



Outcome of delirium in critically ill patients: systematic review and meta-analysis

Jorge I F Salluh,¹ Han Wang,² Eric B Schneider,² Neeraja Nagaraja,² Gayane Yenokyan,³ Abdulla Damluji,⁴ Rodrigo B Serafim,^{1,5} Robert D Stevens⁶

¹D'OR Institute for Research and Education, Rio de Janeiro, Brazil

²Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA

³Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

⁴Elaine and Sydney Sussman Cardiac Catheterization Laboratories, Cardiovascular Division, University of Miami Miller School of Medicine, Miami, FL, USA

⁵Department of Internal Medicine, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

⁶Department of Anesthesiology and Critical Care Medicine, Neurology, Neurosurgery, and Radiology, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA

Correspondence to: R D Stevens rstevens@jhmi.edu

Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/bmj.h2538>)

Cite this as: *BMJ* 2015;350:h2538 doi: 10.1136/bmj.h2538

Accepted: 7 April 2015

ABSTRACT OBJECTIVES

To determine the relation between delirium in critically ill patients and their outcomes in the short term (in the intensive care unit and in hospital) and after discharge from hospital.

DESIGN

Systematic review and meta-analysis of published studies.

DATA SOURCES

PubMed, Embase, CINAHL, Cochrane Library, and PsychINFO, with no language restrictions, up to 1 January 2015.

ELIGIBILITY CRITERIA FOR SELECTION STUDIES

Reports were eligible for inclusion if they were prospective observational cohorts or clinical trials of adults in intensive care units who were assessed with a validated delirium screening or rating system, and if the association was measured between delirium and at least one of four clinical endpoints (death during admission, length of stay, duration of mechanical ventilation, and any outcome after hospital discharge). Studies were excluded if they primarily enrolled patients with a neurological disorder or patients admitted to intensive care after cardiac surgery or organ/tissue transplantation, or centered on sedation management or alcohol or substance withdrawal. Data were extracted on characteristics of studies, populations sampled, identification of delirium, and outcomes. Random effects models and meta-regression analyses were used to pool data from individual studies.

RESULTS

Delirium was identified in 5280 of 16 595 (31.8%) critically ill patients reported in 42 studies. When compared with control patients without delirium, patients with delirium had significantly higher mortality during admission (risk ratio 2.19, 94% confidence interval 1.78 to 2.70; $P<0.001$) as well as longer durations of mechanical ventilation and lengths of stay in the intensive care unit and in hospital (standard mean differences 1.79 (95% confidence

interval 0.31 to 3.27; $P<0.001$), 1.38 (0.99 to 1.77; $P<0.001$), and 0.97 (0.61 to 1.33; $P<0.001$), respectively). Available studies indicated an association between delirium and cognitive impairment after discharge.

CONCLUSIONS

Nearly a third of patients admitted to an intensive care unit develop delirium, and these patients are at increased risk of dying during admission, longer stays in hospital, and cognitive impairment after discharge.

Introduction

A high proportion of adults admitted to hospital experience delirium, a pathological alteration in cognition associated with inattention, a fluctuating course, and an underlying systemic illness, metabolic imbalance, or association with a drug (or withdrawal).¹² Delirium has been linked to adverse short term outcomes, including up to threefold increases hospital mortality and length of stay,³⁻⁵ which place considerable burdens on caregivers^{6,7} and healthcare services.^{8,9} Delirium can also have long term consequences, with studies indicating an association between delirium and a higher likelihood of death,¹⁰ functional disability,¹¹ admission to residential care, cognitive impairment,¹² and dementia after discharge.¹³ The risk of delirium is particularly high in selected subsets of hospital patients such as elderly people and those with pre-existing cognitive impairments,¹⁴ people with terminal illnesses,¹⁵ patients undergoing major surgery,¹⁶ and those who are admitted to an intensive care unit.¹⁷

The identification, prevention, and treatment of delirium are increasingly regarded as major public health priorities.¹⁸ Delirium has been described as one of the most common types of organ dysfunction encountered in intensive care, though its prevalence is variable across studies.^{3,19} Delirium can be overlooked, misdiagnosed, and its significance underestimated by healthcare providers working in intensive care.^{20,21} Studies evaluating the relation between delirium and mortality have yielded inconsistent results, some reporting a significant association^{4,22-24} and others not.²⁵⁻²⁷

Knowledge of the true magnitude of delirium and its associated burdens in critically ill patients would allow clinicians, researchers, and policymakers to allocate much needed resources towards reducing morbidity and mortality associated with delirium. We therefore conducted a systematic review of studies evaluating delirium in intensive care. We produced quantitative estimates of the prevalence of delirium in this setting and explored the association between delirium and

WHAT IS ALREADY KNOWN ON THIS TOPIC

Studies evaluating the relations between delirium in critically ill patients and mortality have yielded inconsistent results, some reporting a significant association and others not

WHAT THIS STUDY ADDS

Delirium is strongly associated with increased hospital mortality
Evidence also suggests a relation between delirium in the intensive care unit and long term cognitive impairment

short term clinical outcomes, specifically mortality in the intensive care unit and hospital, length of stay, and duration of mechanical ventilation. We also analyzed data on long term outcomes, including cognitive impairment after admission to intensive care.

Methods

Data sources and study selection

We carried out a systematic review and meta-analysis of prospective observational studies following the recommendations of the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group.²⁸ We searched PubMed (1966-2015), Embase (1974-2015), CINAHL (1982-2015), the Cochrane Library (2015), and PsychINFO (up to 2015). The most recent search was on 1 January 2015. We hand searched reference lists of retrieved articles, relevant review articles, and personal files. There was no language restriction. Search terms included delirium, acute confusional state, encephalopathy, organic brain syndrome, brain dysfunction, brain failure which were cross-referenced to the terms intensive care, intensive care unit, ICU, critical care, critical illness, critically ill, sepsis, acute respiratory distress, multiple organ system failure, and mechanical ventilation (see appendix 1 for details of search strategy). To be considered for inclusion, studies had to meet the following criteria:

- full length reports published in peer reviewed journals
- prospective observational cohorts or clinical trials of adult patients (aged >16) admitted to an intensive care unit
- patients were evaluated for delirium with a **validated screening** or diagnostic instrument: confusion

assessment method (CAM)²⁹, confusion assessment method for the intensive care unit (CAM-ICU)¹⁷, intensive care delirium screening checklist (ICDSC)³⁰, diagnostic and statistical manual of mental disorders 4th and 3th edition (DSM-IV and DSM-III)², and the Neelon and Champagne (NEECHAM) confusion scale³¹

- the relation between delirium and at least one of the following outcomes was reported: death in the intensive care unit or in hospital, length of stay in the intensive care unit or in hospital, duration of mechanical ventilation, or any outcome after hospital discharge.

We excluded articles if they did not have a control group of patients without delirium; if they were case studies or case series; if most enrolled patients (or the largest subgroup) had a primary central nervous system disorder (stroke, traumatic brain injury, central nervous system infections, brain tumors, recent intracranial surgery); if most enrolled patients were undergoing cardiac surgery or organ/tissue transplantation (patient subsets associated with pathophysiologically distinct forms of acute brain dysfunction); if most enrolled patients were experiencing alcohol or substance withdrawal; or if the primary study endpoint was the comparative efficacy or safety of different sedative drugs. RDS, JIFS, and AD screened citations identified by the initial search and selected potentially relevant titles for review of abstracts. From these, RDS, JIFS, and RBS then chose articles for review of full length reports. Figure 1 shows the study selection process.

Data extraction and study quality assessment

Three authors (RBS, JIFS, and AD) independently abstracted data from the selected articles. They recorded the following information (when available): study characteristics (study location, period of enrolment, type of intensive care unit, criteria for patient enrollment, number of patients enrolled, methods used to identify delirium, duration of follow-up); patients' characteristics (age, sex, premorbid cognitive and functional status, severity of illness scores, organ dysfunction scores, mechanical ventilation, renal replacement therapy); and outcomes (death in intensive care and in hospital, duration of mechanical ventilation, length of stay in intensive care, length of stay in hospital, and any reported endpoint after discharge). A fourth author (RDS) verified accuracy and reliability of the abstracted data by sampling 10% of the references selected at each stage the systematic search and evaluating extracted data against the original reference; any discrepancies were resolved by discussion among authors (RBS, JIFS, AD, RDS). If data were not reported, we planned to contact first or senior authors by email; this was not necessary as data points were readily available.

We used the Newcastle-Ottawa Scale to assess methodological quality of included studies. this scale has been validated for the assessment of observational

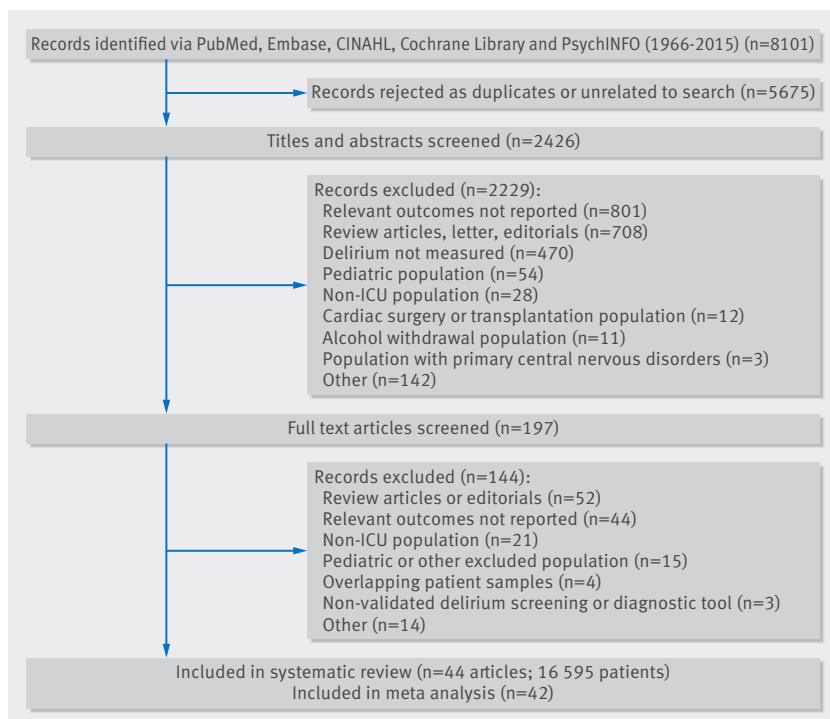


Fig 1 | Selection of studies on outcome of delirium in critically ill patients

studies in systematic reviews and meta-analyses.^{32,33} The scale evaluates three aspects of study methods: the selection of study groups (range 0-4), the comparability of groups (range 0-1), and the quality of outcome ascertainment (range 0-3). The total score ranges from 0 to 8, and an acceptable methodological design is reflected by a score of >5. To rate the quality of randomized controlled trials we used the validated Cochrane Risk of Bias Tool.³⁴

Patient involvement

There was no patient involvement in the design and development of this study.

Analytical approach

We estimated patients' characteristics and outcomes (mortality (in intensive care unit and hospital), length of stay (in intensive care unit and hospital), and duration of mechanical ventilation) in those with and without delirium. The principal outcome of interest was mortality (in intensive care unit and hospital). The strength of the relation between delirium and mortality was expressed as risk ratios with 95% confidence intervals. We selected risk ratio as a measure of effect for the binary outcome (death) as it is less prone to artificial inflation from heterogeneity than risk difference.³⁵ Studies with zero events were entered in the analysis to include all data and reduce bias.³⁶ To handle studies that reported zero outcomes for mortality, we performed a series of sensitivity analyses comparing Peto, Mantel-Haenszel, and inverse variance statistical methods with fixed and random effect with 0.5 continuity correction.^{37,38} Inverse variance and Mantel-Haenszel methods yielded identical results; we have shown the Mantel-Haenszel data in the mortality forest plot. For continuous outcomes, we calculated weighted standard mean difference based on reported means or medians. Standard deviations were imputed as summarized by Thiesen Philbrook and colleagues.³⁹ Long term outcomes (mortality and cognitive impairment) were extracted from the selected studies; these results were summarized and crude data included in the systematic review.

We assessed heterogeneity by means of I^2 statistic, which reflects the amount of heterogeneity between studies over and above the sampling variation and is robust to the number of studies and choice of effect measure.⁴⁰ If the I^2 statistic indicated considerable heterogeneity (Cochrane Handbook, section 9.5.2, <http://handbook.cochrane.org/>), we combined the summary measures across the studies using a random effects model that assumed that the included studies represent a sample from a larger population of studies.⁴¹ To explore heterogeneity between studies, we estimated the effect of study specific characteristics on outcome variables using meta-regression with the following predictors: age, proportion of women, and illness severity or organ failure score (either APACHE II or SOFA). The values of predictors were averaged across the groups with and without delirium. The outcome variable was the risk ratio of

mortality, with age, sex, and severity as predictors. We assessed publication bias by inspecting funnel plots and using the modified Egger test for binary data.⁴² Analyses were performed with STATA version 12 and RevMan version 5.0.

Results

The literature search produced 8101 citation titles, of which we screened 2426 potentially relevant abstracts, yielding 197 articles for detailed analysis; of the latter, 44 articles (16595 patients) met our criteria and were included in the systematic review. In two instances (Ely and colleagues³ and Milbrandt and colleagues,⁸ and Marquis and colleagues⁴³ and Ouimet and colleagues⁴⁴), a single study population was reported on in two separate articles. Hence, the final systematic review included 44 reports on 42 patient samples; only those 42 samples were included in the meta-analysis.

Study characteristics

Detailed characteristics of the included studies are shown in appendix 2. There were 40 prospective observational cohorts^{3,4,10,12,19,21-27,43-67} and two randomized controlled trials.^{47,68} Study populations ranged in size from 37 to 1824 (mean 384, median 185) patients. Twenty nine studies were conducted in mixed medical-surgical intensive care units, five studies evaluated only surgical intensive care units and two studies evaluated only medical intensive care units; seven studies evaluated only mechanically ventilated patients. Most studies (34) evaluated short term outcomes (recorded at hospital discharge or earlier). Seven studies extended follow-up to later time points, including 60 days,⁴ 180 days,³ 12 months,^{45,46,59,69} and 18 months.⁴⁸ Twenty five studies used multivariable approaches to adjust for the association between delirium and mortality.^{3,4,10,12,22,23,25,43-45,47,49,50,54,56,57,60,61,64,66-68,70,71} Details of methodological quality of included studies according to the Newcastle-Ottawa Scale are provided in appendix 3. The data originally from two randomized trials^{47,68} were evaluated as low risk of bias on all five components of the Cochrane tool.³⁴ The funnel plot suggested moderate publication bias in studies reporting on mortality (fig 2).

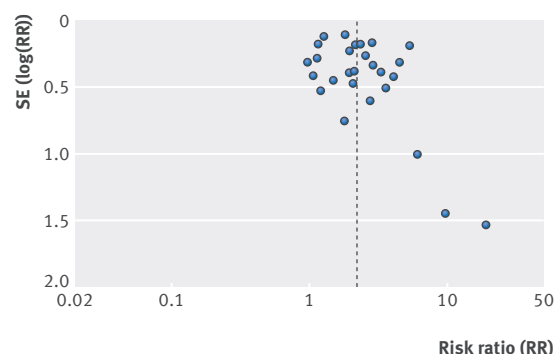


Fig 2 | Funnel plot of mortality in critically ill patients with delirium

Delirium identification and prevalence

The table shows delirium screening and prevalence data. Delirium was identified in 5280 of 16 595 patients (31.8%). Five studies reported on cognitive or psychological function before the index admission,^{3 4 16 23 72} and three studies reported on pre-existing functional status.^{3 16 23} The most common tool used for the diagnosis of delirium was the CAM-ICU, which was used in 28

studies,^{3 4 9 10 12 16 21 24 26 45 47-50 53-58 60 63-67 69 71} while five studies used the ICDSC^{25 27 43 68 70}. Other studies used CAM, DSM-IV, DSM-III, and the NEECHAM confusion scale.

Short term outcome

Figure 3 shows the association between delirium and mortality in the intensive care unit or in hospital. Twenty eight studies reported on mortality, and the

Delirium screening and prevalence data from studies of critically ill patients

Author	No of patients enrolled	Pre-existing cognitive or psychological function assessed (assessment method)?	Pre-ICU functional status assessed (assessment method)?	Delirium assessment tool	Physiologic scoring system	No of patients with delirium (%)
Kishi et al, 1995	238	No	No	DSM-III-R	NR	38 (15.97)
Aldemir et al, 2001	818	No	No	DSM-III-R	NR	90 (11.00)
Dubois et al, 2001	198	No	No	ICDSC	APACHE II	38 (19.19)
Ely et al, 2004; Milbrandt et al, 2004	224	Yes (mBDRS)	Yes (ADL)	CAM-ICU	APACHE II	183 (81.70)
Lin et al, 2004	102	No	No	CAM-ICU, DSM	APACHE III	22 (21.57)
Micek et al, 2005	93	No	No	CAM-ICU;	APACHE II	44 (47.31)
Roberts et al, 2005	185	No	No	ICDSC	APACHE II	84 (45.41)
Thomason et al, 2005	261	No	No	CAM-ICU	APACHE II	125 (47.89)
Ranhoff et al, 2006	401	Yes (MMSE)	Yes (ADL, APS)	CAM	APACHE II	117 (29.18)
Balas et al, 2007 a 2008	114	Yes (IQCODE, surrogate interview)	Yes (ADL, Katz)	CAM-ICU	APACHE II	34 (29.82)
Marquis et al, 2007; Ouimet et al, 2007a	537	No	No	ICDSC	APACHE II	189 (35.20)
Ouimet et al, 2007b	764	No	No	ICDSC	APACHE II	243 (31.81)
Plaschke et al, 2008	37	Yes	No	CAM-ICU	APACHE II	17 (45.95)
Angles et al, 2008	69	No	No	CAM-ICU	NR	41 (59.42)
Lin et al, 2008	151	Yes (BDRS)	No	CAM-ICU	APACHE III	31 (20.53)
Van Rompaey et al, 2008	172	No	No	CAM-ICU, NEECHAM	NR	34 (19.77)
Lat et al, 2009	134	No	No	CAM-ICU	APACHE II	84 (62.69)
Page et al, 2009	71	No	No	CAM-ICU	APACHE II	22 (30.99)
Spronk et al, 2009	46	Yes	No	CAM-ICU,	APACHE II	23 (50.00)
Van Rompaey et al, 2009	523	Yes (diagnosis of dementia)	No	NEECHAM	APACHE II	155 (29.64)
Van den Boogaard et al, 2010	1740	No	No	CAM-ICU	APACHE II	332 (19.08)
Tsuruta 2010	103	No	No	CAM-ICU	APACHE II	21 (20.39)
Shehabi 2010	354	No	No	CAM-ICU	NR	228 (64.41)
Salluh 2010	232	No	No	CAM-ICU	SAPS III	75 (32.33)
Heymann 2010	418	No	No	DDS	APACHE II	204 (48.80)
Girard 2010	77	No	No	CAM-ICU	APACHE II	65 (84.00)
Van den Boogaard et al, 2011	1613	No	No	CAM-ICU	APACHE II	411 (26.00)
Van den Boogaard et al, 2012 (CCM)	915	No	No	CAM-ICU	APACHE II	171 (18.60)
Sharma et al (2012)	140	No	No	DSM-IV	APACHE II	75 (54.00)
Tomasí et al (2011)	162	No	No	CAM-ICU, ICDSC	APACHE II	43 (26.50)
Serafim et al (2012)	467	No	No	CAM	APACHE II	43 (9.20)
Tsuruta et al, 2014	180	No	No	CAM-ICU	APACHE II	115 (64.00)
Almeida t al, 2014	170	No	No	CAM-ICU	SAPS II, SOFA,	161* (91.00)
Van den Boogaard et al, 2014	1824	No	No	CAM-ICU	APACHE II	410 (22.50)
Lahariya et al, 2014	309	No	No	CAM-ICU, DSM-IV-TR	APACHE II, SOFA	81 (18.77)
Pisani et al, 2009	309	Yes	Yes	CAM-ICU	APACHE II	N/A
Pandharipande et al, 2013	821	Yes	Yes	CAM-ICU	APACHE II, SOFA	606 (74.00)
Brummel et al, 2014	126	Yes	Yes	CAM-ICU	APACHE II	105 (84.00)
Wolters et al, 2013	1101	No	No	CAM-ICU	APACHE IV, SOFA	412 (37.00)
Mehta et al, 2014	420	No	No	ICDSC	APACHE II	226 (53.80)
Klein Klouwenberg et al, 2014	1112	No	No	CAM-ICU	APACHE II	558 (50.20)
Yamaguchi et al, 2014	126	No	No	ICDSC	NR	35 (27.80)

DSM=diagnostic and statistical manual of mental disorders; ICDSC=intensive care delirium screening checklist; BDRS=Blessed dementia rating scale; mBDRS=modified Blessed dementia rating scale; CAM=confusion assessment method; CAM-ICU=confusion assessment method for the intensive care unit; IQCOD=informant questionnaire on cognitive decline in the elderly; NEECHAM=Neelon and Champagne confusion scale; MMSE=mini-mental status examination; APACHE=acute physiology and chronic health evaluation score; SOFA=sequential organ failure assessment score; ADL=activity of daily living

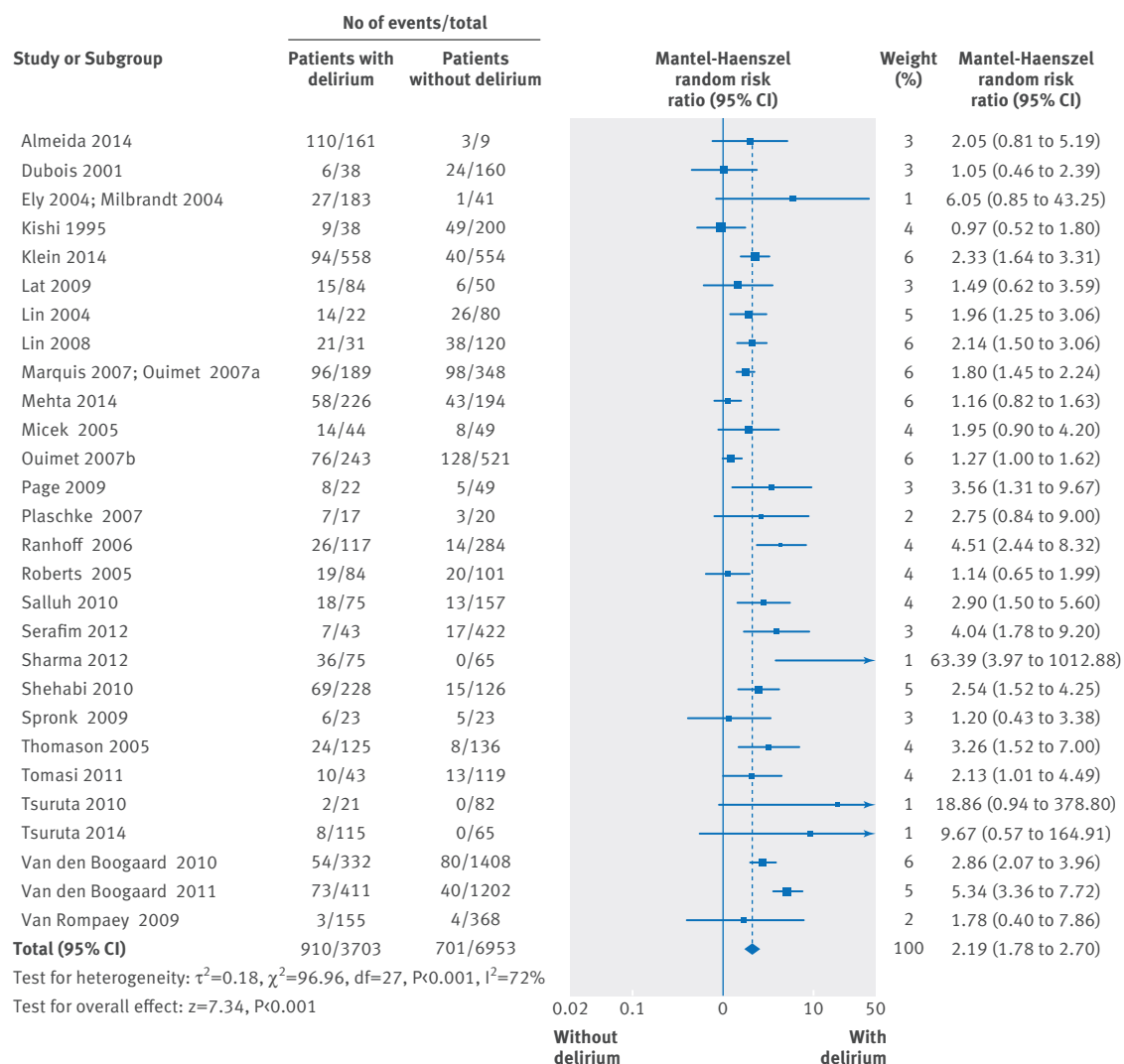


Fig 3 | Impact of delirium on hospital mortality in critically ill patients

overall risk ratio for death in patients with delirium was 2.19 (95% confidence interval 1.78 to 2.70; $P<0.001$). Severity of illness was rated with the APACHE II score in 31 studies and was higher in patients with delirium (mean 18.28 (SD 3.6) v 15.72 (SD 3.7); $P=0.017$). After adjustment for age, the proportion of female patients, and APACHE scores, the adjusted risk of mortality remained higher in the delirium group (effect size 2.72, 95% confidence interval 1.75 to 3.69).

Twenty eight studies reported length of stay in intensive care, which was significantly longer in patients with delirium (standardized mean difference 1.38, 95% confidence interval 0.99 to 1.77; $P<0.001$) compared with those without delirium (fig 4). This means that patients with delirium had a mean length of stay in intensive care that was 1 day and 9 hours longer than patients without delirium. Twenty two studies reported length of stay in hospital, which was significantly longer in patients with delirium (standardized mean difference 0.97, 0.61 to 1.33; fig 5).

Ten studies reported duration of mechanical ventilation, with point estimates indicating a longer duration

of mechanical ventilation in patients with delirium than in those without (1.79, 0.31 to 3.27; $P<0.001$; fig 6)—that is, the mean duration of mechanical ventilation was 1.79 days longer in patients with delirium.

Outcome after discharge

Eight studies reported follow-up after hospital discharge.^{4 10 12 46 48 49 69 72} Two studies found increased mortality by six months in patients who had delirium when they were in intensive care (41.2% v 15.4%, $P<0.001$,⁶⁹ and 34% v 15%, $P=0.03$), and one study showed that the number of days of delirium in intensive care was significantly associated with time to death within one year after admission to intensive care unit (hazard ratio 1.10, 95% confidence interval 1.02 to 1.18).¹⁰ In a recent prospective cohort of 1101 people who survived a critical illness, no significant association was found between delirium in intensive care and mortality or quality of life at one year, after adjustment for sex, type of admission, APACHE IV score, and the cumulative SOFA score throughout the stay in intensive care.⁴⁹

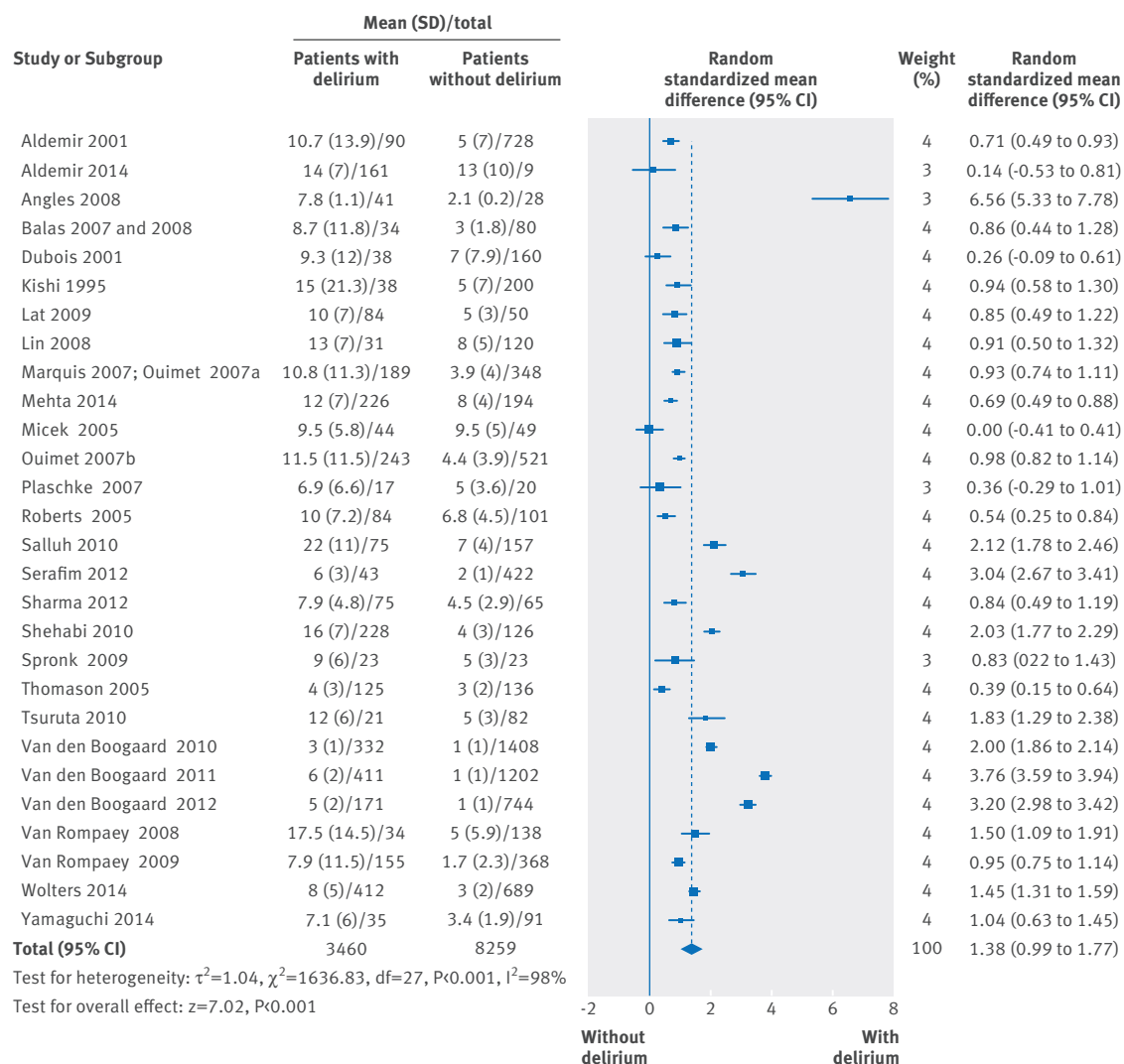


Fig 4 | Impact of delirium on length of stay (days) in intensive care unit in critically ill patients

Regarding cognitive function after hospital discharge, Girard and colleagues reported that delirium was an independent predictor of worse scores on neuropsychological testing at follow-up at three months ($P=0.02$) and 12 months ($P=0.03$).⁴⁶ Pandharipande and colleagues found that longer duration of delirium was independently associated with worse global cognition at three and 12 months ($P=0.001$ and $P=0.04$, respectively) and worse executive function at three and 12 months ($P=0.004$ and $P=0.007$, respectively).¹² Van den Boogaard and colleagues found that duration of delirium was significantly correlated to memory and naming impairments 18 months after discharge.⁴⁸ Brummel and colleagues reported that in patients who survived after mechanical ventilation evaluated at 12 months, duration of delirium was associated with worse scores on activities of daily living and impaired perception of motor sensory function.⁴⁵

Discussion

Principal findings

This systematic review and meta-analysis synthesized data on the prevalence of delirium in patients admitted

to an intensive care unit and the association between delirium and outcomes of critically ill patients. We identified 42 studies enrolling a total of 16 595 patients. Delirium was detected in nearly a third of critically ill patients and was associated with increased hospital mortality, an association that persisted after adjustment for severity of illness. Delirium was also associated with longer length of stay and longer duration of mechanical ventilation. Despite the small number of studies that evaluated outcomes at more than one time point, available data suggest an association between delirium and cognitive impairment and mortality after discharge.

Strengths and limitation of study

Our study indicates that delirium identified in the intensive care unit is strongly associated with adverse outcomes, even after adjustment for illness severity. These findings are consistent with results of a previous systematic review⁷³ and expand them to include a much larger number of studies and patients (42 v 14 studies; 16 595 v 5891 patients). Our data, however, still do not clarify the nature of this association,

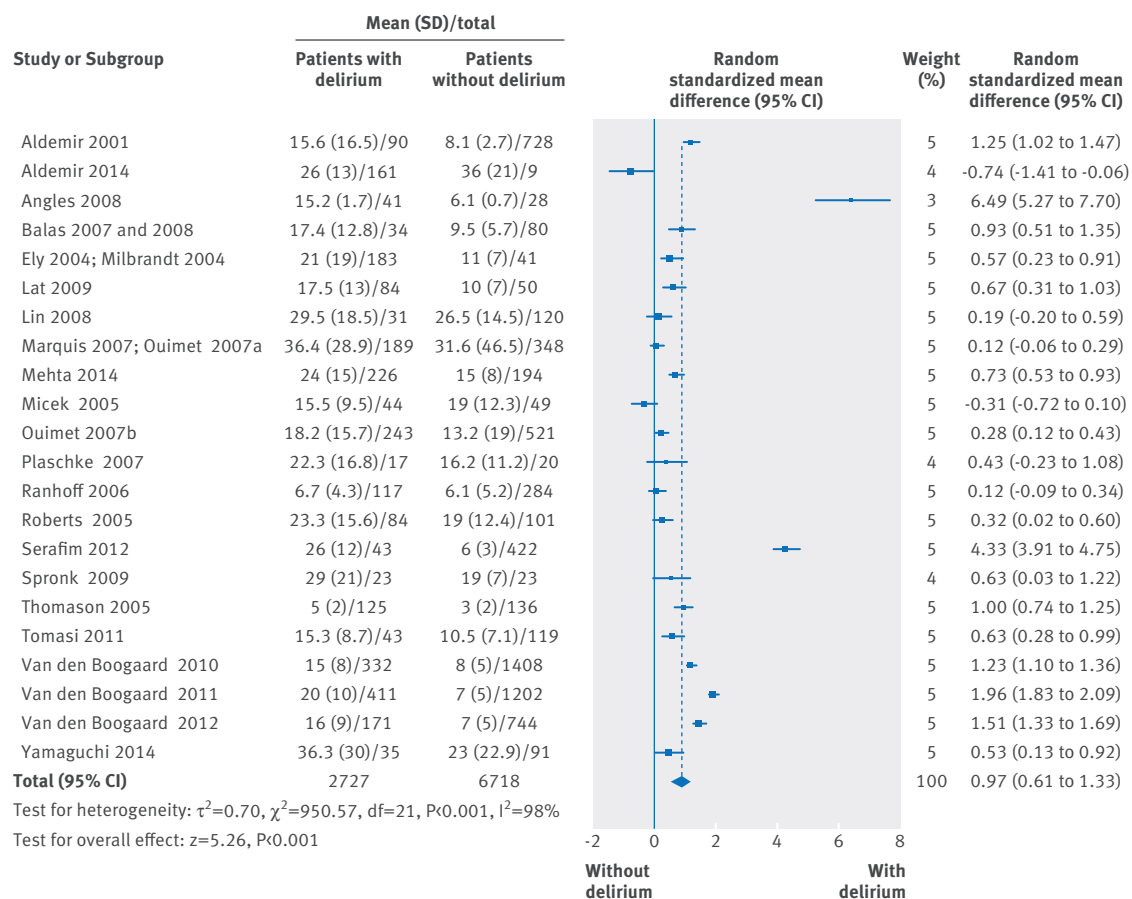


Fig 5 | Impact of delirium on length of stay (days) in hospital in critically ill patients

specifically whether delirium is a condition that is causatively linked to adverse outcome or whether it is a marker of severity of disease whose link to outcome is confounded by other measured or unmeasured variables. Despite this uncertainty, the results have major practical implications and provide an evidentiary basis for the recommendations of the PAD (pain,

agitation, and delirium) guidelines recently put forward by the American College of Critical Care Medicine.⁷⁴ The burden of delirium could be reduced by a range of interventions such as rational titration of sedation and anesthesia,⁷⁵ reduced exposure to benzodiazepines,⁷⁶⁻⁷⁸ promotion of sleep,⁷² early implementation of mobility and occupational therapy in

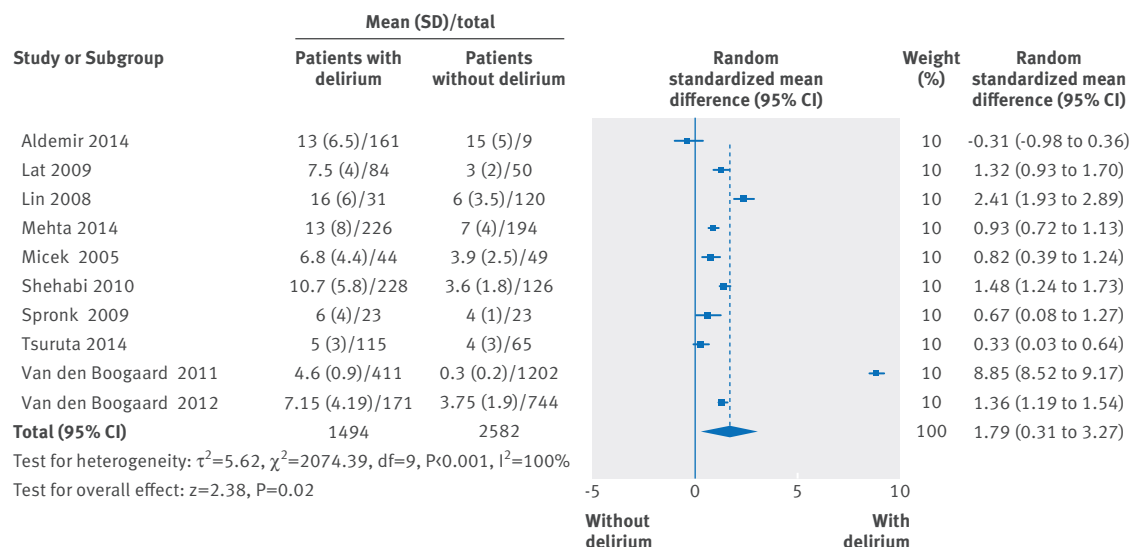


Fig 6 | Impact of delirium on duration (days) of mechanical ventilation in critically ill patients

the intensive care unit,⁷⁹ use of antipsychotic agents particularly in specific subgroups,^{80–82} and bundled interventions.^{83,84} Delirium is therefore a potentially modifiable risk factor for adverse outcomes in critically ill patients in hospital.

Given the prevalence and adverse consequences of delirium, our results underscore the need for prospective cohort studies with standardized methods to accurately and reliably detect and rate delirium and to characterize short and long term outcomes. Such studies need to be stringent in identifying all factors that could contribute to the onset, pathogenesis, and resolution of delirium associated with critical illness. Studies should be designed to allow discriminative analysis of subgroups of patients in intensive care who have different causes, severities, and durations of delirium.^{71,85–87} Specific attention should be devoted to determining endpoint measures that are relevant from a biological, clinical, and process of care standpoints. The latter might include resource utilization, long term cognitive function, psychological status, functional status, and quality of life. Additionally, large and appropriately designed clinical trials are needed to evaluate the efficacy and safety of single and bundled interventions in reducing the incidence and burden of delirium in acutely ill populations.

The present study has some limitations. First, there was considerable heterogeneity in the meta-analysis, as reflected by the I^2 statistic. This is not unexpected as there were major differences between studies in the patient populations, the methods used to detect and rate delirium, and the timeframes for mortality—such differences could account for substantial differences in prevalence and mortality. Second, funnel plot asymmetry suggests the possibility of moderate publication bias in studies reporting on mortality, though this was observed in a small proportion of all patients (11%) and was not likely to have an important impact on the conclusions. Third, we did not conduct a grey literature search, which could lead to an overestimation of the effect size. Fourth, we excluded studies of patients after cardiac surgery and organ transplantation. Phenotypes of brain dysfunction or encephalopathy in these settings are each highly distinctive in terms of epidemiology, genetic and biological determinants, pathophysiology, natural history, and outcomes; we therefore decided to remove these groups and plan to report on them separately.

Another constraint in this study is that there are potentially unmeasured confounders such as differences in the timing and frequency of assessment of delirium, in the use of sedatives, and in the medical management of critically ill patients. While advances have been made in identifying delirium in such patients, it is also apparent that the construct of delirium and the currently available assessment tools for delirium do not sufficiently characterize the range of central nervous system alterations that could be encountered in the intensive care unit.⁸⁸ Subtypes of delirium including hypoactive

delirium or subsyndromal delirium, for example, might not be accurately or reliably detected with available delirium instruments.^{117,21} Criteria used in defining and scoring delirium differ between studies and could overlap with those used to describe other syndromes of impaired cognitive function or consciousness. In particular, patients whose level of consciousness is depressed or who are comatose might be misclassified as having delirium or alternatively might be excluded altogether from neurocognitive assessment.⁷⁹

Recent work has shown that the impact of delirium on mortality in intensive care is reduced after adjustment for time varying confounders, with most of the negative impact on outcomes confined to the group with persistent delirium.^{71,85} Although this does not diminish the overall importance of the present data, it certainly points in a new direction for clinical research. Future studies should focus on patients with persistent delirium and its impact on neurocognitive outcomes and survival. Notwithstanding these limitations, the results of this meta-analysis show a robust association between the occurrence of delirium in the intensive care unit and adverse short term outcomes.

Conclusion

Delirium is common in a broad sample of critically ill patients and is strongly associated with increased hospital mortality even after adjustment for severity of disease. Evidence also suggests a relation between delirium in the intensive care unit and long term cognitive impairment. Research is needed to unravel the biological mechanisms governing these relations and to discover strategies and treatments that will reduce the burden of acute and long term brain dysfunction in critically ill populations.

Contributors: JS and RDS designed the study, analyzed and interpreted data, and wrote the manuscript. ES, NN, and GY did the statistical analysis and interpreted the data. AD collected data. RS collected, analyzed, and interpreted data, and wrote the manuscript. RDS is guarantor.

Funding: The study was performed with institutional funding.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/doi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required.

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing: No additional data available.

This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

1 Inouye SK, Viscoli CM, Horwitz RJ, et al. A predictive model for delirium in hospitalized elderly medical patients based on admission characteristics. *Ann Intern Med* 1993;119:474–81.

- 2 Task Force on DSM-IV. Diagnostic and statistical manual of mental disorders: DSM-IV-TR. 4th ed. American Psychiatric Association, 2000.
- 3 Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA* 2004;291:1753-62.
- 4 Lin S, Liu C, Wang C, et al. The impact of delirium on the survival of mechanically ventilated patients. *Crit Care Med* 2004;32:2254-59.
- 5 Pompei P, Foreman M, Rudberg MA, et al. Delirium in hospitalized older persons: outcomes and predictors. *J Am Geriatr Soc* 1994;42:809-15.
- 6 Buss MK, Vanderwerker LC, Inouye SK, et al. Associations between caregiver-perceived delirium in patients with cancer and generalized anxiety in their caregivers. *J Palliat Med* 2007;10:1083-92.
- 7 Shankar KN, Hirschman KB, Hanlon AL, et al. Burden in caregivers of cognitively impaired elderly adults at time of hospitalization: a cross-sectional analysis. *J Am Geriatr Soc* 2014;62:276-84.
- 8 Milbrandt EB, Deppen S, Harrison PL, et al. Costs associated with delirium in mechanically ventilated patients. *Crit Care Med* 2004;32:955-62.
- 9 Leslie DL, Marcantonio ER, Zhang Y, et al. One-year health care costs associated with delirium in the elderly population. *Arch Intern Med* 2008;168:27-32.
- 10 Pisani MA, Kong SY, Kasl SV, et al. Days of delirium are associated with 1-year mortality in an older intensive care unit population. *Am J Respir Crit Care Med* 2009;180:1092-7.
- 11 O'Keeffe S, Lavan J. The prognostic significance of delirium in older hospital patients. *J Am Geriatr Soc* 1997;45:174-8.
- 12 Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. *N Engl J Med* 2013;369:1306-16.
- 13 Witlox J, Eurelings LS, de Jonghe JF, et al. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA* 2010;304:443-51.
- 14 Levkoff SE, Evans DA, Liptzin B, et al. Delirium. The occurrence and persistence of symptoms among elderly hospitalized patients. *Arch Intern Med* 1992;152:334-40.
- 15 Lawlor PG, Gagnon B, Mancini IL, et al. Occurrence, causes, and outcome of delirium in patients with advanced cancer: a prospective study. *Arch Intern Med* 2000;160:786-94.
- 16 Balas MC, Happ MB, Yang W, et al. Outcomes associated with delirium in older patients in surgical ICUs. *Chest* 2009;135:18-25.
- 17 Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 2001;286:2703-10.
- 18 Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet* 2014;383:911-22.
- 19 Aldemir M, Ozen S, Kara IH, et al. Predisposing factors for delirium in the surgical intensive care unit. *Crit Care* 2001;5:265-70.
- 20 Van Eijk MM, van Marum RJ, Klijn IA, et al. Comparison of delirium assessment tools in a mixed intensive care unit. *Crit Care Med* 2009;37:1881-5.
- 21 Spronk PE, Riekerk B, Hofhuis J, et al. Occurrence of delirium is severely underestimated in the ICU during daily care. *Intensive Care Med* 2009;35:1276-80.
- 22 Thomason JW, Shintani A, Peterson JF, et al. Intensive care unit delirium is an independent predictor of longer hospital stay: a prospective analysis of 261 non-ventilated patients. *Crit Care* 2005;9:R375-81.
- 23 Ranhoff AH, Rozzini R, Sabatini T, et al. Delirium in a sub-intensive care unit for the elderly: occurrence and risk factors. *Aging Clin Exp Res* 2006;18:440-5.
- 24 Page VJ, Navarange S, Gama S, et al. Routine delirium monitoring in a UK critical care unit. *Crit Care* 2009;13:R16.
- 25 Dubois MJ, Bergeron N, Dumont M, et al. Delirium in an intensive care unit: a study of risk factors. *Intensive Care Med* 2001;27:1297-304.
- 26 Micek ST, Shintani A, Laible BR, et al. Delirium as detected by the CAM-ICU predicts restraint use among mechanically ventilated medical patients. *Crit Care Med* 2005;33:1260-5.
- 27 Roberts B, Rickard CM, Rajbhandari D, et al. Multicentre study of delirium in ICU patients using a simple screening tool. *Aust Crit Care* 2005;18:6-14.
- 28 Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. *JAMA* 2000;283:2008-12.
- 29 Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med* 1990;113:941-8.
- 30 Bergeron N, Dubois MJ, Dumont M, et al. Intensive care delirium screening checklist: evaluation of a new screening tool. *Intensive Care Med* 2001;27:859-64.
- 31 Neelon VJ, Champagne MT, Carlson JR, et al. The NEECHAM confusion scale: construction, validation, and clinical testing. *Nurs Res* 1996;45:324-30.
- 32 Wells GA SB, O'Connell D, Peterson J, Welch V, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute, 2000. www.ohrica/programs/clinical_epidemiology/oxford.htm.
- 33 Stevens RD, Dowdy DW, Michaels RK, et al. Neuromuscular dysfunction acquired in critical illness: a systematic review. *Intensive Care Med* 2007;33:1876-91.
- 34 Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
- 35 Fleiss JL. The statistical basis of meta-analysis. *Stat Methods Med Res* 1993;2:121-45.
- 36 Friedrich JO, Adhikari NK, Beyene J. Inclusion of zero total event trials in meta-analyses maintains analytic consistency and incorporates all available data. *BMC Med Res Methodol* 2007;7:5.
- 37 Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med* 2004;23:1351-75.
- 38 Sankey SS, Weissfeld LA, Fine MJ, et al. An assessment of the use of the continuity correction for sparse data in meta-analysis. *Commun Stat Simul Comput* 1996;25:1031-56.
- 39 Thiessen Philbrook H, Barrowman N, Garg AX. Imputing variance estimates do not alter the conclusions of a meta-analysis with continuous outcomes: a case study of changes in renal function after living kidney donation. *J Clin Epidemiol* 2007;60:228-40.
- 40 Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.
- 41 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.
- 42 Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Stat Med* 2006;25:3443-57.
- 43 Marquis F, Ouimet S, Riker R, et al. Individual delirium symptoms: do they matter? *Crit Care Med* 2007;35:2533-7.
- 44 Ouimet S, Kavanagh BP, Gottfried SB, et al. Incidence, risk factors and consequences of ICU delirium. *Intensive Care Med* 2007;33:66-73.
- 45 Brummel NE, Jackson JC, Pandharipande PP, et al. Delirium in the ICU and subsequent long-term disability among survivors of mechanical ventilation. *Crit Care Med* 2014;42:369-77.
- 46 Girard TD, Jackson JC, Pandharipande PP, et al. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. *Crit Care Med* 2010;38:1513-20.
- 47 Shehabi Y, Riker RR, Bokesch PM, et al. Delirium duration and mortality in lightly sedated, mechanically ventilated intensive care patients. *Crit Care Med* 2010;38:2311-8.
- 48 Van den Boogaard M, Schoonhoven L, Evers AW, et al. Delirium in critically ill patients: impact on long-term health-related quality of life and cognitive functioning. *Crit Care Med* 2012;40:112-8.
- 49 Wolters AE, van Dijk D, Pasma W, et al. Long-term outcome of delirium during intensive care unit stay in survivors of critical illness: a prospective cohort study. *Crit Care* 2014;18:R125.
- 50 Angles EM, Robinson TN, Biffi WL, et al. Risk factors for delirium after major trauma. *Am J Surg* 2008;196:864-70.
- 51 Heymann A, Radtke F, Schiemann A, et al. Delayed treatment of delirium increases mortality rate in intensive care unit patients. *J Int Med Res* 2010;38:1584-95.
- 52 Kishi Y, Iwasaki Y, Takezawa K, et al. Delirium in critical care unit patients admitted through an emergency room. *Gen Hosp Psychiatry* 1995;17:371-9.
- 53 Lat I, McMillan W, Taylor S, et al. The impact of delirium on clinical outcomes in mechanically ventilated surgical and trauma patients. *Crit Care Med* 2009;37:1898-905.
- 54 Lin SM, Huang CD, Liu CY, et al. Risk factors for the development of early-onset delirium and the subsequent clinical outcome in mechanically ventilated patients. *J Crit Care* 2008;23:372-9.
- 55 Plaschke K, von Haken R, Scholz M, et al. Comparison of the confusion assessment method for the intensive care unit (CAM-ICU) with the Intensive Care Delirium Screening Checklist (ICDSC) for delirium in critical care patients gives high agreement rate(s). *Intensive Care Med* 2008;34:431-6.
- 56 Salluh JJ, Soares M, Teles JM, et al. Delirium epidemiology in critical care (DECCA): an international study. *Crit Care* 2010;14:R210.
- 57 Tsuruta R, Nakahara T, Miyauchi T, et al. Prevalence and associated factors for delirium in critically ill patients at a Japanese intensive care unit. *Gen Hosp Psychiatry* 2010;32:607-11.
- 58 Van den Boogaard M, Peters SA, van der Hoeven JG, et al. The impact of delirium on the prediction of in-hospital mortality in intensive care patients. *Crit Care* 2010;14:R146.
- 59 Van Rompaey B, Schuurmans MJ, Shortridge-Baggett LM, et al. Long term outcome after delirium in the intensive care unit. *J Clin Nurs* 2009;18:3349-57.
- 60 Almeida IC, Soares M, Bozza FA, et al. The impact of acute brain dysfunction in the outcomes of mechanically ventilated cancer patients. *PLoS One* 2014;9:e85332.

- 61 Serafim RB, Dutra MF, Saddy F, et al. Delirium in postoperative nonventilated intensive care patients: risk factors and outcomes. *Ann Intensive Care* 2012;2:51.
- 62 Sharma A, Malhotra S, Grover S, et al. Incidence, prevalence, risk factor and outcome of delirium in intensive care unit: a study from India. *Gen Hosp Psychiatry* 2012;34:639-46.
- 63 Tomasi CD, Grandi C, Salluh J, et al. Comparison of CAM-ICU and ICDSC for the detection of delirium in critically ill patients focusing on relevant clinical outcomes. *J Crit Care* 2012;27:212-7.
- 64 Tsuruta R, Oda Y, Shintani A, et al. Delirium and coma evaluated in mechanically ventilated patients in the intensive care unit in Japan: a multi-institutional prospective observational study. *J Crit Care* 2014;29:472.e1-5.
- 65 Van den Boogaard M, Kox M, Quinn KL, et al. Biomarkers associated with delirium in critically ill patients and their relation with long-term subjective cognitive dysfunction; indications for different pathways governing delirium in inflamed and noninflamed patients. *Crit Care* 2011;15:R297.
- 66 Van den Boogaard M, Schoonhoven L, Maseda E, et al. Recalibration of the delirium prediction model for ICU patients (PRE-DELIRIC): a multinational observational study. *Intensive Care Med* 2014;40:361-9.
- 67 Lahariya S, Grover S, Bagga S, et al. Delirium in patients admitted to a cardiac intensive care unit with cardiac emergencies in a developing country: incidence, prevalence, risk factor and outcome. *Gen Hosp Psychiatry* 2014;36:156-64.
- 68 Mehta S, Cook D, Devlin JW, et al. Prevalence, risk factors, and outcomes of delirium in mechanically ventilated adults. *Crit Care Med* 2015;43:557-66.
- 69 Van Rompaey B, Schuurmans MJ, Shortridge-Baggett LM, et al. A comparison of the CAM-ICU and the NEECHAM Confusion Scale in intensive care delirium assessment: an observational study in non-intubated patients. *Crit Care* 2008;12:R16.
- 70 Yamaguchi T, Tsukioka E, Kishi Y. Outcomes after delirium in a Japanese intensive care unit. *Gen Hosp Psychiatry* 2014;36:634-6.
- 71 Klein Klouwenberg PM, Zaal IJ, Spitoni C, et al. The attributable mortality of delirium in critically ill patients: prospective cohort study. *BMJ* 2014;349:g6652.
- 72 Kamdar BB, King LM, Collop NA, et al. The effect of a quality improvement intervention on perceived sleep quality and cognition in a medical ICU. *Crit Care Med* 2013;41:800-9.
- 73 Zhang Z, Pan L, Ni H. Impact of delirium on clinical outcome in critically ill patients: a meta-analysis. *Gen Hosp Psychiatry* 2013;35:105-11.
- 74 Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med* 2013;41:263-306.
- 75 Sieber FE, Zakriya KJ, Gottschalk A, et al. Sedation depth during spinal anesthesia and the development of postoperative delirium in elderly patients undergoing hip fracture repair. *Mayo Clin Proc* 2010;85:18-26.
- 76 Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA* 2009;301:489-99.
- 77 Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA* 2007;298:2644-53.
- 78 Fraser GL, Devlin JW, Worby CP, et al. Benzodiazepine versus nonbenzodiazepine-based sedation for mechanically ventilated, critically ill adults: a systematic review and meta-analysis of randomized trials. *Crit Care Med* 2013;41(suppl 1):S30-8.
- 79 Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet* 2009;373:1874-82.
- 80 Wang W, Li HL, Wang DX, et al. Haloperidol prophylaxis decreases delirium incidence in elderly patients after noncardiac surgery: a randomized controlled trial*. *Crit Care Med* 2012;40:731-9.
- 81 Devlin JW, Roberts RJ, Fong JJ, et al. Efficacy and safety of quetiapine in critically ill patients with delirium: a prospective, multicenter, randomized, double-blind, placebo-controlled pilot study. *Crit Care Med* 2010;38:419-27.
- 82 Kalisvaart KJ, de Jonghe JF, Bogaards MJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. *J Am Geriatr Soc* 2005;53:1658-66.
- 83 Inouye SK, Bogardus ST Jr, Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med* 1999;340:669-76.
- 84 Reston JT, Schoelles KM. In-facility delirium prevention programs as a patient safety strategy: a systematic review. *Ann Intern Med* 2013;158:375-80.
- 85 Patel SB, Poston JT, Pohlman A, et al. Rapidly reversible, sedation-related delirium versus persistent delirium in the intensive care unit. *Am J Respir Crit Care Med* 2014;189:658-65.
- 86 Widmann CN, Heneka MT. Long-term cerebral consequences of sepsis. *Lancet Neurol* 2014;13:630-6.
- 87 Hsieh SJ, Soto GJ, Hope AA, et al. The association between acute respiratory distress syndrome, delirium, and in-hospital mortality in intensive care unit patients. *Am J Respir Crit Care Med* 2015;191:71-8.
- 88 Stevens RD, Sharshar T, Ely EW. Brain disorders in critical illness: mechanisms, diagnosis, and treatment. Cambridge University Press, 2013.

Appendix 1: Search strategy

Appendix 2: Characteristics of included studied

Appendix 3: Newcastle-Ottawa Scale ratings of included observational studies

© BMJ Publishing Group Ltd 2015