTRACT

*Background:* Delirium is common in critically ill patients and may lead to severe complications, such as falls and injuries. Nonpharmacological interventions have been widely suggested to prevent delirium, yet the effects remain uncertain.

*Objectives:* The aim of the study was to determine the effects of nonpharmacological interventions on preventing delirium and improving critically ill patients' clinical, psychological, and family outcomes.

*Methods:* Ten databases were searched from their inception to September 2020. Two reviewers assessed the methodological quality and extracted details of the included studies. The data were narratively or statistically pooled where appropriate. Dichotomous variables are presented as odds ratio (OR), and continuous variables are presented as mean difference (MD). The Grading of Recommendations Assessment, Development, and Evaluation criteria were used to assess the quality of evidence for each review outcome.

*Results:* Thirty-four studies (10 randomised controlled trials, eight controlled clinical trials, and 16 before-and-after studies) were included in the analysis. Low-certainty evidence indicated that nonpharmacological interventions reduced delirium incidence (OR = 0.43, 95% confidence interval [CI] [0.33, 0.55]), delirium duration (MD = −1.43 days, 95% CI [−1.94, 0.92]), and length of stay in the intensive care unit (MD = −1.24 days, 95% CI [−2.05, −0.43]). Moderate-certainty evidence demonstrated no effect on mortality. Narrative synthesis further implied improvements in patients' psychological recovery (two studies, very low-certainty evidence) and families' satisfaction with care (two studies, very low-certainty evidence) through nonpharmacological interventions. As for effective intervention types, moderate-certainty evidence demonstrates that early mobilisation (OR = 0.33, 95% CI [0.24, 0.46], five studies, 859 participants, $I^2$ = 24%), family participation (OR = 0.25, 95% CI [0.18, 0.34], four studies, 997 participants, $I^2$ = 21%), and use of multicomponent interventions (OR = 0.48, 95% CI [0.34, 0.69], 13 studies, 3172 participants, $I^2$ = 77%) are associated with reduced incidence of delirium.

*Conclusions:* Healthcare professionals are recommended to apply early mobilisation, family participation, or multicomponent interventions in clinical practice to prevent delirium. Further studies investigating the effects of nonpharmacological interventions on patients' psychological and family outcomes are warranted.



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## 1. Introduction

Delirium is defined by the American Psychiatric Association as an acute confusion state characterised by attention disturbance and cognitive changes, developing over a short period of time and exhibiting fluctuations in severity during the course of the day. Delirium can be induced by a physiological consequence, such as a medical condition, substance intoxication, or substance withdrawal.[1]

Delirium is particularly common in intensive care units (ICUs), where it has been reported to occur in 40–60% of patients not requiring mechanical ventilation and 60–80% of patients requiring mechanical ventilation.[2] Risk factors of delirium have been broadly classified into patient factors (e.g., old age, cognitive status, and alcohol abuse), disease-associated factors (e.g., surgery, mechanical ventilation, sepsis, and comorbidity), and iatrogenic factors (e.g., immobilisation, social isolation, sensory deprivation, and sleep deprivation).[3–5]

ICU delirium is highly associated with adverse clinical outcomes, such as increased cognitive impairment, duration of intubation, ICU length of stay (LOS) and mortality, as well as increased healthcare costs.[6,7] A systematic review of 42 studies found that compared with patients without delirium, patients with delirium had significantly higher mortality (risk ratio: 2.19) and ICU (risk ratio: 1.38).[8] Furthermore, family members experience stress when caring for their loved ones with delirium.[2]

The high incidence and severe outcomes of ICU delirium have prompted clinicians to focus on its prevention. Primary prevention strategies of ICU delirium encompass both pharmacological and nonpharmacological interventions. However, pharmacological interventions tend to be costly owing to the complexity of delirium.[2] Furthermore, reports of adverse effects, such as fatigue and concerns about safety in drug-induced hypotension, have inhibited translation into clinical practice.[9] Therefore, simple, safe, effective, and feasible interventions targeting the risk factors of delirium are urgently needed. A previous systematic review investigating the effects of nonpharmacological interventions on the prevention of delirium in ICUs found that nonpharmacological interventions targeting risk factors of delirium could positively influence patients' clinical outcomes, as well as resulting in a reduction in the incidence and duration of delirium.[10] Such interventions can be multicomponent or single-component interventions, such as early mobilisation, family participation, patient education, and changes to the patient's physical environment. Multicomponent interventions are a combination of several single-component interventions.[11] For instance, another systematic review found that the implementation of the ABCDE (Awakening and Breathing Coordination, Delirium Monitoring/Management, and Early Exercise/Mobility) bundle and delirium guideline reduced delirium incidence.[12] However, these two reviews focused only on the patients' clinical outcomes.[10,12] A comprehensive understanding of the effects of nonpharmacological interventions on patients' psychological outcomes (such as the level of anxiety) and family caregivers' outcomes (such as satisfaction with care and the level of anxiety) is needed. Furthermore, these two reviews were limited by their combination of all categories of nonpharmacological interventions into a single category. It is necessary to identify effective interventions for clinical practice. Given these knowledge gaps, the aims of the current review were (i) to determine the effects of nonpharmacological interventions on preventing delirium and improving patients' clinical, psychological, and family outcomes and (ii) to examine the efficacy of different categories of nonpharmacological interventions on preventing delirium.

## 2. Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[13] The review protocol was registered on PROSPERO on July 16, 2019 (reg. no.: CRD42019135395).

### 2.1. Eligibility criteria

Eligible studies met the criteria described in the following section:

#### 2.1.1. Participants

The eligible participants included ICU patients ≥18 years of age, regardless of sex, ethnicity, or socio-economic status and those patients admitted to surgical, medical, trauma, or cardiac ICUs or a high-dependency unit. Studies involving ICU patients with a history of a neurologic condition such as dementia, traumatic brain injury, stroke, or hepatic encephalopathy or who had undergone neurosurgery were excluded because these conditions hinder the accurate assessment of delirium.[14]

#### 2.1.2. Intervention(s)

The eligible nonpharmacological interventions included multicomponent or single-component interventions aimed at preventing delirium and improving outcomes among ICU patients. The interventions included, but were not limited to, early mobilisation, family participation, patient education, music, sleep promotion, changes to the physical environment, and multicomponent interventions (the combination of two or more of the single interventions listed). Studies that included pharmacological interventions (e.g., use of haloperidol, risperidone, or quetiapine) offered in addition to nonpharmacological interventions were excluded.

#### 2.1.3. Comparator(s)

The comparison group received usual care, including, but not limited to, a spontaneous breathing trial, indwelling catheter, feeding, and bowel care.

#### 2.1.4. Outcome(s)

Patients' clinical outcomes included the incidence and duration of delirium, the LOS in the ICU, and mortality. Patients' psychological outcomes included the level of anxiety and the quality of recovery. Family outcomes included the level of family satisfaction with the care provided and anxiety.

#### 2.1.5. Types of study

Randomised controlled trials (RCTs), controlled clinical trials, and controlled or uncontrolled before-and-after studies were included. Discussion papers, literature reviews, commentaries, abstracts, protocols, and conference papers were excluded.

### 2.2. Search strategy

Studies published in the English or Chinese language were considered. Six English electronic databases including Medical Literature Analysis and Retrieval System Online (MEDLINE), Cummulative Index of Nursing and Allied Health Literature CINAHL), Excerpta Medica dataBASE (EMBASE), Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and PsycINFO) and four Chinese electronic databases (China National Knowledge Infrastructure, Wanfang Data, Weipu, and China Biomedical Literature Database) were searched from their inceptions to September

2020. The reference lists of relevant systematic reviews and guidelines were also screened to identify potentially relevant studies.

The initial keywords were 'delirium', 'non?pharmacological intervention*', 'critical care unit*', and 'intensive care unit*'. Variations of these terms were used for a comprehensive search.[15] A librarian was consulted to refine the search strategy. The detailed search of MEDLINE is shown in Supplementary Material 1. Similar search combinations were used for the other databases.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart was used to guide the selection of studies included in this review.[13]

### 2.3. Study selection

After removing duplicate records, the titles and abstracts were assessed by two independent reviewers. For the remaining records, the full texts of the studies were retrieved and assessed to determine eligibility. Queries regarding inclusion were resolved by discussion. The reference lists of eligible articles were reviewed to identify additional potentially eligible studies.

### 2.4. Risk-of-bias assessment

Two independent reviewers assessed the risk of bias. JBI Critical Appraisal Checklists for RCTs and nonrandomised experimental studies were used to assess the risk of bias of different types of studies.[16] Any disagreement was resolved by discussion. If a consensus could not be reached, the third reviewer made the deciding judgement. The risk for each item was graded 'yes', 'no', or 'unclear' based on the comprehensiveness of the information reported. The overall study was labelled high risk if two or more items were graded 'no' and/or 'unclear', moderate risk if one item was graded 'no' or 'unclear', and low risk if no items were labelled 'no' or 'unclear'.

### 2.5. Data extraction

A data extraction form was designed. Four included studies were randomly selected to pilot test the appropriateness of the form. One reviewer extracted the details of the included articles (author, methods, sample characteristics, intervention, outcomes, and measurement), and the second reviewer checked the extracted data. Any disagreement was resolved by consensus between the two reviewers; otherwise, the third reviewer was consulted. If the studies provided insufficient or ambiguous information, the original study investigators were contacted for clarification.

### 2.6. Data synthesis

The effect estimates for each outcome of the included studies were synthesised by meta-analysis using RevMan 5.3, whenever appropriate. The effect sizes of the implementation of nonpharmacological interventions were expressed as odds ratio (OR) together with 95% confidence interval (CI) for dichotomous outcomes (such as delirium incidence and mortality) and pooled using a Mantel–Haenszel model and as mean difference (MD) with 95% CI for continuous variables (such as delirium duration and LOS in the ICU) and pooled using the inverse variance method. A fixed-effects model was used for statistical pooling if there were adequate studies with sufficient homogeneity as per the $I^2$ statistic ($I^2 \leq 50\%$). When substantial heterogeneity existed ($I^2 > 50\%$), a random-effects model was used.[17] A random-effects model was also adopted when the number of studies ($k < 5$) was small.[18] For the primary comparison between nonpharmacological interventions and the control intervention, data from all relevant studies were pooled without stratification. A pooled analysis based on the categories of nonpharmacological interventions was also conducted. If there were more than two studies for the same outcome of each intervention category, the data were pooled. Otherwise, narrative summaries were provided. Sensitivity/subgroup analysis was planned where appropriate to explore the influence of the intervention dose and risk of bias on the effect estimate.[19,20] The funnel plot was planned for detecting the publication bias.

### 2.7. Assessing the certainty of evidence and 'summary of findings' tables

We used the Grading of Recommendations Assessment, Development, and Evaluation approach to assess the quality of evidence for each outcome and assessed the certainty of the evidence as 'high', 'moderate', 'low', or 'very low' depending on the presence and extent of five factors including risk of bias, inconsistency of the effect, indirectness, imprecision, and publication bias and three factors that can increase the quality of evidence, namely, the large magnitude of an effect, a dose–response gradient, and the effect of plausible residual confounding.[21] The evidence was first rated as high if all designs included in the study were RCTs or as moderate if both RCTs and non-RCTs were included. It was then downgraded accordingly depending on assessments of risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates, and potential publication bias.[21] Specific assessments of each evidence are shown in Supplementary Material 2.

We prepared 'summary of findings' tables featuring the seven listed outcomes for the umbrella comparison (nonpharmacological interventions [all types] versus control) and delirium incidence, delirium duration, LOS in the ICU, and mortality for the primary nonpharmacological intervention categories versus the control comparisons, when the data were available.

## 3. Results

### 3.1. Search results

The initial search of six English and four Chinese databases identified 2425 articles. Five additional articles were found through manual searching. After removal of duplicates, 1765 articles remained and were screened via review of their titles and abstracts. A total of 1603 articles were excluded owing to lack of relevance. Of the 162 records that were subjected to full-text assessment, 22 were excluded because they were review articles or because they used a cohort study or a qualitative study design. A total of 64 studies were excluded because the intervention was not related to delirium prevention. Forty-two studies were excluded because they involved combined pharmacological and nonpharmacological interventions. The reasons and the respective number of studies for exclusion are presented in Fig. 1. Finally, 34 articles were included in this review.[9,14,22–53]

We attempted to contact three investigators to obtain further details of their studies. The investigators of one study provided further data.[35] No response was obtained from the other two investigators.[33,51]

### 3.2. Characteristics of the included studies

Thirty-four studies involving 7159 ICU patients met the inclusion criteria of this review. The studies were conducted in Asia (n = 15), the USA (n = 10), the UK (n = 2), and Europe (n = 7). The settings included the general ICU (n = 21), medical ICU (n = 4),

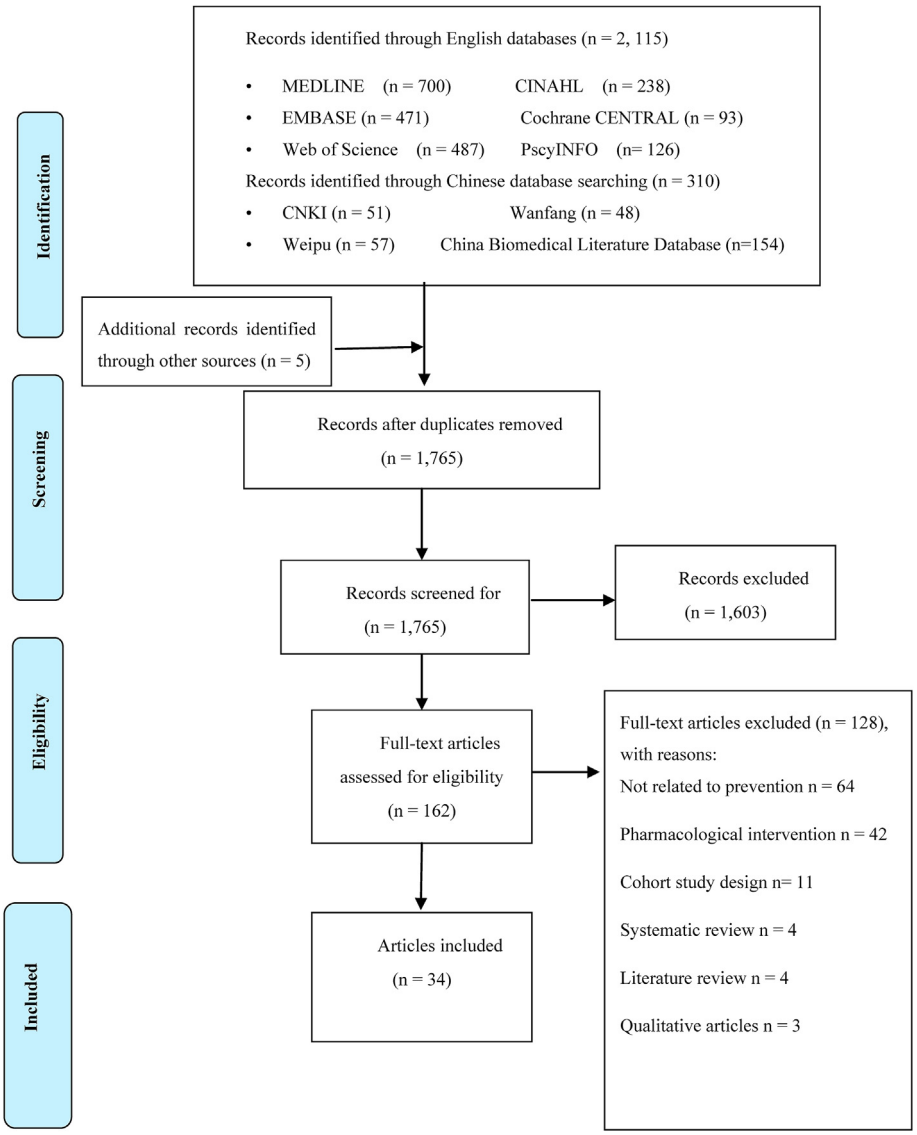


**Fig. 1.** The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart. CNKI = China National Knowledge Infrastructure.

surgical ICU (n = 3), and medical–surgical ICU (n = 6). Twenty studies did not limit the participants to a specific group, whereas the remaining 14 studies limited the participants to the following groups: postoperation (n = 5), use of mechanical ventilators (n = 5), age (n = 2), and duration of ICU stay (n = 2). The sample size for each study ranged from 80 to 734 participants. Of the studies that provided details, the mean age of the participants ranged from 50.7 to 73.7 years (Table 1).

### 3.3. Characteristics of the interventions

Table S1 summarises the intervention details of the included studies. Nonpharmacological interventions were classified into one of the seven categories: multicomponent interventions (n = 15), early mobilisation (n = 7), family participation (n = 5), music (n = 2), patient education (n = 2), the physical environment (n = 2), and sleep promotion (n = 1).

In the aforementioned classification, multicomponent interventions refer to a multifaceted intervention involving a combination of several single-component interventions, such as awakening and breathing coordination, delirium monitoring, early mobilisation, family participation, physical environment, sleep promotion, sensory stimulation, and music.[11] Eight of the 15 studies involved sensory stimulation, which was a core component of three studies.[24,45,52] However, no study determined the effects of sensory stimulation alone on the prevention of delirium in ICUs. Other single-component interventions, such as changes to the physical environment and sleep promotion, were evaluated in an individual study.[42,53]

For early mobilisation, the doses ranged from two to four times per day during the ICU stay, 15–30 min each, and the components included performing range-of-motion exercises, sitting at the edge of the bed, transferring from bed to chair, and early ambulation.[54] Strategies for family participation included extended family visitation time and offering psychological support to family members.[22,25] Music interventions included playing the patients' favourite music three times a day during the ICU stay for 20–40 min each time.[48] Patients' education included equipping patients with knowledge about delirium and familiarising them with the ICU environment before they had an operation or were admitted to an ICU.[34] Changes to the physical environment refers to a modification of the physical environment (e.g., single-bed room

**Table 1**
Characteristics of the included studies (N = 36).

| Author (year)/country | Design | Type of the ICU | Type of participants | Sample size | Mean age (years) | Delirium measurement | Intervention types | Outcomes |
|---|---|---|---|---|---|---|---|---|
| Balas et al., (2014)/USA | CBA | M-SICU | N-S | I:150 C:146 | I:56 C:60 | CAM-ICU | Multicomponent | a, b, c, d |
| Black et al., (2011)/UK | CCT | ICU | N-S | I: 69 C: 69 | I: NA C: NA | ICDSC | Family participation | e |
| Bounds et al., (2016)/USA | CBA | ICU | N-S | I: 79 C: 80 | I: 65 C: 67 | ICDSC | Multicomponent | a, b, c |
| Bryczkowski et al., (2014)/USA | CBA | SICU | Age ≧50 years | I: 66 C:57 | I: 67 C:66 | CAM-ICU | Multicomponent | a, b, c, d |
| Chen et al., (2018)/China | CBA | ICU | N-S | I:85 C:71 | I: NA C: NA | CAM-ICU | Family participation | a, c, f |
| Chevillon et al., (2015)/USA | RCT | M-SICU | After pulmonary operation | I: 63 C:66 | I: 53 C:55 | CAM-ICU | Patient education | a, c, e |
| Colombo et al., (2012)/Italy | CBA | ICU | N-S | I:144 C:170 | I: NA C: NA | CAM-ICU | Multicomponent | a |
| Dou et al., (2018)/China | CBA | ICU | N-S | I:248 C:245 | I: NA C: NA | CAM-ICU | Early mobilisation | a |
| Fraser et al., (2015)/USA | CCT | ICU | N-S | I: 66 C:66 | I: 66 C: 64 | CAM-ICU | Early mobilisation | b, c, |
| Gan et al., (2017)/China | CBA | ICU | N-S | I:213 C:178 | I: NA C: NA | CAM-ICU | Family participation | a, c, f |
| Guo et al., (2016)/China | RCT | SICU | After oral cancer | I: 81 C:79 | I:73 C:74 | CAM-ICU | Multicomponent | a, b, e |
| Guo and Fan (2016)/China | CCT | ICU | After abdominal surgery | I: 59 C:63 | I: 54 C:52 | DDS | Multicomponent | a |
| Huang et al., (2014)/China | CCT | ICU | MV | I:46 C:46 | I: NA C: NA | CAM-ICU | Early mobilisation | a |
| Huang et al., (2017)/China | CCT | ICU | MV | I:40 C:40 | I: 56 C:55 | CAM-ICU | Early mobilisation | a, b |
| Jacob (2017)/USA | CBA | MICU | N-S | I:150 C:151 | I:65 C : 66 | CAM-ICU | Multicomponent | a, c |
| Karadas et al.,(2016)/Turkey | RCT | MICU | Age ≥65 years | I: 47 C:47 | I: 75 C:73 | CAM-ICU | Early mobilisation | a, b |
| Kram et al., (2015)/USA | CBA | ICU | N-S | I: 36 C:47 | I: NA C: NA | ICDSC | Multicomponent | a, c, |
| Lee and Kim (2014)/Korea | CCT | ICU | After liver surgery | I: 68 C:62 | I: 51 C: 52 | Neurological physicians | Multicomponent | a, c, |
| Lee et al., (2013)/Korea | CBA | SICU | After cardiac surgery | I: 49 C:46 | I:59 C:62 | DSM-IV | Patient education | a, c |
| Ma et al., 2015/China | RCT | ICU | N-S | I:84 C:80 | I:53 C:47 | ICDSC | Family participation | a |
| Martinez (2017)/Chile | CBA | M-SICU | N-S | I:227 C: NA | I:64 C: NA | CAM-ICU | Multicomponent | a |
| Moon et al., (2015)/Korea | RCT | ICU | N-S | I: 60 C:63 | I:70 C:69 | CAM-ICU | Multicomponent | a, c |
| Patel et al., (2014)/UK | CBA | M-SICU | Admitted ≧24 h | I:171 C:167 | I:61 C:60 | CAM-ICU | Multicomponent | a, b |
| Rivosecchi et al., (2016)/USA | CBA | MICU | N-S | I:253 C:230 | I: 59 C:59 | ICDSC | Multicomponent | a, b, c |
| Rosa (2017)/Brazil | CBA | M-SICU | N-S | I:145 C:141 | I:61 C:62 | CAM-ICU | Family participation | a, b, c, d |
| Schweickert (2009)/USA | RCT | MICU | MV ≧ 24 h | I: 49 C:55 | I:58 C:54 | CAM-ICU | Early mobilisation | b, c |
| Simon et al., (2016)/ Netherlands | RCT | ICU | N-S | I:361 C:373 | I:66 C:64 | CAM-ICU | Physical environment | a, b, c, d |
| Smith (2017)/USA | CCT | M-SICU | N-S | I:149 C: 298 | I: NA C: NA | CAM-ICU | Multicomponent | a |
| Van et al., (2012)/Belgium | RCT | ICU | N-S | I: 69 C:67 | I: 57 C:62 | NEECHAM | Sleep promotion | a |
| Wang et al., (2016)/China | RCT | ICU | MV | I:50 C:50 | I:51 C:51 | CAM-ICU | Early mobilisation | a, b |
| Zaal et al., (2013)/Netherlands | CBA | ICU | Admitted ≧ 24 h | I: 75 C:55 | I:58 C:60 | CAM-ICU | Physical environment | a, c, d |
| Zhang et al., (2015)/China | CBA | ICU | MV > 12 h | I:84 C:83 | I:52 C:54 | CAM-ICU | Multicomponent | a, b |
| Zhang et al., (2017)/China | RCT | ICU | N-S | I:116C:115 | I:56 C:59 | CAM-ICU | Music | a |
| Zhao et al., (2018)/China | CCT | ICU | N-S | I:40 C:40 | I: NA C: NA | CAM-ICU | Music | a, c |

a = delirium incidence; b = delirium duration; c = the length of ICU stay (days); d = ICU mortality; e = psychological outcomes; f = satisfaction of care; RCT = randomised controlled trial; CCT = controlled clinical trial; CBA = controlled before-and-after study; I = intervention; C = control; NA = not available; N-S = nonspecific; ICU = intensive care unit; SICU = surgical intensive care unit; MICU = medical intensive care unit; CICU = cardiac ICU; CABG = coronary artery bypass grafting; CAM-ICU = Confusion Assessment Method for the Intensive Care Unit; ICDSC = Intensive Care Delirium Screening Checklist; DDS = Delirium Detection Score; DSM IV = Diagnostic and Statistical Manual of Mental Disorders IV; NEECHAM = Neelon and Champagne.

and use of dynamic light).[42] Sleep promotion interventions included the provision of earplugs or reducing noise during the night[53] (Table S2).

### 3.4. Risk-of-bias assessment

Table S3 summarises the methodological quality assessment of the RCTs. Among 10 RCTs, one study lacked details about the randomisation method used, namely, blocked or simple randomisation.[34] Allocation concealment was not performed in five studies, which made them subject to selection bias.[32–34,38,43] The blinding of participants and people who delivered the intervention was not possible in any study as the participants could easily identify the group they had been allocated to because of the nature of the intervention. This could have introduced performance bias. Detection bias was also a concern because insufficient details on assessor blinding were found in seven studies.[29,32–34,38,43,47] Unclear comparability at baseline was found in one study.[38]

Tables S4 and S5 summarise the methodological quality assessment of the nonrandomised experimental studies. Among 24 nonrandomised experimental studies, baseline comparability was judged to be adequate in three studies,[27,49,51] and unclear in seven studies.[24,31,35,36,39,42,45] There were statistically significant baseline differences between the intervention and comparison groups in terms of sex, admission type, severity of the disease, and comorbidity, which may influence the interpretation of the results. However, none of the studies reported the adjusted OR values for baseline confounding.[24,27,31,35,36,39,42,45,49,51] In addition, no significant baseline comparability was observed in the other 14 studies.[9,14,22,23,25,26,28,30,37,44,46,48,50,52]

Overall, the risk of bias was prevalent among the randomisation process, assessor blinding, and confounding control. In addition, only two studies estimated the appropriate sample size by performing a power analysis.[38,53]

### 3.5. Effects of interventions

Only studies measuring clinical outcomes were subjected to meta-analysis (Table 2). Owing to the scarcity of the included studies, the patients' psychological outcomes, family outcomes, and other outcomes were narratively described. Pooled analyses of different intervention categories were conducted (Supplementary Material 3). The OR values of multicomponent interventions were higher than those of single-component interventions.

### 3.5.1. Nonpharmacological interventions vs control

*3.5.1.1. Delirium incidence, duration, ICU LOS, and mortality.* In a comparison between all types of nonpharmacological intervention and the control group, the pooled analysis demonstrated a statistically significant effect on decreasing the delirium incidence (OR = 0.43, 95% CI [0.33, 0.55], 28 studies, 6427 participants, $I^2$ = 78%, low-certainty evidence) and duration (MD = −1.43 days, 95% CI [−1.94, −0.92], 11 studies, 2082 participants, $I^2$ = 97%, low-certainty evidence) as well as the ICU LOS (MD = −1.24 days, 95% CI [−2.05, −0.43], 18 studies, 4239 participants, $I^2$ = 89%, low-certainty evidence). The pooled analysis of the four studies found insufficient evidence for an effect on decreasing mortality (OR = 0.77, 95% CI [0.55, 1.09], four studies, 1283 participants, $I^2$ = 28%, moderate-certainty evidence) (Analysis S1).

*3.5.1.2. Level of anxiety and quality of psychological recovery.* Three studies reported the psychological outcomes of the patients. One study reported that preoperative education did not reduce the levels of trait and state anxiety of patients upon intervention completion ($p > 0.05$).[34] Guo and Fan[36] used the 40-item Quality of Recovery Score questionnaire based on five dimensions (emotional state, physical comfort, psychological support, physical independence, and pain). A significant improvement ($p < 0.05$) was found at three different time points (the first 3 days upon admission to an ICU) in the intervention group. Black et al.[22] used the Sickness Impact Profile based on three dimensions (physical, psychosocial, and emotional activities) and also found a significant improvement at three time points (the first 3 days upon admission to an ICU) in the intervention group ($p < 0.05$).

As per the summary of findings for main comparison, the narrative synthesis indicated nonpharmacological interventions improved patients' quality of psychological recovery during the first 3 days upon admission to an ICU (two studies, 298 participants, very low-certainty evidence). However, an insufficient evidence for an effect on patients' anxiety was observed upon completion of the intervention (one study, 129 participants, low-certainty evidence).

*3.5.1.3. Families' satisfaction with care.* Two studies used the Chinese version of Critical Care Family Satisfaction Survey to investigate the family satisfaction.[27,51] The Chinese version of Critical Care Family Satisfaction Survey includes 27 items: information (seven items), guarantees (seven items), acceptance (three items), support (six items), and comfort (four items), and each item is scored from 1 to 5 points. The results could not be pooled because one study reported on the total satisfaction level with care scores,[27] and another only reported the score for each item rather than the total scores;[51] the authors did not respond to attempts to contact them. Significant improvement in satisfaction with care ($p < 0.05$) was found in the intervention group upon completion of the intervention in both studies.

As per summary of findings for main comparison, there is very low-certainty evidence that the nonpharmacological interventions led to statistically significant improvement in the families' satisfaction with care (two studies, 547 participants).

### 3.5.2. Nonpharmacological multicomponent interventions vs control

Of the 15 studies that investigated the effects of multicomponent interventions, 13 measured delirium incidence,[9,14,28,30,36,37,41,44–47,52,55] seven measured delirium duration,[14,37,41,42,44,45,52] 10 measured LOS in the ICU,[9,14,30,31,37,42,44,45,47,52] and two measured mortality.[9,37]

The pooled analyses showed statistically significant effects on decreasing delirium incidence (OR = 0.48, 95% CI [0.34, 0.69], 13 studies, 3172 participants, $I^2$ = 77%, moderate-certainty evidence) and duration (MD = −1.47 days, 95% CI [−2.2, −0.75], seven studies, 1666 participants, $I^2$ = 98%, low-certainty evidence), the LOS in the ICU (MD = −1.01 days, 95% CI [−1.77, −0.25], 10 studies, 2036 participants, $I^2$ = 70%, low-certainty evidence), and mortality (OR = 0.51, 95% CI [0.26, 0.97], two studies, 419 participants, $I^2$ = 0%, low-certainty evidence) (Analysis S2).

### 3.5.3. Early mobilisation vs control

Of the seven studies that investigated the effects of early mobilisation, five measured delirium incidence,[26,38,43,49,50] four measured delirium duration,[39,40,43,49] and two measured the LOS in the ICU.[39,40]

The pooled analyses demonstrated statistically significant effects on decreasing delirium incidence (OR = 0.33, 95% CI [0.24, 0.46], five studies, 859 participants, $I^2$ = 24%, moderate-certainty

**Table 2**
Summary of effect size (nonpharmacological interventions versus control).

| Intervention type | Outcome | k | Effect size (OR* or MD) | 95% CI | | p | $I^2$ | Quality of evidence (GRADE) |
|---|---|---|---|---|---|---|---|---|
| | | | | Lower | Upper | | | |
| Multicomponent | Delirium incidence | 13 | 0.48* | 0.34 | 0.69 | <0.0001 | 77% | Moderate |
| | Delirium duration | 7 | −1.35 | −1.68 | −1.02 | <0.0001 | 98% | Low |
| | ICU LOS | 9 | −1.01 | −1.77 | −0.25 | 0.009 | 70% | Low |
| | Mortality | 2 | 0.51* | 0.26 | 0.97 | 0.04 | 0% | Low |
| Early mobilisation | Delirium incidence | 5 | 0.33* | 0.24 | 0.46 | <0.0001 | 24% | Moderate |
| | Delirium duration | 4 | −1.24 | −1.43 | −1.04 | <0.0001 | 0% | Moderate |
| | ICU LOS | 2 | −1.02 | −2.88 | 0.84 | 0.28 | 54% | Very low |
| Family participation | Delirium incidence | 4 | 0.25* | 0.18 | 0.34 | <0.0001 | 21% | Moderate |
| | ICU LOS | 3 | −2.31 | −4.14 | −0.48 | 0.01 | 92% | Very low |
| Music | Delirium incidence | 2 | 0.47* | 0.28 | 0.79 | 0.004 | 0% | Low |
| Patient education | Delirium incidence | 2 | 0.45* | 0.24 | 0.83 | 0.01 | 38% | Low |
| | ICU LOS | 2 | −5.3 | −13.11 | 2.5 | 0.18 | 86% | Very low |
| Physical environment | Delirium incidence | 2 | 1.16* | 0.88 | 1.53 | 0.3 | 23% | Low |
| | Mortality | 2 | 0.92* | 0.61 | 1.39 | 0.69 | 16% | Very low |
| | ICU LOS | 2 | 0.15 | −0.49 | 0.79 | 0.65 | 48% | Very low |
| Overall | Delirium incidence | 28 | 0.43* | 0.33 | 0.55 | <0.0001 | 78% | Low |
| | Delirium duration | 11 | −1.43 | −1.94 | −0.92 | <0.0001 | 97% | Low |
| | ICU LOS | 18 | −1.24 | −2.05 | −0.43 | 0.003 | 89% | Low |
| | Mortality | 4 | 0.77* | 0.55 | 1.09 | 0.14 | 28% | Low |

Note: * = OR; LOS in the ICU = length of stay in the intensive care unit; OR = odds ratio; MD = mean difference; k = number of studies; CI = confidence interval; GRADE = Grading of Recommendations Assessment, Development, and Evaluation.

evidence) and duration (MD = −1.24 days, 95% CI [−1.43, −1.04], four studies, 416 participants, $I^2$ = 0%, moderate-certainty evidence). A positive effect on decreasing the LOS in the ICU was found, but statistical significance was not reached (MD = −1.02 days, 95% CI [−2.88, 0.84], two studies, 282 participants, $I^2$ = 54%, very low-certainty evidence) (Analysis S3).

#### 3.5.4. Family participation vs control

Of the five studies that investigated the effects of family participation, four measured delirium incidence,[25,27,32,51] and three measured LOS in the ICU.[25,27,51]

The pooled analysis of these four studies demonstrated a statistically significant effect on decreasing the delirium incidence (OR = 0.25, 95% CI [0.18, 0.34], four studies, 997 participants, $I^2$ = 21%, moderate-certainty evidence). The pooled analysis of three of these studies indicated positive effect on the LOS in the ICU (MD = −2.31 days, 95% CI [−4.14, −0.48], three studies, 833 participants, $I^2$ = 92%, very low-certainty evidence) (Analysis S4).

#### 3.5.5. Music vs control

Two studies investigated the effects of music on delirium incidence.[29,48] The pooled analysis indicated a statistically significant effect of music on decreasing delirium incidence (OR = 0.47, 95% CI [0.28, 0.79], two studies, 311 participants, $I^2$ = 0%, low-certainty evidence) (Analysis S5).

#### 3.5.6. Patient education vs control

Two studies investigated the effects of patient education on delirium incidence and the LOS in the ICU.[23,34] The pooled analysis indicated that patient education resulted in a statistically significant decrease in delirium incidence (OR = 0.45, 95% CI [0.24, 0.83], two studies, 224 participants, $I^2$ = 38%, low-certainty evidence) but had no significant effect on LOS in the ICU (MD = −5.3 days, 95% CI [−13.11, 2.5], two studies, 224 participants, $I^2$ = 86%, very low-certainty evidence) (Analysis S6).

#### 3.5.7. Physical environment vs control

Two studies investigated the effects of the physical environment on delirium incidence, ICU LoS and mortality.[33,42] The pooled analysis demonstrated an insignificant effect on all patients' clinical outcomes, including delirium incidence (OR = 1.16, 95% CI [0.88, 1.53], two studies, 864 participants, $I^2$ = 23%, low-certainty evidence), the ICU LOS (MD = 0.15 day, 95% CI [−0.49, 0.79], two studies, 864 participants, $I^2$ = 16%, very low-certainty evidence), and mortality (OR = 0.92, 95% CI [0.61, 1.39], two studies, 864 participants, $I^2$ = 48%, very low-certainty evidence) (Analysis S7).

#### 3.5.8. Sleep promotion vs control

Only one study investigated the effect of sleep promotion.[53] It reported that the use of earplugs decreased the risk of delirium or confusion by 53% for the participants in the intervention group.

### 3.6. Publication bias

A funnel plot of the included studies reporting ICU LoS was generated (Fig. 2). All studies were observed to lie inside the 95% CIs, with an even distribution around the vertical. Consequently, there was no obvious publication bias.

## 4. Discussion

### 4.1. Effects of nonpharmacological interventions

To the best of our knowledge, this systematic review is the first to explore and quantitatively analyse the effects of nonpharmacological interventions on patients' psychological outcomes (level of anxiety, quality of psychological recovery) and family outcomes (satisfaction with care). For patients' psychological outcomes, narrative synthesis indicated that nonpharmacological interventions exerted a positive effect on patients' psychological recovery during the first 3 days upon ICU admission. However, there was insufficient evidence on the effect of nonpharmacological interventions in reducing patients' anxiety. For the family outcome, very low-certainty evidence demonstrates a significant improvement in families' satisfaction with care upon completion of the interventions.

Psychological outcomes are important for a patient's quality of life.[56] Studies have reported that patients who suffered delirium during an ICU stay experienced a higher prevalence of post-traumatic stress disorder (19–33%)[57] and depression (17–43%)[58] after their discharge. Family caregivers were found to have a significant increase in the level of anxiety and a decrease in the level of satisfaction when caring for their loved ones with delirium symptoms.[2] The evidence for patients' quality of psychological recovery and families' satisfaction with care is limited by imprecision owing to small sample sizes. More studies are required before recommendations can be made about the effects of nonpharmacological interventions on patients' psychological outcomes and family outcomes.

For patients' clinical outcomes, the results of this review are consistent with two previous reviews. A review by Kang et al.[10] suggested that nonpharmacological interventions were effective in reducing delirium incidence and delirium duration. A review conducted by Trogrlić et al.[12] reported beneficial effects of the ABCDE bundle in reducing delirium incidence. Although consistent with these two reviews, the findings of our review must be interpreted with caution because the evidence quality was downgraded owing to nonrandomisation, absence of allocation concealment, and substantial statistical heterogeneity among nonpharmacological interventions. For example, we graded the outcome as moderate certainty of evidence if nonrandomised experimental studies were involved. Furthermore, we downgraded the level as per heterogeneity and imprecision (small sample size). See details in Supplementary Material 2.

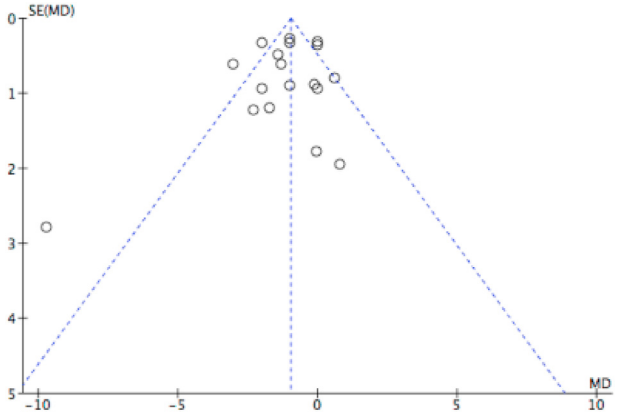


**Fig. 2.** Funnel plot illustrating meta-analysis of ICU length of stay. SE = standard error; MD = mean difference; ICU = intensive care unit.

### 4.2. Effects of different categories of nonpharmacological intervention

Moderate-certainty evidence shows that various nonpharmacological interventions (early mobilisation, family participation, and use of multicomponent interventions) are effective in improving ICU patients' clinical outcomes.

Nonpharmacological multicomponent interventions had a higher OR value than single-component interventions (such as early mobilisation and family participation). The risk factors for delirium are complex, and multicomponent interventions, in comparison with single-component interventions, use more diverse methods to deal with these risk factors and are, therefore, better at reducing delirium incidence and duration.[14] Among the various identified components of multicomponent interventions, sensory stimulation was adopted in eight of 15 studies. Although the studies suggested that sensory stimulation was a core component of these multicomponent interventions, no study tested its effect in isolation on delirium prevention.[24,45,52] Sensory deprivation is a prevalent risk factor for delirium onset from a patient's admission to an ICU owing to the unfamiliar environment and the effects of sedation, an artificial airway, and lack of communication.[24] Sensory stimulation aimed at promoting sensory input by stimulating patients' vision and hearing was effective in reducing patients' confusion, thus decreasing the occurrence of delirium.[35] Future trials for assessing sensory stimulation are needed to enable a comprehensive understanding of its effects on the prevention of ICU delirium.

Our review also shows that early mobilisation and family participation are associated with decreased delirium incidence and duration. With regard to early mobilisation, the dose (three times every day, 30 min each time) and main content (performing range-of-motion exercises, sitting at the edge of the bed, transferring from bed to chair, and early ambulation) indicated significant effects in preventing delirium. However, more investigation into them is needed. Immobility is highly associated with delirium, and patients in an ICU are less likely to be mobilised owing to factors such as tubes, sedation, vasopressor medications, and physical restraints.[59] Some early mobilisation programmes showed positive effects on reducing delirium incidence by implementing goal-directed mobility management.[60,61]

For family participation, extended family visitation or offering psychological support seems to be beneficial. Rosa et al.[25] engaged the family in delirium prevention through an extended visitation model, which resulted in a reduced delirium incidence (9.6% vs 25%) and duration (1.5 vs 3 days) in the intervention group compared with the control group. Furthermore, according to Murno et al.,[62] psychological support from family caregivers was both potentially beneficial in reducing family members' level of anxiety and managing and preventing delirium. Explicit descriptions of the development and application of early mobilisation and family participation interventions are crucial for their replications and hence the transferability of the results. This review also found that family participation might be effective in reducing delirium incidence and improving family satisfaction with care. However, owing to the small sample size, a lack of concealment of the group allocation, and outcome assessor blinding, we are uncertain about the pooled effect size. Enhancing family caregivers' physical and psychological wellbeing is also of great importance and deserves further attention.[63] This finding might suggest that more trials of delirium-preventive interventions with family support are warranted.

Conclusions could not be drawn with regard to the effects of patient education, music, and change in the physical environment on delirium incidence, delirium duration, and ICU LoS due owing to the limited number of eligible studies and very low quality of evidence. Further trials are necessary.

### 4.3. Limitations

Several limitations of this systematic review have been identified. First, some outcomes, such as delirium duration and ICU LOS, may not follow normal distribution. The individual study effects estimated by MDs may therefore violate normality assumption in the statistical pooling method used, particularly in the DerSimonian–Laird random-effects model.[64] Regardless, a simulation study by Kontopantelis and Reeves[65] previously revealed that commonly used fixed- or random-effects methods in meta-analysis could still yield robust results amid severe violations of normality assumption of individual study effects.

Second, the number of studies in some meta-analyses in the study, such as patient education and music, is small ($k < 5$). The use of the DerSimonian–Laird random-effects method may consequently lead to narrower CIs and flawed *P* values.[18] Hence, caution is needed when interpreting such meta-analysis results.

Third, in view of the limited number of RCTs available (one or two), we combined RCTs and non-RCTs in the meta-analysis of each intervention type. Furthermore, as some intervention types were covered by fewer than five studies, we largely reported on the combined meta-analysis results, providing the forest plot of subgroup analysis in Supplementary Material 4. Nevertheless, our findings were supported by the subgroup analysis, which showed that the result of the only RCT did not deviate from the overall effect from combining all studies.

Fourth, the Grading of Recommendations Assessment, Development, and Evaluation estimates implied that most evidence was of low quality. However, this was due to the inclusion of mostly nonrandomised experimental studies. We limited the grading of an outcome for nonrandomised experimental studies to moderate certainty of evidence. In addition, we downgraded the evidence level based on the degree of heterogeneity and imprecision ($I^2 > 50\%$ or small sample size) as high heterogeneity of the included population and settings in individual studies may affect the generalisability of results. Therefore, this resulted in the generally low rating of the evidence level. In conclusion, studies of all methodological quality (including low-quality studies wherein results are less reliable) were combined in meta-analysis, and thus, the findings must be interpreted accordingly.

Finally, this review was limited to journal articles written in English and Chinese. As we omitted non-English and non-Chinese evidence, there may be additional bias in our reported findings.

### 4.4. Implications for research

The included studies investigated the effects of nonpharmacological interventions on patients' outcomes but rarely focused on patients' psychological outcomes, which are important for improving the quality of care. More research studies should be conducted that focus on the psychological wellbeing of ICU patients. Allocation concealment methods and assessor blinding were not sufficiently reported in several RCTs, and confounding factors were not identified for several controlled clinical trials, which makes it difficult for readers to judge the studies' reliability and validity. Researchers are thus urged to report their studies in line with the CONSORT statement. Owing to heterogeneity among nonpharmacological interventions, future well-designed studies that follow standardised intervention protocols are necessary. Multicomponent interventions enhanced the reduction of delirium incidence with moderate-certainty evidence; however, it is unclear which components of these interventions contributed to the effects. No study tested the effect of sensory

stimulation alone on the prevention of delirium in ICU patients, although it was reported to be a core component of multicomponent interventions. Trials are thus needed to test the effects of sensory stimulation on the prevention of delirium.

### 4.5. Implications for practice

Given that the OR value of multicomponent interventions was higher than that of single-component interventions, a multicomponent intervention should be the priority for the prevention of ICU delirium in clinical practice. There is low-certainty evidence that music and patient education lower delirium incidence. These can be implemented in clinical practice by offering the patient delirium-related knowledge, introducing the ICU environment to patients and family members before patients have an operation or are admitted to the ICU, and playing the patients' favourite music during their ICU stay. The findings of this review suggest that family participation and early mobilisation may be effective non-pharmacological interventions for delirium prevention in ICU patients. Three 30-min interventions a day, comprising range-of-motion exercises, sitting at the edge of the bed, transferring from bed to chair, and early ambulation, are associated with significant effects. Further exploration of them would be beneficial. Extended family visitation and offering psychological support by communicating with and encouraging patients are also suggested.

## 5. Conclusions

Healthcare professionals are encouraged to apply single-component (e.g., early mobilisation, family participation) or multicomponent interventions in clinical practice to prevent delirium onset in ICU patients. Further studies investigating the effects of nonpharmacological interventions on patients' psychological and family outcomes are warranted.

## Conflict of 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.

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## CRediT authorship contribution statement

**Liang Surui:** Conceptualisation, Methodology, Data curation, Writing - original draft preparation.

**Janita Pak Chun Chau:** Conceptualisation, Methodology, Writing - reviewing and editing.

**Suzanne Hoi Shan Lo:** Conceptualisation, Methodology, Writing - reviewing and editing.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.aucc.2020.10.004.

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