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Non-pharmacological interventions for preventing delirium in hospitalised non-ICU patients (Review)

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[Intervention Review]

Non-pharmacological interventions for preventing delirium in hospitalised non-ICU patients

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ABSTRACT

Background

Delirium is an acute neuropsychological disorder that is common in hospitalised patients. It can be distressing to patients and carers and it is associated with serious adverse outcomes. Treatment options for established delirium are limited and so prevention of delirium is desirable. Non-pharmacological interventions are thought to be important in delirium prevention.

Objectives

To assess the effectiveness of non-pharmacological interventions designed to prevent delirium in hospitalised patients outside intensive care units (ICU).

Search methods

We searched ALOIS, the specialised register of the Cochrane Dementia and Cognitive Improvement Group, with additional searches conducted in MEDLINE, Embase, PsycINFO, CINAHL, LILACS, Web of Science Core Collection, ClinicalTrials.gov and the World Health Organization Portal/ICTRP to 16 September 2020. There were no language or date restrictions applied to the electronic searches, and no methodological filters were used to restrict the search.

Selection criteria

We included randomised controlled trials (RCTs) of single and multicomponent non-pharmacological interventions for preventing delirium in hospitalised adults cared for outside intensive care or high dependency settings. We only included non-pharmacological interventions which were designed and implemented to prevent delirium.

Data collection and analysis

Two review authors independently examined titles and abstracts identified by the search for eligibility and extracted data from full-text articles. Any disagreements on eligibility and inclusion were resolved by consensus. We used standard Cochrane methodological procedures. The primary outcomes were: incidence of delirium; inpatient and later mortality; and new diagnosis of dementia. We included secondary and adverse outcomes as pre-specified in the review protocol. We used risk ratios (RRs) as measures of treatment effect for

dichotomous outcomes and between-group mean differences for continuous outcomes. The certainty of the evidence was assessed using GRADE. A complementary exploratory analysis was undertaker using a Bayesian component network meta-analysis fixed-effect model to evaluate the comparative effectiveness of the individual components of multicomponent interventions and describe which components were most strongly associated with reducing the incidence of delirium.

Main results

We included 22 RCTs that recruited a total of 5718 adult participants. Fourteen trials compared a multicomponent delirium prevention intervention with usual care. Two trials compared liberal and restrictive blood transfusion thresholds. The remaining six trials each investigated a different non-pharmacological intervention. Incidence of delirium was reported in all studies.

Using the Cochrane risk of bias tool, we identified risks of bias in all included trials. All were at high risk of performance bias as participants and personnel were not blinded to the interventions. Nine trials were at high risk of detection bias due to lack of blinding of outcome assessors and three more were at unclear risk in this domain.

Pooled data showed that multi-component non-pharmacological interventions probably reduce the incidence of delirium compared to usual care (10.5% incidence in the intervention group, compared to 18.4% in the control group, risk ratio (RR) 0.57, 95% confidence interval (CI) 0.46 to 0.71, I^2 = 39%; 14 studies; 3693 participants; moderate-certainty evidence, downgraded due to risk of bias).

There may be little or no effect of multicomponent interventions on inpatient mortality compared to usual care (5.2% in the intervention group, compared to 4.5% in the control group, RR 1.17, 95% CI 0.79 to 1.74, I^2 = 15%; 10 studies; 2640 participants; low-certainty evidence downgraded due to inconsistency and imprecision).

No studies of multicomponent interventions reported data on new diagnoses of dementia.

Multicomponent interventions may result in a small reduction of around a day in the duration of a delirium episode (mean difference (MD) -0.93, 95% CI -2.01 to 0.14 days, I^2 = 65%; 351 participants; low-certainty evidence downgraded due to risk of bias and imprecision). The evidence is very uncertain about the effect of multicomponent interventions on delirium severity (standardised mean difference (SMD) -0.49, 95% CI -1.13 to 0.14, I^2=64%; 147 participants; very low-certainty evidence downgraded due to risk of bias and serious imprecision). Multicomponent interventions may result in a reduction in hospital length of stay compared to usual care (MD -1.30 days, 95% CI -2.56 to -0.04 days, I^2=91%; 3351 participants; low-certainty evidence downgraded due to risk of bias and inconsistency), but little to no difference in new care home admission at the time of hospital discharge (RR 0.77, 95% CI 0.55 to 1.07; 536 participants; low-certainty evidence downgraded due to risk of bias and imprecision). Reporting of other adverse outcomes was limited.

Our exploratory component network meta-analysis found that re-orientation (including use of familiar objects), cognitive stimulation and sleep hygiene were associated with reduced risk of incident delirium. Attention to nutrition and hydration, oxygenation, medication review, assessment of mood and bowel and bladder care were probably associated with a reduction in incident delirium but estimates included the possibility of no benefit or harm. Reducing sensory deprivation, identification of infection, mobilisation and pain control all had summary estimates that suggested potential increases in delirium incidence, but the uncertainty in the estimates was substantial.

Evidence from two trials suggests that use of a liberal transfusion threshold over a restrictive transfusion threshold probably results in little to no difference in incident delirium (RR 0.92, 95% CI 0.62 to 1.36; I^2 = 9%; 294 participants; moderate-certainty evidence downgraded due to risk of bias).

Six other interventions were examined, but evidence for each was limited to single studies and we identified no evidence of delirium prevention.

Authors' conclusions

There is moderate-certainty evidence regarding the benefit of multicomponent non-pharmacological interventions for the prevention of delirium in hospitalised adults, estimated to reduce incidence by 43% compared to usual care. We found no evidence of an effect on mortality. There is emerging evidence that these interventions may reduce hospital length of stay, with a trend towards reduced delirium duration, although the effect on delirium severity remains uncertain. Further research should focus on implementation and detailed analysis of the components of the interventions to support more effective, tailored practice recommendations.

PLAIN LANGUAGE SUMMARY

Non-drug approaches for preventing delirium in adults receiving care in hospital outside of intensive care and high dependency units

Review question

We reviewed the evidence for non-pharmacological (non-medication-based) approaches to prevent delirium in adults in hospital, not including those treated in intensive care units (ICU, specialised wards for the care of critically ill patients).

Background

Delirium is an important illness which is common among adults, especially older adults who are in hospital. It is sometimes referred to as an 'acute confusional state'. Typically, a person with delirium has sudden onset of confusion, which fluctuates, and often includes impaired concentration, memory and thinking skills; reduced awareness of surroundings; drowsiness or agitation and restlessness; and hallucinations, which are usually visual (seeing things which are not really there). It can be distressing for the individual with delirium and their family. It is also associated with increased risks of complications, such as dying in hospital, having a longer hospital stay, and requiring more care after discharge. Increasingly, there is evidence that delirium is associated with an increased risk of permanent worsening of memory and thinking skills, including development or worsening of dementia.

Non-pharmacological approaches are approaches which do not use medications, but which focus on other aspects of care. They are already recognised as important in reducing the risk of delirium, particularly multicomponent interventions which target several of the common risk factors for delirium. It is not known which components of these complex interventions are most important in preventing delirium and this was something we wanted to find out.

Study characteristics

We searched up to 16 September 2020 for reports of studies in which people in hospital were randomly allocated to a non-pharmacological intervention intended to prevent delirium or to usual hospital care. We found 22 studies with 5718 participants. Fourteen of the studies were of multicomponent approaches; two studies looked at different cut-offs for giving a blood transfusion after an orthopaedic operation; the remaining six studies all considered different approaches.

Key findings

Multicomponent approaches probably reduce occurrence of delirium by 43% compared to usual hospital care. This means that two in five cases of delirium in adults in hospital wards (other than ICU) can be prevented by multicomponent, non-pharmacological approaches. These interventions may also reduce the length of time people stay in hospital and, if delirium does occur, they may reduce the duration of the delirium episode by about a day. However, these approaches may have little or no effect on the risk of dying in hospital. The studies did not investigate the effect of multicomponent interventions on the development or worsening of dementia. There was little information about whether the interventions had any harmful effects.

Using a new statistical technique, we found that the following components within each intervention were most important for preventing delirium: (a) trying to keep people well-oriented to their surroundings and making their surroundings more familiar, (b) providing stimulation to memory and thinking skills, and (c) trying to improve sleep (through sleep hygiene measures). We could not be so certain about the effect of other components, largely because not enough evidence was available. More research is needed comparing the specific components included in multicomponent interventions to help determine the most effective and efficient ways to prevent delirium.

The evidence for other, single-component, non-pharmacological interventions was very limited.

Certainty of the evidence

There were some limitations in the studies which may affect the results. In many included studies the people in the study and sometimes researchers were aware of who was and was not receiving the intervention.

There was very little information about people living with dementia, who are at greater risk of experiencing delirium.

External funding

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SUMMARY OF FINDINGS

Summary of findings 1. Non-pharmacological multicomponent interventions for preventing delirium in hospitalised non-ICU patients

Multicomponent delirium prevention intervention compared with usual care for hospitalised adults					
Patients: adults (aged 18 years and over) in hospital for any reason **Settings: receiving care in general hospital settings (excluding those in intensive care or high dependency units; also known as level 3 and level 2 critical care settings)** **Intervention: multicomponent interventions designed to prevent delirium** **Comparison: usual hospital care**					
Outcomes **No of participants** **(studies)**	**Illustrative comparative risks* (95% CI)**		**Relative effect** **(95% CI)**	**Certainty of the evidence** **(GRADE)**	**Comments**
	Assumed risk **Risk with usual care**	**Corresponding risk** **Risk with multicomponent intervention**			
Incidence of delirium during hospital admission validated diagnostic instruments[1] 3693 participants (14 studies)	**184 per 1000** [2]	**105 per 1000** (85 to 216)	**RR 0.57** (0.46 to 0.71)	⊕⊕⊕◯ MODERATE[3]	
Inpatient mortality 2640 participants (10 studies)	**45 per 1000** [2]	**52 per 1000** (37 to 73)	**RR 1.17** (0.79 to 1.74)	⊕⊕◯◯ LOW[4]	
New diagnosis of dementia (at any time point after randomisation) Not measured	No relevant studies	No relevant studies	No relevant studies	No relevant studies	
Duration of delirium (days) (any time during hospital admission)	The mean duration of delirium in	The mean duration of delirium in the intervention groups was **0.93**		⊕⊕◯◯	

351 participants (6 studies)	the control groups ranged from **2.1 to 10.2 days**	**days shorter** (2.01 days shorter to 0.14 days longer)		LOW[5]	
Delirium severity (any time during hospital admission) validated diagnostic instruments[6] 147 participants (5 studies)		The standardised mean severity of delirium in the intervention groups was **0.49 standard deviations lower** (1.13 lower to 0.14 higher)[10]		⊕◯◯◯ VERY LOW[7]	A standardised mean severity of 0.49 standard deviations represents a moderate effect. The 95% confidence interval encompasses a very large effect and little or no effect, indicating serious imprecision.
Length of hospital admission (days) 3351 participants (10 studies)	The mean length of hospital admission in the control groups ranged from **5 to 38 days**	The mean length of admission in the intervention groups was **1.30 days shorter** (2.56 days shorter to 0.04 days shorter)		⊕⊕◯◯ LOW[8]	
Discharge from hospital to new long-term care placement 536 participants (1 study)	**247 per 1000** [2]	**190 per 1000** (136 to 264)	**RR 0.77** (0.55 to 1.07)	⊕⊕◯◯ LOW[9]	

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95%CI).
CI: Confidence interval; **RR**: Risk ratio;
GRADE Working Group grades of evidence
HHigh certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

1. Delirium was diagnosed using the CAM, DRS-R-98, DSM-IV, DSM-V criteria
2. The assumed risk is the risk in the control group
3. Downgraded one level for study limitations (high risk of performance bias due to the lack of blinding of participants and personnel in all studies (due to the nature of the intervention) and outcome assessors unblinded in 6 studies)
4. Downgraded one level for inconsistency and one level for imprecision (pooled estimate includes both no effect, appreciable benefit and appreciable harm)

5. Downgraded one level for study limitations (high risk of performance bias due to lack of blinding of participants and personnel) and one level for imprecision (Minimal important difference (MID) of 1 day assumed. 95% confidence limits around the pooled estimate of mean difference includes both 'no difference', and the MID)
6. Delirium severity was assessed using CAM, CAM-S, DRS-R-98
7. Downgraded one level for study limitations (high risk of performance bias due to lack of blinding of participants and personnel and outcome assessors unblinded in 3 studies) and two levels for serious imprecision (based on small, pooled sample size of 147 participants)
8. Downgraded one level for study limitations (high risk of performance bias due to lack of blinding of participants and personnel; outcome assessors unblinded in 4 studies) and one level for inconsistency (significant statistical heterogeneity, with $I^2 = 91\%$)
9. Downgraded one level for study limitations (high risk of performance bias due to lack of blinding of participants, personnel and outcome assessors) and one level for imprecision (based on results from a single study)

BACKGROUND

Description of the condition

Delirium is a disturbance of consciousness and cognition, which usually has a rapid onset and a fluctuating course. The core features of delirium are defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, and include "disturbance in attention, awareness and cognition, which develops over a short period of time and tends to fluctuate in severity during the course of a day. It represents an acute change from baseline and is not better explained by a pre-existing, established or evolving neurocognitive disorder or a severely reduced level of arousal such as coma. There should be evidence from history, physical examination or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal, or exposure to a toxin, or is due to multiple etiologies" (American Psychiatric Association 2013). The *International Statistical Classification of Diseases and Related Health Problems 10th Revision* (ICD-10) definition of delirium is similar, but also includes disturbance of the sleep-wake cycle and does not specify that there is a definitive underlying aetiology (World Health Organization 2016).

Delirium is highly prevalent across all inpatient hospital settings, with an estimated occurrence of 23% (Gibb 2020). The highest prevalence rates were found in patients who had experienced cardiac surgery, neurosurgery, trauma, radiotherapy and neurology (36% to 41%) (Schubert 2018). However, delirium was also common in geriatric medicine, internal medicine, general surgery, reconstructive plastic surgery and cranio-maxillo-facial surgery (22% to 29%) (Schubert 2018). A point prevalence study conducted in Ireland found that 20% of adult hospital inpatients had delirium on a single day and that age was associated with higher prevalence (5% in those under 50 years of age, versus 35% in those aged over 80) (Ryan 2013). Pooled prevalence of delirium from meta-analysis of 25 studies was 15% with cumulative incidence of new delirium of 9% over two weeks (Gibb 2020). This ranges from 11% to 14% in general medicine, 20% to 29% in geriatric medicine, 10% to 27% in stroke units, 47% in palliative care settings and 12% to 51% in orthopaedic units (Inouye 2014).

Delirium is associated with a range of serious adverse health outcomes. Factors associated with poorer outcomes after an episode of delirium include: longer duration and severity; hypoactive delirium subtype; and the presence of comorbid dementia and depression (Jackson 2016a). A meta-analysis of observational study data from older adults found those with delirium were at an increased risk of death (hazard ratio (HR) 1.95, 95% confidence interval (CI) 1.51 to 2.52), after adjusting for age, sex, comorbidity illness or illness severity and baseline dementia (Witlox 2010). Evidence indicates increased hospital length of stay is both a risk factor for developing delirium and an outcome associated with experiencing delirium (Ahmed 2014; Aitken 2017; Pendlebury 2015).

Delirium can have irreversible effects on an individual's function. A UK cohort of hospital admissions with mental health problems found only 25% of those experiencing delirium had a clinically important recovery in their activities of daily living six months after the episode (Whittamore 2013). Delirium is also associated with an increased risk in overall dependency (odds ratio (OR) 2.56, 95% CI 1.37 to 4.76) (Pendlebury 2015). This can lead to an increased risk of requiring formal institutional care (Witlox 2010), particularly for those with delirium superimposed on an existing dementia (Burton 2018).

Undiagnosed cognitive impairment and dementia are common in older adults presenting with delirium (Jackson 2016b). In adults with Alzheimer's disease, an episode of delirium was found to accelerate cognitive decline, compared to those who did not experience delirium (Fong 2009). Combined neuropathological and clinical cohort study data have confirmed that delirium both accelerates existing cognitive decline and is a risk factor for developing dementia (Davis 2012). Delirium symptoms experienced in early older age (60 to 69 years) are associated with poorer cognitive function after adjustment for other dementia risk factors (Tsui 2018).

An important consideration in evaluating the impact of an episode of delirium is both the duration of the episode and the severity, and validated measures are available to quantitatively assess both parameters (Vasunilashorn 2016). Persistent delirium (lasting beyond hospital discharge) is common, estimated to affect "25.6% (95% CI 7.9% to 43.3%)" of older hospitalised patients at three months follow-up (Cole 2009). Dementia, malignancy, multi morbidity, increased delirium severity, hypoactive subtype and hypoxic illness have been independently associated with persistent delirium (Cole 2015; Dasgupta 2010).

Significantly, delirium is distressing, particularly to family members who witness episodes (Finucane 2017), and also may have lasting effects on the individual patient if they recall their in-hospital experiences (Grover 2015; Partridge 2013). It can also cause distress to staff caring for these patients (Agar 2012; Partridge 2013; Waterfield 2018).

Delirium has considerable economic impact on healthcare systems and society (Leslie 2011). Estimates suggest the costs for those with delirium are two and a half times greater per day than for those without delirium (Leslie 2008). The cost-effectiveness of multicomponent delirium-prevention interventions has been demonstrated using data from a non-randomised study (Akunne 2012), however there is a lack of data on cost-effectiveness from randomised trials (Siddiqi 2016).

Description of the intervention

This review assesses the effectiveness of non-pharmacological interventions for preventing delirium in hospitalised patients outside the intensive care unit (ICU) and high dependency unit (HDU) setting. Non-pharmacological interventions can be broadly divided into single component interventions, which often target a specific risk factor, and multicomponent interventions, which target multiple risk factors for delirium. Multicomponent interventions are often based around care delivered according to specific protocols, and target risk factors such as sleep deprivation, immobility, dehydration and sensory impairment (Inouye 1999a). The National Institute for Health and Care Excellence (NICE) recommend assessing for the presence of delirium risk factors in adults aged 65 years and older; those with cognitive impairment; those with a hip fracture; and those with severe illness at the time of hospital presentation (NICE 2010). Thereafter, it recommends a multicomponent intervention tailored to needs and care setting, delivered by a multidisciplinary team (NICE 2010).

How the intervention might work

A number of risk factors for delirium have been identified (Ahmed 2014; Pendlebury 2015; Wilson 2020). While some of these are non-modifiable factors such as age and comorbidity, there are others which are potentially modifiable, including dehydration, sensory impairment and urinary catheterisation (Ahmed 2014). Predictors of incident delirium during a hospital admission include dementia, dependence in activities of daily living, and increased illness severity (O'Regan 2018). Delirium has been described as the interaction between an individual's baseline vulnerability (based on predisposing factors such as age and cognitive function) and precipitating factors or insults occurring during the hospital admission (Inouye 1996). These precipitating factors can be further divided into those which are related to the presenting illness an individual is experiencing and those occurring after admission, which include environmental factors, pain management interventions, and sleep deprivation (Wilson 2020). Furthermore, it has been suggested that a combination of risk factors for delirium may interact to increase vulnerability and that susceptibility can be scored at the time of admission (Pendlebury 2017). It is thought that non-pharmacological interventions can be used to address these risk factors, targeting those vulnerable to developing delirium, as an effective prevention strategy.

Why it is important to do this review

Delirium is common across all inpatient settings and, in view of the serious complications, costs and consequences arising, it is a priority for healthcare practitioners and providers. Establishing the degree to which delirium can be prevented, and identifying evidence-based strategies for prevention, will help inform evidence-based care pathways.

Multicomponent interventions have been shown in randomised controlled trials to reduce the incidence of delirium (Martinez 2015; Siddiqi 2016). However, the reductions seen in delirium incidence have not been associated with statistically significant reductions in length of stay or in longer-term sequelae, including mortality or the need for admission to long-term care (Hshieh 2015; Martinez 2015). There is uncertainty about the precision and certainty of these findings and the extent to which frailty influences outcomes (Teale 2015). Delirium and frailty (defined as '"a diminished ability to compensate for stressors") are conditions associated with poor outcomes in older people and they have been postulated to be different manifestations of "shared vulnerability to stress" (Quinlan 2011). This relationship is complex and poorly understood; recent evidence suggests that mortality risk in delirium is greatest in those with lower levels of frailty (Dani 2018), although the role of illness severity in mediating this association is not known. It would, however, be helpful to identify if those with frailty are differentially affected by delirium-prevention interventions.

Some of the risk factors for delirium — including malnutrition, dehydration, restraint use, and iatrogenic events (condition caused by medical or surgical interventions) — can be seen as measures of the quality of hospital care. The occurrence of delirium has been linked to the quality of care delivered to inpatients, which can highlight areas for improvement (Inouye 1999b). Clinical adverse events which have been associated with delirium, such as falls and pressure ulcers, are also priorities for reduction within inpatient settings. The associations between delirium and dementia mean that interventions to prevent delirium are of interest to the wider public health agenda of dementia prevention (Fong 2015).

Over the past decade there has been a rapid increase in the number of randomised trials of delirium-prevention interventions. In 2007, a Cochrane Review identified six trials evaluating six interventions to prevent delirium, only one of which was a non-pharmacological intervention (Siddiqi 2007). The 2016 update identified 39 trials of 22 interventions, including seven trials of multicomponent interventions and two other non-pharmacological interventions (Siddiqi 2016). There was heterogeneity among the multicomponent interventions studied, with the number of components ranging from two to 13. In this review, we focused on non-pharmacological interventions only to allow a more detailed synthesis of the current evidence in this area. We also add a component network meta-analysis to try to develop understanding of which components are necessary and most effective. This should allow more robust recommendations for practice and future research to be made.

OBJECTIVES

To assess the effectiveness of non-pharmacological interventions designed to prevent delirium in hospitalised non-intensive care unit (ICU) patients.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs), including cluster-RCTs.

Types of participants

We included studies of adult participants (aged 18 years and over) who were admitted to general hospital settings. This included acute and rehabilitation hospitals and sub-acute care provided in hospital. We excluded studies conducted in community settings, such as long-term care or nursing homes; these are considered in a separate Cochrane Review (Woodhouse 2019). If settings were mixed, we only included the study if data could be extracted specifically for the hospitalised patients.

We excluded studies conducted in intensive care unit (ICU) and high dependency unit (HDU) settings, due to the different populations and interventions likely to be found in such environments. ICU settings, also known as Level 3 settings, are those where patients require either respiratory support alone, or support of a minimum of two organs (Intensive Care Society 2009). HDU settings, also known as Level 2 settings, are those where patients either receive single-organ support or are stepping down from Level 3 care; need preoperative optimisation using invasive monitoring; or need extended postoperative care (Intensive Care Society 2009). The evidence for delirium prevention in ICU settings is evaluated in a separate Cochrane Review (Herling 2018).

We excluded studies of delirium associated with psychoactive substance misuse or withdrawal, as these presentations are clinically distinct.

We considered studies of delirium prevention in patients receiving only in-hospital specialist palliative care and evaluated them using

a sensitivity analysis within this review. Delirium prevalence in specialist palliative care settings can be very high (approximately 42% of admissions to specialist palliative care units) and the goals of care may be different in this context (Bush 2017).

Types of interventions

We only included non-pharmacological interventions which were designed and implemented to prevent delirium. We did not include studies targeting those with "geriatric syndromes", rather than delirium specifically.

Eligible interventions were multicomponent interventions or single-component interventions targeting a specific risk factor for delirium (e.g. sleep disturbance, dehydration, disorientation). Interventions could be implemented at the level of the ward or department providing care, or at the individual level.

We excluded studies of pharmacological interventions to prevent delirium. Specifically, this included tablets, infusions, injectable medications, inhaled medications, or anaesthetic gases, given to all participants in active treatment arms with the intention of preventing delirium. Studies that included correction of abnormal physiology using a pharmacological intervention as part of a multicomponent intervention, e.g. administration of oxygen in presence of low oxygen saturations, were eligible for inclusion.

Comparators could be usual care or an active control intervention.

Types of outcome measures

We included all studies which fulfilled our other eligibility criteria and which measured any of the primary or secondary outcomes. We prespecified clinically important secondary outcomes and adverse outcomes which are relevant to patients, families and healthcare providers.

Primary outcomes

1. Incidence of delirium during hospital admission, using a validated diagnostic method. (Studies using only a positive screening test in the absence of a formal diagnosis were excluded.)
2. Mortality as an inpatient, between one and three months, six and 12 months, and beyond 12 months from randomisation.
3. New diagnosis of dementia, made between one and three months, six and 12 months, and beyond 12 months from randomisation.

Secondary outcomes

1. Duration of delirium episode, measured in days.
2. Severity of delirium, measured using validated instruments including the Memorial Delirium Assessment Scale (MDAS) (Breitbart 1997), Delirium Rating Scale (DRS) (Trzepacz 1988), and Delirium Rating Scale Revised 1998 (DRS-R-98) (Trzepacz 2001).
3. Length of hospital admission, measured in days.
4. Use of new psychotropic medication during hospital admission.
5. Activities of daily living, measured using a validated instrument including the Barthel Index (Mahoney 1965) and Katz Index (Katz 1963), between one and three months, six and 12 months, and beyond 12 months from randomisation.
6. Quality of life, measured using a validated patient reported measure, between one and three months, six and 12 months, and beyond 12 months from randomisation.
7. Carer's quality of life, using a validated carer-reported measure, between one and three months, six and 12 months, and beyond 12 months from randomisation.
8. Withdrawal from protocol by participants.

Adverse outcomes

1. Readmission to hospital within 30 days of discharge.
2. Progression of existing dementia, measured using a validated instrument, between one and three months, six and 12 months, and beyond 12 months from randomisation.
3. New care-home admission at discharge and between one and three months, six and 12 months, and beyond 12 months from randomisation.
4. Falls.
5. Pressure ulcers.

Search methods for identification of studies

Electronic searches

We searched ALOIS (www.medicine.ox.ac.uk/alois), the Cochrane Dementia and Cognitive Improvement Group's Specialised Register, up to the 16th September 2020. ALOIS is maintained by the Information Specialists of the Cochrane Dementia and Cognitive Improvement Group and contains studies in the areas of dementia (prevention and treatment), mild cognitive impairment and cognitive improvement. The studies are identified from:

1. monthly searches of a number of major healthcare databases: MEDLINE, Embase, CINAHL, PsycINFO and LILACS;
2. monthly searches of the trial registers: the WHO International Clinical Trials Registry Platform (which covers ClinicalTrials.gov, ISRCTN, the Chinese Clinical Trials Register, the German Clinical Trials Register, the Iranian Registry of Clinical Trials, and the Netherlands National Trials Register, plus others) and ClinicalTrials.gov;
3. quarterly search of the Cochrane Library's Central Register of Controlled Trials (CENTRAL);
4. six-monthly searches of a number of grey literature sources from ISI Web of Science Core Collection.

Details of the search strategies used for the retrieval of reports of trials from the healthcare databases, CENTRAL and conference proceedings can be viewed in the 'Methods used in reviews' section within the editorial information about the Dementia and Cognitive Improvement Group. We performed additional searches in many of the sources listed above, to cover the timeframe from the last searches performed for ALOIS to ensure that the search for the review was as up-to-date and as comprehensive as possible.

The search strategies used are described in Appendix 1. The most recent search was carried out on the 16 September 2020.

Searching other resources

We examined reference lists from identified articles and relevant systematic reviews to identify any additional potential trials to review for eligibility. We searched the ClinicalTrials.gov database,

to identify any relevant ongoing trials. We compared the trials that meet our review inclusion criteria with the trials register to identify any trials where results have been unpublished. We contacted the lead author of any unpublished trials, to ask if they are prepared to share their results (we examined these against the published protocols to ensure they have been consistently analysed).

Data collection and analysis

Selection of studies

We directly imported the results of the literature searches into Covidence software (Covidence 2017). This automatically removed direct duplicate records. Thereafter, two review authors, with experience in conducting systematic reviews, independently screened the titles and abstracts of all identified articles and removed irrelevant results. We resolved any disagreements by discussion, involving a third review author if necessary. Two review authors then independently examined the full-text articles of potentially relevant articles against the review eligibility criteria. We resolved any disagreements by consensus with a third review author. If we were unable to determine eligibility based on the available information, for example if only an abstract was identified, we contacted the study authors for clarification and additional data as necessary. We listed all articles excluded after full-text assessment in the Characteristics of included studies table, with reasons for exclusion. We present a PRISMA diagram to summarise the study selection process (Figure 1).

Figure 1.

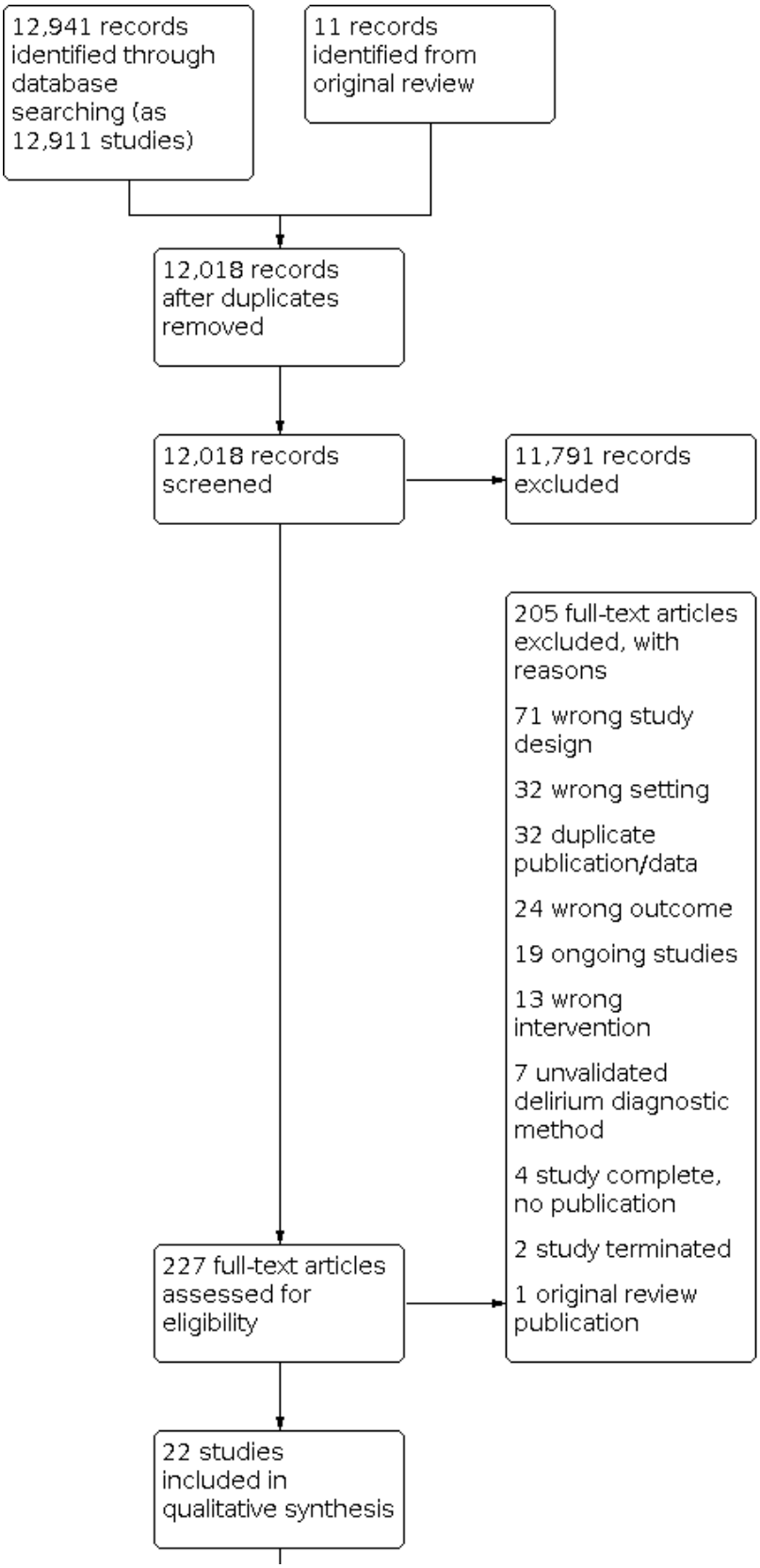
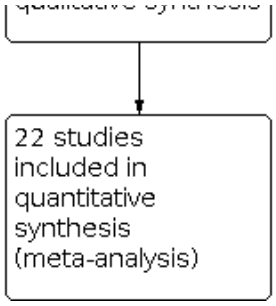


Figure 1. (Continued)



Data extraction and management

We created a data extraction tool, adapted from the version used in the previous version of this review (Siddiqi 2016). Two review authors extracted data using this tool, discussing any disagreements and involving a third author if necessary.

To allow use of more of the reported data for syntheses, where medians and Interquartile ranges (IQR) or ranges were presented rather than means and standard deviations, we converted values as follows. We assumed the median value was equivalent to the mean. We estimated the standard deviation as 'IQR/1.35' or 'range/4' (small studies, n < 70) or 'range/6' (larger studies, n > 70).

For delirium incidence and severity, where results were presented for multiple time points and no summary data were available, we used the highest recorded number or peak values for the intervention and control arm. This was because we were interested in interventions that reduced the overall burden of delirium. For example, if delirium severity was ascertained on days one, three, and five of the hospital stay, then we included only the highest of the three scores (most severe) in our analysis of delirium severity. For severity and duration of delirium, data were included only from patients with delirium.

We used RevMan Web to produce tables documenting the characteristics of included, excluded and ongoing trials (RevMan Web 2021). We created a summary of findings table using GRADE Pro Software (GRADEpro 2014).

Component network meta-analysis

The previous version of this review (Siddiqi 2016), included a descriptive table of multicomponent intervention components, with 20 components described from the seven included studies (Abizanda 2011; Bonaventura 2007; Hempenius 2013; Jeffs 2013; Lundstrom 2007; Marcantonio 2001; Martinez 2012). These 20 'components' were: individualised care; checklists/protocols; structured education/training of staff or carers; reorientation; attention to sensory deprivation; familiar objects; cognitive stimulation; nutrition/hydration; identification of infection; mobilisation; sleep hygiene; multidisciplinary care; comprehensive geriatric assessment; oxygenation; electrolytes; pain control; medication review; mood (assessment for depression/anxiety); bowel/bladder care and postoperative complications.

To undertake our exploratory component network meta-analysis we extracted text from each of the included studies about their specific multicomponent intervention and the components included in each study (Appendix 2). We mapped the 14 included studies to the originally described 20 components and then reviewed these. Due to the small number of identified studies relative to the number of potential components, components had to be grouped to enable analysis to be undertaken. This was done by clinical review authors and experts in network meta-analysis to ensure clinical and methodological integrity in the approach.

We recognised that some of these components described how the intervention was delivered (e.g. individualised care (often described as tailoring), or use of checklists/protocols) as distinct from components of the intervention itself. Thus we considered tailored/individualised care, use of protocol/checklist, staff education and multidisciplinary care as modes of delivery, rather than components. We also considered comprehensive geriatric assessment for inclusion in the network as it was reported in three trials (Hempenius 2013; Lundstrom 2007; Partridge 2017), but clinically this entity encapsulated several of the components already specified (Welsh 2014) and thus we classified it as a mode of delivery, rather than an individual component. Similarly, family involvement, reported in three studies, covered both the delivery of the intervention (Hosie 2020; Martinez 2012; Wang 2020) and a component of the intervention itself (Hosie 2020) so we did not include it as a component in the analysis. Inclusion of family involvement resulted in the model failing to achieve convergence.

Management of postoperative complications was identified in a single study (Marcantonio 2001) and we did not consider it to be analogous to other components, so excluded it. Fluid and electrolyte balance was also only considered in a single study (Marcantonio 2001). Considering the clinical context, we combined this with the nutrition/hydration component and included it in the analysis in this format. Finally, use of familiar objects was reported in two studies (Bonaventura 2007; Martinez 2012). These were only delivered in studies which included a reorientation component and we considered it clinically appropriate to combine these components as reorientation (including use of familiar objects).

Assessment of risk of bias in included studies

Two review authors independently performed a risk of bias assessment. We evaluated each study using the criteria described in the original Cochrane tool for assessing risk of bias (Higgins 2011). We assessed trials for the domains of: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting and other bias.

Cluster-RCTs are subject to additional biases: recruitment bias (recruitment of individual study participants after randomisation of clusters), chance between-cluster baseline imbalances due to a

small number of clusters, loss of clusters (e.g. withdrawal of a study site), not accounting for clustering during the analysis (incorrect unit of analysis issues), or bias introduced through combining data from cluster-randomised and individually-randomised trials in meta analyses (risk of underestimation of treatment effects). We considered those which extended beyond the traditional risk of bias domains under the heading of 'other bias'.

We judged each study as being at either high, low or unclear risk of bias in each domain. We resolved any disagreements by discussion between the two review authors, involving a third author if necessary. We produced summary tables and figures of the risk of bias assessment, with justification, in RevMan Web (RevMan Web 2021). When using GRADE methods to assess the certainty of the evidence from pooled analyses, we downgraded certainty for risk of bias, or study limitations, where the majority or all of included studies had limitations likely to be relevant to the outcome of interest (e.g. we downgraded for high risk of performance and detection bias for outcomes such as delirium incidence; whereas ascertainment of mortality would probably not be affected by lack of blinding but could be subject to important selection or attrition bias).

Measures of treatment effect

For continuous outcomes, we calculated between-group (intervention versus control) mean differences (MDs) with 95% confidence intervals (CIs). If studies used different instruments to measure the same continuous outcome, we calculated the standardised mean difference (SMD). SMD was interpreted in accordance with the Cochrane Handbook. For dichotomous outcomes, we calculated risk ratios (RRs) with 95% CIs.

Unit of analysis issues

Where cluster-randomised studies had analysed data using statistical methods that account for clustering, we extracted the adjusted effect measures (RRs) and their 95% CIs. If an included study reported only unadjusted analyses, then we approximated corrected analyses by extracting data on the number of clusters, mean size of each cluster, primary outcome data and estimates of intra-cluster correlation coefficient (ICC). If approximately corrected analyses were not possible, then we extracted the primary data and calculated RRs with 95% CIs.

Dealing with missing data

We contacted study authors to try to obtain data not reported in the publication. We reported missing data for each included study, including reporting the number of participants included in the final analysis as a proportion of all participants in the study. We performed available-case analysis, including data on those participants whose outcomes were known. We reported incomplete outcome assessment in the risk of bias table for each study, including an assessment of the potential impact of missing data on the results.

Assessment of heterogeneity

We described clinical heterogeneity. If we considered the data to be appropriate for quantitative synthesis, we calculated statistical heterogeneity and described it using the I^2 statistic (Higgins 2002). Interpretation of the I^2 statistic was in accordance with guidance in the Cochrane Handbook (Deeks 2019). Assessment of heterogeneity was based on visual analysis of the forest plot, directions of effect at individual study level and the I^2 statistic, with I^2 of 75% to 100% indicating considerable heterogeneity (Guyatt 2011).

Assessment of reporting biases

We compared the studies included in our review with clinical trial registries, to identify trials with unpublished results. We compared the published studies included in the review against their protocols to check adherence to planned methods.

We used funnel plots to assess for possible publication bias for our two primary outcomes with pooled data (incidence of delirium and in-hospital mortality) for multicomponent interventions and used these to inform our GRADE assessments.

Data synthesis

Where it was appropriate, we performed meta-analysis of extracted data using RevMan Web (RevMan Web 2021). We used a random-effects model. We calculated pooled RRs with 95% CIs for dichotomous outcomes (intervention versus control), and pooled MDs with 95% CIs for continuous outcomes. If studies used different instruments to measure the same continuous outcome, we calculated the SMD. We synthesised outcomes from appropriately adjusted cluster-RCTs. We performed data synthesis only where it was considered that the identified studies were clinically homogenous, such that pooling of data was appropriate and valid comparisons could be made. If the clinical heterogeneity was significant, we reported a narrative evidence synthesis.

Component network meta-analysis

We used a Bayesian component network meta-analysis fixed-effect model to evaluate the comparative effectiveness of the individual components of interventions and to draw conclusions about which components were most strongly associated with reducing the incidence of delirium. A fixed-effect model was used because there were not enough data to estimate between-study heterogeneity. Models were constructed as described by Welton 2009, using code from Freeman 2018 adapted to include a binomial likelihood with logit link for binary outcomes. We fitted an additive effects model which assumes the effects of components add together directly when combined. If data allowed we planned to fit a model relaxing the assumption of additivity through the inclusion of pairwise interactions between components which would allow combinations of components to have synergistic or antagonistic effects. However, due to the small number of trials relative to the number of component parameters in the model we were unable to fit this model.

Bayesian analyses were run using WinBUGS version 1.4.3 and R version 4.0.1 through the R2WinBUGS package (Sturtz 2005). Models were run with a burn in of at least 20,000 iterations and a sample of 30,000 iterations. Convergence was assessed through history and density plots. We used vague prior distributions for trial-specific baselines (e.g. the log-odds of the outcome in the control group) and component effects. Results are reported as odds ratios (ORs) with 95% credibility intervals with component effects reported relative to treatment-as-usual.

Subgroup analysis and investigation of heterogeneity

From our main meta-analysis results we performed subgroup analyses for participants in trials conducted in medical versus surgical inpatient settings; and for those with and without a diagnosis of dementia (measured using a validated diagnostic instrument). We were unable to undertake the planned analysis of those who were considered to have frailty versus those who were not (measured using a validated instrument) due to lack of available data in the included studies.

Sensitivity analysis

Sensitivity analysis to remove studies in which participants were receiving palliative care only versus those receiving other medical or surgical treatment was undertaken as planned.

We did not undertake our planned sensitivity analysis around risk of methodological bias, as all studies were considered at high risk of bias in at least one domain.

In the protocol, we planned sensitivity analyses to address two possible scenarios: uncertainty about the optimal way to define components, and an intervention component being delivered to only a fraction of a trial arm. However, we did not encounter either of these scenarios.

Summary of findings and assessment of the certainty of the evidence

We used GRADEpro Guideline Development Tool software (GRADEpro 2014) to determine the overall certainty of the evidence and to generate a summary of findings table for the outcomes: incidence of delirium, inpatient mortality, new diagnosis of dementia (at any time point after randomisation), duration of delirium, peak delirium severity, length of hospital admission, and discharge to new long-term care placement. We created a summary of findings table only for the multicomponent intervention analysis as the other interventions had too few included studies to draw conclusions.

RESULTS

Description of studies

See Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies

Results of the search

The search results are summarised in a PRISMA diagram (Figure 1). Of the 227 full-text articles retrieved, 26 were considered eligible for inclusion; 182 were excluded (see Excluded studies); and 19 are ongoing (see Characteristics of ongoing studies). Of the 26 studies considered eligible for inclusion, four had no published results available including searching for publications based on author names and study titles from within trial registry entries. We were unsuccessful in attempts to contact the named study contacts identified in the Trial Registry entries by email. These four studies have been listed as 'Studies awaiting classification' and are described in Characteristics of studies awaiting classification. Twenty-two studies are included in the review.

Included studies

The 22 studies included a total study population of 5718 randomised participants. The trials assessed multicomponent and seven different single-component non-pharmacological interventions.

Study design

All 22 studies were randomised controlled trials (RCTs). Four of them were cluster-randomised in design (Chen 2017; Hosie 2020; Wang 2020; Young 2020).

Eighteen studies evaluated a delirium prevention intervention against usual care (Abizanda 2011; Avendano-Cespedes 2016; Bonaventura 2007; Boustani 2012; Cetinkaya 2019; Chen 2017; Dong 2020; Hempenius 2013; Hosie 2020; Jeffs 2013; Lundstrom 2007; Marcantonio 2001; Martinez 2012; Martinez-Velilla 2019; Nadler 2017; Partridge 2017; Wang 2020; Young 2020). Two studies compared use of different thresholds for physiological correction (Fan 2014; Gruber-Baldini 2013). One study compared a delirium prevention intervention to a placebo (Gao 2018). One study compared two different interventions (Watne 2014).

Sample size

The sample size of included studies ranged from 50 to 713 randomised participants. Five studies randomised fewer than 100 participants (Avendano-Cespedes 2016; Bonaventura 2007; Cetinkaya 2019; Gao 2018; Hosie 2020).

Setting

Thirteen studies were conducted in patients under the care of surgical teams for elective or emergency surgical or procedural interventions and care. Orthopaedic settings were the commonest, in eight of the included studies (Cetinkaya 2019; Fan 2014; Gao 2018; Gruber-Baldini 2013; Lundstrom 2007; Marcantonio 2001; Nadler 2017; Watne 2014). In one study, participants were undergoing elective surgery for known cancer (Hempenius 2013). Four studies were conducted in other surgical settings (Chen 2017; Dong 2020; Partridge 2017; Wang 2020). Seven studies were conducted in a general medical or specialist geriatric medical hospital environment (Abizanda 2011; Avendano-Cespedes 2016; Bonaventura 2007; Boustani 2012; Jeffs 2013; Martinez 2012; Martinez-Velilla 2019). One study was conducted in inpatient palliative care settings for individuals with a diagnosis of cancer (Hosie 2020). One study was conducted in both specialist wards for older adults and orthopaedic trauma wards (Young 2020).

Participants

Age

In 12 studies the mean age of included participants was between 70 to 79 years in one or both arms. Seven studies had a mean age in both allocation arms of more than 80 years (Abizanda 2011; Avendano-Cespedes 2016; Gruber-Baldini 2013; Lundstrom 2007; Martinez-Velilla 2019; Watne 2014; Young 2020). Two studies had a mean age of less than 70 years in both allocation arms (Cetinkaya 2019; Nadler 2017). One study did not report data on the mean age of included participants (Bonaventura 2007).

Co-morbidities

Eight studies used the Charlson Index (Charlson 1994) to compare co-morbidities between intervention and control groups

(Avendano-Cespedes 2016; Boustani 2012; Chen 2017; Jeffs 2013; Marcantonio 2001; Martinez 2012; Wang 2020; Young 2020). One study (Boustani 2012) reported higher Charlson Index scores in the usual care group. One study used the Cumulative Illness Rating Scale (Martinez-Velilla 2019), and another the American Society of Anesthesiologists (ASA) score (Gao 2018) to quantify the co-morbidity of participants. Four studies reported a count of conditions experienced by participants (Abizanda 2011; Bonaventura 2007; Cetinkaya 2019; Hempenius 2013). Three studies considered specific co-morbidities and described the distribution of these among recruited participants at baseline (Fan 2014; Gruber-Baldini 2013; Lundstrom 2007). Lundstrom 2007 reported a higher rate of depression among those allocated to the control arm of their study. Four studies did not report co-morbidities at baseline (Dong 2020; Hosie 2020; Nadler 2017; Watne 2014).

Dementia

Three studies excluded all participants with dementia (Bonaventura 2007; Dong 2020; Gao 2018), and three excluded those assessed as having severe dementia (Avendano-Cespedes 2016; Martinez-Velilla 2019; Wang 2020). Six studies reported an imbalance in the proportion of those with dementia between their intervention and control arms, with higher rates in the control arms in Gruber-Baldini 2013; Lundstrom 2007; Marcantonio 2001; Nadler 2017; Partridge 2017 and higher rates in the intervention arm in Young 2020. Three studies did not report specifically on dementia (Boustani 2012; Cetinkaya 2019; Hosie 2020).

Frailty

Only one study included a baseline assessment of the frailty of recruited participants (Wang 2020). This used the Chinese adaptation of the FRAIL scale score (Dong 2018) - with a higher proportion of the intervention group classed as healthy and a higher proportion of the control group considered as frail (Wang 2020).

Interventions

Multicomponent interventions versus usual care

Fourteen studies evaluate multicomponent interventions for delirium prevention, compared to usual hospital care.

We identified characteristics associated with the delivery of the intervention, with the use of tailored interventions mentioned in nine trials (Abizanda 2011; Avendano-Cespedes 2016; Dong 2020; Hempenius 2013; Jeffs 2013; Lundstrom 2007; Marcantonio 2001; Partridge 2017; Wang 2020); protocols/checklists used in 10 trials (Chen 2017; Dong 2020; Hempenius 2013; Hosie 2020; Jeffs 2013; Lundstrom 2007; Martinez 2012; Partridge 2017; Wang 2020; Young 2020). Ten trials had a specific education component as part of the intervention (Abizanda 2011; Avendano-Cespedes 2016; Bonaventura 2007; Chen 2017; Hempenius 2013; Hosie 2020; Lundstrom 2007; Martinez 2012; Wang 2020; Young 2020) and five specified multidisciplinary involvement (Hosie 2020; Lundstrom 2007; Martinez 2012; Partridge 2017; Wang 2020) with three trials specifying family involvement as a key characteristic (Hosie 2020; Martinez 2012; Wang 2020). Many of the delirium risk factors targeted with multi-component interventions relate to good fundamental care, supporting staff within the care team to deliver these aspects consistently.

We identified 12 distinct components of the interventions that could be entered in the network meta-analysis: re-orientation (including use of familiar objects); reducing sensory deprivation (for example hearing aids, spectacles); cognitive stimulation; nutrition and hydration (including electrolyte balance); identification of infection; mobilisation; sleep hygiene; oxygenation; pain control; medication review; bladder and bowel care and assessment of mood. Individual studies included between two and 10 components with a mean and median of six components included in each study. The distribution of these components across the included studies is summarised in Table 1 and Appendix 2 summarises how components were selected.

Liberal versus restrictive blood transfusion thresholds

Intraoperative blood transfusion has been implicated as a risk factor for postoperative delirium (Carson 2011). Subset analysis from a multicentre RCT identified that anaemia was associated with delirium and blood transfusion was associated with reduced risk of delirium (van der Zanden 2016). Gruber-Baldini 2013 and Fan 2014 tested the use of liberal versus restrictive blood transfusion thresholds on risk of incident delirium. Fan 2014 classified liberal transfusion strategy as transfusing to maintain haemoglobin ≥10g/dL and restrictive strategy as only transfusing when haemoglobin < 8 g/dL or when symptoms of anaemia developed. Gruber-Baldini 2013 gave their liberal transfusion group one unit of packed red blood cells and as much as needed to maintain haemoglobin ≥10 g/dL; their restrictive group was treated in the same way as described by Fan 2014.

Care in geriatric medicine unit versus in orthopaedic unit following hip fracture

Individuals admitted following a fracture are typically placed under the care of an orthopaedic surgeon, pending operative intervention. However, the complex nature of the predominantly older adult population who experience a hip fracture has led to the emergence of orthogeriatric medicine services, where input is also received from physicians specialist in the care of older adults. Comprehensive geriatric assessment (CGA) is an evidence-based "multidimensional interdisciplinary diagnostic process used to determine the medical, psychological and functional capabilities of a frail older person to develop a coordinated and integrated plan for treatment and long-term follow-up" associated with improved outcomes, particularly when delivered in a dedicated ward (Ellis 2017). Watne 2014 designed their trial around their local service reconfiguration where older adults were admitted to their specialist geriatric medicine unit and received CGA comparing this to the care received in the orthopaedic unit.

Exercise therapy versus usual care

Observational data support a link between physical activity and incidence of delirium in hospitalised adults (Yang 2008), with those unable to undertake such activity at increased risk (Marcantonio 1998). Ability to undertake physical activity while in hospital is likely to be complex, with associations with illness severity important to consider. Emerging evidence from intensive care unit settings supports mobilisation strategies to reduce delirium (Banerjee 2011). Martinez-Velilla 2019 undertook a multicomponent exercise intervention targeted towards hospitalised older adults and prevention of delirium was one of their secondary end-points of interest.

Computerised clinical decision support system versus usual care

Computerised clinical decision support software (CCDS) has been reported as an effective tool in prompting healthcare practitioners to comply with established protocols and preventive measures (Dexter 2001). One study in our review (Boustani 2012), investigated the use of CCDS in medical inpatients with alerts to identify cognitive impairment or individuals who would benefit from specialist assessment and prompts around urinary catheters, physical restraints and anticholinergic medications.

Listening to music versus usual care

Cetinkaya 2019 evaluated listening to classical Turkish music as a postoperative intervention to reduce delirium. Music has been proposed as a potential intervention for delirium research in intensive care unit settings, with limited empirical data (Guerra 2019) and for postoperative orthopaedic surgery (Sibanda 2019).

Transcutaneous electrical acupoint stimulation versus placebo

Complementary medicine approaches, including techniques such as acupoint stimulation, have been postulated as helpful in the management of agitation and delirium, although evidence of their effectiveness has been lacking (Levy 2017). Gao 2018 examined the use of transcutaneous electrical acupoint stimulation among older adults with evidence of silent lacunar infarction on imaging as a modality to prevent postoperative delirium.

Continuous positive airway pressure versus usual care (CPAP)

Nadler 2017 evaluated the use of continuous positive airway pressure (CPAP) for those identified as at risk of obstructive sleep apnoea (OSA) as a potential intervention to prevent postoperative delirium. CPAP is an evidence-based treatment for OSA, known to reduce sleepiness symptoms and improve quality of life (Giles 2006). An association between postoperative delirium and OSA has been identified in elective surgical patients (Flink 2012).

Outcomes

Primary outcomes

Incidence of delirium was measured using a range of validated diagnostic methods. The commonest approach was use of the Confusion Assessment Method (CAM) (Inouye 1990), used in 15 of the included studies (Abizanda 2011; Avendano-Cespedes 2016; Boustani 2012; Chen 2017; Dong 2020; Gruber-Baldini 2013; Jeffs 2013; Marcantonio 2001; Martinez 2012; Martinez-Velilla 2019; Nadler 2017; Partridge 2017; Wang 2020; Watne 2014; Young 2020). The CAM-ICU (Ely 2001) was used in two studies (Fan 2014; Gao 2018). Diagnostic and Statistical Manual (DSM-IV) criteria were used in Lundstrom 2007. Hempenius 2013 used theDelirium. Observation Screening) Scale (DOSS) which, if positive, resulted in an assessment using DSM-IV criteria and the Delirium Rating Scale Revised 1998 (DRS-R-98). Bonaventura 2007 used the CAM and DRS-R-98 (Trzepacz 2001). Cetinkaya 2019 used the NEECHAM confusion scale (Nelson 1996), assessed on postoperative days one, two and three, comparing scores between intervention and control groups. They categorise the score as 0 to 19 indicating moderate to severe confusion, 20 to 24 moderate or early confusion, 25 to 26 as high risk for confusion and 27 to 30 as normal function (Cetinkaya 2019). Hosie 2020 used the Nursing Delirium Screening Scale (NuDESC) (Gaudreau 2005) and the DSM-V criteria and DRS-R-98.

Only 13 studies reported data on mortality, either in-hospital or at follow-up of one and three, six and 12 months (Abizanda 2011; Avendano-Cespedes 2016; Boustani 2012; Chen 2017; Dong 2020; Hempenius 2013; Hosie 2020; Lundstrom 2007; Martinez-Velilla 2019; Partridge 2017; Wang 2020; Watne 2014; Young 2020). No study evaluated mortality beyond 12 months from randomisation.

One study evaluated new diagnosis of dementia at 12 months (Watne 2014).

Secondary outcomes

Seven studies reported on the duration of delirium (in days) experienced by participants (Avendano-Cespedes 2016; Jeffs 2013; Lundstrom 2007; Marcantonio 2001; Martinez 2012; Watne 2014; Young 2020).

Eight studies reported on severity of delirium episodes (Avendano-Cespedes 2016; Dong 2020; Hempenius 2013; Hosie 2020; Jeffs 2013; Wang 2020; Watne 2014; Young 2020) using the CAM, CAM-S, DRS-R-98 and Memorial Delirium Assessment Scale (MDAS). Only one study (Hempenius 2013) reported the peak severity of delirium, with others reporting mean or median over the duration of the study. Avendano-Cespedes 2016 reported mean severity data at multiple time points, but the denominator for analysis was not clear and thus these figures were not included in the quantitative synthesis. Wang 2020 reported severe delirium (defined as MDAS ≥18) as a dichotomous outcome only.

Length of hospital admission was reported by 16 studies (Abizanda 2011; Boustani 2012; Chen 2017; Dong 2020; Fan 2014; Gruber-Baldini 2013; Hempenius 2013; Jeffs 2013; Lundstrom 2007; Marcantonio 2001; Martinez 2012; Martinez-Velilla 2019; Partridge 2017; Wang 2020; Watne 2014; Young 2020). Partridge 2017 reported only the mean length of stay, without standard deviation, so this could not be included in quantitative synthesis. Avendano-Cespedes 2016 reported data on length of stay for their whole sample and then for those who did or did not experience delirium, rather than those in the intervention and control groups, again these data could not be pooled.

None of the included studies evaluated use of new psychotropic medications during admission.

Activities of daily living were reported in six studies (Abizanda 2011; Dong 2020; Martinez-Velilla 2019 Wang 2020; Watne 2014; Young 2020).

Quality of life was reported by only two studies (Hempenius 2013; Martinez-Velilla 2019).

None of the included studies evaluated carer's quality of life.

Seven studies included data on individuals withdrawal from protocol (Chen 2017; Fan 2014; Hosie 2020; Marcantonio 2001; Partridge 2017; Wang 2020; Young 2020).

Adverse outcomes

Only two studies examined hospital readmission (Hempenius 2013; Partridge 2017).

None of the included studies evaluated progression of existing dementia.

Two studies reported on new care home admission, one at the time of hospital discharge (Young 2020) and one at follow-up of four and 12 months (Watne 2014).

Nine of the included studies looked at the incidence of in-hospital falls (Boustani 2012; Hempenius 2013; Hosie 2020; Lundstrom 2007; Martinez 2012; Martinez-Velilla 2019; Partridge 2017; Watne 2014; Young 2020), and four evaluated the incidence of in-hospital pressure ulcers (Boustani 2012; Hempenius 2013; Lundstrom 2007; Watne 2014).

Exclusion of prevalent delirium at baseline

Failure to exclude delirium at enrolment to the study was a common problem. Only seven studies clearly excluded or accounted for prevalent cases of delirium at baseline (Abizanda 2011; Fan 2014; Gao 2018; Jeffs 2013; Martinez 2012; Wang 2020; Young 2020). Avendano-Cespedes 2016 reported multiple measures of delirium, including exclusion of delirium present on the first day of admission, but there was uncertainty around the denominators for each group, making it difficult to use in pooled comparisons.

Funding sources and declarations of interest

The majority of included studies (18 of 22) were funded through academic or governmental research institutions or grant funding schemes. In three studies, the source of funding was not reported (Boustani 2012; Cetinkaya 2019; Martinez 2012), and one study received no specific funding, but was loaned equipment from a health technology company (Nadler 2017).

Four studies reported potential interest to declare related to their study (Boustani 2012; Gruber-Baldini 2013; Hosie 2020; Wang 2020). Three studies did not provide a declaration of interest statement in their publication (Bonaventura 2007; Lundstrom 2007; Marcantonio 2001).

Excluded studies

We excluded 182 records. Thirty-two duplicate records (either duplicate publications or publications reporting the same underlying data) were excluded. Studies were excluded for the following reasons: n=71 wrong study design; n=32 wrong setting; n=24 wrong outcome (not delirium prevention); n=13 wrong intervention (not non-pharmacological); n=7 unvalidated delirium diagnostic method; n=2 study terminated and n=1 previous version of review (Figure 1). Excluded studies for which a full text was available are listed in Characteristics of excluded studies. Details of 19 studies identified as ongoing are given in Characteristics of ongoing studies.

Risk of bias in included studies

Risk of bias assessments are presented for each study in the Characteristics of included studies table and are summarised in the text below and graphically in Figure 2. We assessed no study to be at low risk of bias across all domains.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

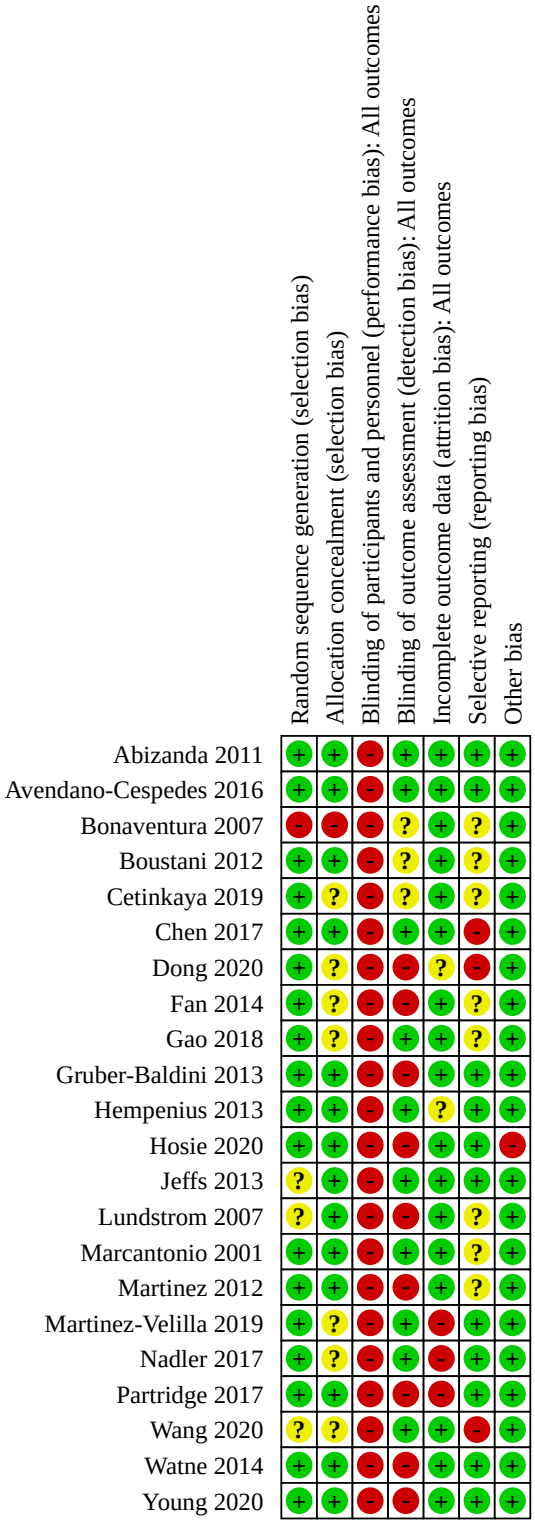


Figure 2. (Continued)

Young 2020 

Allocation

We considered 12 of the included studies to be at low risk of selection bias with appropriate random methods for sequence generation and allocation concealment reported (Abizanda 2011; Avendano-Cespedes 2016; Boustani 2012; Cetinkaya 2019; Chen 2017; Gruber-Baldini 2013; Hempenius 2013; Hosie 2020; Marcantonio 2001; Martinez 2012; Partridge 2017; Watne 2014; Young 2020).

Bonaventura 2007 was at high risk of selection bias due to use of day of admission in allocation to intervention or control. Wang 2020 was at unclear risk of selection bias due to the method of allocating individuals to groups and concealment of the allocation. Two studies were at unclear risk in terms of their random sequence generation (Jeffs 2013; Lundstrom 2007). Six studies were at unclear risk in their allocation concealment (Cetinkaya 2019; Dong 2020; Fan 2014; Gao 2018; Martinez-Velilla 2019; Nadler 2017).

Blinding

All studies were at high risk of performance bias as none were able to blind participants and study personnel.

Ten studies were at low risk of detection bias due to blinding of outcome assessors (Abizanda 2011; Avendano-Cespedes 2016; Chen 2017; Gao 2018; Hempenius 2013; Jeffs 2013; Marcantonio 2001; Martinez-Velilla 2019; Nadler 2017; Wang 2020). Three studies were at unclear risk of detection bias (Bonaventura 2007; Boustani 2012; Cetinkaya 2019). The remaining nine studies were at high risk of detection bias (Dong 2020; Fan 2014; Gruber-Baldini 2013; Hosie 2020; Lundstrom 2007; Martinez 2012; Partridge 2017; Watne 2014; Young 2020).

Incomplete outcome data

Seventeen studies were at low risk of attrition bias (Abizanda 2011; Avendano-Cespedes 2016; Bonaventura 2007; Boustani 2012; Cetinkaya 2019; Chen 2017; Fan 2014; Gao 2018; Gruber-Baldini 2013; Hosie 2020; Jeffs 2013; Lundstrom 2007; Marcantonio 2001; Martinez 2012; Wang 2020; Watne 2014; Young 2020). Two studies were at unclear risk of attrition bias (Dong 2020; Hempenius 2013) and the remaining three studies were considered to be at high risk of attrition bias (Martinez-Velilla 2019; Nadler 2017; Partridge 2017).

Selective reporting

Eleven studies were at low risk of reporting bias having published protocols and reporting as per their protocol (Abizanda 2011; Avendano-Cespedes 2016; Gruber-Baldini 2013; Hempenius 2013; Hosie 2020; Jeffs 2013; Martinez-Velilla 2019; Nadler 2017; Partridge 2017; Watne 2014; Young 2020). Eight studies were at unclear risk of reporting bias as a result of an absence of a published protocol (Bonaventura 2007; Boustani 2012; Cetinkaya 2019; Fan 2014; Gao 2018; Lundstrom 2007; Marcantonio 2001; Martinez 2012). Three studies were at high risk of reporting bias due to inconsistency in reporting between protocol and paper or between methods and results (Chen 2017; Dong 2020; Wang 2020).

Other potential sources of bias

The other bias domain was used to assess the four cluster-randomised trials (Chen 2017; Hosie 2020; Wang 2020; Young 2020). These were assessed for recruitment bias, baseline imbalance, loss of clusters and incorrect analysis, with full details provided in the study-level risk of bias tables. Three of the cluster-randomised trials were considered at low risk of bias (Chen 2017; Wang 2020; Young 2020), and one study (Hosie 2020) was considered at high risk, as no specific analytical consideration was made to account for the cluster design. To investigate the fifth parameter of assessing risk of bias in cluster-randomised trials, comparability with individually randomised trials, a sensitivity analysis was undertaken of the primary outcome (incidence of delirium), removing the cluster-randomised trials. Removing the cluster-randomised trials results in a change to the effect estimate (risk ratio (RR) 0.65 compared to 0.57) and associated uncertainty (95%CI 0.55 to 0.77, compared to 0.46 to 0.71 for all studies), but the direction and nature of the effect was the same. This analysis does not suggest an important bias from inclusion of the cluster-randomised trials in the summary estimate.

Visual inspection of funnel plots for incidence of delirium and inpatient mortality for multicomponent interventions did not suggest publication bias.

The four studies in which trials are completed but the results are not publicly available are summarised in Studies awaiting classification. They include four interventions (family intervention (n = 79 participants), care bundle (n = 80 participants), preventative care protocol (n = 80 participants) and passive cycling (n = 230 participants) with a total planned sample size of 469 participants. From the information available in the trial registry entries it is difficult to categorise these studies and estimate how they would influence the published results.

Effects of interventions

See: **Summary of findings 1** Non-pharmacological multicomponent interventions for preventing delirium in hospitalised non-ICU patients

1. Multicomponent interventions versus usual care

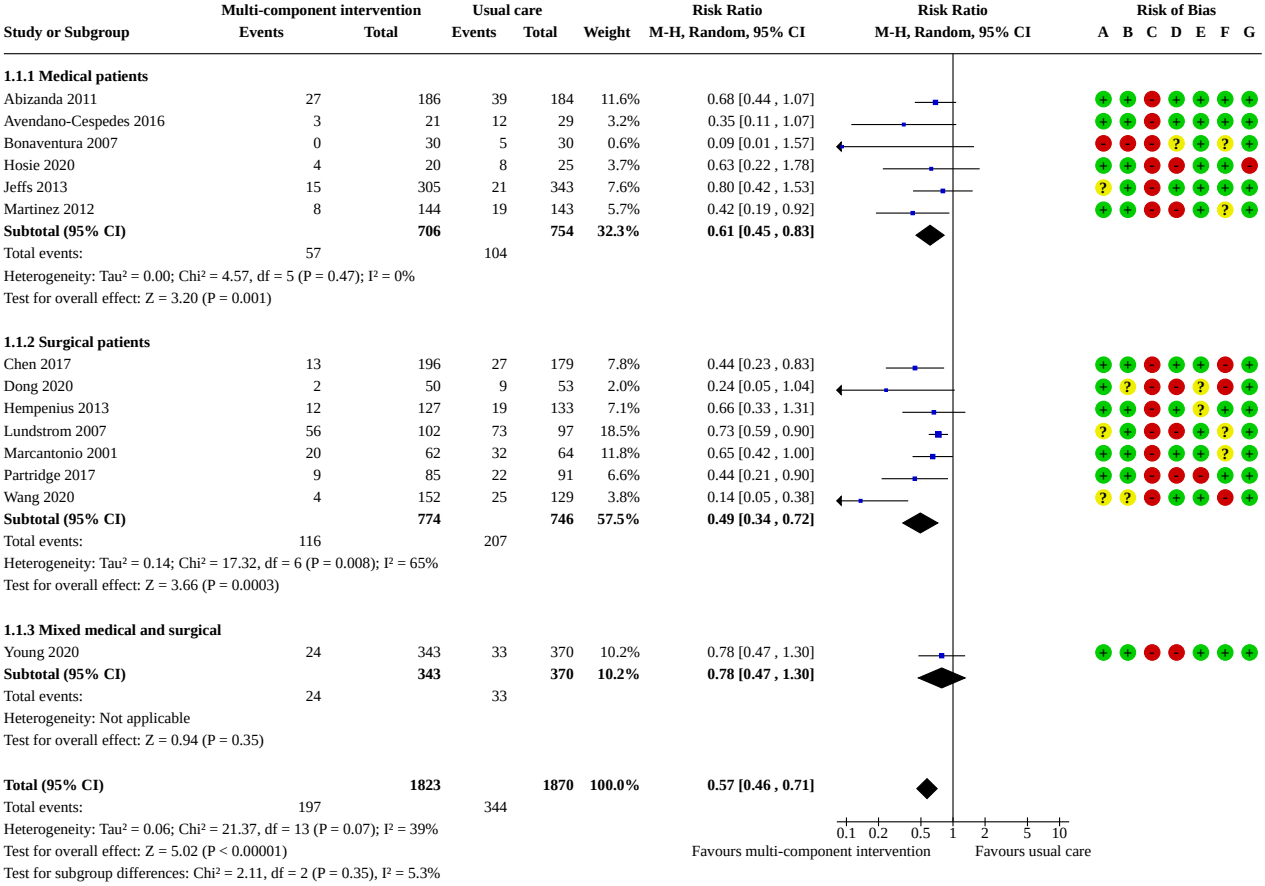
Fourteen trials investigated the effectiveness of multicomponent interventions for the prevention of delirium (Abizanda 2011; Avendano-Cespedes 2016; Bonaventura 2007; Chen 2017; Dong 2020; Hempenius 2013; Hosie 2020; Jeffs 2013; Lundstrom 2007; Marcantonio 2001; Martinez 2012; Partridge 2017; Wang 2020; Young 2020). A summary of findings table for the seven key outcomes is presented in Summary of findings 1.

a. Primary outcomes

Pooled analysis showed that multi-component non-pharmacological interventions probably reduce the incidence of delirium compared to usual care (risk ratio (RR) 0.57, 95% confidence interval (CI) 0.46 to 0.71, I^2=39%; 3693 participants;

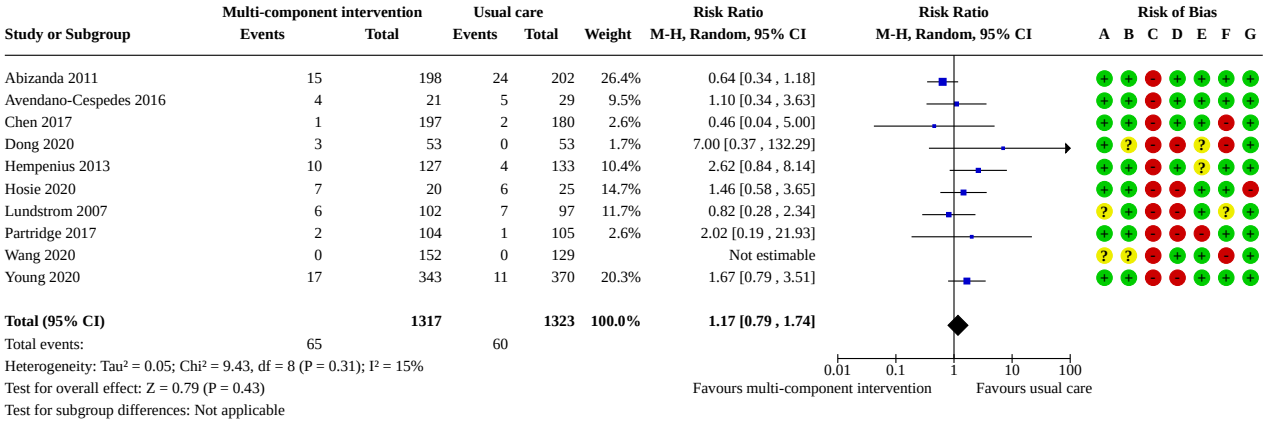
downgraded to moderate certainty due to risk of bias) (Analysis 1.1, Figure 3).

Figure 3. Forest plot: Multi-component delirium prevention intervention (MCI) versus usual care for incident delirium



Ten studies reported data on inpatient mortality; there may be little or no effect of multicomponent interventions on inpatient mortality compared to usual care (RR 1.17, 95% CI 0.79 to 1.74, I^2=15%; 2640 participants; low-certainty evidence downgraded due to inconsistency and imprecision) (Analysis 1.2; Figure 4).

Figure 4. Forest plot: Multi-component delirium prevention intervention (MCI) versus usual care for inpatient mortality



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Three studies reported mortality data between one and three months. Multicomponent interventions likely result in little to no difference in mortality at one to three months compared to usual care (RR 1.26, 95% CI 0.92 to 1.75, I^2=0%; 1200 participants; moderate-certainty evidence downgraded due to imprecision) (Analysis 1.3).

Only one study (Lundstrom 2007) reported mortality data between six and 12 months. There may be little or no effect of multicomponent interventions on mortality at 12 months compared to usual care (RR 0.85, 95% CI 0.46 to 1.56; 199 participants; low-certainty evidence downgraded due to imprecision and risk of bias within the study) (Analysis 1.4).

None of the included studies reported mortality data beyond 12 months from randomisation.

None of the included studies of multicomponent interventions reported data on new diagnosis of dementia at any point following randomisation.

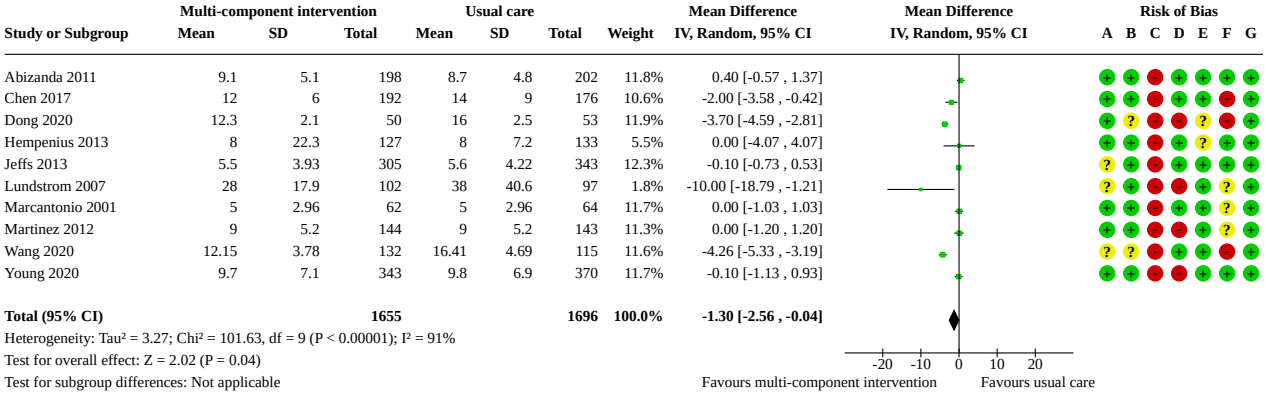
b. Secondary outcomes

Six studies reported data on the duration of delirium episodes. Multicomponent interventions may result in a small reduction of around a day in the duration of a delirium episode (mean difference (MD) -0.93, 95% CI -2.01 to 0.14 days, I^2 = 65%; 351 participants; low-certainty evidence downgraded due to risk of bias and imprecision) (Analysis 1.5).

Five studies compared delirium severity between intervention and usual care groups. The evidence is very uncertain about the effect of multicomponent interventions on delirium severity (standardised mean difference (SMD) -0.49, 95% CI -1.13 to 0.14, I^2 = 64%; 147 participants; very low-certainty evidence downgraded due to risk of bias and serious imprecision) (Analysis 1.6). A standardised mean severity of 0.49 standard deviations represents a moderate effect. The 95% confidence interval encompasses a very large effect and little or no effect, indicating serious imprecision.

Pooled analysis of 10 studies showed multicomponent interventions may result in a reduction in hospital length of stay compared to usual care (MD -1.30 days, 95% CI -2.56 to -0.04 days, I^2=91%; 3351 participants; low-certainty evidence downgraded due to risk of bias and inconsistency) (Analysis 1.7; Figure 5).

Figure 5. Forest plot: Multi-component delirium prevention intervention (MCI) versus usual care for length of hospital stay



Heterogeneity: Tau² = 3.27; Chi² = 101.63, df = 9 (P < 0.00001); I² = 91%
Test for overall effect: Z = 2.02 (P = 0.04)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

None of the included studies evaluated use of new psychotropic medication during hospital admission.

Activities of daily living, measured using a validated instrument were evaluated in four trials (Abizanda 2011; Dong 2020 Wang 2020; Young 2020). However, these were reported using different measures as post-intervention values and change scores or as a dichotomous variable determining improvement/not (Abizanda 2011) and it was not considered appropriate to pool these data.

Quality of life, measured using a validated patient reported measure was reported in two trials (Hempenius 2013; Martinez-Velilla 2019). However, these data were not considered suitable to pool as Hempenius 2013 dichotomised results based on presence/absence of change and Martinez-Velilla 2019 derived results from a linear mixed-effects model.

None of the included studies evaluated carer's quality of life.

Withdrawal from protocol by participants was reported in six studies. The evidence suggests that multicomponent interventions result in little to no difference in withdrawal from protocol compared to usual care (RR 1.03, 95% CI 0.60 to 1.75, I^2=0%; 1751 participants; low-certainty evidence downgraded due to risk of bias and imprecision) (Analysis 1.8).

c. Adverse outcomes

Only two studies reported on readmission to hospital (Hempenius 2013; Partridge 2017). The evidence is very uncertain about the effect of multicomponent interventions on hospital readmission (RR 1.35, 95% CI 0.89 to 2.07, I^2=0%; 401 participants; very low-certainty evidence downgraded due to risk of bias and serious imprecision) (Analysis 1.9).

None of the included studies evaluated progression of existing dementia.

New care home admission at the time of hospital discharge was only reported in a single study (Young 2020). The evidence suggests that multicomponent interventions result in little to no difference in new care home admission at the time of hospital discharge compared to usual care (RR 0.77, 95% CI 0.55 to 1.07; 536 participants; low-certainty evidence downgraded due to risk of bias and imprecision) (Analysis 1.10).

Rates of falls were reported in six studies, the evidence is very uncertain about the effect of multicomponent interventions on the rate of falls (RR 0.89, 95% CI 0.42 to 1.88, I^2=55%; 1680 participants; very low-certainty evidence downgraded due to risk of bias, imprecision and inconsistency) (Analysis 1.11).

Rates of pressure ulcers were only reported in two studies (Hempenius 2013; Lundstrom 2007). The evidence suggests multicomponent interventions result in a reduced risk of pressure ulcer formation compared to usual care (RR 0.48, 95% CI 0.26 to 0.89, I^2 = 0%; 457 participants; low-certainty evidence downgraded, due to risk of bias and imprecision) (Analysis 1.12).

Subgroup analysis by setting

Pre-planned subgroup analysis was conducted to evaluate the effectiveness of delirium prevention interventions based on clinical setting. The 14 trials were divided into the six conducted in medical settings (Abizanda 2011; Avendano-Cespedes 2016; Bonaventura 2007; Hosie 2020; Jeffs 2013; Martinez 2012), seven conducted in surgical settings including orthopaedics (Chen 2017; Dong 2020; Hempenius 2013; Lundstrom 2007; Marcantonio 2001; Partridge 2017; Wang 2020) and one conducted in both medical and surgical settings (Young 2020). There were similar effect sizes in medical (RR 0.61, 95% CI 0.45 to 0.83; I^2= 0%; 1460 participants) and surgical including orthopaedic (RR 0.49, 95% CI 0.34 to 0.72; I^2 = 65%; 1520 participants) settings in favour of multicomponent interventions in reducing incidence delirium (moderate certainty evidence downgraded due to risk of bias. (Analysis 1.1)

Subgroup analysis by dementia diagnosis

Only one trial (Marcantonio 2001) reported incident delirium in patients with pre-existing dementia. Delirium incidence estimates appeared different between individuals with dementia (RR 0.90, 95% CI 0.59 to 1.36; 50 participants; low-certainty evidence, downgraded due to risk of bias and imprecision) and those without dementia (RR 0.50, 95% CI 0.22 to 1.13; 76 participants; low-certainty evidence, downgraded due to risk of bias and imprecision). However, the results are too imprecise to allow a conclusion to be drawn.

Subgroup analysis by frailty status

It was not possible to evaluate the impact of frailty as no studies reported numerical delirium data stratified by frailty status.

Sensitivity analysis removing specialist palliative care

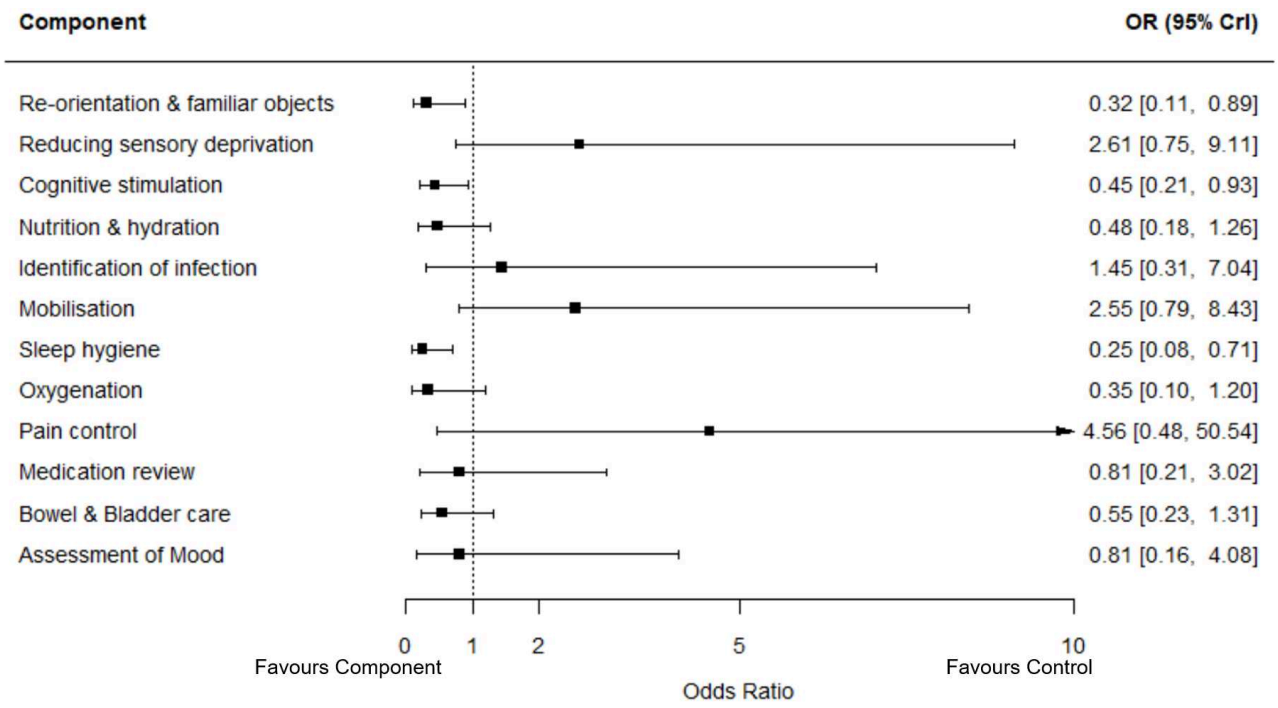
Pre-planned sensitivity analysis to remove the trial conducted in specialist palliative care (Hosie 2020) did not make any significant difference to the observed estimate of the effectiveness of multicomponent delirium prevention interventions (RR 0.56, 95% CI 0.45 to 0.71; 3648 participants; moderate-certainty evidence downgraded due to risk of bias).

Component network meta-analysis

We created a component network using data from the 14 trials (n = 3693 participants) of multicomponent interventions included in the main review.

The forest plot of component effects is given in Figure 6. Based on our data, re-orientation (odds ratio (OR) 0.32, 95% Credible Intervals (CrI) 0.11 to 0.89), cognitive stimulation (OR 0.45, 95% CrI 0.21 to 0.93) and sleep hygiene (OR 0.25, 95% CrI 0.08 to 0.71) were associated with reduced risk of incident delirium. Attention to nutrition and hydration (OR 0.48, 95% CrI 0.18 to 1.26), oxygenation (OR 0.35, 95% CrI 0.10 to 1.20), and bowel and bladder care (OR 0.55, 95% CrI 0.23 to 1.31) suggested probable reduction in incident delirium, but estimates included the possibility of no effect or harm. For most other components the 95% credible intervals were too wide to comment on potential effects. This is likely a result of lack of data, both a low number of trials and low heterogeneity in the composition of components included in the trials. Medication review and assessment of mood both had imprecise summary estimates, favouring the interventions, although harms could not be excluded. On the other hand, reducing sensory deprivation, identification of infection, mobilisation, pain control and assessment of mood all had summary estimates that suggested potential increase in delirium, but the uncertainty in these estimates was very substantial, including potential benefits as well as harms. We compared estimates based on the network against data from the original trials and found that most of the component network meta-analysis estimates were similar to the individual trial estimates, providing some evidence of validity to the component network analysis.

Figure 6. Forest plot summarising component network meta-analysis results



2. Liberal versus restrictive blood transfusion thresholds

Two trials (Fan 2014; Gruber-Baldini 2013) evaluated blood transfusion thresholds. Fan 2014 included 192 participants undergoing elective hip replacement and Gruber-Baldini 2013 included 139 participants undergoing surgical repair of hip fracture. Both compared liberal versus restrictive blood transfusion thresholds. There was significant overlap in the volume of blood received by participants in both studies and in other products administered.

a. Primary outcomes

The evidence suggests that use of a liberal transfusion threshold over a restrictive transfusion threshold results in little to no difference in incident delirium (RR 0.92, 95% CI 0.62 to 1.36; I^2 = 9%; 294 participants; moderate-certainty evidence downgraded due to risk of bias) (Analysis 2.1).

Neither study reported on mortality or new diagnosis of dementia.

b. Secondary outcomes

The evidence suggests that liberal transfusion thresholds does not affect the severity of delirium (MD - 0.10, 95% CI -2.99 to 2.79; 38 participants; low-certainty evidence downgraded due to imprecision and risk of bias) (Analysis 2.2).

The evidence suggests that liberal transfusion thresholds do not affect the length of hospital stay (MD 0.28, 95% CI -0.49 to 1.04 days; I^2 = 0%; 324 participants; low-certainty evidence downgraded due to imprecision and risk of bias) (Analysis 2.3).

The evidence is very uncertain about the effect of liberal transfusion thresholds on the risk of withdrawal from the study (RR 2.00, 95% CI 0.38 to 10.66; 192 participants; very low-certainty evidence downgraded due to serious imprecision and risk of bias) (Analysis 2.4).

The studies did not report on duration of delirium, use of new psychotropic medications, activities of daily living, quality of life or carer's quality of life.

c. Adverse outcomes

Neither study reported on hospital readmission, progression of existing dementia, new care home admission at discharge, falls or pressure ulcers.

3. Geriatric unit care versus orthopaedic unit care

One trial of 329 older adults following hip fracture compared care in a specialist geriatric unit to care in their orthopaedic unit (Watne 2014).

a. Primary outcomes

The evidence suggests that care in the geriatric unit does not affect the incidence of delirium compared to care in the orthopaedic unit (RR 0.98, 95% CI 0.79 to 1.22; 329 participants; low-certainty evidence downgraded due to risk of bias and imprecision) (Analysis 3.1).

Care in the geriatric unit likely results in little to no difference in the rate of in-hospital mortality (RR 0.56, 95% CI 0.21 to 1.47; 329 participants; moderate-certainty evidence downgraded due to imprecision) compared to the orthopaedic unit. (Analysis 3.2).

Care in the geriatric unit appeared to increase the rate of incident dementia at 12 months (RR 2.26, 95% CI 0.60 to 8.49; 193 participants). However, the evidence was deemed to be of low certainty and was downgraded two levels due to serious imprecision. (Analysis 3.3).

b. Secondary outcomes

The evidence suggests that care in the geriatric unit results in little to no difference in the duration of delirium (MD -1.00 days, 95% CI -2.03 to 0.03 days; 166 participants) (Analysis 3.4), or severity of delirium episodes (MD 1.50 points, 95% CI -0.97 to 3.97 points; 166 participants) (Analysis 3.5) compared to the orthopaedic unit, low-certainty evidence for both outcomes, downgraded due to risk of bias and imprecision.

Care in the geriatric unit probably increases length of hospital admission by a mean of three days (RR 3.00, 95% CI 1.94 to 4.06 days; 329 participants; moderate-certainty evidence downgraded due to risk of bias) compared to the orthopaedic unit (Analysis 3.6).

The study did not report on use of new psychotropic medications, quality of life, carer's quality of life or withdrawal from protocol by participants.

c. Adverse outcomes

The evidence suggests that care in the geriatric unit does not affect the rate of falls (RR 1.30, 95% CI 0.61 to 2.77; 329 participants; low-certainty evidence downgraded due to risk of bias and imprecision) (Analysis 3.7), or pressure ulcer formation (RR 0.38, 95% CI 0.10 to 1.41; 329 participants; low-certainty evidence downgraded due to risk of bias and imprecision) (Analysis 3.8).

Care in the geriatric unit probably does not affect the risk of new care home admission at 12 months (RR 0.86, 95% CI 0.47 to 1.59; 193 participants; moderate-certainty evidence downgraded due to imprecision) (Analysis 3.9).

The study did not report on hospital readmission or progression of existing dementia.

4. Exercise therapy versus usual care

One trial Martinez-Velilla 2019 evaluated the effect of an exercise intervention on 370 older adults hospitalised in an acute elderly care unit.

a. Primary outcomes

The evidence suggests that an exercise intervention does not affect the incidence of delirium compared to usual care (RR 1.80, 95% CI 0.99 to 3.27; 370 participants; lo- certainty evidence downgraded due to risk of bias and imprecision) (Analysis 4.1).

Exercise intervention likely results in little to no difference on mortality at one to three months (RR 1.22, 95% CI 0.68 to 2.20; 370 participants; moderate-certainty evidence downgraded due to imprecision). (Analysis 4.2)

The study did not report on new diagnosis of dementia.

b. Secondary outcomes

Exercise intervention results in little to no difference on length of hospital admission compared to usual care (MD 0.00 days, 95%CI -0.60 to 0.60; 370 participants; high-certainty evidence). (Analysis 4.3)

Activities of daily living data were reported, as a change in Barthel Index score from two weeks prior to hospital admission to hospital discharge. These data were derived from linear mixed-effects modelling and reported as time coefficient and 95% CI, thus they could not be entered into RevMan Web.

The study did not report on duration or severity of delirium, use of new psychotropic medications, quality of life, carer's quality of life or withdrawal from protocol by participants.

c. Adverse outcomes

The evidence suggests that an exercise intervention does not affect the likelihood of new care home admission at hospital discharge (RR 2.00, 95% CI 0.37 to 10.79; 370 participants; low-certainty evidence downgraded due to serious imprecision). (Analysis 4.4)

The evidence suggests that an exercise intervention does not affect the rate of falls experienced by participants (RR 8.57, 95% CI 0.47 to 157.75; 285 participants; low-certainty evidence downgraded due to serious imprecision). (Analysis 4.5)

The study did not report on hospital readmission, progression of existing dementia or pressure ulcers.

5. Computerised clinical decision support system versus usual care

One trial Boustani 2012 assessed the use of a computerised clinical decision support system (CCDSS) on the management of 427 older adults with cognitive impairment, compared to usual care.

a. Primary outcomes

Use of CCDSS probably results in little to no difference in delirium incidence (RR 1.08, 95% CI 0.82 to 1.43; 424 participants; moderate-certainty evidence downgraded due to risk of bias) (Analysis 5.1).

The evidence suggests that use of CCDSS does not affect the rate of mortality within one to three months (30 days of discharge) (RR 1.04, 95% CI 0.49 to 2.23; 424 participants; low-certainty evidence downgraded due to serious imprecision) (Analysis 5.2).

The study did not report on new diagnosis of dementia.

b. Secondary outcomes

The evidence suggests that CCDSS does not affect the length of admission (MD 0.90 days, 95% CI -0.35 to 2.15 days; 424 participants; low-certainty evidence, downgraded due to serious imprecision (Analysis 5.3).

The study did not report on duration of delirium, severity of delirium, use of new psychotropic medications, activities of daily living, quality of life, carer's quality of life or withdrawal from protocol by participants.

c. Adverse outcomes

Use of CCDSS probably does not affect rates of falls (RR 0.93, 95% CI 0.39 to 2.19; 424 participants; moderate-certainty evidence downgraded due to imprecision) or pressure ulcers (RR 1.09, 95% CI 0.64 to 1.84; 424 participants; moderate-certainty evidence downgraded due to imprecision) (Analysis 5.4; Analysis 5.5).

The study did not report on hospital readmission, progression of existing dementia or new care home admission at discharge.

6. Listening to music versus usual care

One trial Cetinkaya 2019 included 60 individuals undergoing hip or knee surgery and evaluated listening to classical Turkish music in the postoperative period, compared to usual care.

a. Primary outcomes

Using the postoperative day one (peak in severity) NEECHAM scores, the evidence is very uncertain about the effect of music listening on the incidence of delirium (MD 1.47, 95% CI 0.16 to 2.78; 60 participants; very low-certainty evidence downgraded due to risk of bias, imprecision and indirectness due to type of music) (Analysis 6.1).

The study did not report on mortality or new diagnosis of dementia.

b. Secondary outcomes

The study did not report on duration of delirium, severity of delirium, length of hospital admission, use of new psychotropic medications, activities of daily living, quality of life, carer's quality of life or withdrawal from protocol by participants.

c. Adverse outcomes

The study did not report on hospital readmission, progression of existing dementia, new care home admission at discharge, falls or pressure ulcers.

7. Transcutaneous electrical acupoint stimulation versus placebo

One trial Gao 2018 evaluated the use of transcutaneous electrical acupoint stimulation during surgery in a sample of 64 adults who had experienced silent lacunar infarction and were undergoing spinal surgery, compared to placebo.

a. Primary outcomes

The evidence is very uncertain about the effect of transcutaneous electrical acupoint stimulation on incident delirium (RR 0.25, 95% CI 0.06 to 1.09; 64 participants; very low-certainty evidence downgraded due to risk of bias, indirectness and imprecision) (Analysis 7.1).

The study did not report on mortality or new diagnosis of dementia.

b. Secondary outcomes

The study did not report on duration of delirium, severity of delirium, length of hospital admission, use of new psychotropic medications, activities of daily living, quality of life, carer's quality of life or withdrawal from protocol by participants.

c. Adverse outcomes

The study did not report on hospital readmission, progression of existing dementia, new care home admission at discharge, falls or pressure ulcers.

8. Continuous positive airway pressure versus usual care

One trial Nadler 2017 evaluated the use of peri-operative continuous positive airway pressure (CPAP) for 135 adults considered at risk of obstructive sleep apnoea, undergoing elective hip or knee arthroplasty, compared to usual care. CPAP was given during sleep before surgery and on postoperative days zero, one1 and tw0.

a. Primary outcomes

The evidence is very uncertain about the effect of peri-operative CPAP on incident delirium (RR 1.29, 95% CI 0.59 to 2.82; 114

participants; very low-certainty evidence downgraded due to risk of bias and serious imprecision) (Analysis 8.1).

The study did not report on mortality or new diagnosis of dementia.

b. Secondary outcomes

The study did not report on duration of delirium, severity of delirium, length of hospital admission, use of new psychotropic medications, activities of daily living, quality of life, carer's quality of life or withdrawal from protocol by participants.

c. Adverse outcomes

The study did not report on hospital readmission, progression of existing dementia, new care home admission at discharge, falls or pressure ulcers.

DISCUSSION

Summary of main results

We identified 22 randomised trials of eight non-pharmacological interventions for the prevention of delirium in hospitalised adults, not in intensive care unit (ICU) or high dependency unit (HDU) settings. Most of these evaluated multicomponent interventions, with two trials evaluating the use of blood transfusion thresholds and the others evaluating interventions in a single study.

We found moderate-certainty evidence from 14 randomised controlled trials that multicomponent interventions probably reduce delirium incidence in hospitalised adults by 40% compared with usual care. This evidence holds across different settings and populations within the hospital, broadly categorised as medical versus surgical (including orthopaedics). We found low-certainty evidence that these interventions may result in a reduction in hospital length of stay. Delirium duration may be reduced by around a day, although evidence was of low certainty. The evidence is very uncertain around the effect on delirium severity. There may be little or no effect of multicomponent interventions on inpatient mortality. The need for care home placement at discharge was only evaluated in a single multicomponent intervention study.

Our component network meta-analysis identified 12 distinct components of the interventions; studies included between two and 10 components with a mean of six components in each study. Re-orientation, cognitive stimulation and sleep hygiene were associated with reduced risk of incident delirium. Attention to nutrition and hydration, oxygenation, medication review, assessment of mood and bowel and bladder care suggested probable reduction in incident delirium, but estimates included the possibility of no benefit or harm. For most other components the 95% credible intervals were too wide to comment on potential effect.

We found no evidence for any single component intervention affecting delirium incidence.

Overall completeness and applicability of evidence

The majority of the evidence in this review is about the use of multicomponent delirium prevention interventions (14 of the 22 included trials). This reflects a significant increase in research evidence in this area, with the previous iteration of this review published five years ago identifying only seven trials (Siddiqi 2016). The other eight interventions identified in this review were investigated in only one or two small studies each, precluding meaningful synthesis of these results.

Multicomponent interventions have previously been shown to be effective in reducing the incidence of delirium, however, this is the first review that has attempted to define the components which should be considered for inclusion. This question is relevant for clinical practice in terms of operationalising the implementation of delirium prevention interventions as part of hospital care. This exploratory analysis sought to describe if there are some components which are necessary and if any are harmful or non-contributory to the effectiveness of prevention. Our analysis was novel, but limited by the total number of included studies and the range of components included. Aspects of intervention delivery were not considered as components in the model, but these are clearly worthy of further systematic exploration. Interventions in future trials could include re-orientation, cognitive stimulation and sleep hygiene. However, it would be helpful to have future trials directly comparing different combinations of components, rather than one combination compared with usual care, as having trials directly comparing interventions would increase the benefit of the component network meta-analysis approach over pairwise meta-analyses.

Implementation of evidence-based delirium prevention interventions in healthcare settings globally is recognised to be complex, but critical to improve outcomes for individuals (Wilson 2020). One of the included studies (Young 2020) had a parallel implementation study using Normalization Process Theory to articulate how the intervention was implemented and delivered within clinical hospital settings, identifying key contextual factors for successful implementation (Godfrey 2019). Implementation science approaches such as this are likely to be required to understand how to apply evidence from randomised trials in clinical care settings, ensuring the fundamental aspects of care are delivered consistently for all.

Only one study specifically reported on the impact of their intervention on adults living with dementia, an important subgroup to study in delirium prevention. Four studies actively excluded those with dementia and a further three excluded those with severe dementia.The effectiveness of delirium interventions might be expected to differ given the higher prevalence of delirium and poorer outcomes in dementia. Only one study reported progression of existing dementia and no studies evaluated new diagnosis of dementia. This is an important limitation in light of the growing epidemiological evidence associating delirium with the development of dementia (Richardson 2020), and recurrent delirium with worsening cognitive decline (Richardson 2021). Only one study included a measure of the frailty of recruited participants and results were not presented stratified by frailty. This may be an important variable to consider within the population targeted by delirium prevention interventions. There were limited data on quality of life of patients and no data on quality of life of carers/families. Data on new care home admission were limited with one study reporting need for care at time of hospital discharge and another at later follow-up. These outcomes are important for individuals, their families and healthcare services and would benefit from further research.

A core outcomes set for studies evaluating interventions to prevent delirium among adults requiring an acute care hospital admission

has recently been published, incorporating the perspectives of multiple stakeholders (Rose 2021). This includes cognition, emotional distress and health-related quality of life. It is hoped that this will inform future data collection in delirium prevention research, with researchers focusing on measuring outcomes which matter and in a less heterogeneous way to support evidence synthesis.

We note there are 19 ongoing studies whose findings may be eligible for inclusion in future updates of this review.

Future trials and reviews should consider the health economic implications of multicomponent interventions.

Quality of the evidence

We undertook risk of bias assessment for each included trial and used GRADEpro software (GRADEpro 2014) to inform the generation of evidence certainty statements. None of the included trials were considered to be at low risk of bias across all domains. All of the included interventions were conducted without blinding of participants and personnel and fewer than half of the studies attempted to reduce detection bias through use of blinded outcome assessors. Multi-component delirium prevention interventions are complex and thus arguably a double-blind design is not realistic. However, independent outcome assessment may be feasible.

Evidence is typically of moderate or low certainty, downgraded as a result of the risk of bias in the included studies, imprecision or inconsistency of results. Delirium incidence was the only outcome used in all of the included studies and reporting on other delirium variables, such as duration and severity were more limited. Delirium incidence was measured at any time point during hospital admission. It is therefore possible that where interventions were effective in reducing length of hospital stay, delirium may not be detected. Hospital readmission with delirium would be a way to identify if this was occurring, however this outcome was not commonly reported in the included studies.

Heterogeneity in the measurement of outcomes limited the pooling of results.

We note that there were four studies identified which cannot be classified for inclusion or exclusion (Characteristics of studies awaiting classification). These studies appear to have been completed based on information in trial registry entries. However, results remain unpublished and no further information was identified from correspondence using contact details recorded in the trial registries.

Failure to exclude prevalent delirium at enrolment was a common limitation in the majority of studies (16/22). This has the potential to reduce precision in the results as interventions cannot prevent cases of delirium already present in recruited participants. However, ruling out prevalent delirium in busy, clinical settings is difficult and it is perhaps more representative of real-world delirium care that those with and without delirium are included at the baseline of intervention studies. This likely increases external validity of the evidence.

Potential biases in the review process

This review was conducted in accordance with Cochrane procedures and there were only a small number of amendments to the review process, which are outlined in Differences between protocol and review.

Agreements and disagreements with other studies or reviews

Our findings are consistent with the previous version of this review which included all interventions to prevent delirium, pharmacological and non-pharmacological (Siddiqi 2016). That version included seven randomised controlled trials (RCTs) of multicomponent interventions; the additional seven trials now included provide consistent and stronger results than the earlier estimate of a reduction of a third in the rate of incident delirium (Siddiqi 2016).

These data from RCTs are consistent with the evidence seen in non-randomised studies, most notably studies of the Hospital Elder Life Program (HELP) (Inouye 1999). The programme targets six delirium risk factors (cognitive impairment, sleep deprivation, immobility, dehydration, vision or hearing impairment) and provides targeted interventions to address these factors involving specialist nurses and clinicians and volunteers (Inouye 2000a). The HELP approach has been studied extensively, with 44 articles informing a review of effectiveness and implementation (Hshieh 2018). The data from these clinical studies are consistent with reduced costs and reduced rate of falls as well as reduced delirium incidence (Hshieh 2018). Our review did not find evidence for a reduction in falls.

Heim 2017 reported on the experience of undertaking a planned, stepped-wedge design, randomised trial of the HELP intervention within Dutch hospitals. Difficulty accessing electronic records to ascertain outcomes and missing data from these care records were identified as particular challenges which contributed to the termination of their study. The authors note the challenges of trying to evaluate a complex intervention using a pragmatic study design, highlighting selection bias due to recruitment procedures as another contributing factor (Heim 2017). This is an important contribution to the delirium prevention research landscape in terms of generating evidence in clinical practice.

One study included in the previous version of the review was excluded as it reported a mixed pharmacological and non-pharmacological intervention (Jia 2014). The 'fast-track surgery' intervention described shared components with those studies which described themselves as multicomponent delirium prevention studies, including focus on bowels/bladder care, nutrition and hydration, and early mobilisation (Jia 2014). However, the intervention also included a different mode of anaesthesia and type of analgesia regimen from the control group, rendering it ineligible for inclusion in this non-pharmacological review. This multicomponent, mixed pharmacological and non-pharmacological intervention was also reported to be associated with reductions in the incidence of delirium and the length of hospital stay.

Other systematic reviews have found similar results to those reported here. Most recently these include León-Salas 2020 pooling data in older adults (aged ≥ 65 years) across medical, surgical and ICU populations and identifying 10 randomised trials,

and Ludolph 2020 who included studies of adults in all hospital settings, and similarly found no evidence of an effect of interventions intended to prevent delirium on either duration of delirium or mortality. Martinez 2015 identified that multi-component interventions were effective in reducing incident delirium and accidental falls among hospitalised older adults (aged > 60 years), compared to usual care.

Evidence for delirium prevention in other settings does not allow such consistent conclusions. The Cochrane review of delirium prevention in long-term care settings identified only three trials for inclusion, each considering different non-pharmacological interventions, with considerable uncertainty about the results (Woodhouse 2019). In ICU settings, most studies have been conducted on the effects of pharmacological interventions. A Cochrane Review in the ICU setting, included four non-pharmacological intervention studies, but there was heterogeneity in the interventions and outcomes and no clear conclusions could be drawn from the available evidence (Herling 2018).

AUTHORS' CONCLUSIONS

Implications for practice

Non-pharmacological delirium prevention interventions are probably effective across all (non-intensive care unit (ICU)) hospital settings in reducing the incidence of delirium by around 43%.

These interventions may include reorientation and use of familiar objects, cognitive stimulation and sleep hygiene, with consideration for support for nutrition, hydration and electrolyte balance, oxygenation and bowel and bladder care.

Implications for research

Given the strength of evidence to support non-pharmacological multicomponent interventions, there is a need for research to understand how these can be implemented in practice. The randomised-trial evidence to support single-component interventions for delirium prevention in non-ICU settings remains limited and this may reflect the nature of the condition, necessitating complex intervention approaches. Future evidence synthesis may benefit from focusing on multicomponent approaches alone, taking time and attention on the specific included components in greater detail, both their content and delivery. There is a need to evaluate cost-effectiveness to make the case for investment to implement interventions.

There is a lack of evidence involving people with delirium superimposed on dementia, who are often excluded from trials and for whom specific subgroup reporting would be beneficial. These individuals must be included in delirium prevention research.

Routine assessment of frailty status and reporting stratified by this variable would also be helpful in future research studies to test hypotheses about the role of frailty in delirium.

Outcome assessment focused on variables which matter to individuals, particularly around cognitive outcomes including progression of dementia and the development of dementia would be informative as part of the wider dementia prevention agenda.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abizanda 2011

Study characteristics	
Methods	Design: RCTof a short-term occupational therapy intervention in an acute geriatric unit Date of study: November 2002 to June 2003 Power calculation: yes Inclusion criteria: all patients aged 65 and over consecutively admitted to the acute geriatric unit with an acute medical illness or exacerbation of existing chronic condition Exclusion criteria: none reported
Participants	Number in study: 400 Country: Spain Setting: one acute geriatric unit Age: mean age 83.7 years (SD 6.1) in intervention group, 83.3 years (SD 6.5) in control group Sex: 43.4% male in intervention group, 43.1% male in control group Co-morbidity: number of previous chronic conditions 3.8 in intervention group, 3.5 in control group Dementia: 35.3% in intervention group, 31.4% in control group Frailty: not reported
Interventions	Intervention: occupational therapy intervention schedule consisted of a daily 45-minute session with patient and relative/caregiver Monday-Friday for the duration of admission. Activities were carried out according to needs and day of admission. Therapeutic plan included: cognitive stimulation; instruction on preventing complications including immobility, confusion, falls, urinary incontinence, pressure sores; retraining in ADL; assessment of technical aids for home.

Abizanda 2011 *(Continued)*

	Control: all participants received medical treatment, nursing care, physical therapy and social assistance.
Outcomes	Outcomes reported: - Incident delirium, measured daily using CAM - In-hospital mortality - Length of admission - Activities of daily living (ADL), measured using Barthel index - Adverse events Outcomes not reported: none Frequency of outcomes assessment: daily during hospitalisation
Notes	Funding source: Institute of Health Sciences, Junta de Comunidades de Castilla-La Mancha. Declarations of interest: quote: "All authors declare that there is not any personal, financial or potential conflict of interest, and therefore have nothing to declare." Delirium excluded at enrolment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised randomisation system
Allocation concealment (selection bias)	Low risk	Assignment to randomised group by a geriatrician who did not participate in the clinical management of participants
Blinding of participants and personnel (performance bias) All outcomes	High risk	The geriatricians caring for the patients and providing their routine care were blinded to allocated group. Participants were not blinded due to the nature of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor and the individual performing data analysis were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number with missing data are balanced between groups and there do not appear to be any systematic differences between the groups
Selective reporting (reporting bias)	Low risk	No changes were made to trial outcomes after the trial was initiated
Other bias	Low risk	No evidence of other bias

Avendano-Cespedes 2016

Study characteristics

Methods	Design: RCT

Avendano-Cespedes 2016 *(Continued)*

	Date of study: Oct 13 to Feb 14 Power calculation: pilot sample calculated to detect 10% reduction in delirium from 20% in control group with upper 1 sided 80% confidence limit (power not specified) – sample size of 50 selected Inclusion criteria: >=65, Hospitalised on acute geriatric unit of participating hospital (single-site) between Oct 13 and Feb 14, Valid informed consent (patient or their legal representative) Exclusion criteria: quote: "Agonic situation" (presume palliative care), Non-Spanish speaking Severe cognitive decline (Reisberg's Global Deterioration Scale = 7), patient sharing a room with a previously included participant (to avoid contamination bias)
Participants	Sample size: 50 Country: Spain Setting: acute geriatric unit in one tertiary University hospital Age: Mean age 85.8 (SD = 6.2) in intervention, mean age 87.0 (SD 4.9) in control Overall 86.5 (5.5) Sex: Males, 10 (47.6%) in intervention, males 16 (32%) in control Overall males 26 (52%) Co-morbidity: mean Charlson comorbidity index score 2.1 (1.7) in intervention group, 2.2 (1.3) in control group. Data reported on physiological parameters including blood pressure, temperature and oxygen saturation– no major imbalances between groups. Dementia: patients with 'severe' cognitive impairment were excluded – Reisberg's Global Deterioration scale = 7 (end-stage dementia). Other stages of dementia are included. Frailty: not reported
Interventions	Intervention:the intervention was carried out exclusively by the "intervention nurses", and was composed of two main parts, being the first one a risk factor analysis, and the second one the a daily multicomponent non-pharmacologic intervention (orientation, sensorial deficit, sleep, mobilisation, hydration, nutrition, drug chart review, elimination, oxygenation, pain), on the risk factors detected. The intervention nurses identified the principal caregiver in the first 24 hours from admission, and provided an informative booklet about strategies and recommendations to prevent delirium incidence, including ambient strategies, orientation abilities, and identification of alert signs. Participants received the initial intervention in the first 24 hours from admission, and thereafter daily until hospital discharge. Control: Usual medical and nursing care throughout the hospitalisation process. No booklet
Outcomes	Outcomes reported: - Incident delirium using CAM - Prevalent delirium, at any point during hospitalisation, using CAM - New diagnosis of dementia using Pfeiffer Short Portable Mental Status Questionnaire and Reisberg Global Deterioration Scale - Duration of delirium episode (days) - Peak severity of delirium using validated instruments - Length of hospital admission (days) - Use of new psychotropic medication during admission - Withdrawal from protocol by participants

Avendano-Cespedes 2016 *(Continued)*

	Outcomes not reported: none Frequency of outcomes assessment: daily assessment for delirium whilst in hospital
Notes	Funding source: Funded by RD12/0043RETICEF, Instituto de Salud Carlos III, Ministerio de Economíay Competitividad Declarations of interest: none declared Multiple measures of delirium reported. Those with delirium on first day are highlighted in various analyses presented, but difficult to ascertain denominator and use the data presented in narrative and tables as some inconsistency in reporting.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was computer-based using computer-generated random numbers with a proportion of 1:1 between control group and intervention group.
Allocation concealment (selection bias)	Low risk	After randomisation before participant allocation, opaque envelopes were used to store the data with sequential study numbers
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of investigator and participants was not possible due to nature of intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessment was conducted blinded to allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Reporting in accordance with pre-registered trial protocol
Other bias	Low risk	No evidence of other bias

Bonaventura 2007

Study characteristics

Methods	Design: RCT of a multi-component intervention, the Intervention to Prevent Delirium (IPD) in older patients admitted to medical and geriatric wards Date of study: 2005 to 2006 Power calculation: no Inclusion criteria: age > or = to 65 years admitted to medical and geriatric wards in one hospital Exclusion criteria: MMSE score < or =25, at least 1 relative not present, transfer out of ward, pre-existing dementia, blindness, deafness, aphasia or unable to understand Italian
Participants	Number in study: 60

Bonaventura 2007 *(Continued)*

	Country: Italy Setting: medical and geriatric wards Age: not given Sex M:F: Intervention 12/18, Control 12/18 Co-morbidity: comparable P = 0.77 Dementia: excluded Frailty: not reported
Interventions	Intervention: Intervention to Prevent Delirium (IPD), a series of structured and standardised welfare actions based on existing guidelines, including support in the following areas: cognitive re-orientation, sensory and environmental, mobilisation, hydration, and 'socio-emotional' Control: usual care, not described further
Outcomes	Outcomes reported: - Incident delirium measured using CAM & DRS-R-98 - Functional performance using Barthel Index Outcomes not reported: none Frequency of outcomes assessment: days 1, 2, 4 and 7 of admission
Notes	Funding source: not reported Declarations of interest: not reported Delirium not excluded at enrolment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Sequence generated using day of admission
Allocation concealment (selection bias)	High risk	Odd and even days of admission used so concealment unlikely
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel not blinded, not possible given nature of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcome assessment blinding not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants included in the analysis
Selective reporting (reporting bias)	Unclear risk	Insufficient information presented to make judgment
Other bias	Low risk	No evidence of other bias

Boustani 2012

Study characteristics	
Methods	Design: RCT of a clinical decision support system to improve the care of hospitalised older adults with cognitive impairment Date of study: July 2006 to March 2008 Power calculation: no Inclusion criteria: at least 65 years of age, hospitalised on a medical ward, English-speaking, and cognitive impairment at the time of hospital admission. Exclusion criteria: pPatients were excluded if they had previously been enrolled in the study, were aphasic, or unresponsive at the time of screening
Participants	Number in study: 427 Country: USA Setting: medical wards of Wishard Memorial University Hospital Age: Mean age 76.8 years (SD 7.9 years) in intervention group, 77.6 years (SD 8.3 years) in control group Sex: 39.7% male in intervention group, 28.9% male in control group Co-morbidity: mean Charlson comorbidity index 1.8 (SD 1.8) in intervention group, 2.4 (SD 2.1) in control group Dementia: not reported Frailty: not reported
Interventions	Intervention: electronically-delivered clinical decision support system (CDSS) (1) Each time a physician enters an order for a patient randomised to the intervention arm, the physician received non-interruptive alerts of the presence of CI, catheter, physical restraints, anticholinergic drugs, or the need for ACE services; (2) If the physician orders a urinary catheter, s/he will receive interruptive alerts to recommending discontinuing the catheter; (3) If the physician orders physical restraints, s/he will receive interruptive alerts recommending substituting physical restraints with the use of a professional sitter or low dose trazodone; (4) If the physician orders any of the 18 inappropriate anticholinergics, s/he will receive interruptive alerts recommending stopping the drug, suggesting an alternative, or recommending dose modification. (5) The physician was required to make a decision to accept, reject, or modify any of the interruptive alerts. Control: patients randomised into usual care did not receive CDSS
Outcomes	Outcomes reported: - Incident delirium, measured using CAM - Mortality - Length of hospital stay - Falls - Pressure ulcers Outcomes not reported: None

Boustani 2012 *(Continued)*

	Frequency of outcomes assessment: every weekday during hospital admission
Notes	Funding source: NIA Paul B. Beeson K23 Career Development Award Declarations of interest: quote: "Dr Boustani has work supported by grants from the NIA and AHRQ. He is also a member of the Pfizer speakers' bureau. Dr Buckley has provided expert testimony for local law firms. Mr Perkins owns stock in several pharmaceutical firms" Delirium assessed but not excluded at enrolment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated process was employed for sequence generation in a 1:1 ratio
Allocation concealment (selection bias)	Low risk	Central process following computer generation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind personnel treating the patients in the CDSS group
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of research assistants conducting outcome assessments not known
Incomplete outcome data (attrition bias) All outcomes	Low risk	427 enrolled into trial, outcome data available for 424 with no account given for missing participants or to which group they were assigned. However, small as proportion of total sample
Selective reporting (reporting bias)	Unclear risk	Insufficient information presented to make judgment
Other bias	Low risk	No evidence of other bias

Cetinkaya 2019

Study characteristics

Methods	Design: RCT Date of study: February and June 2018 Power calculation: no Inclusion criteria: the inclusion criteria for the study were 65 years of age or older, no complications during the 3 days of the postoperative period, and willingness to participate in the study. Exclusion criteria: the exclusion criteria were mental retardation that hinders communication, dementia (defined as a Mini-Mental State Examination [MMSE] score of <23), age < 65 years, hearing problem, development of postoperative complications and unable to speak Turkish.
Participants	Sample size: 60 Country: Turkey

Cetinkaya 2019 *(Continued)*

	Setting: orthopaedics clinic in an educational research hospital Age: Mean age 69.86 (± 7.59) Sex: male, 10 (33.3%) in Intervention group, male, 5 (16.7%) in control group Overall: male (15, 25%) Co-morbidity: there were no differences between groups for the number of chronic diseases, previous surgery or regular use if medication. Dementia: not reported Frailty: not reported
Interventions	Intervention: patients were exposed to music for 3 postoperative days after hip or knee surgery. The patients listening to music were supplied with an Mp3 player in their room, in bed. A separate headset was used for each patient. The patients listened to Acemasiran-type classical Turkish music. Acemasiran-type music affects the human brain and provides a sense of creativity of people. Each patient in the intervention group listened to the music for 20-minute sessions three times a day for 3 postoperative days. Control: routine nursing care – no other description provided.
Outcomes	Outcomes reported: -Incident delirium using The Neecham Confusion Scale Outcomes from study not reported: none Frequency of outcomes assessment: three days postoperatively
Notes	Funding source: not reported Declarations of interest: none reported by authors Delirium not excluded at enrolment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly allocated into two groups by drawing lots using closed envelopes with numbers from 0 to 9. However, authors state – quote: "Those who selected single numbers were allocated to the control group, and those with double numbers formed the intervention group". Assumed to reflect typographical error in the paper.
Allocation concealment (selection bias)	Unclear risk	Unclear how the allocation to groups was concealed based on method used to generate random allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients receiving the intervention were supplied with an MP3 player in their room, blinding not possible. States nurses were blinded, although their role in study is unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Those in the intervention group visited by the researcher. States statistician was blinded to assignment, but role of researcher and statistician not defined in terms of outcome assessment.

Cetinkaya 2019 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcome data reported – no losses to follow-up
Selective reporting (reporting bias)	Unclear risk	No published protocol available for review
Other bias	Low risk	No evidence of other bias

Chen 2017

Study characteristics	
Methods	Design: cluster-RCT Date of study: August 1 2009 to October 31 Power calculation: not calculated before data collection Inclusion criteria: scheduled for elective abdominal surgery and expected LOS longer than 6 days (≥ 65 years of age) Exclusion criteria: not reported
Participants	Sample size: 557 Country: Taiwan Setting: two 36-bed gastrointestinal wards of a 2000-bed urban medical centre in Taipei Age: mean age 74.3 years (SD= 5.8) in intervention group, Mean age 74.8 (SD=6.0) in control group Sex: male, 111 (56.4%) in intervention group, male, 103 (57.2%) in control group Co-morbidity: mean Charlson comorbidity index - IG (1.6, 1.9), CG (1.5, 1.7) Dementia: cognitive, MMSE score range, 0-30; 30 indicates no impairment, (mean, SD): IG (27.0, 3.8), CG (26.8, 3.1) P-value 0.61 Frailty: not reported
Interventions	Intervention: the intervention was implemented by a mHELP nurse which is registered nurse who had 2 years of medical surgical experience and who was trained on site for 1 month before the intervention start. The intervention consisted of 3 protocols administered daily: orienting communication, oral and nutritional assistance, and early mobilisation. Intervention group participants received all 3 mHELP protocols with a median start time of postoperative day 1 (IQR 1-3), in addition to usual care, as soon as they arrived in the inpatient ward and until hospital discharge. Control: usual care consisted of standard hospital care provided by surgeons, residents, nurses, and physical therapists (as needed) in the general surgery wards. All participants were encouraged to ambulate and did so as tolerated. The mHELP nurses did not provide services to participants assigned to the control group. However, the same attending physicians provided care to participants in the mHELP and control groups.
Outcomes	Outcomes reported: - Incident delirium using CAM - Inpatient mortality

Chen 2017 *(Continued)*

	- Length of hospital admission (days) - Withdrawals (not explicitly included as an outcome but reported) Outcomes from study not reported: - New diagnosis of dementia using change in MMSE at baseline, discharge, 4 and 6 weeks - ADL using Barthel Index Frequency of outcomes assessment: daily from Monday to Saturday
Notes	Funding source: This study was supported in part by grants 98-2314-B-002-113-MY3 from the Ministry of Science and Technology and NHRIEX-9820PC from the National Health Research Institute in Taiwan (Dr C.C.-H. Chen). Dr Inouye's time was covered in part by grants R24AG054259, P01AG031720, K07AG041835, and R01AG044518 from the National Institute on Aging. Dr Inouye holds the Milton and Shirley F. Levy Family Chair. Declarations of interest: none reported Delirium not excluded at enrolment Intervention only delivered once participants discharged from ITU so varied from first postoperative day to after three days postoperatively

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generated based on computer-generated list
Allocation concealment (selection bias)	Low risk	Cluster-randomised to groups with an allocation ratio of 1:1. Cluster randomisation used to reduce risk of cross-contamination due to shared occupancy rooms.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Due to nature of intervention, participants and personnel were unblinded. Intervention delivery was separate from outcome assessment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were masked to group assignment and room assignments were re-randomised every 20 patients to minimise potential unmasking of the randomisation scheme
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted-for and low levels of attrition from analysis of outcomes, clearly described with reasons documented.
Selective reporting (reporting bias)	High risk	NCT protocol specifies other primary outcomes (frailty and bowel dysmotility) not reported here.
Other bias	Low risk	No evidence of recruitment bias or evidence of baseline imbalance associated with cluster methods. No clusters lost. Authors report that the intracluster correlation coefficient (ICC) was calculated for each outcome and were not significantly different from 0 and some were even less than 0, suggesting that the true ICCs are small and adjustment for cluster effect is not indicated. We thus analysed treatment effects using standard statistical methods not accounting for within-cluster correlation.

Dong 2020

Study characteristics	
Methods	Design: RCT Date of study: December 2016 to December 2019 Power calculation: not calculated Inclusion criteria: meets the Severe Acute Pancreatitis diagnostic criteria in the 2013 Chinese Guidelines for the Diagnosis and Treatment of Acute Pancreatitis, aged 70 years or older, expected hospital stay >2 weeks and provision of written informed consent. Exclusion criteria: the exclusion criteria were history of severe acute pancreatitis, coma, complicated with mental disorders or disorders, dementia, low immune function (such as neutrophil deficiency) and end-stage disease.
Participants	Sample size: 106 Country: China Setting: Affiliated Hospital of Jiangnan University, Age: mean age in intervention group 75.87 [+/- 4.32], mean age in control group 76.23 [+/- 4.58] Sex: male, 32 (64%) in intervention group, male 34 (65%), in control group Co-morbidity: not reported Dementia: excluded Frailty: not reported
Interventions	Intervention: all patients received 1. Directional communication plan 2. Cognitive therapy activity plan 3. Early activity plan The following schemes are implemented as needed based on the evaluation results 4. Pain improvement program 5. Sleep improvement program 6. Assisted feeding plan 7. Rehydration program 8. Constipation improvement plan 9. Hearing/vision improvement program 10. Hypoxic improvement program 11. Aspiration pneumonia prevention program 12. Urine-related infection prevention program 13. Delirium improvement program14. Dementia improvement program 15. Multiple medication management plan Control: Routine nursing programmes and procedures.
Outcomes	Outcomes reported: - Incident delirium using CAM - Inpatient mortality - Length of hospital admission (days) - ADL using Barthel Index (pre and post 2-week intervention period only) Outcomes from study not reported: None Frequency of outcomes assessment: pre and post 2 week intervention period
Notes	Funding source:this work was supported by the Translational Medicine Specialty of Wuxi Municipal Health Committee (ZM006). Declarations of interest: No conflicts of interest to declare

Dong 2020 *(Continued)*

	Delirium not excluded at enrolment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Use of random number table to determine if subjects for test group or control
Allocation concealment (selection bias)	Unclear risk	Method of allocation not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants or personnel described
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Three participants in intervention group died, no data presented on them, even at baseline
Selective reporting (reporting bias)	High risk	No protocol available. Length of stay was not pre-specified in methods. Incomplete reporting for cognition and self-care as categories used are not referenced or specified as data derived.
Other bias	Low risk	No evidence of other bias

Fan 2014

Study characteristics

Methods	Design: RCT Date of study: October 2011 to May 2013 Power calculation: no Inclusion criteria: patients older than 65 years undergoing elective unilateral total hip replacement surgery with spinal anaesthetic Exclusion criteria: ASA physical status 3 IV; preoperative delirium; unwilling to comply with the procedures; inability to understand the language (Mandarin Chinese); hearing loss, or a failure in spinal anaesthesia
Participants	Sample size:192 Country: China Setting: hospital inpatient – elective orthopaedics Age: mean age 73 (+/- 7) in the intervention group, 75 (+/- 6) in the control group Sex: male, 30, (31.9%) in the Intervention group, male, 32, (35.9%) in the control group

Fan 2014 *(Continued)*

	Co-morbidity: no baseline between-group differences in CVD, IHD, CHF, hypertension, pulmonary disease, renal insufficiency, PVD, diabetes mellitus, liver disease. Dementia: not mentioned explicitly but cognitive assessment undertaken using MMSE Frailty: not reported
Interventions	Intervention: patients older than 65 years undergoing elective unilateral total hip replacement surgery with spinal anaesthetic. Control: ASA physical status 3 IV; preoperative delirium; unwilling to comply with the procedures; inability to understand the language (Mandarin Chinese); hearing loss, or a failure in spinal anaesthesia
Outcomes	Outcomes reported - Incident delirium using the Confusion Assessment Method for the intensive care unit (CAM-ICU) - Length of stay - Withdrawal Outcomes from study not reported: none Frequency of outcomes assessment: Delirium was assessed by the same attending anaesthesiologist between 8 a.m. and 9 a.m. preoperatively, and 1, 2, 3 days after surgery.
Notes	Funding source: this work was supported by the grants from the National Natural Science Foundation of China (No. 81300946) and the Natural Science Foundation of Jiangsu Province (BK2012778). Declarations of interest: no conflict of interest stated by authors Delirium excluded at enrolment using the (CAM- ICU) criteria (Chinese version) Imbalance between groups om other substances transfused – restrictive group received more Ringer's lactate and hydroxyethyl starch

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned to restrictive or liberal group using a random number table
Allocation concealment (selection bias)	Unclear risk	The method used to was sealed envelope technique, however, there is insufficient detail as to whether these were opaque.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants or personnel described
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessments described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Clear accounting for all participants at follow-up. Loss of 2 from restrictive and 4 from liberal transfusion groups at follow-up due to declined consent for transfusion.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to assess as no published protocol

Fan 2014 *(Continued)*

Other bias	Low risk	No evidence of other bias

Gao 2018

Study characteristics	
Methods	Design: RCT Date of study: July 2017 Power calculation: not reported Inclusion criteria: aged 65+, with silent lacunar infarct, who underwent spinal surgery in July 2017 (at Third Hospital of Hebei Medical University) Exclusion criteria: MMSE score of less than 24 or dementia, due to various aetiologies, preoperative delirium, history of neurological or mental illness, current use of tranquillisers or antidepressants, history of an endocrine or metabolic disorder, recent use of glucocorticoids or other hormones, suffering from infections or chronic inflammatory conditions, intake of anti-inflammatory drugs, unwillingness to complete the experimental procedures, inability to communicate in the preoperative period (language barrier or severe hearing or visual impairment), and alcohol or drug dependence.
Participants	Sample size: 64 Country: China Setting: hospital -post surgery at Third Hospital of Hebei Medical University (China) Age: mean age 71 (SD = 5) in the intervention group, mean age 73 (SD = 4) in the control group Sex: male, 15, 47% in the intervention group, male, 18, 56% in the control group Co-morbidity: no significant differences for the American Society of Anaesthesiologists (physical status) and for BMI Dementia: excluded Frailty: not reported
Interventions	Intervention: transcutaneous electrical acupoint stimulation: TEAS (disperse-dense waves; frequency, 2/100 Hz) on acupoints Hegu and Neiguan of both sides starting from 30 minutes before induction of anaesthesia until the end of surgery, and the intensity was the maximum current that could be tolerated. Control: in the control group, electrodes were placed on the same acupoints before anaesthesia induction, but no current was given.
Outcomes	Outcomes reported -Incident delirium using CAM-ICU/RASS Outcomes from study not reported: none Frequency of outcomes assessment: assessed on day of surgery and twice daily on the 3 days following surgery
Notes	Funding source: National Natural Science Foundation of China (81771134), Natural Science Foundation of Hebei Province (H2018206305), and Hebei Provincial Government Funded Clinical Talents Cultivation and Basic Research Projects (361005).

Gao 2018 *(Continued)*

	Declarations of interest: authors report no conflicts of interest. Delirium excluded at enrolment Statistically significant imbalance in administration of Propofol and Remifentanil with those in the control group receiving more of both. May be related to observed rates of delirium.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Divided into two groups using a random number table
Allocation concealment (selection bias)	Unclear risk	No information provided around how allocations were concealed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants unclear as intervention delivered while under anaesthesia and electrodes places for both groups. Blinding of personnel not described, but intervention would need to be actively administered.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Delirium assessment conducted by researchers blinded to group assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the analysis
Selective reporting (reporting bias)	Unclear risk	Insufficient information to assess as no published protocol
Other bias	Low risk	No evidence of other bias

Gruber-Baldini 2013

Study characteristics

Methods	Design: RCT of liberal blood transfusion thresholds compared to restrictive transfusion practice for hip fracture patients Date of study: April 2008-February 2009 Power calculation: yes Frequency of outcomes assessment: multiple times within 5 days after randomisation or up to hospital discharge (if hospital stay was shorter) Inclusion criteria: aged 50 and older; undergoing surgical repair of hip fracture; Hb < 10 g/dL within 3 days after surgery; clinical evidence of cardiovascular disease or cardiovascular disease risk factors Exclusion criteria: non-English speaking; unable to walk unaided before fracture; declined blood transfusions; multiple traumas; pathological hip fracture; clinical acute myocardial infarction within 30 days pre-randomisation; previous participants in the trial; symptoms associated with anaemia; actively bleeding at time of potential randomisation
Participants	Number in study: 139 Country: USA and Canada Setting: 13 hospitals

Gruber-Baldini 2013 *(Continued)*

	Age: mean age 82.4 (SD 7.4) in intervention group compared to 80.6 (SD 10.4) in control group Sex: 81.8% of intervention group were female compared to 47% of control group Co-morbidity: numbers and percentages of common co-morbidities reported in paper (stroke/TIA, chronic lung disease, cancer, diabetes, atrial fibrillation, Parkinson's disease, hearing problems, visual problems and alcohol abuse or withdrawal) Dementia: 27.3% of intervention group had dementia compared to 36.1% of the control group Frailty: not reported
Interventions	Intervention (aka liberal treatment): one unit of packed red blood cells and as much blood as needed to maintain a Hb concentration >10 g/dL Control (aka restrictive treatment): only transfused if symptoms of anaemia developed or at the study physicians discretion or if Hb < 8 g/dL
Outcomes	Outcomes reported: - Incident delirium, using CAM - Delirium severity, using MDAS - Length of admission - Physical morbidity (post-randomisation adverse events) - Psychoactive medication use Outcomes from study not reported: none Frequency of outcomes assessment: multiple times within 5 days after randomisation or up to hospital discharge.
Notes	Funding source: Research grant from National Heart Lung and Blood Institute Declarations of interest: quote: "Dr Magaziner received support from Amgen, Eli Lilly, Glaxo SmithKline, Merck, Novartis and Sanofi Aventis to conduct research through his institution, provide academic consultation, or serve on an advisory board. Dr Roffey reports working as a consultant for Palladian Health. Dr Cardson reports receiving grant support to his institution from Amgen. Dr Marcantionio is a recipient of a Mid-Career Investigator Award in Patient-Oriented Research from the National Institute on Aging" Delirium assessed at baseline but not excluded >1/3 of the restrictive group received transfusion

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Automated central telephone randomisation system
Allocation concealment (selection bias)	Low risk	No evidence to suggest allocations revealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded

Gruber-Baldini 2013 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Research staff unblinded to treatment status except at one site
Incomplete outcome data (attrition bias) All outcomes	Low risk	139 randomised, outcome assessment data available for 138
Selective reporting (reporting bias)	Low risk	Data reported for all participants included in the study
Other bias	Low risk	No evidence of other bias

Hempenius 2013

Study characteristics	
Methods	Design: multi-centre, RCT Date of study: June 2007-June 2010 Power calculation: yes but study underpowered Inclusion criteria: over 65 yrs; due to undergo elective surgery for a solid tumour, deemed to be frail (using Groningen Frailty Indicator >3) Exclusion criteria: unable to complete protocol; unable to complete follow-up; unable to complete questionnaire
Participants	Sample size: 297 Country: the Netherlands Setting: 3 hospitals (1 university medical centre, 1 teaching hospital and 1 community hospital) Age: Mean age 77.45 (SD 6.72) in intervention group; 77.63 (SD 7.69) in usual care group Sex: 62.2% of intervention group were female compared with 65.8%of usual care group Co-morbidity: stratified into < or equal to 2 co-morbidities (39.6% of intervention group 40.4% of usual care group) or >2 co-morbidities (60.4% in intervention group 59.6% of usual care group) Dementia: MMSE performed at baseline; mean score 26.6 in intervention group versus 26. 33 in usual care group (P = 0.49) Frailty: not reported
Interventions	Intervention: multi-component intervention focused on best supportive care and the prevention of delirium. Preoperative geriatric team assessment with daily monitoring during hospital stay, supported by the use of standardised checklists Control: only had access to geriatric care if treating physician requested referral
Outcomes	Outcomes reported: - Incident delirium, using DOSS - if > 3 then had specialist assessment using DSM-IV. - Delirium severity, using DRS-R-98 - Length of admission - Mortality - Return to independent living - Postoperative complications - Quality of life using Short-Form-36 - Falls - ADL using validated instrument using the Care Dependency Scale (CDS) - Withdrawals

Hempenius 2013 *(Continued)*

	Outcomes not reported: none
	Frequency of outcomes assessment: days 1-10 postoperatively, 3 times per day
Notes	Funding source: Netherlands Organisation for Health Research and Development
	Declarations of interest: quote: “The authors declared that no competing interests exist”
	Delirium not excluded at enrolment
	No record of how many in usual care group received geriatrician input

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Interactive voice response telephone system for randomisation provided by university
Allocation concealment (selection bias)	Low risk	Central allocation system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and research nurses unblinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Delirium assessment blinded to allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	297 participants randomised, outcome assessments available for 260 (n = 127 in intervention group and n = 133 in control group) - no information provided, described as ’lost to follow-up’
Selective reporting (reporting bias)	Low risk	Outcomes reported as per original protocol
Other bias	Low risk	No evidence of other bias

Hosie 2020

Study characteristics

Methods	Design: cluster-RCT
	Date of study: 2017
	Power calculation:dDetails of formal calculation for future phase III cluster study are detailed in the published protocol;
	Inclusion criteria: patients eligible for enrolment were adults (i.e. 18 years of age or older) with advanced (stage 4) cancer.
	Exclusion criteria: none specified.
Participants	Sample size: 65
	Country: Australia

Hosie 2020 *(Continued)*

	Setting: four specialist palliative care inpatient units within hospitals in metropolitan Australia. Age: mean age of 76.0 (SD 11.2) in intervention group, 70.5 (15.5) in control group and 68.1 (12.5) in waitlisted group Sex: 41% of intervention group were male, compared to 65% of the control group and 66% in waitlisted group. Co-morbidity: no specific measure of co-morbidity or health conditions listed by group. Provided breakdown of Australian-modified Karnofsky Performance Scale which suggests there are differences between the group, however, numbers are very small Dementia: not reported Frailty: not reported
Interventions	Intervention: the intervention had six domains (eating and drinking, sleep, exercise, reorientation, vision and hearing, and family partnership), containing 36 strategies overall (4–12 per domain). Team members were asked to enlist family and volunteers and tailor the intervention to patients' needs and wishes. A two-month site engagement and training period, guided by customised information manuals , preceded control and intervention conditions. Sites formed working groups of interested team members to plan implementation in line with their resources and systems. University-based researchers attended working group meetings to ensure intervention fidelity, trial integrity, and timely progress. Sites shared meeting records whenever researchers could not attend in person. Training was provided through four discrete 30– to 40-minute sessions using Biggs' educational model, delivered multiple times for broadest reach. Control: control sites received information about delirium prevention strategies when they transitioned to the intervention phase, along with a summary of learnings from intervention sites about optimising trial processes. A key message was that the checklist was not the intervention per se, but essential to measuring the primary outcome of adherence.
Outcomes	Outcomes reported: - Incident delirium using Nurses Delirium Screening Scale (Nu-DESC) and DSM-V with DRS-R-98. - Inpatient mortality - Severity of delirium (mean, using DRS-R-98) - Falls Outcomes from study not reported: none Frequency of outcomes assessment: each eight-hour shift
Notes	Funding source: the trial was funded by an Australian National Breast Cancer Foundation (NBCF) 2017 Pilot Study Grant (Grant code PS-17-030). Declarations of interest: Drs. A.H., J.P., L.L., S.K., S.L.C., A.G., and M.A. and Ms. L.B., B.F., L.E., J.H., R.A., T.A., M.G. and J.W. report a grant from the National Breast Cancer Foundation during the conduct of the study. Dr. A.H. also reports personal fees from Medtronic, outside the submitted work. Dr. G.A.C. reports grants from Bionomics Pty Ltd., outside the submitted work. Dr. E.W.E. reports personal fees from Masimo, grants from VA/NIH, personal fees from Pfizer/Orion, and grants from Koheler, outside the submitted work. All remaining authors have no disclosures to report. Delirium not excluded at enrolment

Risk of bias

Bias	Authors' judgement	Support for judgement

Hosie 2020 *(Continued)*

Random sequence generation (selection bias)	Low risk	Permuted block randomisation method used
Allocation concealment (selection bias)	Low risk	Allocation performed by trial statistician at University using above randomisation method.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel not possible due to study design and nature of intervention
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessment also unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for – high proportion in waitlisted site (7/27) did not receive intervention or have data collected but reasons provided, and majority relate to nature of the unit of care (palliative/end of life), rather than the intervention
Selective reporting (reporting bias)	Low risk	Outcomes reported in accordance with published protocol (BMJ Open citation)
Other bias	High risk	No evidence of recruitment bias or baseline imbalance associated with cluster design. No loss of clusters. No account made for cluster design in the analytical methods reported.

Jeffs 2013

Study characteristics	
Methods	Design: RCT Date of study: May 2005-December 2007 Power calculation: yes - incorporating incident delirium and absolute risk reduction of 6% Inclusion criteria: aged 65 years or older; admitted to a medical unit in the study area; in hospital < 48 hours Exclusion criteria: severe dysphasia rendering communication impossible; death expected within 24 hours; isolation for infection control; documented contraindication to mobilisation; admission to the Stroke Unit or to critical care; planned admission of < 48 hours; major psychiatric diagnosis; previous inclusion in the study; delirium documented in the admission notes; transfer from another hospital.
Participants	Number in study: 649 Country: Australia Setting: acute medical wards, secondary referral centre Age: mean age of 79.6 (SD 7.5) in intervention group, 79.1 (7.9) in control group Sex: 45% of intervention group were male, compared to 50% of control group Co-morbidity: Charlson index of 2 (1-3) in both groups at baseline Dementia: MMSE recorded at baseline in both groups: 25 (20 to 28) in intervention group versus 26 (19-28) in control group Frailty: not reported

Jeffs 2013 *(Continued)*

Interventions	Intervention: participants randomised to the intervention arm received a graded physical activity and orientation programme twice daily, which was delivered in addition to usual care. A certified Allied Health Assistant, trained in administering exercise programmes, delivered the intervention after initial assessment of the participant by a physiotherapist. The programme started on the same day as the participant was randomised. Commensurate with ability, participants were prescribed one of four exercise programmes: bed, seated, standing or rails. All programmes were customised to the participant's ability and were reviewed daily. Exercise programmes were modified to ensure suitable progression for those participants who made significant gains. The orientation programme comprised formal and informal elements. The formal element of the programme comprised a series of seven questions aimed at assessing and improving orientation (day, month, year, date, ward, bed number and name of primary nurse). The participant was asked the questions in sequence and prompted with the correct answer if they were not able to give a correct response. The informal element of the programme related to engaging in the exercise programme and in the social interaction with the Allied Health Assistant and/or Physiotherapist. Control: Usual care included 24-hour nursing care, daily medical assessment and allied health referral by medical, nursing or other staff. Allied health input was provided on referral only, but daily ward meetings were held to review patient progress and facilitate referrals. Patients with significant functional, cognitive or social issues could be referred to the Aged Care medical consultation service that performed a daily round and could offer advice regarding the recognition, investigation and management of geriatric syndromes including delirium.
Outcomes	Outcomes reported: - Incidence of delirium, using CAM - Duration of delirium - Severity of delirium, using CAM - Length of stay - Return to previous residence Outcomes not reported: none Frequency of outcomes assessment: every 48 hours
Notes	Funding source: HCF Health and Medical Research Foundation Declarations of interest: quote: "No competing interests" Very low rates of delirium in both arms. Authors suggest may be due to 48 hourly assessments or not selecting those at high risk. Delirium excluded at enrolment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not clear, just states 'randomisation was achieved using sealed opaque envelopes'
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes for allocation
Blinding of participants and personnel (performance bias)	High risk	Participants not informed of allocation, but unable to fully blind due to nature of intervention

Jeffs 2013 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded to allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	n = 17 in intervention and n = 18 in control did not receive the intervention, but were assessed on an intention-to-treat analysis basis
Selective reporting (reporting bias)	Low risk	Trial protocol retrospectively registered with Australian New Zealand Clinical Trials Registry ACTRN 012605000044628; outcomes reported in accordance with protocol
Other bias	Low risk	No evidence of other bias

Lundstrom 2007

Study characteristics	
Methods	Design: RCT of multi-component delirium prevention intervention for older hip fracture patients Date of study: May 2000 to December 2002 Power calculation: yes Inclusion criteria: patients aged 70 years and older consecutively admitted to the orthopaedic department in Umea hospital, Sweden. Exclusion criteria: age under 70, severe rheumatoid arthritis, severe hip osteoarthritis, severe renal failure, pathological fracture and patients who were bedridden before the fracture
Participants	Sample size: 199 Country: Sweden Setting: orthopaedic hip fracture patients Age: Mean age 82 years Sex: 74% female Co-morbidity: no baseline between group differences in cardiovascular disease, respiratory disease, hypertension or diabetes. More patients in control group with depression (46% versus 32%, P = 0.03) Dementia: 27.5 % in intervention group, 37.1% in control group Frailty: not reported
Interventions	Intervention: multi-disciplinary team providing comprehensive geriatric assessment, management and rehabilitation on a geriatric ward. Intervention comprising: staff education; teamwork; individual care planning; delirium prevention detection and treatment; prevention and treatment of complications; bowel/bladder function; sleep; decubitus ulcer prevention/treatment; pain management; oxygenation; body temperature measurement; nutrition; rehabilitation; secondary prevention of falls/fractures and osteoporosis prophylaxis Control: usual care on orthopaedic ward.
Outcomes	Outcomes reported: - Incident delirium, diagnosed retrospectively using DSM-IV based on nursing notes (for the duration of the inpatient stay) and organic brain scale (measured once between the 3rd and 5th postoperative day) - Duration of delirium, diagnosed retrospectively using DSM-IV based on nursing notes and OBS - Length of admission - Cognitive status, measured using MMSE - Falls - New pressure ulcers - Psychological morbidity (Depression)

Lundstrom 2007 *(Continued)*

	- Mortality - inpatient and at 12 months Outcomes not reported: None Frequency of outcomes assessment: all patients tested once between day 3 and day 5 postoperatively using organic brain scale, MMSE and geriatric depression scale. Delirium diagnosed retrospectively after the study had finished by specialist in geriatric medicine blind to allocation group on the basis of the nursing assessments by applying the DSM IV criteria
Notes	Funding source: Swedish Research Council & Vardal Foundation Declarations of interest: not reported Prevalent delirium not excluded at enrolment (21.8% intervention group, 30.9% control group) but, patients with prevalent delirium appear to have been included in outcome data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given on how randomisation sequence generated
Allocation concealment (selection bias)	Low risk	Sealed-opaque envelopes to conceal allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	All staff aware of allocation group, patients potentially aware due to nature of intervention
Blinding of outcome assessment (detection bias) All outcomes	High risk	Staff recording outcome measurements not blind to study arm. Blinded specialist made diagnosis of delirium retrospectively based on staff measurements and medical/ nursing records
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients included in the analysis
Selective reporting (reporting bias)	Unclear risk	Insufficient information to assess
Other bias	Low risk	No evidence of other bias

Marcantonio 2001

Study characteristics

Methods	Design: RCT of proactive geriatric consultation in patients with hip fracture Date of study: study dates not reported Power calculation: yes. Study adequately powered for bivariate analyses but not for the multivariate or stratified analyses. Inclusion criteria: all patients aged 65 years and older, admitted for primary surgical repair of hip fracture, who were at intermediate or high risk of delirium (presence of 1 or more delirium risk factors) Exclusion criteria: metastatic cancer or comorbid illness reducing life expectancy to less than 6 months; Unable to obtain consent (or proxy assent) within 24 hours of surgery, or 48 hours of admission

Marcantonio 2001 *(Continued)*

Participants	Number in study: 126 Country: USA Setting: one academic centre orthopaedic department Age mean (SD): Intervention 78 (8), Control 80 (8); P = 0.39 Sex M:F: Intervention 21%, Control 22%; P = 0.9 Co-morbidity: Charlson Index > 4 Intervention 39%, Control 33%; P = 0.49 Dementia: Intervention 37%, Control 51%; P = 0.13. However, dementia assessment only reported for 90% of participants Frailty: not reported
Interventions	Intervention: Proactive consultation by Consultant Geriatrician, with daily visits starting preoperatively or within 24 hours postoperatively for duration of admission. Protocol based targeted recommendations over and above what was already being done by team, limited to 5 at initial visit and 3 at follow-up visits. Controls: usual care, consisting of management by orthopaedic team and consultation by internal medicine or geriatrics on reactive rather than proactive basis.
Outcomes	Outcomes reported: - Delirium incidence- total cumulative during admission, using CAM (performed daily throughout inpatient stay) - Delirium duration - Length of admission - Return to independent living - Withdrawals from protocol Outcomes not reported: none Frequency of outcomes assessment: daily interviews from enrolment to discharge to complete MMSE, DSI, CAM, MDAS
Notes	Funding source: older Americans Independence Center; Charles Farnworth Trust; Declarations of interest: not reported Delirium examined but not reported at enrolment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table used to generate sequence
Allocation concealment (selection bias)	Low risk	Sealed envelopes prepared with allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Nature of intervention precluded blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Independent researchers conducted delirium assessments and timed not to coincide with Geriatrician consultation. States blinding successfully maintained

Marcantonio 2001 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Selective reporting (reporting bias)	Unclear risk	Insufficient information to assess
Other bias	Low risk	No evidence of other bias

Martinez 2012

Study characteristics	
Methods	Design: RCT of a multi-component delirium prevention intervention provided by family members Date of study: September 2009-June 2010 Power calculation: yes Inclusion criteria: all patients at risk for delirium (> 70 years, cognitive impairment (MMSE < 24 prior to admission) alcoholism or metabolic imbalance at admission) Exclusion criteria: delirium at admission, no family support, admitted to ward other than general medicine, those in a room with more than two beds
Participants	Number in study: 287 Country: Chile Setting: internal medicine ward of acute hospital Age: mean age 78.1 years (SD 6.3) in intervention group; 78.3 years (6.1) in control group Sex: 42% female in intervention group; 33% female in control group Co-morbidity: median Charlson comorbidity index (CCI) 2 (interquartile range, IQR, 1-4) in intervention group, median CCI 2 (IQR 1-3) in control group Dementia: 9% in intervention group, 8% in control group Frailty: not reported
Interventions	Intervention: multi-component non-pharmacological intervention provided by family members, including education regarding confusional syndromes; provision of a clock and calendar; avoidance of sensory deprivation (glasses, denture and hearing aids available as needed); presence of familiar objects in the room; re-orientation of patient provided by family members; extended visiting times (5 hours daily). Control: usual care from the attending physician
Outcomes	Outcomes reported: - Incident delirium, measured using CAM performed daily, throughout admission - Duration of delirium - Length of admission - Falls Outcomes not reported: none Frequency of outcomes assessment: Daily during hospital stay
Notes	Funding source: not reported

Martinez 2012 *(Continued)*

	Declarations of interest: quote: "No conflicts of interest declared"
	Delirium excluded at enrolment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Randomisation performed by a statistician who was not involved in data collection
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel unblinded due to the nature of the intervention
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessors unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis performed, 5% loss to follow-up
Selective reporting (reporting bias)	Unclear risk	Insufficient information to assess
Other bias	Low risk	No evidence of other bias

Martinez-Velilla 2019

Study characteristics

Methods	Design: RCT
	Date of study: Feb 1 2015 to Aug 30 2017
	Power calculation: not for delirium outcome
	Inclusion criteria: Age >=75, Barthel index >=60, mobile with/without assistance, able to communicate
	Exclusion criteria: LOS< 6 days, severe cognitive decline, terminal illness, uncontrolled arrhythmias, acute PE, recent MI, recent major surgery, extremity bone fracture in the last 3 months
Participants	Sample size: 370
	Country: Spain
	Setting: Acute elderly care unit
	Age: Mean age 87.6 years (SD 4.6) in intervention group; 87.1 years (SD 5.2) in control group
	Sex: male, 76 (41.1%) in the intervention group, male, 85 (45.9%) in the control group

Martinez-Velilla 2019 *(Continued)*

	Co-morbidity: cumulative Illness Rating Scale similar between groups = Intervention group, 13(5), Control group 12(5). No baseline between-group differences in demographic variables including BMI and number of diseases (includes hypertension, congestive heart failure, osteoarthritis, COPD). Dementia: mean score 22 (SD = 5) in the intervention group, Mean score 23 (SD = 45) in the control group Frailty: not reported
Interventions	Intervention: intervention session supervised by an experienced fitness specialist was conducted twice daily (morning and evening) of 20 minutes' duration during 5 to 7 consecutive days (including weekends). A session was considered completed when 90% or more of the Programmed exercises were successfully performed. Exercises were adapted from the multicomponent physical exercise program Vivifrail to prevent weakness and falls. The morning sessions included individualized supervised progressive resistance, balance, and walking training exercises. The evening session consisted of functional unsupervised exercises using light loads Control: usual care is offered to the patient by the geriatricians of the geriatrics department and consists of standard physiotherapy focused on walking exercises for restoring the functionality conditioned by potentially reversible abnormalities. A formal exercise prescription was not provided at study entry and patients were instructed to continue with the current activity practices through the duration of the study.
Outcomes	Outcomes reported -Incident delirium using CAM -Mortality at 3 months -Length of hospital admission (days) - ADL using Barthel index (2 weeks prior to admission to hospital discharge) - Quality of life using EQ5D (baseline to discharge) - New care home admission at discharge (reported as home/institution) - Falls Outcomes from study not reported: none Frequency of outcomes assessment: not reported.
Notes	Funding source: Gobierno de Navarra project Resolucion grant., Ministerio de Economia, Industria y Cometitividad, ISCIII and Fondos FEDER. Declarations of interest: none reported Delirium measured but not excluded at baseline (control group 12 %, intervention group 17%).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation based on use of online calculator (www.randomizer.org) on a 1:1 ratio without restrictions
Allocation concealment (selection bias)	Unclear risk	No description provided as to how allocations concealed
Blinding of participants and personnel (performance bias)	High risk	Participants were explicitly informed and reminded not to discuss assignment with the assessment staff. Staff providing intervention were unblinded due to the nature of the intervention.

Martinez-Velilla 2019 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessment staff were blinded to main study design and group allocation.
Incomplete outcome data (attrition bias) All outcomes	High risk	Imbalance in discontinuation of intervention with 47% of those dropouts in intervention group due to 'clinical worsening' versus 21% in control – unclear if this due to intervention.
Selective reporting (reporting bias)	Low risk	Study reported in accordance with trial protocol
Other bias	Low risk	No evidence of other bias

Nadler 2017

Study characteristics	
Methods	Design: RCT Date of study: 2014 (unclear - not explicitly reported) Power calculation: yes (study underpowered, baseline rate of delirium lower than expected) Inclusion criteria: aged 50 years or older, at risk of obstructive sleep apnoea as defined by a STOP-Bang score ≥ 3, scheduled for elective knee or hip arthroplasty, able to speak English, understand consent forms and give informed consent. Exclusion criteria: patients with severe tracheal or lung disease (e.g. bullous lung disease, pneumothorax, recent tracheal anastomosis) or contra-indications to nasal-mask CPAP (e.g. facial fractures/lacerations/burns, recent ENT surgery, basilar skull fracture, tracheostomy); Patients with previously diagnosed obstructive sleep apnoea
Participants	Sample size: 135 Country: USA Setting: perioperative hospitalised patients undergoing joint arthroplasty population could be shortened to elective orthopaedic Age: mean age 65.1 (SD = 8.4) in intervention group, mean age 66.3 (SD = 9.4) in control group Sex: male, 22 (32.4%) in intervention group, male 24 (35.8%) in control group Co-morbidity: imbalance in rates of depression and visual or hearing impairment in intervention group compared to control. Dementia: dementia or significant cognitive impairment, 0 in intervention group, 2 (3%) in control group Frailty: not reported
Interventions	Intervention: CPAP before surgery and days 0 1 and 2 postoperative (variable amount of time between enrolment and surgery) Control: usual care
Outcomes	Outcomes reported:

Nadler 2017 *(Continued)*

	-Incident delirium using DRS-R-98 diagnostic assessment tool Outcomes from study not reported: -Incident delirium using CAM Frequency of outcomes assessment: once post op day 2
Notes	Funding source: Equipment loaned by Philips Respironics, Amsterdam. No other funding source Supported by the Department of Psychiatry Duke University Medical Centre, Durham, NC, USA Declarations of interest: none stated. Delirium not excluded at enrolment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation performed by consulting a computer-permuted sequence that guaranteed an equal number of patients in each arm within blocks of 20
Allocation concealment (selection bias)	Unclear risk	No information provided around how allocations were concealed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants not blinded due to nature of intervention.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators performing assessments were blinded to study group assignment and CPA devices were recovered from the group before assessment took place.
Incomplete outcome data (attrition bias) All outcomes	High risk	Assessments not performed in 10% of intervention group and 13% of control group and unclear why.
Selective reporting (reporting bias)	Low risk	Outcomes reported as per NCT protocol
Other bias	Low risk	No evidence of other bias

Partridge 2017

Study characteristics

Methods	Design: RCT Date of study: Nov 2012 to Feb 2014 Power calculation: yes, Assuming 80% power and a two-sided significance level of 5%, a total sample size of 198 patients was required (99 per group). Attrition rates were expected to be negligible from previous observational work that showed no dropouts10; the target sample size was inflated (by 5%) to 208.

Partridge 2017 *(Continued)*

	Inclusion criteria: patients aged at least 65 years scheduled for elective endovascular/open aortic aneurysm repair or lower-limb arterial bypass surgery. Exclusion criteria: admitted directly to the ward from the surgical clinic or emergency department for emergency or very urgent surgery, which precluded the opportunity for outpatient preoperative assessment and optimisation.
Participants	Sample size: 209 Country: UK Setting: teaching hospital with a tertiary referral practice for vascular arterial surgery Age: mean age 75.5 (SD = 6.6) in intervention, Mean age 75.5 (SD = 6.3) Sex: males, 80 (76.9%) in intervention, males, 79 (75.2%) in control Co-morbidity: there were some differences between the randomised groups in relation to CVD (C: 21 of 100 (21·0) versus I: 10 (9·6), falls C: 10(9.5) versus I: 26 of 100 (26.0) Dementia: 2 (1.9%) in intervention, 5 (4.8) in control Frailty: not reported
Interventions	Intervention: comprehensive geriatric assessment and optimisation in an outpatient clinic setting. Patients were assessed and optimised according to peer-reviewed protocols based on current evidence, national and hospital guidelines, and expert opinion. Control: the control group received standard preoperative care. Within the participating centre, this consisted of a nurse led preoperative assessment clinic where a protocolised appraisal of anaesthetic and medical issues was conducted.
Outcomes	Outcomes reported: -Incident delirium using CAM -Inpatient mortality (not explicit included as outcome but data reported in study flow chart) -Length of hospital admission -Withdrawal -Readmission to hospital within 30 days of discharge (unplanned 30-day readmission) -Falls Outcomes from study not reported: None Frequency of outcomes assessment: recorded routinely by hospital staff
Notes	Funding source: Research Into Ageing–Age UK–British Geriatrics Society grant (reference 366) and the Guy's and St Thomas' Charity (EFT120610). Declarations of interest:No conflicts of interest Delirium is not excluded at enrolment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Internet-based randomisation using a 1:1 allocation and stratified according to sex and site of surgical procedure

Partridge 2017 *(Continued)*

Allocation concealment (selection bias)	Low risk	Performed independently by the King's Clinical Trials Unit
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded due to nature of the intervention. Those providing their postoperative care were unaware of the patient's involvement in study, however they had access to individualised care plans generated as part of the intervention.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were recorded by an unblinded research nurse using data collected by the routine clinical teams.
Incomplete outcome data (attrition bias) All outcomes	High risk	Primary outcome data missing for significant proportion of those randomised. Figures in CONSORT diagram do not account for all individuals from allocation to analysis.
Selective reporting (reporting bias)	Low risk	Outcomes reported as per ISRCTN protocol, retrospectively registered.
Other bias	Low risk	No evidence of other bias

Wang 2020

Study characteristics	
Methods	Design: cluster-RCT Date of study: 24/08/2015-28/02/2016 Power calculation: yes Inclusion criteria: patients aged 70 years or older and scheduled for an elective surgical procedure with an anticipated LOS longer than 2 days were eligible for inclusion. Exclusion criteria: included (1) delirium at baseline as assessed with the Confusion Assessment Method (CAM); (2) a terminal condition with life expectancy of less than 6 months (e,g, metastatic cancer, pancreatic cancer, or receiving end-of-life care); (3) inability to perform cognitive tests be- cause of severe dementia, legal blindness, or severe deafness; (4) a documented history of schizophrenia or psychosis; and (5) a documented history of alcohol abuse or withdrawal within the past 6 months and/or reporting consumption of more than 5 drinks per day for men (4 for women).
Participants	Sample size: 281 Country: China Setting: Hospital Age: overall, mean: 74.7 (5.2) years. Mean age 74.20 (SD = 5.33) in intervention group, mean age 75.28 (SD = 4.73) in control group Sex: overall, male: 171 (60.9%). Male, 96 (63.2%) in intervention group, male 75.28 (58.1%) in control group Co-morbidity: no clinically significant differences between groups using the Charlson comorbidity index score Score 0: I: 38(25.0), S: 27 (20.9), Score 1-2: I:56 (36.8), 52(40.3), Score >2: I:58(38.2), C:50 (38.8) Dementia: exclusion included inability to perform cognitive tests because of severe dementia but the number of patients with any level of dementia not defined.

Wang 2020 *(Continued)*

	Frailty: healthy 59.2% of intervention versus 52.7% of control, prefrail32.9% of intervention versus 34.1% of control and frail 7.9% of intervention versus 13.2% of control, assessed using FRAIL scale
Interventions	Intervention: the t-HELP intervention consisted of 3 universal protocols and 8 targeted protocols. The universal protocols, including orientation, therapeutic activities, and early mobilisation protocol, were given to all t-HELP participants. The targeted protocols) were tailored for each patient on the basis of delirium- related risk factors, which were assessed daily. Control: usual care
Outcomes	Outcomes reported: - Incident delirium using CAM - Inpatient mortality - Peak severity of delirium (incidence of severe delirium) - Length of hospital admission - ADL - Withdrawal - Falls Outcomes not reported: ADL at 30 days. Frequency of outcomes assessment: daily up to 7 days, discharge and 30 days
Notes	Funding source: this study was funded by grant 2018YFC1312300 from the National Key Research and Development Program of the Ministry of Science and Technology of China; grant H1403014 from the Milstein Medical Asian American Partnership Foundation; grant 81800092 from the National Natural Science Foundation of China; grant Z2018B03 from the National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University; grant 2018SZ0252 from the Sichuan Science and Technology Program; and grant 2019-109, 2017-111 from the Health Research of Cadres in Sichuan province. Dr Inouye was supported in part by grants P01AG031720, K07AG041835, R24AG054259, and R01AG044518 from the National Institutes of Health and by the Milton and Shirley F. Levy Family Chair. Declarations of interest: Dr Inouye was the creator of the Hospital Elder Life Program (HELP) but receives no income or royalties from the program. The American Geriatrics Society holds the exclusive license to HELP. no other disclosures were reported. Delirium excluded at enrolment using the Confusion Assessment Method (CAM)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Two-step randomisation process - standard computerised randomisation for the nursing units. Random assignment of participants to units co-ordinated by member of staff not involved in study. Unclear how participant sequence generated.
Allocation concealment (selection bias)	Unclear risk	Opening sealed envelopes containing the random assignments'. Unclear if these envelopes were opaque.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and intervention personnel were not blinded due to the nature of the intervention.

Wang 2020 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor and statistical analysts were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted-for via CONSORT diagram. Those discontinuing intervention and lost to 30-day follow-up are balanced between groups.
Selective reporting (reporting bias)	High risk	Adverse events are not reported by group. ADL only reported at discharge
Other bias	Low risk	No evidence of recruitment bias or baseline imbalance associated with cluster design. No loss of clusters reported. Statistical analysis planned and performed to take account of the cluster design including use of multilevel binomial regression model in which two nested models were fitted.

Watne 2014

Study characteristics	
Methods	Design: RCT comparing care in an acute geriatric ward or standard orthopaedic ward following hip fracture Date of study: September 2009 - January 2012 Power calculation: yes but powered for primary outcome of cognitive function not delirium Inclusion criteria: all acute admissions to Oslo University Hospital with a hip fracture Exclusion criteria: hip fracture due to high energy trauma (defined as a fall from higher than one metre) or if they were moribund on admission
Participants	Number in study: 332 randomised; 329 included in analyses Country: Norway Setting: university hospital Age: mean age 84 years (range: 55 to 99) for intervention group and 85 years (range: 46 to 101) Sex: male 42 (26%) for intervention group; 38 (23%) for controls Co-morbidity: not reported Dementia: 49% in both intervention and control groups diagnosis by expert evaluation Frailty: not reported
Interventions	Intervention: acute geriatric ward – 20 bed ward mainly admitting patients suffering from acute medical disorder superimposed upon frailty, co-morbidities and polypharmacy. Comprehensive Geriatric Assessment was the basis for treatment planning. Assessment by geriatrician, nurse, physiotherapist and occupational therapists was expected during their first day on the ward and this team had daily meetings to plan discharge. Checklists and clinical routines based on published literature and previous experience. These included medication reviews, optimal pain control, correction of physiological disturbances preoperatively and postoperatively (hypoxaemia, anaemia, electrolyte disturbances, acid–base disturbances, dehydration, hypotension, blood sugar etc), early and intensive mobilisation, optimising pre- and postoperative nutrition and early discharge planning. Outpatient orthopaedic clinic at 4 months. Control: usual care in orthopaedic ward setting. Staffing levels were similar but there was no multidisciplinary meetings and no geriatric assessments. Early mobilisation was emphasised and patients were seen by a physiotherapist soon after surgery. Outpatient orthopaedic clinic at 4 months.

Watne 2014 *(Continued)*

Outcomes	Outcomes reported: - Incident delirium using CAM - In-hospital mortality - Incident dementia at 12 months - Delirium duration (days) - Delirium severity using MDAS - Length of stay - ADL function using Barthel Index at four months - New care home residence at four and 12 months - Falls - Pressure ulcers - Postoperative complications Outcomes not reported: None Frequency of outcomes assessment: daily using CAM preoperatively and until the fifth postoperative day or for patients with delirium until discharge
Notes	Funding source: Research Council of Norway through the program 'Improving mental health of older people through multidisciplinary efforts' (Grant No: 187980/H10) plus Oslo University Hospital, The Sophies Minde Foundation, The Norweigan Association for Public Health and Civitan's Research Foundation Declaration of interest: the authors declare 'they have no competing interests' Delirium not excluded at enrolment There are concerns about the fidelity of the intervention received as, when a bed was not available in the unit, care was provided in a corridor.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers (blocks of variable and unknown size) carried- out by statistician not involved in clinical service
Allocation concealment (selection bias)	Low risk	Allocation by sealed-opaque numbered envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not possible due to nature of intervention
Blinding of outcome assessment (detection bias) All outcomes	High risk	Delirium assessments were performed by study nurse/geriatrician aware of allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Three moribund patients erroneously randomised were excluded from the analysis (2 from intervention and 1 from control arm)

Watne 2014 *(Continued)*

Selective reporting (reporting bias)	Low risk	Study reported in accordance with published protocol
Other bias	Low risk	No evidence of other bias

Young 2020

Study characteristics	
Methods	Design: cluster-randomised controlled feasibility trial Date of study: August 2014-Feb 2015 Power calculation: no Inclusion criteria: patients were eligible for trial recruitment if they were aged over 65 years and admitted to the study wards during the study period. Exclusion criteria: patients were excluded if delirium was present on admission to the ward, discharge was planned within 48 hours of admission, delirium assessment had not been performed by an RA within 24 hours of admission (older people's care patients) or preoperatively (orthopaedic trauma patients), consent had not been obtained with 48 hours of admission to the ward, end of life care was being provided or the patient was under the care of another ward.
Participants	Sample size: 713 Country: UK Setting: hospital wards - orthopaedic trauma and older people care wards. Imbalance in clinical setting between intervention and control group – 62% in intervention group in Older People's wards and 38% in Orthopaedic Trauma compared to 49% and 51% of those in the control group. Age: 82.5 (7.9) in intervention group, 83.0 (7.8) in intervention group Sex: males, 112 (23.7) in intervention group, males, 114 (31.8) in control group Co-morbidity: no clinically significant difference between groups for overall comorbidities. Comorbidities 236 (68.8) in intervention group 244 (65.9) in control group; Mean (SD) Charlson comorbidity index score 1.7 (2.0) in intervention group, 1.7 (1.9) in control group Dementia: cognitive impairment and/or dementia 83 (24.2) in intervention group, 67 (18.1) in control group Frailty: not reported
Interventions	Intervention: prevention of delirium programme – manualised, multicomponent intervention and systematic implementation process designed to secure ward practice changes, potentially enhanced by the involvement of hospital volunteers. Comprises of actions directly affected to optimise nutrition & hydration, reduce environmental threats, increase orientation to time and place, improve communicative practices, supporting/encouraging mobility and better management of pain and infection. Implementation is supported through raising awareness and training of staff. Control: Usual care
Outcomes	Outcomes reported: - Incident delirium using CAM

Young 2020 *(Continued)*

	- Inpatient mortality (within 10 days) - Mortality (overall) - Peak severity of delirium (mean severity of delirium episode and mean severity of delirium at 30 days) - Length of stay - ADL function using NEADL at 3 months - Withdrawals (not explicitly included as an outcome but reported) - New care home admission at discharge - Falls Outcomes from study not reported: - Quality of Life using EuroQoL EQ-5D Frequency of outcomes assessment: daily up to 10 days from admission, discharge, 30 days and 3 months
Notes	Funding source: National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (grant RP-PG-0108-10037). Declarations of interest: no conflicts to declare Delirium excluded at enrolment using CAM

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation stratified by ward type in a two-stage process, randomised 1:1 between site-level allocation and ward level allocation. Those selected for site-level allocation further randomised 1:1 for their wards to receive intervention or control. Those selected for ward-level allocation randomised 1:1 for intervention or control.
Allocation concealment (selection bias)	Low risk	Performed centrally by the statistician at the Clinical Trials Unit.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were unblinded due to nature of the intervention.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessment conducted by research assistants not involved in intervention development or delivery, but unblinded to treatment allocation. Post-discharge outcomes were blind to allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up at day 10 is comparable between groups. Longer term (30 day and 3 months) follow-up affected by missing questionnaire data and deaths.
Selective reporting (reporting bias)	Low risk	Study reported as per published protocol (Trials)
Other bias	Low risk	No evidence of recruitment bias. Baseline imbalance in study populations (orthopaedic versus older adult wards) between intervention and control noted by reviewers and authors of the study. Not thought to relate to underlying bias

Young 2020 *(Continued)*	associated with randomisation. No loss of clusters reported. Statistical analysis performed to take account of cluster design including calculation of the intracluster correlation coefficient using the incidence of new-onset delirium expressed as a proportion of the recruited study population

ADL: activities of daily living;**BMI:** body mass index; **CAM:** Confusion Assessment Method;**CAM-ICU:** Confusion Assessment Method for Intensive Care Unit; **COPD:** chronic obstructive pulmonary disease; **CPAP:** continuous positive airway pressure;**CVD:** cardiovascular disease; **DOSS:** Delirium. Observation Screening) Scale; **DRS-R-98:** Delirium Rating Scale Revised 98; **DSI:** Delirium Symptom Interview;**DSM:** Diagnostic and Statistical Manual; **ENT:** ear nose and throat;**Hb:** haemoglobin; **IQR:** interquartile range;**IV:** intravascular; **MDAS:** Memorial Delirium Assessment Scale; **mHELP:** modified Hospital Elder Life Program; **MMSE:** Mini Mental State Examination; **Nu_DESC:** Nurses Delirium Screening Scale; **PVD:** peripheral vascular disease; **SD:** standard deviation; **RCT:** randomised controlled trial; **TIA:** transient Ischaemic attack.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alvarez 2012	Wrong setting
Asplund 2000	Wrong outcome
Astaneh 2007	Wrong study design
Avidan 2018	Wrong outcome
Baldwin 2004	Wrong outcome
Bjorkelund 2010	Wrong study design
Blandfort 2017	Unvalidated delirium diagnostic method
Boltz 2014	Wrong study design
Bruera 2013	Wrong setting
Cavalcante 2014	Wrong outcome
Cole 1998	Wrong study design
Cole 1999	Wrong study design
Dalal 2012	Wrong setting
Davies 2015	Wrong setting
Davies 2018	Wrong setting
Deschodt 2012	Wrong study design
Dharmarajan 2017	Wrong study design
Epling 1999	Wrong study design
Ettema 2014	Wrong study design

Study	Reason for exclusion
Fish-Trotter 2018	Wrong intervention
Freter 2017	Wrong intervention
Gorski 2017	Wrong study design
Greaves 2020	Wrong setting
Groshaus 2012	Wrong study design
Gustafson 1991	Wrong study design
Hammond 2017	Wrong outcome
Hea-Jeong 2014	Wrong study design
Heim 2017	Unvalidated delirium diagnostic method
Holly 2019	Wrong study design
Holroyd-Leduc 2010	Wrong study design
Hoolahan 2011	Wrong study design
Hudetz 2015	Wrong setting
Illioska 2014	Wrong setting
Inouye 1999	Wrong study design
Inouye 2000b	Wrong study design
Jia 2014	Wrong intervention (included pharmacological measures)
Ko 2019	Wrong study design
Lei 2017	Wrong setting
Li 2017	Wrong outcome
Lisann 2016	Wrong setting
Llera 2005	Wrong study design
Lundstrom 2005	Wrong outcome
McCaffrey 2004	Unvalidated delirium diagnostic method
Moppett 2017	Unvalidated delirium diagnostic method
Mudge 2008	Wrong study design
Mudge 2017	Wrong outcome
Nikelski 2019	Unvalidated delirium diagnostic method

Study	Reason for exclusion
O'Gara 2020	Wrong setting
Pitkala 2004	Wrong outcome
Rice 2017	Wrong setting
Saltvedt 2012	Wrong outcome
Sandberg 2001	Wrong outcome
Shirvani 2020	Wrong setting
Stromberg 1999	Wrong outcome
Vlisides 2019	Wrong setting
Wang 2018	Wrong setting
Xin 2017	Wrong intervention
Yoo 2013	Wrong study design
Zamvar 2002	Wrong outcome
Zhao 2018	Wrong outcome

Characteristics of studies awaiting classification *[ordered by study ID]*

NCT01998997 2013

Methods	Randomised controlled trial
Participants	79 hospitalised older (≥70 years) medical inpatients
Interventions	Group 1: a family educational, non-pharmacologic intervention will be administered to educate family members on how to prevent delirium. Family members will be encouraged to actively participate in this non-pharmacologic intervention Group 2: the placebo group will be given a brochure on good health habits
Outcomes	Primary outcome: acceptance rate of intervention over 14 weeks Secondary outcome (s): date of incident delirium (14 weeks) Other outcomes: difficulties in performing the intervention (14 weeks)
Notes	ClinicalTrials.gov Identifier: NCT01998997 Status: completed (last update 24/12/2015)

NCT03470662 2018

Methods	Randomised controlled study
Participants	80 patients (≥65 years) with hip fractures treated surgically
Interventions	Group 1: care bundle Group 2: standard care
Outcomes	Primary outcome: incidence of delirium within 3 weeks Secondary outcome(s): VAS, perioperative complications and adverse events
Notes	ClinicalTrials.gov Identifier: NCT03470662 Status: completed

NCT04188795 2019

Methods	Randomised controlled study
Participants	80 patients with hip fracture
Interventions	Group 1: nursing care in accordance with the delirium preventive care protocol developed with the support of literature Group 2: routine nursing care
Outcomes	Primary outcome: Richards-Campbell Sleep Questionnaire on admission, 1st day and 3rd day post-operatively, Barthel Index (BI) on admission, 1st day and 3rd day postoperatively, VAS on admission, 1st day and 3rd day postoperatively, Mini Nutritional Assesment- Short Form on admission Other outcome(s): Confusion Assessment Method- Intensive Care Unit (CAM-ICU) on admission, 1st day and 3rd day postoperatively
Notes	ClinicalTrials.gov Identifier: NCT04188795 Status: completed

UMIN000027181 2017

Methods	Randomised controlled study
Participants	230 patients, (≥ 50 years) undergoing planned head and neck surgery
Interventions	Group 1: passive cycling exercise by bedside ergometer for 20 minutes Group 2: early mobilisation
Outcomes	Primary outcomes: incidence of delirium as determined by the DSM-5 Secondary outcomes: change in cognitive function, depression incidence rate, number of hospital days, mortality rate, presence or absence of other adverse events
Notes	UMIN-CTR Clinical Trial Identifer: UMIN000027181

UMIN000027181 2017 *(Continued)*	Status: completed (last modified 28/10/2017)

DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition;**VAS:** visual analogue scale.

Characteristics of ongoing studies *[ordered by study ID]*

Boltz 2018

Study name	Reducing disability via a family centered intervention for acutely ill persons with Alzheimer's disease and related dementias: protocol of a cluster-randomized controlled trial (Fam-FFC study)
Methods	Cluster randomised trial
Participants	438 patients (≥65 years) with a diagnosis of very mild to moderate stage dementia
Interventions	Group 1: Family centred Function Focused Care nurse (Fam-FFC nurse) which involves the staff nurse, along with the patient and family care givers, in the care planning, delivery, and evaluation process of Fam-FFC interventions. Group 2: control condition (Fam- FFC Ed-only) consists of education of the nursing staff with no other intervention
Outcomes	Primary outcome(s): physical function (activities of daily living, functional performance/ chair rise, physical activity), delirium (occurrence and severity), mood and behavior. All at 6 months post-discharge. Secondary outcome(s): preparedness for caregiving, caregiver strain, caregiver burden, desire to institutionalise scale. All at 6 months post-discharge. Other outcome measures: healthcare cost 12 months after enrolment, post-acute health care utilisation at 6 months after discharge.
Starting date	November 2017
Contact information	Marie Boltz: mpb40@psu.edu The Pennsylvania State University, College of Nursing, 306 Nursing Sciences Building, University Park, PA 16802, USA
Notes	ClinicalTrials.gov, ID: NCT03046121 Status: recruiting Boltz et al. Trials (2018) 19:496 https://doi.org/10.1186/s13063-018-2875-1

ChiCTR1900027115 2019

Study name	Effects of acupuncture on postoperative delirium in elderly patients after laparoscopic surgery
Methods	Randomised controlled trial
Participants	240 (≥ 65 years) undergoing laparoscopic surgery
Interventions	Group 1: acupuncture Group 2: sham acupuncture

ChiCTR1900027115 2019 *(Continued)*

	Group 3: control group
Outcomes	Primary outcome: incidence of postoperative delirium Secondary outcome(s): VAS
Starting date	1/11/2019
Contact information	Shen Qihong, shenqihong1989@163.com The First Hospital of Jiaxing
Notes	ClinicalTrials.gov Identifier: ChiCTR1900027115 Status: recruiting

DRKS00013158 2017

Study name	Influence of perinterventional acupuncture on the incidence of postoperative delirium after elective, endoprosthetic replacement of the hip joint
Methods	Randomised controlled trial
Participants	135 patients (≥ 65 years) scheduled for total endoprosthetic hip
Interventions	Group 1: acupuncture Group 2: control (no treatment)
Outcomes	Primary outcome: incidence of postoperative delirium after total hip joint replacement at 24 hours and 48 hours postoperatively using the CAM for intensive care units. Secondary outcome: activity of acetylcholinesterase (ACHE) and butyrylcholinesterase (BCHE) in the blood, Determination TNFa, NSE, S-100 ß protein, Epigenetic markers such as DNA methylation, acetylation, and histone modifications, hospital length of stay. All measured 4 times (during premedication, directly postoperatively, first and second postoperatively)
Starting date	01/01/2018
Contact information	Lars Bergmann, lars.bergmann@kk-bochum.de. Universitätsklinikum Knappschaftskrankenhaus Bochum, Klinik für Anästhesiologie, Intensivmedizin und Schmerztherapie
Notes	German Clinical Trials Register, Main ID: DRKS00013158 Status: recruiting planned

DRKS00016352 2019

Study name	Evaluation of incidence of delirium in an acute care hospital by engaging an innovative and multidisciplinary approach
Methods	Randomised controlled study

DRKS00016352 2019 *(Continued)*

Participants	190 patients (≥ 65 years) who have been hospitalised for 3 days or longer in trauma surgery.
Interventions	Group 1: innovative standardised management of delirium Group 2: standard care
Outcomes	Primary outcome: incidence of delirium using the CAM (Confusion Assessment Method) on the first three postoperative days/ on the first three days of hospitalisation Secondary outcome(s): cognitive outcome 12 months after discharge by using the MoCA (Montreal Cognitive Assessment) and the i-ADL (instrumental - Activity of Daily Living Scale)
Starting date	14/01/2016
Contact information	Ms. Katharina Iltingreuke, katharina.ilting-reuke@ukmuenster.de Universitätsklinikum Münster
Notes	German Clinical Trials Register ID: DRKS00016352 Status: Complete

Humeidan 2015

Study name	Perioperative cognitivepProtection - Cognitive Exercise and Cognitive Reserve (The Neurobics Trial)
Methods	Randomised clinical trial
Participants	322 patients (≥60 years) who underwent non-cardiac/non-neurological surgery with expected hospital stay of at least 72 hours.
Interventions	Group 1: cognitive exercises consisting of a series of computer games focusing on five categories: memory, speed, attention, flexibility and problem-solving Group 2: standard care
Outcomes	Primary outcome(s): reduction in the incidence of PostOperative Delirium (%) [Time Frame: Postoperative period (Day 0 through Day 7 or discharge, whichever comes first)] as detected by the Confusion Assessment Method (CAM) / Memorial Delirium Assessment Scale (MDAS) Secondary outcome(s): Mini-Mental State Examination, Self-Administered Gerocognitive Examination, Geriatric Depression Scale, Charlson Comorbidity Index, Short Form 36 Health Survey, Confusion Assessment Method, Memorial Delirium Assessment Scale, Postoperative Quality of Recovery Scale
Starting date	July 2015
Contact information	Michelle L Humeidan, michelle.humeidan@osumc.edu Department of Anesthesiology, The Ohio State University Wexner Medical Center, Columbus, Ohio
Notes	ClinicalTrials.gov Identifier: NCT02230605 Status: completed

IRCT20180910040995N1 2019

Study name	Effect of HELP model on prevention of delirium
Methods	Randomised clinical trial
Participants	110 patients (≥70 years) admitted to the internal wards with at least one risk factor for delirium at admission
Interventions	Group 1: interventions such as therapeutic activity, early mobilisation, daily orientation, sleep enhancement, feeding assistance/fluid repletion, and helping to resolve visual and auditory disorders. Group 2: standard care
Outcomes	Primary outcome: incidence of delirium using CAM on everyday until discharge Secondary outcome(s): activities of daily living (Barthel Index) on admission and on discharge, level of frailty (clinical frailty index) on admission and on discharge, number of falls, use of anti-psychotic drugs, number of readmissions after discharge until 3 months after discharge
Starting date	07/10/2018
Contact information	Afsaneh Kogaie Bidgoli, kojaiibidgoli@yahoo.com University of social welfare and rehabilitation sciences
Notes	IRCT registration number: IRCT20180910040995N1 Status: recruitment complete

JPRN 2017

Study name	A multi-center, cluster randomized controlled study comparing usual care and a multidisciplinary intervention such as the DELirium Team Approach program to manage delirium among hospitalized cancer patients
Methods	Cluster-randomised controlled trial
Participants	9600 Hospitalised cancer patients (≥50 years)
Interventions	Group 1: implementation of the DELTA program with six components: (1) education of healthcare providers, (2) screening of delirium, (3) planning for delirium care, (4) prevention of occurrence and worsening of delirium, (5) scheduled assessment of delirium symptoms or risk factors, and (6) management and treatment of delirium. Group 2: standard care
Outcomes	Primary outcome (s): the incidence in events in medical safety such as falls, self-removal of drip infusion or drain tube, restraint Secondary outcome (s): falls, self-removal of drip infusion or drain tube, restraint, Barthel Index, level of nursing care needs, antipsychotic drug use, opioid use, duration of hospital stay, cost of medical care, hospital readmission within 1 month after discharge, mortality within 1 year after discharge
Starting date	11/12/2017

JPRN 2017 *(Continued)*

Contact information	Asao Ogawa, asogawa@east.ncc.go.jp National Cancer Center, Division of Psycho-Oncology, Exploratory Oncology Research&Clinical Trial Center
Notes	Japan Primary Registries Network-UMIN000030062 Status: no longer recruiting

NCT03060174 2017

Study name	Study of prevention of postoperative delirium to reduce Incidence of postoperative cognitive dysfunction
Methods	Randomised controlled trial
Participants	638 patients (≥ 60 years) to undergo cardiac surgery (on-pump/off-pump, standard/minimal invasive)
Interventions	Group 1: monitoring and non-medical prophylaxis of delirium which incorporates reorientation (watches, calendar, family photos, use of hearing aids, glasses and dentures, cognitive stimulation (newspaper, magazines, radio, television), early mobilisation, early enteral nutrition, early removal of drains or catheters, normalizing sleep-awake-rhythm. Group 2: standard care
Outcomes	Primary outcome: postoperative cognitive deficit (POCD) measured by neuropsychological test battery, analysis (change from baseline in cognitive function at day 7, 3 months and 1 year after operation) Secondary outcome: incidence and severity of postoperative delirium (from day of operation until the 7th postoperative day) measured 3 times per day via CAM-ICU, number of patients with cardiac complications (day of operation until 7th postoperative day), length of hospital stay (from day of admission until day of discharge, up to 24 weeks), mortality (1 years), health related quality of life (months, 1 year after operation) using short form health survey, number of patients with respiratory complications (day of operation until 7th postoperative day), number of patients with renal complications (day of operation until 7th postoperative day) daily documentation of renal complications (creatinine, haemo(dia)filtration or haemodialysis), number of patients with complications in the immuno system (day of operation until 7th postoperative day), daily documentation of parameters mirroring the immune answer (C-reactive protein, leukocytes, procalcitonin)
Starting date	May 2014
Contact information	Prof. Alwin E. Goetz Department of Anaesthesiology and Intensive Care Medicine, University Hospital Hamburg Eppendorf
Notes	ClinicalTrials.gov Identifier: NCT03060174 Status: active, not recruiting Estimated completion date: May 2019

NCT03158909 2017

Study name	Trial of a non-pharmacological Intervention to prevent delirium among elderly in-patients
Methods	Randomised controlled study
Participants	284 patients (≥ 60 years) for inpatient stay at a Brazilian Hospital
Interventions	Group 1: patients in this group will receive eyemask and earplugs, for use during the night, and orientations about space and time, every night Group 2: this group will receive orientations about space and time only, every night.
Outcomes	Primary outcome: incidence cases of delirium up to 15 days from the inclusion in the study using the Confusion Assessment Method (Short-CAM) Secondary outcome(s): sleep quality up to 15 days, safety of the intervention up to 15 days, acceptance, comfort and adherence to the intervention up to 15 days, use of psychotropic drugs up to 15 days, time of hospital stay up to 6 months, evaluation of the sleep-wake cycle up to 15 days, urinary 6-sulfatoxymelatonin levels 48 hours after admission
Starting date	15/01/2020
Contact information	Artur Schuh, schuh.afs@gmail.com Hospital de Clínicas de Porto Alegre
Notes	ClinicalTrials.gov Identifier: NCT03158909 Status: recruiting (last update, 14/01/2020)

NCT03541408 2018

Study name	Preventative delirium protocol in elderly patients
Methods	Randomised controlled trial
Participants	Patients (≥65 years) of age undergoing elective surgery.
Interventions	Group 1: preventative delirium protocol Group 2: standard of care without preventative delirium protocol
Outcomes	Primary outcome: presence or absence of delirium (CAM_ICU) (Within one postoperative day) using the validated CAM-ICU measure Secondary outcome:pPostoperative nausea and vomiting within one day postoperatively, numerical rating scale of pain intensity within one postoperative day.
Starting date	May 2016
Contact information	Robert McCarthy, Robert_J_McCarthy@40rush.edu Rush University Medical Center, Chicago, Illinois, United States, 60612
Notes	ClinicalTrials.gov Identifier: NCT03541408 Status: recruiting

NCT03541408 2018 *(Continued)*

	Estimated study completion: 01/12/2020

NCT03573843 2018

Study name	Software-guided cognitive stimulation to prevent delirium (Prevedel)
Methods	Pilot randomised controlled trial
Participants	60 older patients (≥ 65 years) and admitted to medicine room or intermediate care unit > 48 hours
Interventions	Group 1: receive standard prevention measures plus the use of software installed on a mobile device designed to support the prevention of delirium (Prevention software) Group 2: receive the standard prevention measures plus the use of a mobile device without installed delirium prevention software (placebo).
Outcomes	Primary outcome: difference in delirium incidence between both groups at day 5 using the with CAM twice a day Secondary outcome(s): length of stay at 5 days, severity of delirium at 5 days using the CAM-S, time of use of electronic device at 5 days, functionality at discharge at 5 days and at discharge using the Barthel index
Starting date	15/09/2018
Contact information	Eduardo A Tobar, etobar@40hcuch.cl University of Chile
Notes	ClinicalTrials.gov Identifier: NCT03573843 Status: recruitment completed

NCT03704090 2018

Study name	Non-pharmacological Prevention of Postoperative Delirium by Occupational Therapy Teams (PREPODOT)
Methods	Randomised controlled trial
Participants	160 patients (≥75 years) and older admitted to hospital for highly complex elective surgery
Interventions	Group 1: occupational therapy intervention twice a day plus standard non-pharmacological prevention intervention during 5 days after surgery Group 2: standard non-pharmacological intervention during 5 days after surgery
Outcomes	Primary outcome: delirium at 5 days using the CAM, subsyndromal delirium at 5 days using the CAM Secondary outcome(s): length of hospital stay at 30 days, mortality, severity of delirium at 5 days using the CAM-S, duration of delirium at 5 days.
Starting date	1/10/2018

NCT03704090 2018 *(Continued)*

Contact information	Antonello Penna, apenna@40uchile.cl University of Chile
Notes	ClinicalTrials.gov Identifier: NCT03704090 Status: recruiting Estimated completion date: 30/12/2020

NCT03832192 2019

Study name	Care.Coach Avatars for improvement of outcomes in hospitalized elders,iIncluding mitigation of falls and delirium: a multi-site clinical study
Methods	Randomised controlled trial
Participants	2400 patients (≥18 years) at risk of fall/delirium
Interventions	Group 1: care.coach human-in-the-loop avatar system with software-directed protocols based on the Hospital Elder Life Program (HELP) Group 2: standard care
Outcomes	Primary outcome: incidence delirium until day 4 using the CAM, average number of falls until day 4 Secondary outcome(s): delirium resolution until day 4, change in delirium severity until day 4 using the memorial delirium assessment scale (MDAS), patient sitter utilisation until day 4, change in cognitive function until day 4 using the short portable mental status questionnaire, falls with injury until day 4
Starting date	08/01/2019
Contact information	Victor Wang, victor@40care.coach Jamaica Hospital Medical Center
Notes	ClinicalTrials.gov Identifier: NCT03832192 Status: recruiting Estimated completion date: 07/01/2021

NCT03894709 2019

Study name	A care model for elderly hip-fractured persons with cognitive impairment and their family caregivers
Methods	Randomised controlled trial
Participants	304 patients (≥60 years) admitted with one-side hip fracture and requiring surgery.
Interventions	Group 1:family-centred approach to interdisciplinary care and a family caregiving-training component to enhance family caregivers' competence in providing postoperative care and handling behavioural problems of adults with cognitive impairment

NCT03894709 2019 *(Continued)*

	Group 2: patients receive health teaching for exercise while still in bed. The usual care does not involve interdisciplinary care protocols, continuity of care, or specific care for hip-fractured patients with cognitive impairment.
Outcomes	Primary outcome: change from baseline in range of motion to 1 year, change from baseline muscle strength to 1 year, change from baseline flexibility to 1 year, change from baseline physical function to 1 year using the activities of daily livings change from baseline cognitive function to 1 year using the Chinese version Cohen-mansfield agitation inventory, change from baseline caregiver competence to 1 year, change from baseline delirium to 1 year Secondary outcome(s): change from one month service utilisation to 1 year, change from baseline health-related quality of life using the SF-36 Taian version, change from baseline cost of care to 1 year
Starting date	1/1/2015
Contact information	Yea-Ing Lotus Shyu, yeaing@mail.cgu.edu.tw Chang Gung Memorial Hospital
Notes	ClinicalTrials.gov Identifier: NCT03894709 Status: Active, not recruiting Estimated completion date: 31/10/2019

NCT03980782 2019

Study name	The effect of music therapy on delirium
Methods	Randomised controlled trial
Participants	44 acutely ill patients (≥ 65 years) admitted to the progressive care unit
Interventions	Group 1: each participant will receive a 30-minute individual music intervention twice daily Group 2: standard care
Outcomes	Primary outcome: Incidence of delirium at 2-3 months using the confusion assessment method Secondary outcome(s): Severity of delirium at 2-3 months using the CAM-S,
Starting date	5/6/2019
Contact information	Mary Kovaleski Geisinger Clinic
Notes	ClinicalTrials.gov Identifier: NCT03980782 Status: completed

NTR7036 2018

Study name	Effect of Music on the clinical outcome after Hip fracture OPeratIoNs (MCHOPIN): a multicenter randomized controlled trial
Methods	Randomised controlled trial
Participants	508 patients (≥ 65 years) with a proximal femur fracture undergoing surgical treatment
Interventions	Group 1: Perioperative recorded music Group 2: Standard care
Outcomes	Primary outcome: delirium (DOS scale and clinical diagnosis by geriatrician) Secondary outcome(s): pain (NRS), Anxiety (STAI-6), medication use, postoperative complications, neurohormonal stress response (serum cortisol), hospital length of stay, 30-day mortality, nursing home length of stay, 90-day readmission, 90-day functional ability to perform daily living activities (Katz-ADL6), cost analysis (direct medical costs)
Starting date	1/7/2018
Contact information	V.X. Fu, v.fu@erasmusmc.nl Department of Surgery, Erasmus MC University Medical Center
Notes	Netherlands Trial Register Identifier: NTR7036 Status: pPending Estimated completion date: not reported

Piotrowicz 2018

Study name	The “Wholesome Contact” non-pharmacological, volunteer-delivered multidisciplinary programme to prevent hospital delirium in elderly patients: study protocol for a randomised controlled trial
Methods	Randomised controlled trial
Participants	416 patients (≥70 years) and have been hospitalised for medical reasons.
Interventions	Group 1: structured, non-pharmacological care delivered by students of medicine, psychology and nursing, together with standard medical treatment Group 2: standard medical treatment
Outcomes	Primary outcome: incidence of delirium using the CAM Secondary outcome(s): occurrence of in-hospital adverse health outcomes, such as falls and in-hospital deaths, In-hospital changes (i.e. the difference noted between the day of baseline assessment and the day of discharge) in cognition (difference in the Mini- Mental State Examination (MMSE) score), mood and anxiety (difference in the Hospital Anxiety and Depression Scale score (HADS)) and functional status (difference in the Activities of Daily Living Scale (ADL) and the Instrumental Activities of Daily Living Scale score (IADL)),
Starting date	May 2018
Contact information	Karolina Piotrowicz, karolina.piotrowicz@uj.edu.pl

Piotrowicz 2018 *(Continued)*

	Department of Internal Medicine and Gerontology, Faculty of Medicine, Jagiellonian University Medical College
Notes	Polish Science Database Identifer: 317484 Estimated completion date: not reported Piotrowicz et al. Trials (2018) 19:439 https://doi.org/10.1186/s13063-018-2781-6

Sanchez 2019

Study name	Patient safety, cost-effectiveness, and quality of life: reduction of delirium risk and postoperative cognitive dysfunction after elective procedures in older adults-study protocol for a stepped-wedge cluster randomized trial (PAWEL Study)
Methods	Stepped-wedge cluster randomised trial
Participants	1500 patients (≥70 years) undergoing elective operative procedures (cardiac, thoracic, vascular, proximal big joints and spine, genitourinary, gastrointestinal, and general elective surgery procedures)
Interventions	Group 1: cross-sectorial all-encompassing multimodal delirium prevention and management approach Group 2: standard care
Outcomes	Primary outcome: delirium prevalence using the delirium screening (I-Confusion Assessment Method-based scoring system for delirium severity (I-CAM)/CAM-S)) [over 7 days after surgery and after 2 and 6 months, the Nursing Delirium Screening Scale (NuDESC) [(days 2 and 6 after surgery), a chart review at discharge applying the DSM-V delirium criteria as a reference standard and the clinical evaluation. Secondary outcome(s): delirium duration as described in the primary outcome assessment; prevalence of POCD 2 and 6 months after surgery; and persistence of POCD after 12 months. The prevalence of POCD will be measured by the following neuropsychological test battery: the Montreal Cognitive Assessment (MoCA), the digit span backwards, the Trail Making Test A and B (TMT A and B), and cognitive performance measured with the continuous non standardised test values of these scales.
Starting date	November 2017
Contact information	Michael Rapp, michael.rapp@uni-potsdam.de Department of Social and Preventive Medicine, University of Potsdam
Notes	German Clinical Trials Register Identifer: DRKS00013311 Status: not reported. Estimated completion date: December 2020

Wong 2018

Study name	The prevention of delirium in elderly with obstructive sleep apnea (PODESA) study: protocol for a multi-centre prospective randomized, controlled trial

Wong 2018 *(Continued)*

Methods	Randomised controlled trial
Participants	304 patients (≥60 years) scheduled for elective hip or knee replacement surgery at least 4 working days after the preadmission clinic visit
Interventions	Group 1: auto-titrating Continuous Positive Airway Pressure (CPAP) treatment will be given on postoperative days 1, 2, and 3. Group 2: standard care
Outcomes	Primary outcome: incidence of postoperative delirium over 2 months Secondary outcome(s): length of hospital stay, time to ambulate (1 week to 2 months) perioperative complications at 10-14 days
Starting date	24/03/2016
Contact information	Jean Wong, University Health Network, Toronto
Notes	ClinicalTrials.gov Identifier: NCT02954224 Status: Active, not recruiting Estimated completion date: 30/08/2020

CAM: Confusion Assessment Method; **SF-36:** Short Form survey; **STAI-6:** State-Trait Anxiety Inventory;**TNFa:** tumour necrosis factor alpha; **VAS:** visual analogue scale.

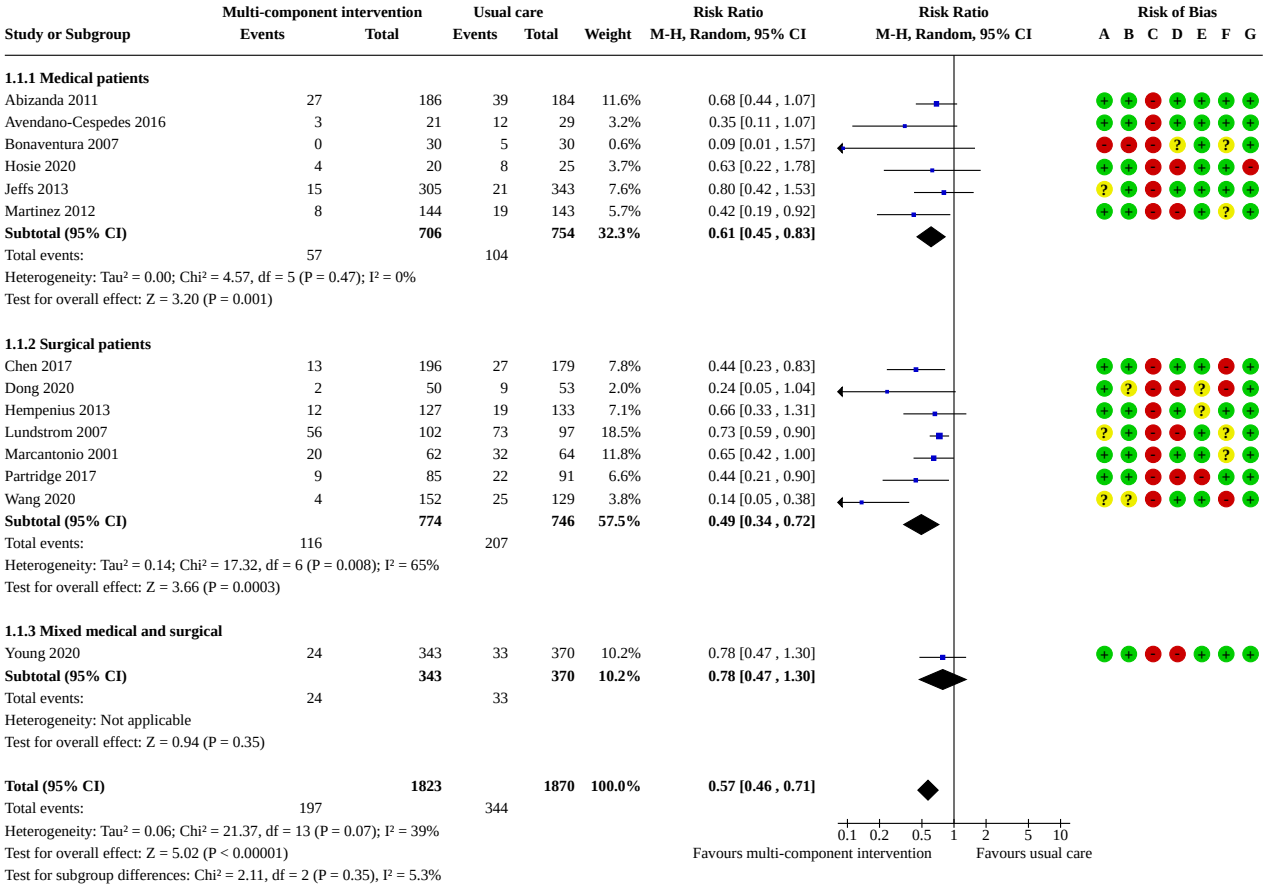
DATA AND ANALYSES

Comparison 1. Multi-component delirium prevention intervention (MCI) versus usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Incident Delirium	14	3693	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.46, 0.71]
1.1.1 Medical patients	6	1460	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.45, 0.83]
1.1.2 Surgical patients	7	1520	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.34, 0.72]
1.1.3 Mixed medical and surgical	1	713	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.47, 1.30]
1.2 Inpatient mortality	10	2640	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.79, 1.74]
1.3 Mortality at 1 to 3 months	3	1200	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.92, 1.75]
1.4 Mortality at 12 months	1	199	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.46, 1.56]
1.5 Duration of delirium episode	6	351	Mean Difference (IV, Random, 95% CI)	-0.93 [-2.01, 0.14]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.6 Peak severity of delirium	5	147	Std. Mean Difference (IV, Random, 95% CI)	-0.49 [-1.13, 0.14]
1.7 Length of hospital stay	10	3351	Mean Difference (IV, Random, 95% CI)	-1.30 [-2.56, -0.04]
1.8 Withdrawal from protocol	6	1751	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.60, 1.75]
1.9 Readmission to hospital	2	401	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.89, 2.07]
1.10 New care home admission on discharge	1	536	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.55, 1.07]
1.11 Falls	6	1680	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.42, 1.88]
1.12 Pressure ulcers	2	457	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.26, 0.89]
1.13 Incidence of delirium in patients with dementia	1	126	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.41, 1.32]
1.13.1 Individuals with dementia	1	50	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.59, 1.36]
1.13.2 Individuals without dementia	1	76	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.22, 1.13]

Analysis 1.1. Comparison 1: Multi-component delirium prevention intervention (MCI) versus usual care, Outcome 1: Incident Delirium



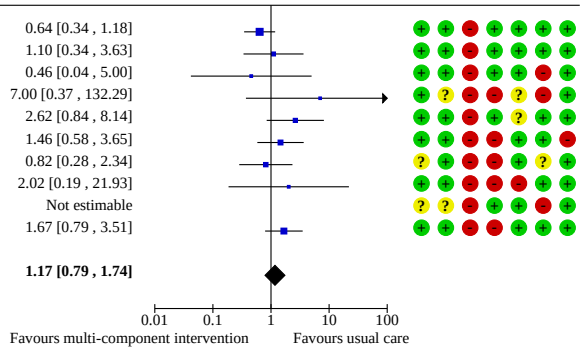
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.2. Comparison 1: Multi-component delirium prevention intervention (MCI) versus usual care, Outcome 2: Inpatient mortality

Study or Subgroup	Multi-component intervention Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Abizanda 2011	15	198	24	202	26.4%	0.64 [0.34 , 1.18]
Avendano-Cespedes 2016	4	21	5	29	9.5%	1.10 [0.34 , 3.63]
Chen 2017	1	197	2	180	2.6%	0.46 [0.04 , 5.00]
Dong 2020	3	53	0	53	1.7%	7.00 [0.37 , 132.29]
Hempenius 2013	10	127	4	133	10.4%	2.62 [0.84 , 8.14]
Hosie 2020	7	20	6	25	14.7%	1.46 [0.58 , 3.65]
Lundstrom 2007	6	102	7	97	11.7%	0.82 [0.28 , 2.34]
Partridge 2017	2	104	1	105	2.6%	2.02 [0.19 , 21.93]
Wang 2020	0	152	0	129		Not estimable
Young 2020	17	343	11	370	20.3%	1.67 [0.79 , 3.51]
Total (95% CI)		**1317**		**1323**	**100.0%**	**1.17 [0.79 , 1.74]**
Total events:	65		60			

Heterogeneity: Tau² = 0.05; Chi² = 9.43, df = 8 (P = 0.31); I² = 15%
Test for overall effect: Z = 0.79 (P = 0.43)
Test for subgroup differences: Not applicable

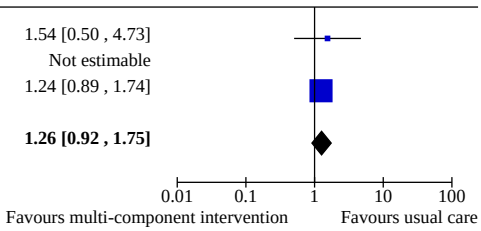


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.3. Comparison 1: Multi-component delirium prevention intervention (MCI) versus usual care, Outcome 3: Mortality at 1 to 3 months

Study or Subgroup	Multi-component intervention Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Hempenius 2013	7	117	5	129	8.3%	1.54 [0.50 , 4.73]
Wang 2020	0	129	0	112		Not estimable
Young 2020	61	343	53	370	91.7%	1.24 [0.89 , 1.74]
Total (95% CI)		**589**		**611**	**100.0%**	**1.26 [0.92 , 1.75]**
Total events:	68		58			

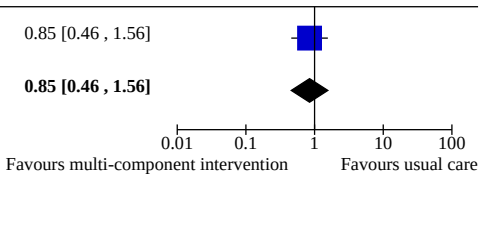
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 1.42 (P = 0.15)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Multi-component delirium prevention intervention (MCI) versus usual care, Outcome 4: Mortality at 12 months

Study or Subgroup	Multi-component intervention Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Lundstrom 2007	16	102	18	97	100.0%	0.85 [0.46 , 1.56]
Total (95% CI)		**102**		**97**	**100.0%**	**0.85 [0.46 , 1.56]**
Total events:	16		18			

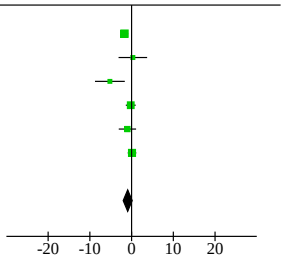
Heterogeneity: Not applicable
Test for overall effect: Z = 0.54 (P = 0.59)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Multi-component delirium prevention intervention (MCI) versus usual care, Outcome 5: Duration of delirium episode

Study or Subgroup	Multi-component intervention Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Avendano-Cespedes 2016	1.7	0.8	21	3.4	2.2	29	25.3%	-1.70 [-2.57 , -0.83]
Jeffs 2013	2.4	5.93	15	2.1	3.85	21	7.5%	0.30 [-3.12 , 3.72]
Lundstrom 2007	5	7.1	56	10.2	13.3	73	7.0%	-5.20 [-8.77 , -1.63]
Marcantonio 2001	2.9	2	20	3.1	2.3	32	22.2%	-0.20 [-1.38 , 0.98]
Martinez 2012	2	0.74	19	3	2.96	8	14.2%	-1.00 [-3.08 , 1.08]
Young 2020	2.3	2	24	2.2	1.9	33	23.8%	0.10 [-0.93 , 1.13]
Total (95% CI)			**155**			**196**	**100.0%**	**-0.93 [-2.01 , 0.14]**

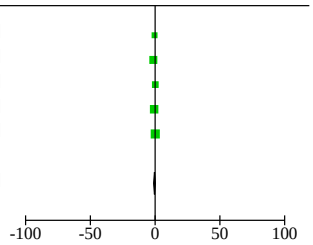
Heterogeneity: Tau² = 0.99; Chi² = 14.23, df = 5 (P = 0.01); I² = 65%
Test for overall effect: Z = 1.70 (P = 0.09)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: Multi-component delirium prevention intervention (MCI) versus usual care, Outcome 6: Peak severity of delirium

Study or Subgroup	Multi-component intervention Mean	SD	Total	Usual care Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Dong 2020	15.54	2.33	2	16.78	2.58	9	11.2%	-0.44 [-1.99 , 1.11]
Hempenius 2013	9	4.5	12	15	4	19	21.8%	-1.39 [-2.20 , -0.58]
Hosie 2020	18.4	8.2	4	16.8	12	8	15.3%	0.13 [-1.07 , 1.34]
Jeffs 2013	3	1.48	15	4	1.11	21	24.2%	-0.77 [-1.46 , -0.08]
Young 2020	3.9	1	24	3.8	1	33	27.5%	0.10 [-0.43 , 0.62]
Total (95% CI)			**57**			**90**	**100.0%**	**-0.49 [-1.13 , 0.14]**

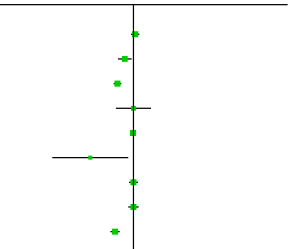
Heterogeneity: Tau² = 0.31; Chi² = 11.03, df = 4 (P = 0.03); I² = 64%
Test for overall effect: Z = 1.52 (P = 0.13)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Multi-component delirium prevention intervention (MCI) versus usual care, Outcome 7: Length of hospital stay

Study or Subgroup	Multi-component intervention Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Abizanda 2011	9.1	5.1	198	8.7	4.8	202	11.8%	0.40 [-0.57 , 1.37]
Chen 2017	12	6	192	14	9	176	10.6%	-2.00 [-3.58 , -0.42]
Dong 2020	12.3	2.1	50	16	2.5	53	11.9%	-3.70 [-4.59 , -2.81]
Hempenius 2013	8	22.3	127	8	7.2	133	5.5%	0.00 [-4.07 , 4.07]
Jeffs 2013	5.5	3.93	305	5.6	4.22	343	12.3%	-0.10 [-0.73 , 0.53]
Lundstrom 2007	28	17.9	102	38	40.6	97	1.8%	-10.00 [-18.79 , -1.21]
Marcantonio 2001	5	2.96	62	5	2.96	64	11.7%	0.00 [-1.03 , 1.03]
Martinez 2012	9	5.2	144	9	5.2	143	11.3%	0.00 [-1.20 , 1.20]
Wang 2020	12.15	3.78	132	16.41	4.69	115	11.6%	-4.26 [-5.33 , -3.19]
Young 2020	9.7	7.1	343	9.8	6.9	370	11.7%	-0.10 [-1.13 , 0.93]
Total (95% CI)			**1655**			**1696**	**100.0%**	**-1.30 [-2.56 , -0.04]**

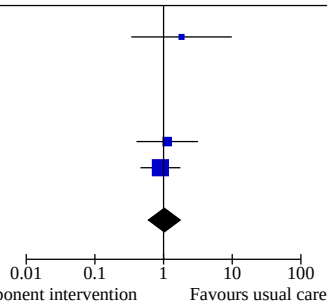
Heterogeneity: Tau² = 3.27; Chi² = 101.63, df = 9 (P < 0.00001); I² = 91%
Test for overall effect: Z = 2.02 (P = 0.04)
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: Multi-component delirium prevention intervention (MCI) versus usual care, Outcome 8: Withdrawal from protocol

Study or Subgroup	Multi-component intervention Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Chen 2017	4	197	2	180	10.0%	1.83 [0.34 , 9.86]
Hosie 2020	0	20	0	25		Not estimable
Marcantonio 2001	0	62	0	64		Not estimable
Partridge 2017	0	104	0	105		Not estimable
Wang 2020	8	152	6	129	26.6%	1.13 [0.40 , 3.18]
Young 2020	15	343	18	370	63.4%	0.90 [0.46 , 1.76]
Total (95% CI)		**878**		**873**	**100.0%**	**1.03 [0.60 , 1.75]**
Total events:	27		26			

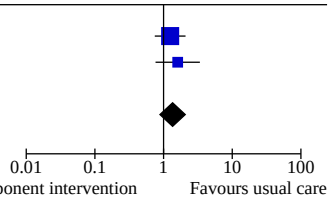
Heterogeneity: Tau² = 0.00; Chi² = 0.64, df = 2 (P = 0.73); I² = 0%
Test for overall effect: Z = 0.09 (P = 0.92)
Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1: Multi-component delirium prevention intervention (MCI) versus usual care, Outcome 9: Readmission to hospital

Study or Subgroup	Multi-component intervention Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Hempenius 2013	24	105	22	120	67.5%	1.25 [0.74 , 2.09]
Partridge 2017	15	85	10	91	32.5%	1.61 [0.76 , 3.38]
Total (95% CI)		**190**		**211**	**100.0%**	**1.35 [0.89 , 2.07]**
Total events:	39		32			

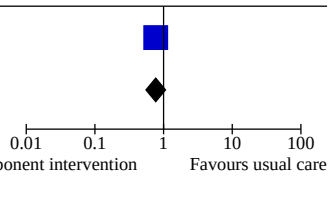
Heterogeneity: Tau² = 0.00; Chi² = 0.30, df = 1 (P = 0.58); I² = 0%
Test for overall effect: Z = 1.40 (P = 0.16)
Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1: Multi-component delirium prevention intervention (MCI) versus usual care, Outcome 10: New care home admission on discharge

Study or Subgroup	Multi-component intervention Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Young 2020	47	248	71	288	100.0%	0.77 [0.55 , 1.07]
Total (95% CI)		**248**		**288**	**100.0%**	**0.77 [0.55 , 1.07]**
Total events:	47		71			

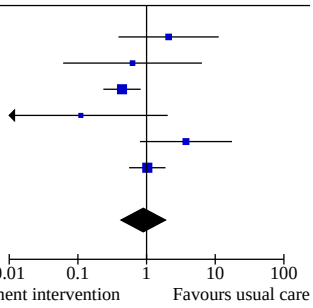
Heterogeneity: Not applicable
Test for overall effect: Z = 1.58 (P = 0.12)
Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1: Multi-component delirium prevention intervention (MCI) versus usual care, Outcome 11: Falls

Study or Subgroup	Multi-component intervention Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Hempenius 2013	4	127	2	133	12.9%	2.09 [0.39 , 11.24]
Hosie 2020	1	20	2	25	8.0%	0.63 [0.06 , 6.41]
Lundstrom 2007	12	102	26	97	29.5%	0.44 [0.23 , 0.82]
Martinez 2012	0	144	4	143	5.6%	0.11 [0.01 , 2.03]
Partridge 2017	7	85	2	91	14.3%	3.75 [0.80 , 17.54]
Young 2020	19	343	20	370	29.8%	1.02 [0.56 , 1.89]
Total (95% CI)		**821**		**859**	**100.0%**	**0.89 [0.42 , 1.88]**
Total events:	43		56			

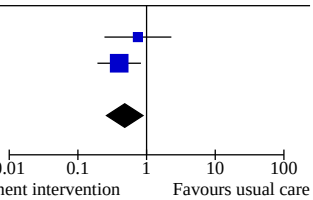
Heterogeneity: Tau² = 0.39; Chi² = 11.09, df = 5 (P = 0.05); I² = 55%
Test for overall effect: Z = 0.29 (P = 0.77)
Test for subgroup differences: Not applicable



Analysis 1.12. Comparison 1: Multi-component delirium prevention intervention (MCI) versus usual care, Outcome 12: Pressure ulcers

Study or Subgroup	Multi-component intervention Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Hempenius 2013	5	127	7	133	29.7%	0.75 [0.24 , 2.30]
Lundstrom 2007	9	102	21	95	70.3%	0.40 [0.19 , 0.83]
Total (95% CI)		**229**		**228**	**100.0%**	**0.48 [0.26 , 0.89]**
Total events:	14		28			

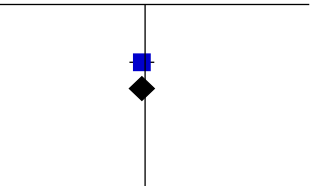
Heterogeneity: Tau² = 0.00; Chi² = 0.85, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 2.35 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 1.13. Comparison 1: Multi-component delirium prevention intervention (MCI) versus usual care, Outcome 13: Incidence of delirium in patients with dementia

Study or Subgroup	Multicomponent intervention Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.13.1 Individuals with dementia						
Marcantonio 2001	13	21	20	29	66.0%	0.90 [0.59 , 1.36]
Subtotal (95% CI)		**21**		**29**	**66.0%**	**0.90 [0.59 , 1.36]**
Total events:	13		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.51 (P = 0.61)						
1.13.2 Individuals without dementia						
Marcantonio 2001	7	41	12	35	34.0%	0.50 [0.22 , 1.13]
Subtotal (95% CI)		**41**		**35**	**34.0%**	**0.50 [0.22 , 1.13]**
Total events:	7		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.68 (P = 0.09)						
Total (95% CI)		**62**		**64**	**100.0%**	**0.73 [0.41 , 1.32]**
Total events:	20		32			

Heterogeneity: Tau² = 0.09; Chi² = 1.84, df = 1 (P = 0.17); I² = 46%
Test for overall effect: Z = 1.03 (P = 0.30)
Test for subgroup differences: Chi² = 1.59, df = 1 (P = 0.21), I² = 37.2%



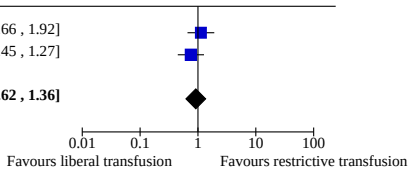
Comparison 2. Liberal versus restrictive blood transfusion thresholds

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Incident delirium	2	294	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.62, 1.36]
2.2 Delirium severity	1	38	Mean Difference (IV, Random, 95% CI)	-0.10 [-2.99, 2.79]
2.3 Length of hospital stay	2	324	Mean Difference (IV, Random, 95% CI)	0.28 [-0.49, 1.04]
2.4 Withdrawal	1	192	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.38, 10.66]

Analysis 2.1. Comparison 2: Liberal versus restrictive blood transfusion thresholds, Outcome 1: Incident delirium

Study or Subgroup	Liberal transfusion threshold Events	Total	Restrictive transfusion threshold Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Fan 2014	22	92	20	94	49.0%	1.12 [0.66 , 1.92]
Gruber-Baldini 2013	16	53	22	55	51.0%	0.75 [0.45 , 1.27]
Total (95% CI)		**145**		**149**	**100.0%**	**0.92 [0.62 , 1.36]**
Total events:	38		42			

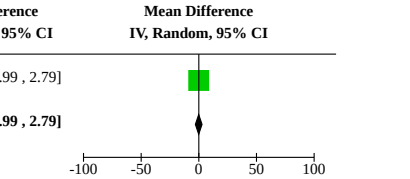
Heterogeneity: Tau² = 0.01; Chi² = 1.10, df = 1 (P = 0.29); I² = 9%
Test for overall effect: Z = 0.43 (P = 0.67)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Liberal versus restrictive blood transfusion thresholds, Outcome 2: Delirium severity

Study or Subgroup	Liberal transfusion threshold Mean	SD	Total	Restrictive transfusion threshold Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Gruber-Baldini 2013	6.8	4.4	16	6.9	4.6	22	100.0%	-0.10 [-2.99 , 2.79]
Total (95% CI)			**16**			**22**	**100.0%**	**-0.10 [-2.99 , 2.79]**

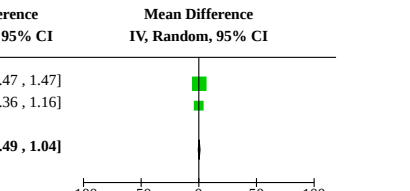
Heterogeneity: Not applicable
Test for overall effect: Z = 0.07 (P = 0.95)
Test for subgroup differences: Not applicable



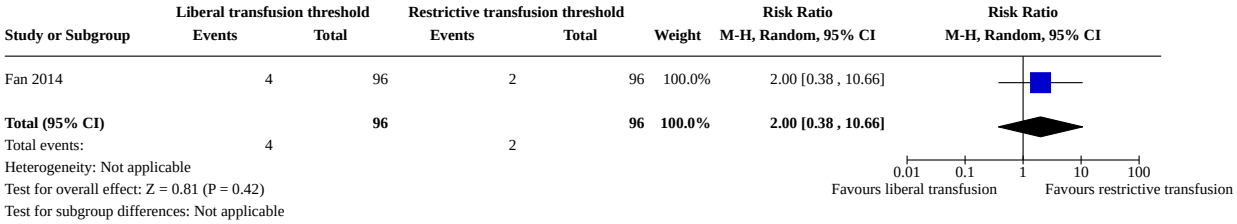
Analysis 2.3. Comparison 2: Liberal versus restrictive blood transfusion thresholds, Outcome 3: Length of hospital stay

Study or Subgroup	Liberal transfusion threshold Mean	SD	Total	Restrictive transfusion threshold Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Fan 2014	9.3	3.9	92	8.8	2.7	94	62.8%	0.50 [-0.47 , 1.47]
Gruber-Baldini 2013	6.6	3.9	66	6.7	3.6	72	37.2%	-0.10 [-1.36 , 1.16]
Total (95% CI)			**158**			**166**	**100.0%**	**0.28 [-0.49 , 1.04]**

Heterogeneity: Tau² = 0.00; Chi² = 0.55, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.71 (P = 0.48)
Test for subgroup differences: Not applicable



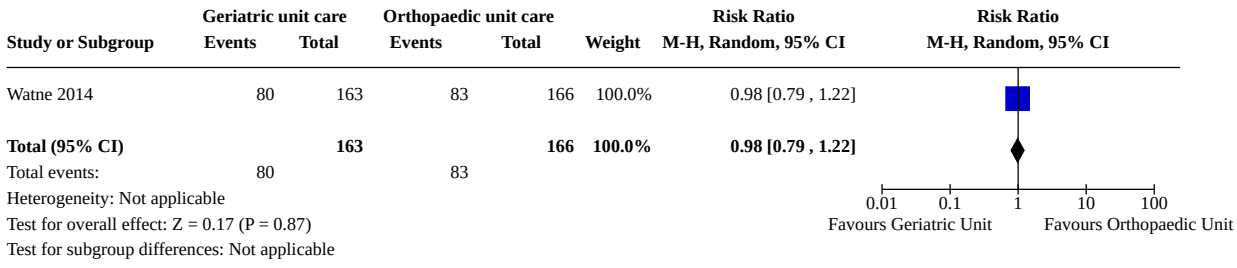
Analysis 2.4. Comparison 2: Liberal versus restrictive blood transfusion thresholds, Outcome 4: Withdrawal



Comparison 3. Geriatric unit care versus orthopaedic unit care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Incident delirium	1	329	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.79, 1.22]
3.2 Inpatient mortality	1	329	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.21, 1.47]
3.3 Incident dementia at 12 months	1	193	Risk Ratio (M-H, Random, 95% CI)	2.26 [0.60, 8.49]
3.4 Duration of delirium	1	166	Mean Difference (IV, Random, 95% CI)	-1.00 [-2.03, 0.03]
3.5 Severity of delirium	1	166	Mean Difference (IV, Random, 95% CI)	1.50 [-0.97, 3.97]
3.6 Length of hospital stay	1	329	Mean Difference (IV, Random, 95% CI)	3.00 [1.94, 4.06]
3.7 Falls	1	329	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.61, 2.77]
3.8 Pressure ulcers	1	329	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.10, 1.41]
3.9 New care home admission at 12 months	1	193	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.47, 1.59]

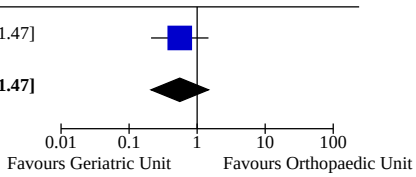
Analysis 3.1. Comparison 3: Geriatric unit care versus orthopaedic unit care, Outcome 1: Incident delirium



Analysis 3.2. Comparison 3: Geriatric unit care versus orthopaedic unit care, Outcome 2: Inpatient mortality

Study or Subgroup	Geriatric unit care Events	Total	Orthopaedic unit care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Watne 2014	6	163	11	166	100.0%	0.56 [0.21 , 1.47]
Total (95% CI)		**163**		**166**	**100.0%**	**0.56 [0.21 , 1.47]**
Total events:	6		11			

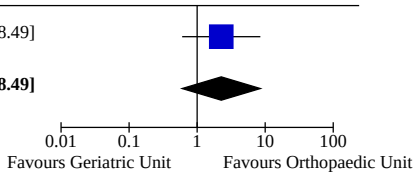
Heterogeneity: Not applicable
Test for overall effect: Z = 1.19 (P = 0.24)
Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3: Geriatric unit care versus orthopaedic unit care, Outcome 3: Incident dementia at 12 months

Study or Subgroup	Geriatric unit care Events	Total	Orthopaedic unit care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Watne 2014	7	98	3	95	100.0%	2.26 [0.60 , 8.49]
Total (95% CI)		**98**		**95**	**100.0%**	**2.26 [0.60 , 8.49]**
Total events:	7		3			

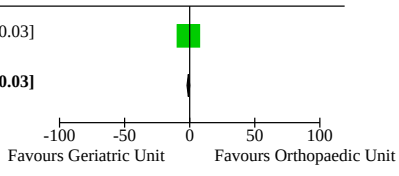
Heterogeneity: Not applicable
Test for overall effect: Z = 1.21 (P = 0.23)
Test for subgroup differences: Not applicable



Analysis 3.4. Comparison 3: Geriatric unit care versus orthopaedic unit care, Outcome 4: Duration of delirium

Study or Subgroup	Geriatric unit care Mean	SD	Total	Orthopaedic unit care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Watne 2014	3	3.7	80	4	3	86	100.0%	-1.00 [-2.03 , 0.03]
Total (95% CI)			**80**			**86**	**100.0%**	**-1.00 [-2.03 , 0.03]**

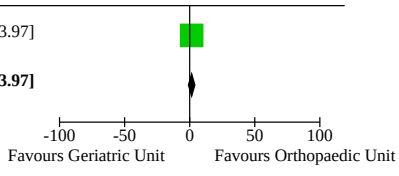
Heterogeneity: Not applicable
Test for overall effect: Z = 1.90 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 3.5. Comparison 3: Geriatric unit care versus orthopaedic unit care, Outcome 5: Severity of delirium

Study or Subgroup	Geriatric unit care Mean	SD	Total	Orthopaedic unit care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Watne 2014	21.5	7.2	80	20	9	86	100.0%	1.50 [-0.97 , 3.97]
Total (95% CI)			**80**			**86**	**100.0%**	**1.50 [-0.97 , 3.97]**

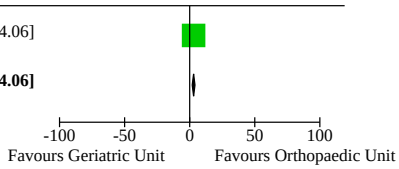
Heterogeneity: Not applicable
Test for overall effect: Z = 1.19 (P = 0.23)
Test for subgroup differences: Not applicable



Analysis 3.6. Comparison 3: Geriatric unit care versus orthopaedic unit care, Outcome 6: Length of hospital stay

Study or Subgroup	Geriatric unit care Mean	SD	Total	Orthopaedic unit care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Watne 2014	11	5.2	163	8	4.6	166	100.0%	3.00 [1.94 , 4.06]
Total (95% CI)			**163**			**166**	**100.0%**	**3.00 [1.94 , 4.06]**

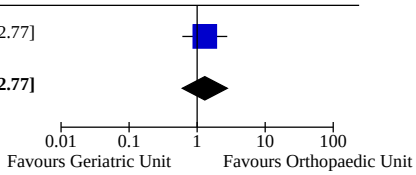
Heterogeneity: Not applicable
Test for overall effect: Z = 5.54 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 3.7. Comparison 3: Geriatric unit care versus orthopaedic unit care, Outcome 7: Falls

Study or Subgroup	Geriatric unit care Events	Total	Orthopaedic unit care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Watne 2014	14	163	11	166	100.0%	1.30 [0.61 , 2.77]
Total (95% CI)		**163**		**166**	**100.0%**	**1.30 [0.61 , 2.77]**
Total events:	14		11			

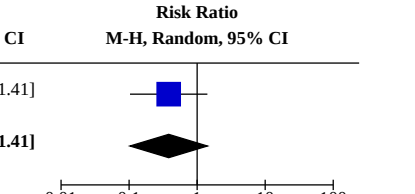
Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.50)
Test for subgroup differences: Not applicable



Analysis 3.8. Comparison 3: Geriatric unit care versus orthopaedic unit care, Outcome 8: Pressure ulcers

Study or Subgroup	Geriatric unit care Events	Total	Orthopaedic unit care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Watne 2014	3	163	8	166	100.0%	0.38 [0.10 , 1.41]
Total (95% CI)		**163**		**166**	**100.0%**	**0.38 [0.10 , 1.41]**
Total events:	3		8			

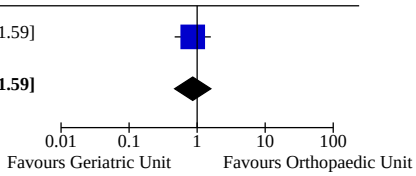
Heterogeneity: Not applicable
Test for overall effect: Z = 1.44 (P = 0.15)
Test for subgroup differences: Not applicable



Analysis 3.9. Comparison 3: Geriatric unit care versus orthopaedic unit care, Outcome 9: New care home admission at 12 months

Study or Subgroup	Geriatric unit care Events	Total	Orthopaedic unit care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Watne 2014	16	98	18	95	100.0%	0.86 [0.47 , 1.59]
Total (95% CI)		**98**		**95**	**100.0%**	**0.86 [0.47 , 1.59]**
Total events:	16		18			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.48 (P = 0.63)
Test for subgroup differences: Not applicable



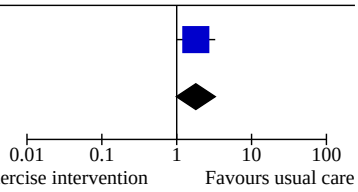
Comparison 4. Exercise therapy versus usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Incident Delirium	1	370	Risk Ratio (M-H, Random, 95% CI)	1.80 [0.99, 3.27]
4.2 Mortality at 1 to 3 months	1	370	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.68, 2.20]
4.3 Length of hospital stay	1	370	Mean Difference (IV, Random, 95% CI)	0.00 [-0.60, 0.60]
4.4 New care home admission on discharge	1	370	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.37, 10.79]
4.5 Falls	1	285	Risk Ratio (M-H, Random, 95% CI)	8.57 [0.47, 157.75]

Analysis 4.1. Comparison 4: Exercise therapy versus usual care, Outcome 1: Incident Delirium

Study or Subgroup	Exercise therapy Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Martinez-Velilla 2019	27	185	15	185	100.0%	1.80 [0.99 , 3.27]
Total (95% CI)		**185**		**185**	**100.0%**	**1.80 [0.99 , 3.27]**
Total events:	27		15			

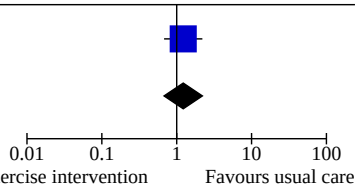
Heterogeneity: Not applicable
Test for overall effect: Z = 1.93 (P = 0.05)
Test for subgroup differences: Not applicable



Analysis 4.2. Comparison 4: Exercise therapy versus usual care, Outcome 2: Mortality at 1 to 3 months

Study or Subgroup	Exercise therapy Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Martinez-Velilla 2019	22	185	18	185	100.0%	1.22 [0.68 , 2.20]
Total (95% CI)		**185**		**185**	**100.0%**	**1.22 [0.68 , 2.20]**
Total events:	22		18			

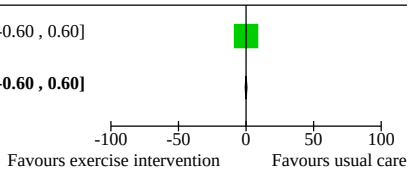
Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.50)
Test for subgroup differences: Not applicable



Analysis 4.3. Comparison 4: Exercise therapy versus usual care, Outcome 3: Length of hospital stay

Study or Subgroup	Exercise therapy Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Martinez-Velilla 2019	8	2.96	185	8	2.96	185	100.0%	0.00 [-0.60 , 0.60]
Total (95% CI)			**185**			**185**	**100.0%**	**0.00 [-0.60 , 0.60]**

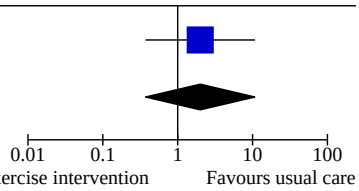
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



Analysis 4.4. Comparison 4: Exercise therapy versus usual care, Outcome 4: New care home admission on discharge

Study or Subgroup	Exercise therapy Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Martinez-Velilla 2019	4	185	2	185	100.0%	2.00 [0.37 , 10.79]
Total (95% CI)		**185**		**185**	**100.0%**	**2.00 [0.37 , 10.79]**
Total events:	4		2			

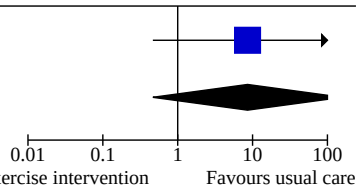
Heterogeneity: Not applicable
Test for overall effect: Z = 0.81 (P = 0.42)
Test for subgroup differences: Not applicable



Analysis 4.5. Comparison 4: Exercise therapy versus usual care, Outcome 5: Falls

Study or Subgroup	Exercise therapy Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Martinez-Velilla 2019	4	146	0	139	100.0%	8.57 [0.47 , 157.75]
Total (95% CI)		**146**		**139**	**100.0%**	**8.57 [0.47 , 157.75]**
Total events:	4		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.45 (P = 0.15)
Test for subgroup differences: Not applicable



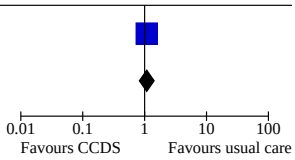
Comparison 5. Computerised clinical decision support system (CCDS) versus usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Incident delirium	1	424	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.82, 1.43]
5.2 Mortality at 1 to 3 months	1	424	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.49, 2.23]
5.3 Length of hospital stay	1	424	Mean Difference (IV, Random, 95% CI)	0.90 [-0.35, 2.15]
5.4 Falls	1	424	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.39, 2.19]
5.5 Pressure sores	1	424	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.64, 1.84]

Analysis 5.1. Comparison 5: Computerised clinical decision support system (CCDS) versus usual care, Outcome 1: Incident delirium

Study or Subgroup	Computerised clinical decision support system Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Boustani 2012	67	199	70	225	100.0%	1.08 [0.82 , 1.43]
Total (95% CI)		**199**		**225**	**100.0%**	**1.08 [0.82 , 1.43]**
Total events:	67		70			

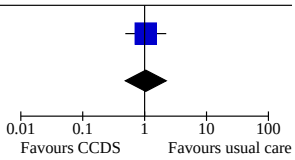
Heterogeneity: Not applicable
Test for overall effect: Z = 0.56 (P = 0.57)
Test for subgroup differences: Not applicable



Analysis 5.2. Comparison 5: Computerised clinical decision support system (CCDS) versus usual care, Outcome 2: Mortality at 1 to 3 months

Study or Subgroup	Computerised clinical decision support system Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Boustani 2012	12	199	13	225	100.0%	1.04 [0.49 , 2.23]
Total (95% CI)		**199**		**225**	**100.0%**	**1.04 [0.49 , 2.23]**
Total events:	12		13			

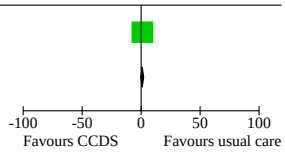
Heterogeneity: Not applicable
Test for overall effect: Z = 0.11 (P = 0.91)
Test for subgroup differences: Not applicable



Analysis 5.3. Comparison 5: Computerised clinical decision support system (CCDS) versus usual care, Outcome 3: Length of hospital stay

Study or Subgroup	Computerised clinical decision support system Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Boustani 2012	7.7	7.4	199	6.8	5.4	225	100.0%	0.90 [-0.35 , 2.15]
Total (95% CI)			**199**			**225**	**100.0%**	**0.90 [-0.35 , 2.15]**

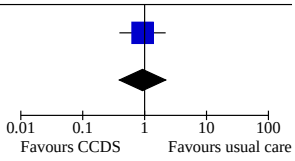
Heterogeneity: Not applicable
Test for overall effect: Z = 1.41 (P = 0.16)
Test for subgroup differences: Not applicable



Analysis 5.4. Comparison 5: Computerised clinical decision support system (CCDS) versus usual care, Outcome 4: Falls

Study or Subgroup	Computerised clinical decision support system Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Boustani 2012	9	199	11	225	100.0%	0.93 [0.39 , 2.19]
Total (95% CI)		**199**		**225**	**100.0%**	**0.93 [0.39 , 2.19]**
Total events:	9		11			

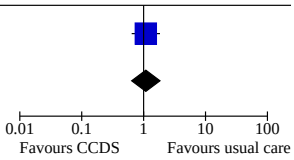
Heterogeneity: Not applicable
Test for overall effect: Z = 0.18 (P = 0.86)
Test for subgroup differences: Not applicable



Analysis 5.5. Comparison 5: Computerised clinical decision support system (CCDS) versus usual care, Outcome 5: Pressure sores

Study or Subgroup	Computerised clinical decision support system Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Boustani 2012	24	199	25	225	100.0%	1.09 [0.64 , 1.84]
Total (95% CI)		**199**		**225**	**100.0%**	**1.09 [0.64 , 1.84]**
Total events:	24		25			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.31 (P = 0.76)
Test for subgroup differences: Not applicable



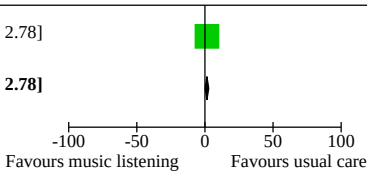
Comparison 6. Listening to music verus usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Incident delirium	1	60	Mean Difference (IV, Random, 95% CI)	1.47 [0.16, 2.78]

Analysis 6.1. Comparison 6: Listening to music verus usual care, Outcome 1: Incident delirium

Study or Subgroup	Music listening Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Cetinkaya 2019	25.57	2.73	30	24.1	2.43	30	100.0%	1.47 [0.16 , 2.78]
Total (95% CI)			**30**			**30**	**100.0%**	**1.47 [0.16 , 2.78]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.20 (P = 0.03)
Test for subgroup differences: Not applicable



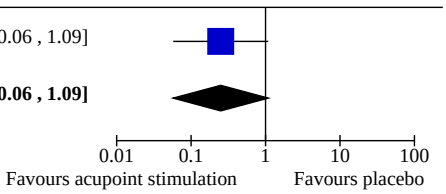
Comparison 7. Transcutaneous electrical acupoint stimulation versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Incident delirium	1	64	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.06, 1.09]

Analysis 7.1. Comparison 7: Transcutaneous electrical acupoint stimulation versus placebo, Outcome 1: Incident delirium

Study or Subgroup	Acupoint stimulation Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Gao 2018	2	32	8	32	100.0%	0.25 [0.06 , 1.09]
Total (95% CI)		**32**		**32**	**100.0%**	**0.25 [0.06 , 1.09]**
Total events:	2		8			

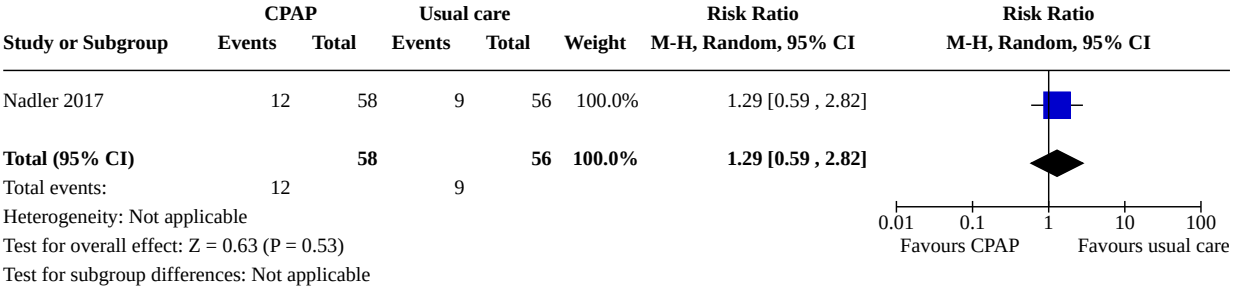
Heterogeneity: Not applicable
Test for overall effect: Z = 1.85 (P = 0.06)
Test for subgroup differences: Not applicable



Comparison 8. Continuous positive airway pressure (CPAP) verus usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Incident delirium	1	114	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.59, 2.82]

Analysis 8.1. Comparison 8: Continuous positive airway pressure (CPAP) verus usual care, Outcome 1: Incident delirium



ADDITIONAL TABLES

Table 1. Distribution of components across included studies

Component name	Number of studies including component	Studies including component
Assessment of mood	2	Hempenius 2013; Partridge 2017
Bowel & bladder care	7	Abizanda 2011; Avendano-Cespedes 2016; Dong 2020; Hempenius 2013; Lundstrom 2007; Marcantonio 2001; Wang 2020
Cognitive stimulation	5	Abizanda 2011; Marcantonio 2001; Martinez 2012; Partridge 2017; Young 2020
Identification of infection	5	Hempenius 2013; Lundstrom 2007; Marcantonio 2001; Wang 2020; Young 2020
Medication review	6	Avendano-Cespedes 2016; Dong 2020; Hempenius 2013; Marcantonio 2001; Partridge 2017; Wang 2020
Mobilisation	12	Abizanda 2011; Avendano-Cespedes 2016; Bonaventura 2007; Chen 2017; Hempenius 2013; Hosie 2020; Jeffs 2013; Lundstrom 2007; Marcantonio 2001; Partridge 2017; Wang 2020; Young 2020
Nutrition & hydration (including electrolyte balance)	11	Avendano-Cespedes 2016; Bonaventura 2007; Chen 2017; Dong 2020; Hempenius 2013; Hosie 2020; Lundstrom 2007; Marcantonio 2001; Partridge 2017; Wang 2020; Young 2020
Oxygenation	5	Avendano-Cespedes 2016; Dong 2020; Lundstrom 2007; Marcantonio 2001; Wang 2020

Table 1. Distribution of components across included studies *(Continued)*

Pain control	7	Avendano-Cespedes 2016; Dong 2020; Hempenius 2013; Lundstrom 2007; Marcantonio 2001; Wang 2020; Young 2020
Re-orientation & familiar objects	10	Avendano-Cespedes 2016; Bonaventura 2007; Chen 2017; Hempenius 2013; Hosie 2020; Jeffs 2013; Marcantonio 2001; Martinez 2012; Wang 2020; Young 2020
Reducing sensory deprivation	8	Avendano-Cespedes 2016; Bonaventura 2007; Dong 2020; Hempenius 2013; Hosie 2020; Marcantonio 2001; Martinez 2012; Young 2020
Sleep hygiene	8	Avendano-Cespedes 2016; Bonaventura 2007; Dong 2020; Hempenius 2013; Hosie 2020; Lundstrom 2007; Wang 2020; Young 2020

APPENDICES

Appendix 1. Sources searched and search strategies

Source	Search strategy	Hits retrieved
ALOIS (Cochrane Dementia and Cognitive Improvement Group Specialised Regsiter, searched via the Cochrane Register of Studies) [Date of most recent search: 16 September 2020]	Deliri* OR DEL [studies that are about delirium trestment or prevention are coded DEL in ALOIS]	June 2019: 240 Jan 2020: 106 Sep 2020: 67
CENTRAL (the Cochrane Library) http://crso.cochrane.org/SearchSimple.php [Date of most recent search: 16 September 2020]	#1 MESH DESCRIPTOR Delirium EXPLODE ALL TREES #2 deliri*:TI,AB,KY #3 ("acute confusion*"):TI,AB,KY #4 ("acute confusion*"):TI,AB,KY #5 ("acute organic psychosyndrome"):TI,AB,KY #6 ("acute brain syndrome"):TI,AB,KY #7 ("metabolic encephalopathy"):TI,AB,KY #8 ("acute psycho-organic syndrome"):TI,AB,KY #9 ("clouded state"):TI,AB,KY #10 ("clouding of consciousness"):TI,AB,KY #11 ("exogenous psychosis"):TI,AB,KY #12 ("toxic psychosis"):TI,AB,KY #13 ("toxic confusion"):TI,AB,KY	June 2019: 1642 Jan 2020: 531 Sep 2020:157

(Continued)

	#14 obnubilat*:TI,AB,KY	
	#15 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	
	#16 MESH DESCRIPTOR Hospitals EXPLODE ALL TREES	
	#17 MESH DESCRIPTOR Patient Care EXPLODE ALL TREES	
	#18 MESH DESCRIPTOR Inpatients EXPLODE ALL TREES	
	#19 Hospital*:TI,AB,KY	
	#20 "In-patient":TI,AB,KY	
	#21 Ward*:TI,AB,KY	
	#22 Inpatient*:TI,AB,KY	
	#23 #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22	
	#24 #15 AND #23	
MEDLINE In-process and other non-indexed citations and MEDLINE 1950-present (Ovid SP) [Date of most recent search: 16 September 2020]	1. Delirium/	June 2019: 1873 Jan 2020: 216 Sep 2020: 136
	2. deliri*.mp.	
	3. "acute confusion*".ti,ab.	
	4. "acute organic psychosyndrome".ti,ab.	
	5. "acute brain syndrome".ti,ab.	
	6. "metabolic encephalopathy".ti,ab.	
	7. "acute psycho-organic syndrome".ti,ab.	
	8. "clouded state".ti,ab.	
	9. "clouding of consciousness".ti,ab.	
	10. "exogenous psychosis".ti,ab.	
	11. "toxic psychosis".ti,ab.	
	12. "toxic confusion".ti,ab.	
	13. Delirium, Dementia, Amnestic, Cognitive Disorders/su [Surgery]	
	14. obnubilat*.ti,ab.	
	15. or/1-14	
	16. Hospitals/	
	17. Inpatients/	
	18. Patient Care/	
	19. Hospital*.ti,ab.	
	20. "In-patient".ti,ab.	
	21. Ward*.ti,ab.	
	22. Inpatient*.ti,ab.	

(Continued)

	23. 16 or 17 or 18 or 19 or 20 or 21 or 22	
	24. randomized controlled trial.pt.	
	25. controlled clinical trial.pt.	
	26. randomi?ed.ab.	
	27. placebo.ab.	
	28. drug therapy.fs.	
	29. randomly.ab.	
	30. trial.ab.	
	31. groups.ab.	
	32. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31	
	33. (animals not (humans and animals)).sh.	
	34. 32 not 33	
	35. 15 and 23 and 34	
EMBASE (Ovid SP)	1. Delirium/	June 2019: 6907
1974 to 15 January 2020	2. deliri*.mp.	Jan 2020: 1117
[Date of most recent search: 16 September 2020]	3. "acute confusion*".ti,ab.	Sep 2020:748
	4. "acute organic psychosyndrome".ti,ab.	
	5. "acute brain syndrome".ti,ab.	
	6. "metabolic encephalopathy".ti,ab.	
	7. "acute psycho-organic syndrome".ti,ab.	
	8. "clouded state".ti,ab.	
	9. "clouding of consciousness".ti,ab.	
	10. "exogenous psychosis".ti,ab.	
	11. "toxic psychosis".ti,ab.	
	12. "toxic confusion".ti,ab.	
	13. Delirium, Dementia, Amnestic, Cognitive Disorders/su [Surgery]	
	14. obnubilat*.ti,ab.	
	15. or/1-14	
	16. Hospitals/	
	17. Inpatients/	
	18. Patient Care/	
	19. Hospital*.ti,ab.	
	20. "In-patient".ti,ab.	
	21. Ward*.ti,ab.	

(Continued)

	22. Inpatient*.ti,ab. 23. 16 or 17 or 18 or 19 or 20 or 21 or 22 24. randomized controlled trial.pt. 25. controlled clinical trial.pt. 26. randomi?ed.ab. 27. placebo.ab. 28. drug therapy.fs. 29. randomly.ab. 30. trial.ab. 31. groups.ab. 32. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 33. (animals not (humans and animals)).sh. 34. 32 not 33 35. 15 and 23 and 34	
PsycINFO (Ovid SP) [Date of most recent search: 16 September 2020]	1 Delirium/ 2 deliri*.mp. 3 "acute confusion*".ti,ab. 4 "acute organic psychosyndrome".ti,ab. 5 "acute brain syndrome".ti,ab. 6 "metabolic encephalopathy".ti,ab. 7 "acute psycho-organic syndrome".ti,ab. 8 "clouded state".ti,ab. 9 "clouding of consciousness".ti,ab. 10 "exogenous psychosis".ti,ab. 11 "toxic psychosis".ti,ab. 12 "toxic confusion".ti,ab. 13 obnubilat*.ti,ab. 14 or/1-13 15 exp HOSPITALS/ 16 exp Hospitalized Patients/ 17 Hospital*.ti,ab. 18 "In-patient".ti,ab. 19 Ward*.ti,ab. 20 Inpatient*.ti,ab.	June 2019: 332 Jan 2020: 21 Sep 2020:365

(Continued)

	21 or/15-20 22 exp Clinical Trials/ 23 randomly.ab. 24 randomi?ed.ti,ab. 25 placebo.ti,ab. 26 groups.ab. 27 "double-blind*".ti,ab. 28 "single-blind*".ti,ab. 29 RCT.ti,ab. 30 or/22-29 31 14 and 21 and 30 32 from 31 keep 1-288	
CINAHL (EBSCOhost) [Date of most recent search: 16 September 2020]	1 deliri* 2 "acute psycho-organic syndrome" or "clouded state" or "clouding of consciousness" or "exogenous psychosis" or "toxic psychosis" or "toxic confusion" 3 "acute brain confusion" or "acute brain failure" or "acute organic psychosyndrome" or "acute brain syndrome" or "metabolic encephalopathy" 4 "Delirium"/ 5 (S1 OR S2 OR S3 OR S4) 6 (MH "Hospitals+") 7 (MH "Inpatients") 8 TX Hospital* 9 TX "In-patient" 10 Ward* 11 Inpatient* 12 (MH "Patient Care") 13 (S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12) 14 MH "Clinical Trials" 15 TX trial 16 TX "single-blind*" 17 TX "double-blind*" 18 TX "treatment as usual" 19 TX randomly 20 S14 OR S15 OR S16 OR S17 OR S18 OR S19	June 2019: 1,498 Jan 2020: 461 Sep 2020: 144

(Continued)

	21 S5 AND S13 AND S20	
ISI Web of Science – core collection [Date of most recent search: 16 September 2020]	TOPIC:(deliri* OR "acute confusion*" OR "acute organic psychosyndrome" OR "acute brain syndrome" OR "metabolic encephalopathy" OR "acute psycho-organic syndrome" OR "clouded state" OR "clouding of consciousness" OR "exogenous psychosis" OR "toxic psychosis" OR "toxic confusion" OR obnubilat*)ANDTOPIC:(hospital* OR Inpatient* OR In-patient* OR ward OR "In patient*")AND TOPIC:(randomly OR randomised OR randomized OR "random allocat*" OR RCT OR CCT OR "double blind*" OR "single blind*" OR "double blind*" OR "single blind*" OR trial)	June 2019: 1612 Jan 2020: 186 Sep 2020: 321
LILACS (BIREME) [Date of most recent search: 16 September 2020]	deliri$ OR delirio OR loucura [Words]and hospital$ OR inpatient$ [Words]	June 2019: 417 Jan 2020: 13 Sep 2020: 9
ClinicalTrials.gov (www.clinicaltrials.gov) [Date of most recent search: 16 September 2020]	HOSPITAL OR INPATIENT | delirium OR toxic psychosis OR toxic confusion	June 2019: 540 Jan 2020: 97 Sep 2020: 68
ICTRP [Date of most recent search: 15 January 2020. Database not available 16 September 2020]	HOSPITAL OR INPATIENT | delirium OR toxic psychosis OR toxic confusion	June 2019: 89 Jan 2020: 18
TOTAL before de-duplication		June 2019: 15,150 Jan 2020: 2766 Sep 2020: 2015
TOTAL after de-duplication		June 2019: 10,810 Jan 2020: 2246 Sep 2020:1682

Appendix 2. Table reporting original study-level description of components forming their multicomponent interventions mapped across to included components in the analysis

Study ID	Description of components within study	Components not included or combined with others	Intervention delivery	Included components
Abizanda 2011	Occupational therapy intervention consisted of a daily session with patient and relative/caregiver Monday-Friday for the duration of admission.		Education Tailored	Bowel/bladder care

(Continued)

	Activities were carried out according to needs and day of admission. Therapeutic plan included: cognitive stimulation; instruction on preventing complications including immobility, confusion, falls, urinary incontinence, pressure sores; retraining in ADL; assessment of technical aids for home			Cognitive stimulation Mobilisation
Avendano-Cespedes 2016	The intervention was carried out exclusively by the intervention nurses and was composed of two main parts, being the first one a risk factor analysis, and the second one the intervention on the risk factors detected. Risk factors: orientation, sensorial deficit, sleep, mobilisation, hydration, nutrition, drugs, oxygenation, elimination, and pain		Education Tailored	Bowel/bladder care Medication review Mobilisation Nutrition & hydration Oxygenation Pain control Re-orientation & familiar objects Reducing sensory deprivation Sleep hygiene
Bonaventura 2007	Intervention to Prevent Delirium (IPD), a series of structured and standardised welfare actions based on existing guidelines, including support in the following areas: cognitive re-orientation, sensory and environmental, mobilisation, hydration, and 'socio-emotional'	Familiar objects	Education	Mobilisation Nutrition & hydration Re-orientation & familiar objects Reducing sensory deprivation Sleep hygiene
Chen 2017	Modified Hospital Elder Life Program comprising of three standardised protocols: orienting communication (i.e., orientation and engaged conversation), oral and nutritional assistance (i.e., brushing teeth, oral-facial exercise, and postoperative dietary education), and early mobilization.		Education Protocol/checklist	Mobilisation Nutrition & hydration Re-orientation & familiar objects
Dong 2020	All patients received 1. Directional communication plan 2. Cognitive therapy activity plan 3. Early activity plan The following schemes are implemented as needed based on the evaluation results		Protocol/checklist Tailored	Bowel/bladder care Medication review Mobilisation Nutrition & hydration

(Continued)

	4. Pain improvement program 5. Sleep improvement program 6. Assisted feeding plan 7. Rehydration program 8. Constipation improvement plan 9. Hearing/vision improvement program 10. Hypoxic improvement program 11. Aspiration pneumonia prevention program 12. Urine-related infection prevention program 13. Delirium improvement program 14. Dementia improvement program 15. Multiple medication management plan		Oxygenation Pain control Reducing sensory deprivation Sleep hygiene
Hempenius 2013	Multi-component intervention focused on best supportive care and the prevention of delirium. Preoperative geriatric team assessment with daily monitoring during hospital stay, supported by the use of standardised checklists. This checklist consisted of nine items: orientation, mobility, anxiety, senses, pain, sleep, intake, defecation and infection.	Comprehensive Geriatric Assessment Education Protocol/checklist Tailored	Assessment of mood Bowel/bladder care Identification of infection Medication review Mobilisation Nutrition & hydration Pain control Re-orientation & familiar objects Reducing sensory deprivation Sleep hygiene
Hosie 2020	The intervention had six domains 1. Preserve natural sleep 2. Maintain optimal sensory perception 3. Optimise hydration 4. Stimulate communication, orientation and cognition 5. Optimise mobility 6. Family partnership	Education Family involvement Multidisciplinary Protocol/checklist	Mobilisation Nutrition & hydration Re-orientation & familiar objects Reducing sensory deprivation Sleep hygiene

(Continued)

	For each domain there are 4-12 strategies provided and their implementation is described We asked team members to enlist family and volunteers and tailor the intervention to patients' needs and wishes.			
Jeffs 2013	Participants received a graded physical activity and orientation programme twice daily, which was delivered in addition to usual care. A certified Allied Health Assistant, trained in administering exercise programmes, delivered the intervention after initial assessment of the participant by a physiotherapist. Commensurate with ability, participants were prescribed one of four exercise programmes: bed, seated, standing or rails. All programmes were customised to the participant's ability and were reviewed daily. Exercise programmes were modified to ensure suitable progression for those participants who made significant gains. The orientation programme comprised formal and informal elements. The formal element of the programme comprised a series of seven questions aimed at assessing and improving orientation (day, month, year, date, ward, bed number and name of primary nurse). The participant was asked the questions in sequence and prompted with the correct answer if they were not able to give a correct response. The informal element of the programme related to engaging in the exercise programme and in the social interaction with the Allied Health Assistant and/or Physiotherapist.		Protocol/checklist	Mobilisation Re-orientation & familiar objects
Lundstrom 2007	The staff worked as a team, applying comprehensive geriatric assessment, management and rehabilitation. Main content of the intervention - Prevention and treatment of complications, bowel and bladder function, sleep, decubitus ulcers, pain, saturation, body temperature, Blood pressure, nutrition, rehabilitation, Secondary prevention of falls and fractures and osteoporosis prophylaxis. Other – staff education, teamwork, individual care planning, delirium		Comprehensive Geriatric Assessment Education Multidisciplinary Protocol/checklist Tailored	Bowel/bladder care Identification of infection Mobilisation Nutrition & hydration Oxygenation Pain control Sleep hygiene
Marcantonio 2001	Proactive geriatrics consultation. The consultation included 10 modules – adequate CNS oxygen delivery, fluid electrolyte balance, treatment of severe pain, elimination of unnec-	Electrolytes Postoperative complications	Tailored	Bowel/bladder care Cognitive stimulation

(Continued)

	essary medications, regulation of bowel/bladder function, adequate nutritional intake, early mobilisation and rehabilitation, prevention, early detection and treatment of major postoperative complications, appropriate environmental stimuli, treatment of agitated delirium.			Identification of infection Medication review Mobilisation Nutrition & hydration (including electrolyte balance) Oxygenation Pain control Re-orientation & familiar objects Reducing sensory deprivation
Martinez 2012	Multicomponent management protocol. The intervention was delivered by family members and consisted of 6 elements: 1. Education 2. Provision of a clock 3. Avoidance of sensory deprivation 4. Presence of familiar objects in the room 5. Reorientation of patient provided by family members 6. Extended visitation time.	Familiar objects	Education Family involvement Multidisciplinary Protocol/checklist	Cognitive stimulation Re-orientation & familiar objects Reducing sensory deprivation
Partridge 2017	Comprehensive geriatric assessment delivered by a multidisciplinary team (geriatrician, clinical nurse specialist, social worker, occupational therapist) according to individual patient. Patients were assessed and optimised according to peer-reviewed protocols based on current evidence, national and hospital guidelines, and expert opinion. The domains that were included cognition, general health status, function independence, social support, medication use, nutrition and mood.		Comprehensive Geriatric Assessment Multidisciplinary Tailored	Assessment of mood Cognitive stimulation Medication review Mobilisation Nutrition & hydration
Wang 2020	t-Hospital Elder Life Program (HELP) (tailored, family-involved HELP), which involved family members instead of volunteers and applied a tailored approach to assigning HELP protocols. The t-HELP intervention consisted of 3 universal protocols and 8 targeted protocols.		Education Family involvement Multidisciplinary Protocol/checklist	Bowel/bladder care Identification of infection Medication review Mobilisation

(Continued)

	The universal protocols, including orientation, therapeutic activities, and early mobilisation protocol (universal protocols), were given to all t-HELP participants. The targeted protocols were tailored for each patient on the basis of delirium related risk factors, which were assessed daily and comprised of pain management, sleep enhancement, nutrition assistance/aspiration prevention, fluid repletion/constipation, vision/hearing enhancement, hypoxia Improvement, catheter associated UTI (CAUTI) prevention and multiple medications management.	Tailored	Nutrition & hydration Oxygenation Pain control Re-orientation & familiar objects Sleep hygiene
Young 2020	The Prevention of Delirium (POD) programme is a manualised, multicomponent intervention and systematic implementation process designed to secure ward practice changes consistent with a reduction in delirium. POD comprises actions centred on ten risk factors associated with the development of delirium among those who are vulnerable on of the basis of predisposing risk (NICE 2010). These interventions directly affect the patient experience of care and include optimising hydration and nutrition, reducing environmental triggers (excessive noise, multiple moves), increasing orientation to time and place, improving communicative practices (personally meaningful interaction and cognitive stimulation), supporting and/or encouraging mobility and better management of pain and infection.	Education Protocol/checklist	Cognitive stimulation Identification of infection Mobilisation Nutrition & hydration Pain control Re-orientation & familiar objects Reducing sensory deprivation Sleep hygiene

Additional detail on each of the multicomponent interventions is provided at study level within Characteristics of included studies.

ADL: activities of daily living; **CNS:** central nervous system.

HISTORY

Protocol first published: Issue 4, 2019

CONTRIBUTIONS OF AUTHORS

JKB - title and abstract screening; full-text retrieval and review; data extraction; risk of bias assessment; data entry; network meta-analysis and interpretation of findings; drafting of review and co-ordination of comments

LC - data extraction; risk of bias assessment; data entry; network meta-analysis and interpretation of findings

SQY - title and abstract screening; full-text retrieval and review; data extraction

NS - title and abstract screening; full-text review; data extraction

EAT - title and abstract screening; full-text review

RW - full text review; data extraction

AJB - title and abstract screening; data extraction

AMS - full-text review; data extraction

AB - data extraction

SCF - network meta-analysis and interpretation of findings

AJS - network meta-analysis and interpretation of findings

TJQ - network meta-analysis and interpretation of findings; support in responding to editorial and peer-reviewer comments

LC, NS, AJB, AB, SCF, AJS, TJQ provided comments and critical review of the manuscript

All review authors approved the manuscript

DECLARATIONS OF INTEREST

JKB has no known conflicts of interest

LC has no known conflicts of interest

SQY has no known conflicts of interest

NS is an author on a study included in the review (Young 2020), she played no part in the study selection, data extraction or quality assessment of the work

EAT is an author on a study included in the review (Young 2020), she played no part in the study selection, data extraction or quality assessment of the work

RW has no known conflicts of interest

AJB has no known conflicts of interest

AMS has no known conflicts of interest

AB has no known conflicts of interest

SCF has no known conflicts of interest

AJS has no known conflicts of interest

TJQ has no known conflicts of interest

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Internal sources

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  Support for author EAT
- Department of Geriatric Medicine, University of Edinburgh, UK

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- Department of Health Sciences, University of Leicester, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The review protocol (Burton 2019) specified the primary outcome was 'Incidence of delirium, using a validated diagnostic method'. Following a peer review comment, we added text to clarify that this outcome is measured during hospital admission.

The review protocol specified 'peak severity of delirium' as a defined secondary outcome. It was not possible to evaluate this outcome due to the heterogeneity of methods to report delirium severity. Thus, the review includes delirium severity and comments on how this has been measured.

The review protocol referenced using the Risk of Bias-2 (RoB-2) (Higgins 2018) and listed the domains for RoB-2 utilisation. The review has used the original risk of bias tool (Higgins 2011) - the references and domains have been updated to reflect this change.

The review protocol referenced use of Review Manager 5 (Review Manager 2014), however the review has been drafted and submitted using RevMan Web (RevMan Web 2021).

The review protocol described subgroup analysis to remove studies in which individuals were receiving palliative care only versus those receiving other medical or surgical treatment. This should have been described as a sensitivity analysis and is reported here correctly as a sensitivity analysis.

An additional sensitivity analysis was undertaken removing studies which used a cluster-randomised design from the analysis of delirium incidence; this was not planned in the protocol, but done to address reviewer comments.

INDEX TERMS

Medical Subject Headings (MeSH)

Bias; Blood Transfusion; Combined Modality Therapy [methods]; Delirium [epidemiology] [*prevention & control]; Hospital Mortality; Incidence; *Inpatients; Length of Stay; Network Meta-Analysis; Randomized Controlled Trials as Topic

MeSH check words

Aged; Aged, 80 and over; Humans