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Review article

Interventions to prevent and treat delirium: An umbrella review of randomized controlled trials

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ABSTRACT

Delirium is a common condition across different settings and populations. The interventions for preventing and managing this condition are still poorly known. The aim of this umbrella review is to synthesize and grade all preventative and therapeutic interventions for delirium. We searched five databases from database inception up to March 15th, 2023 and we included meta-analyses of randomized controlled trials (RCTs) to decrease the risk of/the severity of delirium. From 1959 records after deduplication, we included 59 systematic reviews with meta-analyses, providing 110 meta-analytic estimates across populations, interventions, outcomes, settings, and age groups (485 unique RCTs, 172,045 participants). In surgery setting, for preventing delirium, high GRADE evidence supported dexmedetomidine (RR=0.53; 95%CI: 0.46–0.67, k=13, N=3988) and comprehensive geriatric assessment (OR=0.46; 95%CI=0.32–0.67, k=3, N=496) in older adults, dexmedetomidine in adults (RR=0.33, 95%CI=0.24–0.45, k=7, N=1974), A2-adrenergic agonists after induction of anesthesia (OR= 0.28, 95%CI= 0.19–0.40, k=10, N=669) in children. High certainty evidence did not support melatonergic agents in older adults for delirium prevention. Moderate certainty supported the effect of dexmedetomidine in adults and children (k=4), various non-pharmacological interventions in adults and older people (k=4), second-generation antipsychotics in adults and mixed age groups (k=3), EEG-guided anesthesia in adults (k=2), mixed pharmacological interventions (k=1), five other specific pharmacological interventions in children (k=1 each). In conclusion, our work indicates that effective treatments to prevent delirium differ across populations, settings,

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and age groups. Results inform future guidelines to prevent or treat delirium, accounting for safety and costs of interventions. More research is needed in non-surgical settings.

1. Introduction

Celsus first used the word "DELIRIUM" in medical writing in the first century AD to describe (either as a symptom or as a syndrome) mental disorders during fever or head trauma.(Adamis et al., 2007) Successively, Hippocrates identified delirium in severely ill patients as a bad omen and used about 16 different words to refer to and call the clinical syndrome which we now call delirium.(Adamis et al., 2007) In this light, the word delirium derives from the Latin *delirare* (de-lira, to go out of the furrow) – therefore, to deviate from a straight line, to be mad, deranged, out of one's senses, to be foolish.(Adamis et al., 2007)

Delirium is an acute brain dysfunction characterized by a sudden change in cognitive performance, mainly attention and awareness, with impaired arousal and a fluctuating course, which can be triggered by multiple potential causes, including acute illnesses, drug use or withdrawal, trauma and surgery. (Lolk, 2013; Vlisides and Avidan, 2019)

Delirium may present with various psychomotor subtypes, including hyperactive, hypoactive and mixed.(Wilson et al., 2020) The hyperactive is characterized by restlessness, agitated behavior and/or aggressiveness; the hypoactive is characterized by sluggishness (or lethargy) and reduced psychomotor activity; and the mixed subtype is characterized by the transition from hyperactivity to hypoactivity or *vice versa*. (Bellelli et al., 2021) Delirium is associated with increased mortality, cognitive and functional decline, longer hospital length of stay, and substantial annual health-care costs. (Hamilton et al., 2017; Jackson et al., 2004; Leslie et al., 2008; McCusker et al., 2003) This condition can present in all hospital settings from pediatrics to geriatrics.(Bellelli et al., 2016; Gibb et al., 2020; Morandi et al., 2019) However, it is especially common in surgical settings, with an incidence of postoperative delirium ranging from 20% to 50% in those older than 60 after major surgery (Dasgupta and Dumbrell, 2006), and in critical care settings the prevalence of delirium is estimated to be 31.8% worldwide, increasing to 80% in mechanically ventilated patients.(Ely et al., 2004; Krewulak et al., 2018; la Cour et al., 2022)

With the goal of decreasing the incidence of delirium and reducing the disease burden in various patient populations, several guidelines for the prevention and treatment of delirium have been developed.(Davis et al., 2019; Devlin et al., 2018; Potter and George, 2006) To date, most systematic reviews and meta-analyses on the treatment and prevention of delirium have analyzed management options in isolation.(Joshi and Tampi, 2022; Tian et al., 2022) Network meta-analyses have compared different treatment options for delirium, but the heterogeneity of included evidence, the indirect nature of such analyses, and the restrictions to specific clinical settings due to heterogeneity and transitivity concerns limit the clinical impact of such results.(Wu et al., 2019; Yang et al., 2020)

Umbrella reviews pool evidence from systematic reviews. Currently, there are no umbrella reviews comprehensively synthesizing and analyzing the meta-analyses for all preventative and therapeutic interventions for delirium, reporting their effect sizes, measuring the quality of evidence, without any restrictions on patient population, intervention, and clinical settings. We aimed to conduct the first umbrella review of meta-analyses of interventions for prevention and treatment of delirium according to the different settings in which delirium is present and according to age. The objectives of this umbrella review were to comprehensively review the available evidence regarding the interventions for reducing delirium incidence and severity, accounting for the quality and certainty of evidence, informing future guidelines.

2. Methods

2.1. Protocol and reporting guidance

This umbrella review followed a pre-registered protocol (https://osf.io/5ku93/). Protocol amendments are listed in the supplementary material. We followed the guidance of the Preferred Reporting Items for Overviews of Reviews (PRIOR) statement.(Gates et al., 2022)

2.2. Search and study selection process

We searched Cumulative Index to Nursing and Allied Health Literature, Embase, Medline, PsycINFO and Scopus up to March 15thth, 2023. A manual search was conducted, including screening the references of all eligible systematic reviews, and searching the Cochrane Database of Systematic Reviews (Ovid CDSR) and the COSMIN Database of Systematic Reviews. The full search key is available in the supplementary material. Screening at the title/abstract and full text level was conducted by several independent authors, with a third member resolving any conflicts. Covidence software (https://www.covidence.org/) was used to manage the study selection process.

2.3. Eligibility criteria

Inclusion criteria were i) systematic reviews with meta-analyses, of ii) randomized controlled trials (RCTs), iii) investigating the effect of pharmacological and non-pharmacological interventions versus placebo or standard/usual care, iv) for preventing delirium or decreasing delirium severity, defined according to validated scales, or as per clinical records. Excluded were individual studies, narrative reviews, systematic reviews without meta-analyses, and meta-analyses using active groups, such as a control group taking benzodiazepines (wrong comparators). In case of mixed controls (i.e., active and placebo), the data were extracted at single study level and then the meta-analyses we run ex novo.

2.4. Data extraction

The following data were extracted by two independent authors (LS, FB): first author, year of publication, digital object identifier, country, sample size, mean age, sex, setting (e.g., medical unit, intensive care unit, surgery unit), diagnostic criteria for delirium diagnosis or severity measure, sample size, number of RCTs for a prespecified outcome (k), the effect size and dispersion measures, heterogeneity, publication bias, and GRADE assessment.(Guyatt et al., 2011) Any inconsistency was resolved by consensus or with a third author (NV).

2.5. Quality assessment of included meta-analyses

The quality of included meta-analyses was assessed by two independent authors (LS, FB) and checked by one senior author (MS) with A MeaSurement Tool to Assess systematic Reviews (AMSTAR)-PLUS. AMSTAR-PLUS uses 11 items of AMSTAR, plus six additional content items measuring the quality of the individual RCTs included in a systematic review.(Shea et al., 2007)

2.6. Data analysis and grading of evidence

We re-ran meta-analyses if meta-analyses mixed RCTs with other study designs. We assessed certainty of evidence applying the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework. (Guyatt et al., 2011) Details on the GRADE are available in

the eMethods.

3. Results

3.1. Search results

After deduplication, we screened 1959 articles, assessing 281 articles at the full text level, ultimately including 59 systematic reviews with meta-analysis. The study selection flow and the reasons for exclusion of the 222 studies are summarized in Fig. 1. The references of excluded studies after full text assessment are available in Supplementary Table 1.

3.2. Characteristics of included studies

The eligible 59 meta-analyses (references reported in Supplementary Material) included a total of 485 unique RCTs and 172,045 participants.

As shown in the Table 1, most of the meta-analyses included were of high quality according to the AMSTAR-PLUS evaluation (k=31), whilst 17 meta-analyses were considered of moderate quality and 11 of low quality.

The geographic distribution of individual RCTs is reported in Fig. 2. RCTs were mainly conducted in China (k=120) followed by the USA (k=86),India (k=29) and South Korea (k=22). The other countries included less than 20 RCTs each.

Overall, across 110 meta-analytic estimates, regarding the setting, 68 outcomes were analyzed in surgical settings, 23 in intensive care unit (ICU), 12 in mixed settings and 7 in medical wards. Virtually all results regarded prevention of delirium, with only five of the 68 outcomes in surgery settings considering severity of delirium as an outcome. Regarding age groups, adults were the most studied (k=46) followed by mixed age groups (k=21).

Supplementary Table 2 shows the meta-analyses with interventions

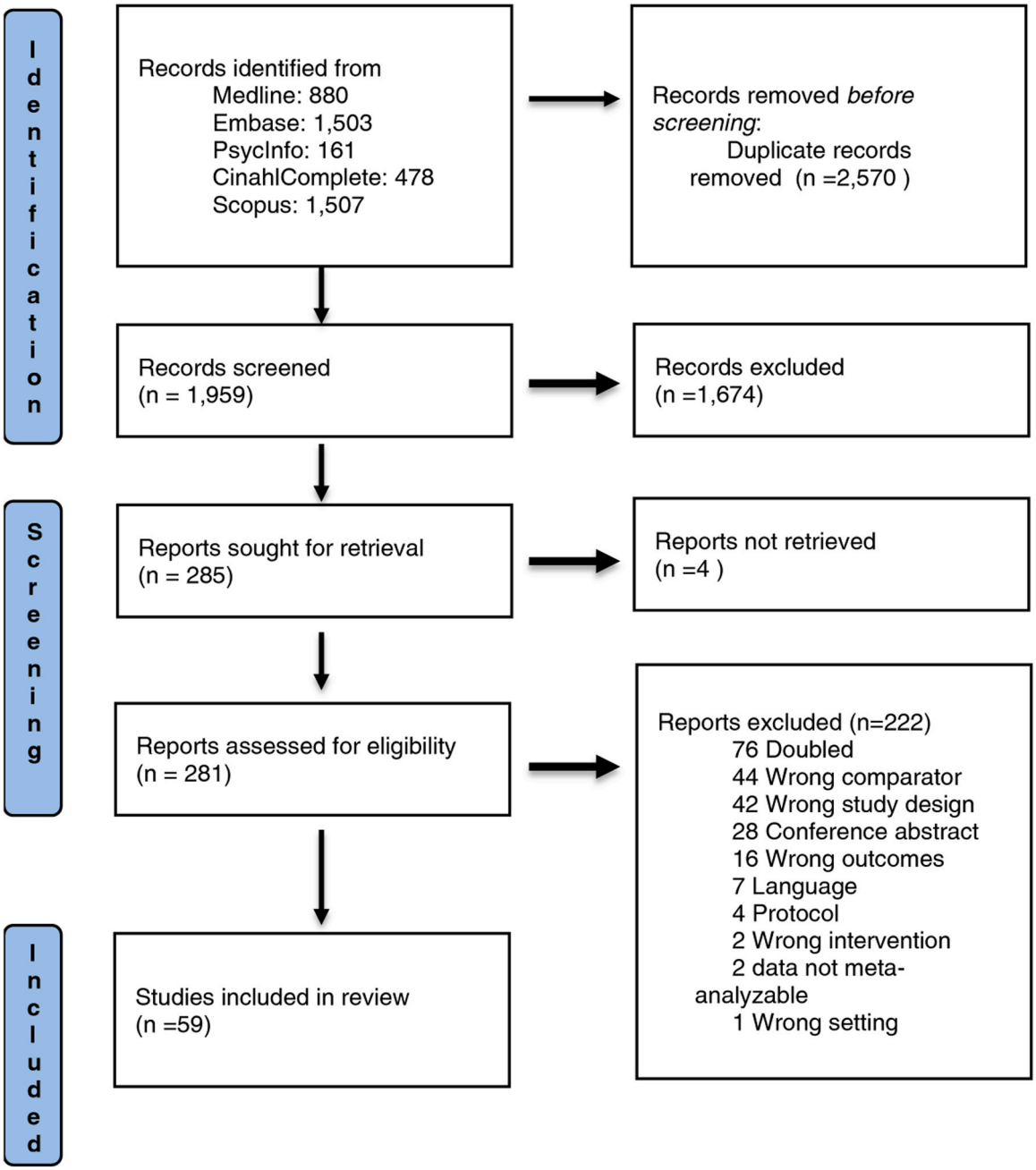

Fig. 1. Study selection flow-chart.

Table 1
Population, intervention, control, outcome, and quality in included meta-analyses of randomized controlled trials to prevent and treat delirium.

Author, year	Prevention or treatment/ severity of delirium	Age Population	Setting	Condition/ population	Type of intervention	Comparison group	Outcome	AMSTAR
Abraha, 2015	Prevention	Mixed	Surgery	Mixed	Multicomponent therapy	Standard care	Delirium	H
Bannon, 2019	Prevention	Mixed	ICU	Mixed	Bright light therapy	Standard care	Delirium	H
Bi, 2021	Prevention	Elderly	Surgery	Mixed	Dexmedetomidine	Placebo	Delirium	L
Bocskai, 2020	Prevention	Elderly	Surgery	Mixed	Bispectral index monitoring	Placebo	Delirium	H
Burton, 2021	Prevention	Mixed	Medical	Mixed	Non pharmacological multicomponent interventions	Standard care	Severity of delirium	H
	Prevention	Mixed	Medical	Mixed	Non pharmacological multicomponent interventions	Standard care	Delirium	H
Chen, 2020	Prevention	Adult	ICU	Mixed	Haloperidol	Placebo	Delirium	H
Ding, 2020	Prevention	Mixed	Surgery	Cardiac surgery	EEG guided anesthesia	Standard care	Delirium	M
	Prevention	Mixed	Surgery	Cardiac surgery	Regional cerebral oxygen saturation monitoring	Standard care	Delirium	M
Eamer, 2018	Prevention	Elderly	Surgery	Mixed	Comprehensive geriatric assessment	Standard care	Delirium	H
Fan, 2017	Prevention	Mixed	Surgery	Mixed	Dexmedetomidine	Placebo	Delirium	M
Fox, 2012	Prevention	Elderly	Medical	Mixed	Acute geriatric unit care, based on all or part of the Acute Care for Elders model	Standard care	Delirium	L
Fuke 2018	Prevention	Mixed	ICU	Intensive care	Early rehabilitation	Standard care	Delirium	H
Hirota, 2013	Prevention	Mixed	Surgery	Mixed	Risperidone	Placebo	Delirium	L
	Prevention	Mixed	Surgery	Mixed	Haloperidol	Placebo	Delirium	L
	Prevention	Mixed	Surgery	Mixed	Second generation antipsychotic	Placebo	Delirium	L
	Prevention	Mixed	Surgery	Mixed	First generation antipsychotic	Placebo	Delirium	L
	Treatment	Mixed	Surgery	Mixed	Antipsychotic (all)	Placebo	Delirium	L
Hovaguimian 2018	Prevention	Mixed	Surgery	Mixed	Ketamine	Placebo or no intervention	Delirium	H
Hshieh, 2018	Prevention	Elderly	Mixed	Mixed	Hospital Elder Life Program	Standard care	Delirium	L
Hshieh, 2015	Prevention	Adult	Medical	Mixed	Multicomponent nonpharmacological delirium interventions	Standard care	Delirium	L
Hu, 2015	Prevention	Mixed	ICU	Intensive care	Multi-component non-pharmacologic delirium prevention interventions	Standard care	Delirium	H
Janssen, 2019	Prevention	Elderly	Surgery	Mixed	Haloperidol	Placebo or standard care	Delirium	H
	Prevention	Elderly	Surgery	Mixed	Antipsychotics (all)	Placebo or standard care	Delirium	H
	Prevention	Elderly	Surgery	Mixed	Sleep-wake cycle	Placebo or standard care	Delirium	H
	Prevention	Elderly	Surgery	Mixed	Dexmedetomidine	Placebo	Delirium	H
	Prevention	Elderly	Surgery	Mixed	Post-operative pain management	Standard care	Delirium	H
	Prevention	Elderly	Surgery	Mixed	Multicomponent interventions	Standard care	Delirium	H
Jiang 2021	Prevention	Mixed	Surgery	Mixed	Intensive glucose control	Standard care	Delirium	M
Khan, 2019	Prevention	Mixed	Mixed	Mixed	Delirium Preventive Models of Care (mixed non-pharmacological and sleep disruption)	Standard care	Delirium	L
	Prevention	Mixed	Mixed	Mixed	Delirium Preventive Models of Care (mixed non-pharmacological interventions and analgesia)	Standard care	Delirium	L
Koo, 2021[75]	Prevention	Children	Surgery	Mixed	Intraoperative magnesium sulfate	Standard care	Delirium	L
Leon-Salas, 2020	Prevention	Elderly	Mixed	Mixed	Hypnotics/sedatives	Placebo	Delirium	M
	Prevention	Elderly	Mixed	Mixed	Pharmacological intervention (anti-epileptics, anti-inflammatories, antipsychotics, cholinesterase inhibitors, opioids, psychostimulants/nootropics, yokukansan)	Placebo	Delirium	M
	Prevention	Elderly	Mixed	Mixed	Multicomponent interventions (mainly non pharmacological but also pain control, hydration, electrolytes control)	Placebo	Delirium	M
Leon-Salas, 2020	Prevention	Elderly	Mixed	Mixed	Multicomponent interventions	Standard care	Delirium	M
Li, 2019	Prevention	Adult	Surgery	Mixed	Dexamethasone	Placebo or no intervention	Delirium	H
Litton, 2016	Prevention	Adult	ICU	Intensive care	Earplugs or noise-canceling headphones for sleep	Standard care	Delirium	L
Liu, 2021	Prevention	Adult	Surgery	Cardiac surgery	Dexamethasone	Placebo	Delirium	H
	Prevention	Adult	Surgery	Cardiac surgery	Glucocorticoids	Placebo or not mentioned	Delirium	H
Lu, 2019	Prevention	Adult	Surgery	Mixed	Melatonin	Placebo	Delirium	H
	Prevention	Adult	Surgery	Mixed	Timed bright light	Standard care	Delirium	H
	Prevention	Adult	Surgery	Mixed	Dexmedetomidine	Placebo	Delirium	H

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Table 1 (*continued*)

Author, year	Prevention or treatment/ severity of delirium	Age Population	Setting	Condition/ population	Type of intervention	Comparison group	Outcome	AMSTAR
Ludolph, 2020	Prevention	Adult	Surgery	Mixed	Non-pharmacologic multicomponent interventions (cognitive stimulation, daily orientation, early mobilization, vision and hearing protocols, fluid repletion, feeding assistance, sleep improvement, family involvement)	Standard care	Delirium	M
	Prevention	Adult	ICU	Mixed	Non-pharmacologic multicomponent interventions (cognitive stimulation, daily orientation, early mobilization, vision and hearing protocols, fluid repletion, feeding assistance, sleep improvement, family involvement)	Standard care	Delirium	M
	Prevention	Adult	Medical	Mixed	Non-pharmacologic multicomponent interventions (cognitive stimulation, daily orientation, early mobilization, vision and hearing protocols, fluid repletion, feeding assistance, sleep improvement, family involvement)	Standard care	Delirium	M
	Prevention	Adult	Mixed	Mixed	Non-pharmacologic multicomponent interventions (cognitive stimulation, daily orientation, early mobilization, vision and hearing protocols, fluid repletion, feeding assistance, sleep improvement, family involvement)	Standard care	Delirium	M
Marra, 2021	Prevention	Adult	ICU	Intensive care	Haloperidol	Placebo	Delirium	L
Moyce, 2014	Treatment	Adult	Surgery	Non cardiac-surgery	Donepezil	Placebo	Post-Operative Delirium	H
	Treatment	Adult	Surgery	Non cardiac-surgery	Gabapentin	Placebo	Post-Operative Delirium	H
	Treatment	Adult	Surgery	Non cardiac-surgery	Haloperidol	Placebo	Post-Operative Delirium	H
	Treatment	Adult	Surgery	Non cardiac-surgery	Bright light therapy	Standard care	Post-Operative Delirium	H
	Treatment	Adult	Surgery	Non cardiac-surgery	Comprehensive geriatric assessment	Standard care	Post-Operative Delirium	H
Mu, 2015	Treatment	Adult	ICU	Cardiac surgery	Dexamethasone	Placebo	Delirium	H
	Treatment	Adult	ICU	Cardiac surgery	Ketamine	Placebo	Delirium	H
	Treatment	Adult	ICU	Cardiac surgery	Risperidone	Placebo	Delirium	H
	Treatment	Adult	ICU	Cardiac surgery	Rivastigmine	Placebo	Delirium	H
Neufeld, 2016	Treatment	Adult	Surgery	Mixed	Antipsychotics (all)	Placebo	Severity of delirium	H
	Prevention	Adult	Surgery	Mixed	Antipsychotics (all)	Placebo	Delirium	H
Ng, 2019	Prevention	Children	Mixed	Surgery	Ketamine	Placebo	Delirium	H
Ng, 2020	Prevention	Adult	Medical	Mixed	Melatonin	Placebo	Delirium	H
Pan, 2016	Prevention	Children	Surgery	Cardiac surgery	Dexmedetomidine	Placebo	Delirium	H
Pickard, 2014	Prevention	Children	Surgery	Mixed	A2-adrenergic agonists after induction of anesthesia	Placebo	Delirium	M
Yang, 2020	Prevention	Adult	Surgery	Mixed	Dexmedetomidine	Placebo	Delirium	H
Qi, 2021	Prevention	Adult	ICU	Mixed	Nurse-led sedation protocol (Attending physician defined daily dose of sedation and sedative and analgesic doses were adjusted by nurses as per algorithm)	Standard care	Delirium	H
Qin, 2022	Prevention	Adult	ICU	Mixed	Family intervention	Standard care	Delirium	L
Rao, 2020	Prevention	Children	ICU	Mixed	Dexmedetomidine	Placebo	Delirium	H
Sedhai, 2021	Prevention	Adult	ICU	Mixed	Thiamine	Placebo or standard care	Delirium	M
Shen, 2018	Prevention	Adult	Surgery	Mixed	Haloperidol	Placebo	Delirium	L
Siddiqi, 2016	Prevention	Adult	Surgery	Non-ICU patients	Antipsychotics	Placebo	Delirium	H
	Treatment	Adult	Surgery	Non-ICU patients	Antipsychotics	Placebo	Severity of delirium	
Sun, 2020	Prevention	Adult	ICU	Mixed	EEG based-monitor	Standard care	Delirium	H

(*continued on next page*)

Table 1 (*continued*)

Author, year	Prevention or treatment/ severity of delirium	Age Population	Setting	Condition/ population	Type of intervention	Comparison group	Outcome	AMSTAR
Tan, 2019	Prevention	Children	Surgery	Ophthalmic Surgery	Dexmedetomidine	Placebo	Delirium	H
	Prevention	Children	Surgery	Ophthalmic Surgery	Ketamine	Placebo	Delirium	H
	Prevention	Children	Surgery	Ophthalmic Surgery	Midazolam	Placebo	Delirium	H
	Prevention	Children	Surgery	Ophthalmic Surgery	Remifentanil	Placebo	Delirium	H
	Prevention	Children	Surgery	Ophthalmic Surgery	Clonidine	Placebo	Delirium	H
Thillainadesan, 2020	Prevention	Elderly	Surgery	Non-orthopedic Surgery	Multicomponent inpatient geriatric program	Standard care	Delirium	H
	Prevention	Elderly	Surgery	Non-orthopedic Surgery	Pre-operative comprehensive geriatric assessment	Standard care	Delirium	H
Thillainadesan, 2021	Prevention	Elderly	Surgery	Colorectal surgery	Enhanced recovery after surgery (ERAS)	Standard care	Delirium	M
Van Heghe, 2022	Prevention	Adult	Surgery	Hip fracture	Geriatric medicine consultant service	Standard care	Delirium	M
	Prevention	Adult	Surgery	Hip fracture	Geriatric medical ward with orthopedic surgeon consultant service	Standard care	Delirium	M
	Prevention	Adult	Surgery	Hip fracture	Integrated care model	Standard care	Delirium	M
Wang, 2022	Prevention	Elderly	Surgery	Mixed	Melatonergic agonist	Placebo	Delirium	M
Wang, 2019	Prevention	Mixed	ICU	Mechanically ventilated	Alpha agonist	Placebo	Delirium	H
Wang, 2020	Prevention	Adult	ICU	Critically ill	Early mobilization	Standard care	Delirium	H
Wang, 2016	Treatment	Children	Surgery	Surgery	Fentanyl	Placebo	Severity of delirium	M
	Treatment	Children	Surgery	Surgery	Propofol	Placebo	Severity of delirium	M
Wang, 2017	Prevention	Elderly	Surgery	Mixed	Comprehensive geriatric care	Standard care	Delirium	H
Xiong 2021	Prevention	Adult	Surgery	Cardiac surgery	Dexmedetomidine	Placebo	Delirium	H
Xu, 2022	Prevention	Adult	ICU	Critically ill	Cognitive exercise	Standard care	Delirium	M
Yuntai, 2020	Prevention	Adult	Surgery	Mixed	Penehyclidine hydrochloride	Placebo	Delirium	M
Zayed, 2019	Prevention	Adult	ICU	Surgery	Haloperidol	Placebo	Delirium	H
Zhang, 2013	Prevention	Adult	Surgery	Mixed	Antipsychotic	Placebo	Delirium	M
	Prevention	Adult	Surgery	Mixed	Acetylcholinesterase	Placebo	Delirium	M
Zhang, 2019	Prevention	Adult	ICU	Mixed	Exogenous melatonin and melatonin receptor agonists	Placebo	Delirium	M
Zhang, 2021	Prevention	Adult	ICU	Mixed	Bundle interventions	Standard care	Delirium	M

Legend. H, high; ICU, intensive care unit; L, low; M, medium

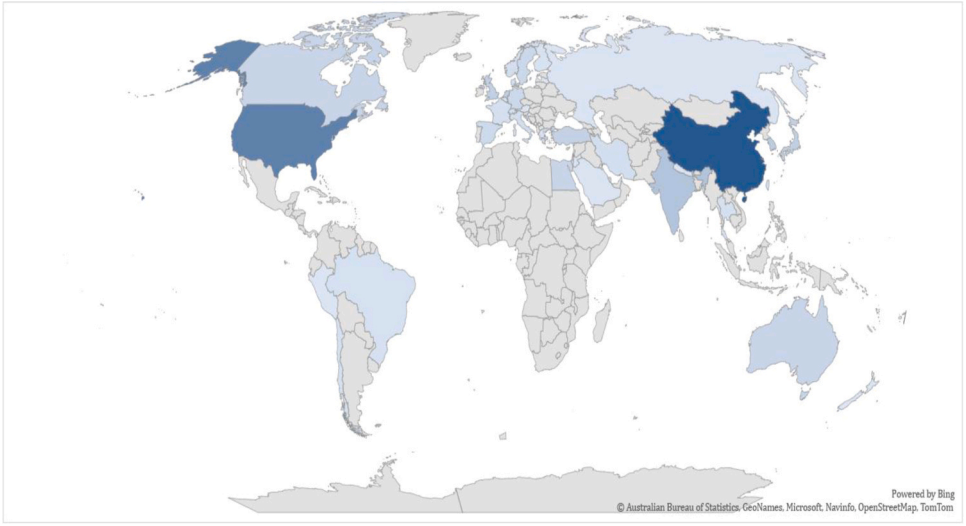

Fig. 2. Geographical distribution of randomized controlled trial to prevent or treat delirium. *Legend. Number of studies in each country ranged from one (several countries) to 120 (China).*

significantly superior to control group in preventing or treating delirium, whilst non-statistically significant results are reported in Supplementary Table 3, both with the GRADE assessment. A summary of findings supported by moderate and high GRADE are visualized in Fig. 3 (ICU and medical unit settings) and Fig. 4 (surgery and mixed settings).

3.3. Findings in surgery setting

Among the 63 outcomes that considered prevention of delirium, 49 included mixed populations undergoing surgery, six studies that underwent orthopedic surgery, five ophthalmic surgery, two cardiac surgery, one colorectal surgery. Most of the outcomes included adults (k=27), followed by older people (k=22). The five analyses on the treatment of delirium included mixed populations, two in children, three in mixed age groups.

Overall, 38 of the 63 meta-analytic associations yield statistically significant results, i.e., the active intervention outperformed the control group, with six results meeting criteria for high certainty of evidence according to GRADE (Fig. 3). The other interventions had in 22/63 a moderate strength of evidence, 12 low and 24 very low.

For the prevention of delirium, five were rated as high certainty of evidence, all in surgical settings. Specifically, among pharmacological interventions, dexmedetomidine, mainly as loading dose at induction of anesthesia followed by a continuous infusion during surgery, outperformed placebo in older adults (RR=0.53; 95%CI: 0.46–0.67, k=13, N=3988), and in adults (RR=0.33, 95%CI=0.24–0.45, k=7, N=1974) in preventing delirium. In children, α2-adrenergic agonists after induction of anesthesia outperformed placebo (OR= 0.28, 95%CI= 0.19–0.40, k=10, N=669). In older people, high certainty supported the lack of efficacy of melatonergic agents in prevention delirium. Finally, among the non-pharmacological interventions, the comprehensive geriatric assessment was superior to standard care and supported by a high certainty of evidence according to the GRADE (OR=0.46; 95% CI=0.32–0.67, k=3, N=496). The other 34 meta-analyses with interventions significantly outperforming the control group were rated as moderate (k=21, 20 for prevention of delirium, only one for treatment of delirium), low (k=10, all prevention of delirium), or very low (k=3, one for prevention of delirium, only two for treatment of delirium) according to GRADE.

Interventions meeting criteria for GRADE moderate certainty and outperforming the control indication were, across age groups, as follows: in adults, dexmedetomidine in orthopedic (k=1) and mixed conditions (k=1), risperidone (k=1), second-generation antipsychotics (k=1), EEG-guided anesthesia in mixed (k=1) and non-cardiac (k=1) surgery, non-pharmacological multi-component interventions (k=1) in mixed clinical populations; in older patients, mixed pharmacological interventions (k=1), mixed non-pharmacological interventions (k=1), pre-operative geriatric assessment (k=1) for mixed conditions, early mobilization, pain management, nutrition, and hydration protocol for colorectal surgery (k=1); in children, dexmedetomidine (k=1) in cardiac surgery, dexmedetomidine (k=1), clonidine (k=1), remifentanil (k=1), ketamine (k=1), midazolam (k=1) in ophthalmic surgery, intraoperative magnesium sulfate (k=1) in mixed conditions in children, and antipsychotics (=1) in mixed age groups.

3.4. Findings in intensive care unit setting

Considering the 23 outcomes in ICU, all focused on the prevention of delirium, for the majority in adults (k=15) (Fig. 4).

Overall, in 12 meta-analyses a statistically significant difference emerged for the active intervention compared with controls, with no results meeting criteria for high certainty according to GRADE, eighth for moderate certainty, five for low certainty, and ten for very low certainty.

Among pharmacological interventions, six reached moderate certainty according to GRADE, all indicating superiority of the

Intervention/Age groups	Setting	Population	k	N	GRADE	eOR (95% CI)
Children						
A2-adrenergic agonists after induction of anaesthesia	Surgery	Mixed	10	669	H	0.28 (0.19, 0.40)
Ketamine(0,25 mg kg−1 to 0,5)	Surgery	Mixed	13	1125	M	0.02 (0.01, 0.05)
Dexmedetomidine (dosage range**)	Surgery	Ortho	3	306	M	0.26 (0.08, 0.84)
Dexmedetomidine (dosage NR)	Surgery	Ophta	7	517	M	0.26 (0.17, 0.39)
Clonidine (dosage NR)	Surgery	Ophta	2	170	M	0.29 (0.13, 0.66)
Remifentanil (dosage NR)	Surgery	Ophta	2	182	M	0.35 (0.17, 0.73)
Midazolam (dosage NR)	Surgery	Ophta	2	150	M	0.40 (0.21, 0.75)
Ketamine (dosage NR)	Surgery	Ophta	2	82	M	0.41 (0.20, 0.86)
Adult						
Dexmedetomidine (dosage range*)	Surgery	Mixed	7	1974	H	0.33 (0.24, 0.45)
2nd generation antipsychotics	Surgery	Mixed	3	627	M	0.36 (0.26, 0.50)
Risperidone (1 mg/die)	Surgery	Mixed	2	227	M	0.38 (0.22, 0.66)
Dexmedetomidine (infusion rate 0,1-0,7 ug/kg/hour)	Surgery	Mixed	6	1320	M	0.43 (0.31, 0.59)
Non-Pharmacologic Multicomponent Interventions	Surgery	Mixed	14	3693	M	0.57 (0.46, 0.71)
EEG guided anesthesia	Surgery	Non-cardio surg	8	3600	M	0.73 (0.57, 0.95)
EEG guided anesthesia	Surgery	Mixed	10	4451	M	0.75 (0.60, 0.93)
Penehyclidine hydrochloride	Surgery	Mixed	3	272	M	1.53 (0.81, 2.90)
Elderly						
Comprehensive geriatric assessment	Surgery	Mixed	3	496	H	0.46 (0.32, 0.67)
Dexmedetomidine (dosage NR)	Surgery	Mixed	13	3988	H	0.53 (0.46, 0.67)
Melatonergic agonist	Surgery	Mixed	9	1452	H	0.93 (0.70, 1.24)
Early mobilization, pain management, nutrition, and hydration	Surgery	Colorectal	3	690	M	0.45 (0.21, 0.98)
Pre-operative comprehensive geriatric assessment	Surgery	Mixed	2	469	M	0.54 (0.33, 0.89)
Pharmacological intervention ($)	Surgery	Mixed	18	4381	M	0.70 (0.55, 0.88)
Non pharmacological interventions (#)	Surgery	Mixed	3	496	M	0.71 (0.60, 0.84)
NS						
Antipsychotics (all)	Surgery	Mixed	6	1592	M	0.37 (0.20, 0.65)

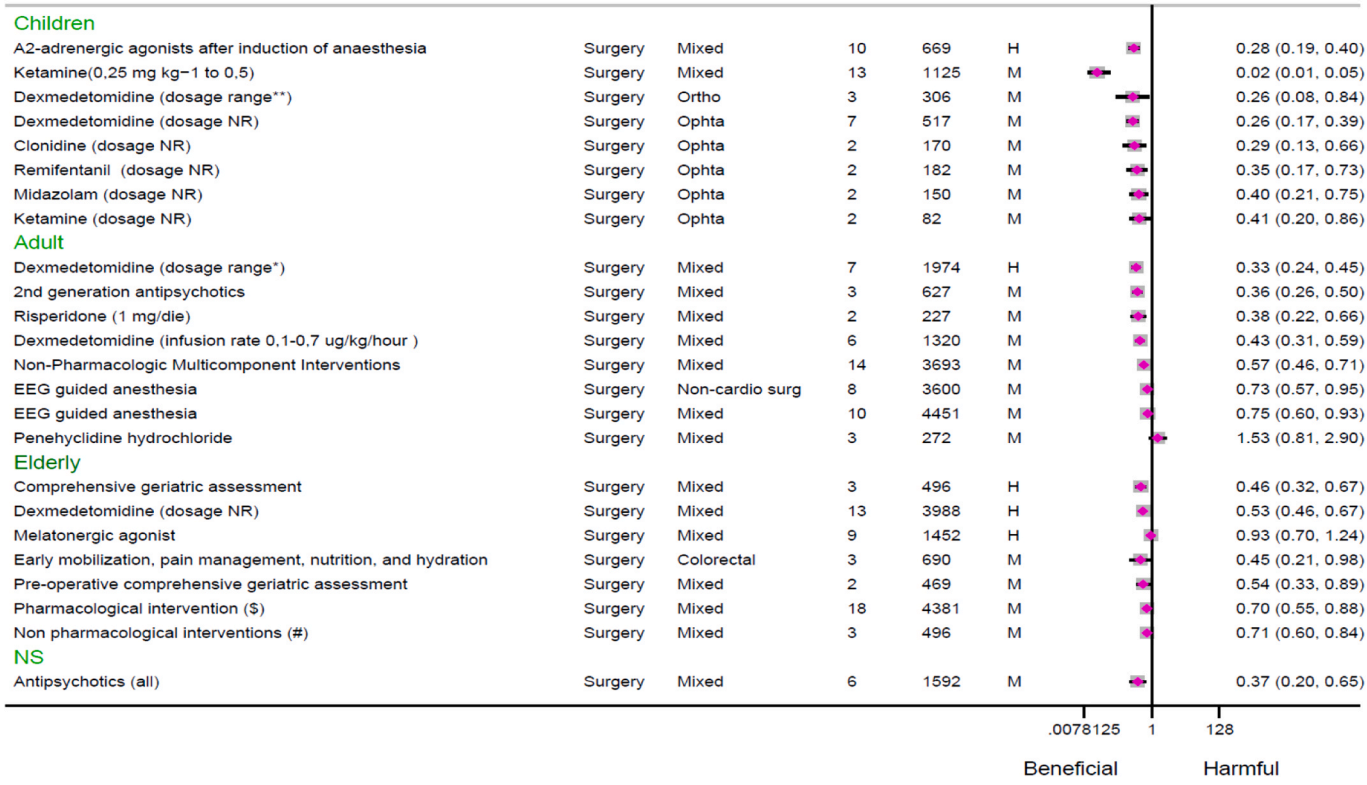

Fig. 3. Summary of findings in surgery for the prevention of delirium. *Legend. K=number of studies; N=sample size; OR= odds ratio; CI= confidence intervals; NS= not specified; M=moderate; H=high.*

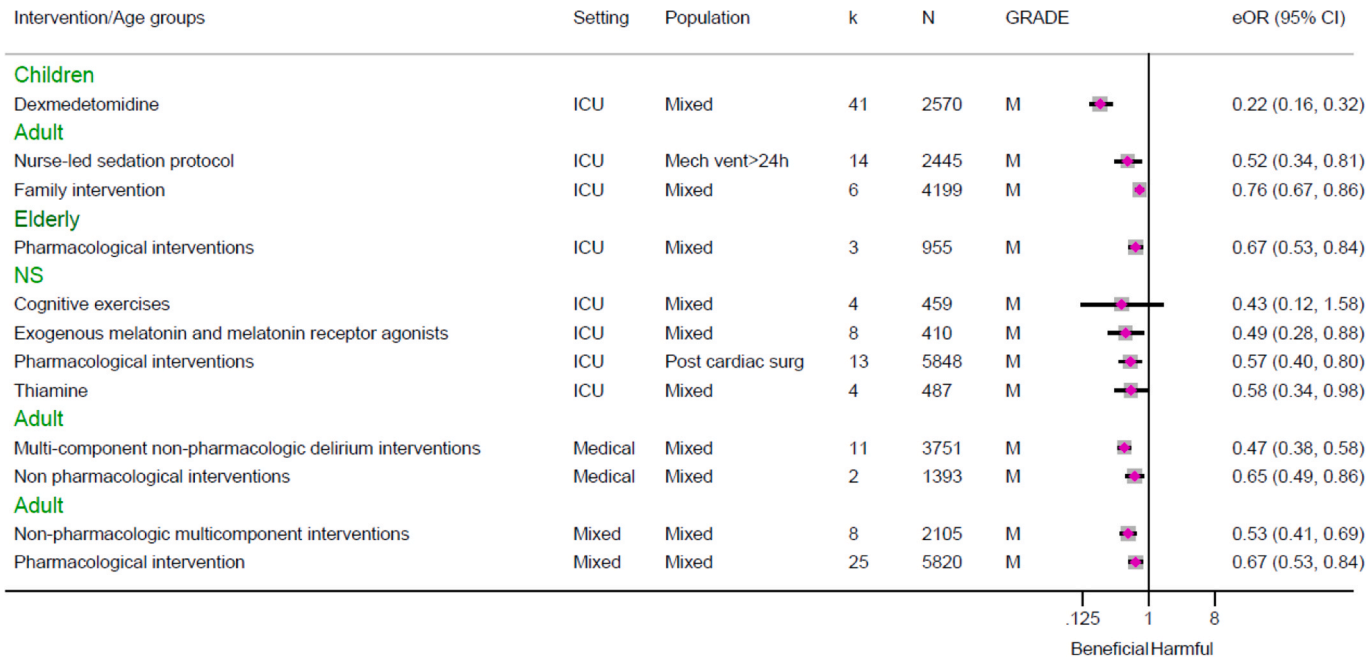

Fig. 4. Summary of findings in Intensive care unit, medical unit and mixed settings for the prevention of delirium. *Legend. K=number of studies; N=sample size; OR= odds ratio; CI= confidence intervals; NS= not specified; M=moderate; H=high.*

interventions over the control group. There were two meta-analyses on mixed pharmacological interventions in persons who underwent mixed or cardiac surgery, nurse-led sedation protocol in those receiving mechanical ventilation for over 24 hours, dexmedetomidine, thiamine and melatonergic agents all in persons with mixed clinical conditions. Among non-pharmacological interventions, family intervention and cognitive exercise also decreased the risk of delirium onset.

3.5. Findings in medical wards setting

The seven outcomes in medical wards included mixed populations in terms of medical conditions, whilst, considering age, for included adults, eighth focused in older people.

Overall, two results met GRADE criteria for moderate certainty, two for low, and three for very low certainty (Fig. 4).

Interventions reaching GRADE moderate certainty were both mixed non-pharmacological interventions.

3.6. Findings in mixed settings

The 12 outcomes in mixed settings all included mixed populations in terms of medical conditions, whilst, considering age, three included adults, two mixed populations, and only one older people. Overall, two results met GRADE criteria for moderate certainty, two for low, and eighth for very low certainty (Fig. 4). Interventions reaching GRADE moderate certainty were mixed pharmacological interventions and mixed non-pharmacological interventions.

4. Discussion

4.1. Principal findings

In this umbrella review, we included 59 meta-analyses and 485 RCTs across the globe, that tested different interventions across populations, settings, and age groups for the prevention and treatment of delirium. Overall, the available interventions for preventing and treating delirium in daily clinical practice are numerous, but only a few are supported by a high or moderate level of certainty, overall indicating a high risk of bias affecting certainty around the effects of most available interventions.

Regarding the pharmacological interventions for the prevention of delirium, dexmedetomidine, a selective A-2 agonist, seems to be the most promising approach able to prevent and treat delirium.(Burry et al., 2021) Due to its A-adrenergic activity, dexmedetomidine reduces the activity of the sympathetic nervous system (which is responsible for the 'fight or flight' response) with various beneficial effects, including a decrease in the release of excitatory neurotransmitters in the brain, such as noradrenaline. As a result, patient activation and stress levels are reduced, contributing to delirium prevention. Furthermore, dexmedetomidine induces sedation while preserving some arousability, and its use has resulted in a shorter time to extubation in ICU (Constantin et al., 2016), an increased number of days free from coma or delirium (Pandharipande et al., 2007), a reduced incidence of hyperactive delirium (Reade et al., 2016), and lower mortality than other agents administered in certain populations.(Shehabi et al., 2019) Notably, the use of dexmedetomidine is generally considered as an alternative to benzodiazepines(Shehabi et al., 2019), which have a deliriogenic effect, especially in older adults. One possible explanation of the consistent efficacy of dexmedetomidine across underlying conditions, settings and age groups might be that in delirium an excessive noradrenergic drive can be treated using noradrenaline release-limiting α2- adrenergic receptor agonists (such as dexmedetomidine), similarly to that observed in alcohol withdrawal.(Wilson et al., 2020) Benzodiazepines appear to be effective in preventing delirium, but limited to specific populations (e.g., children in ophthalmology). Indeed, in other populations, these drugs have shown to be potentially harmful and probably should be not prescribed.(Burry et al., 2021) Finally, among pharmacological interventions, second-generation antipsychotics, such as risperidone, were found effective in preventing and treating delirium among adults recruited from surgical settings and non-specified age groups, although with a strength of evidence from moderate to low in terms of efficacy. Our findings are partly in agreement with common guidelines (Davis et al., 2019; Devlin et al., 2018; Potter and George, 2006), which advice against the use of antipsychotics, primarily due to safety concerns. (Papola et al., 2019)

Among non-pharmacological interventions for preventing delirium, there is increasing evidence that light sedation compared with deep

sedation can decrease the incidence of post-operative delirium.(Shehabi et al., 2018; Sieber et al., 2018) In this perspective, EEG-guided anesthesia can allow for the use of lighter sedation compared to deeper sedation. EEG-guided anesthesia is a technique that monitors the brain's electrical activity (via EEG) to assess the level of consciousness and anesthesia depth during surgical procedures or medical interventions (Hughes et al., 2020). In older patients, Comprehensive Geriatric Assessment (CGA) and non-pharmacological multicomponent interventions (such as, early mobilization, pain management, nutrition, and hydration) demonstrated their efficacy in preventing delirium. To support these considerations, Inouye et al. demonstrated in a seminal paper that a multicomponent approach, consisting of standardized protocols for the management of six risk factors for delirium (cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration) was effective in reducing by nearly 40% the incidence of delirium in older hospitalized patients.(Inouye et al., 1999) The results of our review strongly support the use of such an approach for delirium prevention in adults and older adults.(Hshieh et al., 2018) The use of non-pharmacological approaches for the prevention of delirium seems to be confirmed in the ICU and medical units.

Considering the safety and ethics involved in preventative medicine, in surgery and other settings, non-pharmacological interventions might be preferred as first-line treatment. For example, comprehensive geriatric assessment could be useful for the prevention of delirium since this intervention integrates an approach focused on some important risk factors for delirium such as malnutrition, polypharmacy, bedridden syndrome, and pain trying to correct them, mainly using non-pharmacological interventions.(Veronese et al., 2022) Considering ICU, it seems that some non-pharmacological treatments (cognitive exercises and family interventions) are supported by a moderate strength of evidence, whilst no interventions reached a high certainty of level. Among pharmacological interventions, the most supported by a moderate strength of evidence were dexmedetomidine, exogenous melatonin and melatonin receptor agonists, thiamine and nurse-led sedation protocols. Similarly in medical wards, the use of multidisciplinary non-pharmacological treatments is better than standard care in decreasing delirium incidence, whilst no pharmacological or non-pharmacological approaches are available for delirium severity.

From a clinical perspective, our findings overall suggest that non-pharmacological approaches could be the first line in the prevention of delirium. In particular, as discussed before, some of them such as CGA, family involvement and cognitive training are highly effective in decreasing delirium incidence as well as some medications (such as dexmedetomidine and alpha2-adrenergic agents) could be used in some settings such as ICU. These findings overall indicate that delirium is a complex phenomenon characterized by clinical characteristics such as severity and duration and not only incidence. Recently, Andersen-Ranberg et al. in an RCT including 1000 patients affected by delirium in ICU showed that haloperidol could have an efficacy on delirium compared to placebo, but no effect on survival and number of days alive was observed. (Andersen-Ranberg et al., 2022) Altogether, these findings suggest that antipsychotics may lead to a decrease in delirium onset, considered as yes/no event, but that should be used carefully since no beneficial final effect is really observed by their use.

Finally, in our umbrella review, we identified only a minority of outcomes (n=11) addressing treatment strategies. All of these interventions were often not efficacious in reducing delirium severity and supported by a limited body of literature.

4.2. Strengths and limitations

Our umbrella review gives an overview of the current treatments' options for delirium, including a large number of RCTs and patients. However, the findings of this work must be interpreted within its limitations. First, even if not anticipated, only hospitalized people were included, whilst it is known that other settings, such as nursing homes, have a high prevalence of delirium.(Morichi et al., 2018) Second, we included only pairwise comparisons: therefore not giving a hierarchy of the options for delirium, as head-to-head comparisons are typically explored in network meta-analyses. However, the transitivity assumption would likely not be met in network meta-analyses combining trials from different populations, settings, and/or age groups. Third, we were not able to divide the psychomotor subtypes of delirium, namely hyperactive, hypoactive, or mixed since largely not available in the meta-analyses included in our work. Fourth, most of the evidence comes from surgical settings, yet it is in ICU and medical settings that delirium prevalence is the highest. More trials are thus warranted in these settings. Challenges to develop RCTs to prevent or treat delirium in medical settings can be the heterogeneity of the population. Focusing on populations with increased risk of delirium could provide a risk-enriched and homogeneous populations. Finally, we cannot exclude that the same RCT was included in one or more analyses: however, since we stratified our analyses for setting and population, we believe that this bias is unlikely.

5. Conclusions

Our umbrella review of systematic reviews and meta-analyses of randomized controlled trials regarding how to prevent and treat delirium indicate that a few options are supported by a high certainty of evidence and therefore should be considered from future guidelines for the prevention and treatment of delirium. Safety and health economic considerations should be accounted for in evidence-based guidelines, also involving stakeholders including patients, family members, and caregivers.

Authors' contribution

Marco Solmi and Nicola Veronese designed the protocol. All authors screened the literature, revised, contributed, and approved to the protocol. Marco Solmi, Francesco Bolzetta, Laura Solimando, Arnav Gupta, Nicholas Fabiano, Stanley Wong, Nicola Veronese, screened the literature and extracted the data. Marco Solmi, Nicola Veronese, drafted the first version of the manuscript. All authors revised, contributed, and approved the final version of the manuscript.

Conflict of interest

Marco Solmi received honoraria/has been a consultant for AbbVie, Angelini, Lundbeck, Otsuka. Nicola Veronese reports personal fees from MYLAN, FIDIA, IBSA, VIATRIS, BAYER, MSD, NESTLE'. Other authors declare no conflict of interest.

Declaration of Competing Interest

Marco Solmi received honoraria/has been a consultant for AbbVie, Angelini, Lundbeck, Otsuka. Nicola Veronese reports personal fees from MYLAN, FIDIA, IBSA, VIATRIS, BAYER, MSD, NESTLE'. Other authors declare no conflict of interest.

Data Availability statement

The data underlying this article will be shared on reasonable request to the corresponding author. All authors declare manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained in published protocol.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the

online version at doi:10.1016/j.arr.2024.102313.

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