BJA

British Journal of Anaesthesia, xxx (xxx): xxx (xxxx)

doi: 10.1016/j.bja.2023.05.004
Advance Access Publication Date: xxx
Review Article

REVIEW ARTICLE

Effect of inhaled anaesthetics on cognitive and psychiatric outcomes in critically ill adults: a systematic review and meta-analysis

Sean Cuninghame[1], Angela Jerath[2,3,4,5], Kevin Gorsky[2], Asaanth Sivajohan[7], Conall Francoeur[8], Davinia Withington[9,10], Lisa Burry[11,12], Brian H. Cuthbertson[4,6], Beverley A. Orser[2,3], Claudio Martin[1], Adrian M. Owen[13,14], Marat Slessarev[1,13,*], for the Sedating with Volatile Anesthetics Critically Ill COVID-19 Patients in ICU: Effects on Ventilatory Parameters and Survival study investigators

[1]Department of Medicine, Western University, London, ON, Canada, [2]Department of Anesthesiology and Pain Medicine, Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada, [3]Department of Anesthesia, Sunnybrook Health Sciences Centre, Toronto, ON, Canada, [4]Schulich Heart Program, Sunnybrook Research Institute, Toronto, ON, Canada, [5]Institute for Health Policy, Management and Evaluation, University of Toronto, ON, Canada, [6]Department of Critical Care Medicine, Sunnybrook Health Sciences Centre, Toronto, ON, Canada, [7]Schulich School of Medicine and Dentistry, Western University, London, ON, Canada, [8]Centre de Recherche CHU de Québec–Université Laval, Quebec City, QC, Canada, [9]Department of Anesthesia, Montreal Children's Hospital, Montreal, QC, Canada, [10]Department of Anesthesia, McGill University, Montreal, QC, Canada, [11]Departments of Pharmacy and Medicine, Mount Sinai Hospital, Toronto, ON, Canada, [12]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada, [13]Western Institute for Neuroscience, Western University, London, ON, Canada and [14]Department of Psychology and Department of Physiology and Pharmacology, Western University, London, Canada

*Corresponding author. E-mail: marat.slessarev@lhsc.on.ca

Abstract

Background: Sedation of critically ill patients with inhaled anaesthetics may reduce lung inflammation, time to extubation, and ICU length of stay compared with intravenous (i.v.) sedatives. However, the impact of inhaled anaesthetics on cognitive and psychiatric outcomes in this population is unclear. In this systematic review, we aimed to summarise the effect of inhaled anaesthetics on cognitive and psychiatric outcomes in critically ill adults.

Methods: We searched MEDLINE, EMBASE, and PsycINFO for case series, retrospective, and prospective studies in critically ill adults sedated with inhaled anaesthetics. Outcomes included delirium, psychomotor and neurological recovery, long-term cognitive dysfunction, ICU memories, anxiety, depression, post-traumatic stress disorder (PTSD), and instruments used for assessment.

Results: Thirteen studies were included in distinct populations of post-cardiac arrest survivors (n=4), postoperative noncardiac patients (n=3), postoperative cardiac patients (n=2), and mixed medical–surgical patients (n=4). Eight studies reported delirium incidence, two neurological recovery, and two ICU memories. One study reported on psychomotor recovery, long-term cognitive dysfunction, anxiety, depression, and PTSD. A meta-analysis of five trials found no difference in delirium incidence between inhaled and i.v. sedatives (relative risk 0.95 [95% confidence interval: 0.59–1.54]). Compared with i.v. sedatives, inhaled anaesthetics were associated with fewer hallucinations and faster psychomotor recovery but no differences in other outcomes. There was heterogeneity in the instruments used and timing of these assessments.

Received: 2 March 2023; **Accepted:** 4 May 2023

Conclusions: Based on the limited evidence available, there is no difference in cognitive and psychiatric outcomes between adults exposed to volatile sedation or intravenous sedation in the ICU. Future studies should incorporate outcome assessment with validated tools during and after hospital stay.
Systematic review protocol: PROSPERO CRD42021236455.

Keywords: cognition; critical care medicine; delirium; post-ICU syndrome; psychiatric; sedation

Editor's key points

- There is renewed interest in the use of inhaled agents for sedation in critically ill patients. They reduce lung inflammation, ventilator-free days of mechanical ventilation, and length of stay, but their effect on cognition in this population is unclear.
- In this meta-analysis, the authors found no difference between inhaled and intravenous sedation in the incidence of ICU delirium, and no evidence that inhaled anaesthetics increase the risk of post-traumatic stress disorder, mood disorders, or long-term cognitive dysfunction.
- Further studies are needed to improve understanding of neurocognitive dysfunction in patients in the ICU sedated with inhaled anaesthetics.

Inhaled anaesthetics, such as isoflurane, sevoflurane, and desflurane, are emerging as alternative sedatives for critically ill patients. Compared with intravenous (i.v.) sedatives, inhaled anaesthetics may reduce lung inflammation and improve oxygenation, and they have been associated with faster time to extubation and shorter duration of ICU stay.[1–3] The surge of critically ill patients requiring mechanical ventilation during the COVID-19 pandemic and associated shortage of i.v. sedatives renewed interest in the use of the readily available and inexpensive inhaled anaesthetics for sedation.[4–7] However, the impact of these agents on acute (ICU or in-hospital) and long-term (post-hospitalisation) cognitive and psychiatric outcomes of critically ill patients is less known.

Cognitive vitality is an important patient-centred outcome that impacts work success, levels of happiness, and life expectancy.[8–11] Critically ill patients suffer from high burden of cognitive impairment across the continuum of critical illness ranging from acute (in-hospital) delirium to long-term (after hospital discharge) cognitive impairment.[12,13] ICU delirium is associated with both worse patient (increased mortality and long-term cognitive impairment) and health system (longer duration of mechanical ventilation and hospitalisation and higher healthcare costs) outcomes.[14–16] Although systematic evidence suggests no association between i.v. ICU sedation and cognition,[17] recent prospective cohort studies showed an association between i.v. sedation exposure, long-term cognitive impairment,[16–18] and psychiatric morbidity (i.e. depression, anxiety, and post-traumatic stress disorder [PTSD]).[19–22] Whether the same is true for inhaled anaesthetic drugs is unknown.

In this systematic review and meta-analysis, we collated existing evidence regarding acute (in-hospital) and long-term (after hospital discharge) cognitive and psychiatric outcomes and instruments used for assessment of these outcomes in critically ill adults receiving inhaled anaesthetic or i.v. sedation. Our review provides a timely up-to-date summary of existing evidence to better inform providers, patients, and their families regarding the cognitive and psychiatric effect of inhaled anaesthetic sedation of critically ill patients and identifies research gaps in this emerging field.

Methods

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[23] The protocol followed the International Prospective Register of Systematic Reviews (PROSPERO) checklist and was registered in the PROSPERO database (ID: CRD42021236455). The full study methodology was peer reviewed and published previously.[24]

Search strategy

An initial search of MEDLINE identified relevant keywords in article titles and abstracts. These keywords were then included in an expanded search of the MEDLINE, EMBASE, PsycINFO, and the Cochrane Central Register of Controlled Trials databases; search results were uploaded into the online systematic review system Covidence (Melbourne, VIC, Australia). The search strategy can be viewed in the Supplementary material.

Eligibility criteria

We included studies (i) in adult (≥18 yr) patients admitted to any type of ICU, who received inhaled anaesthetics (sevoflurane, isoflurane, or desflurane) for sedation (ii) reported at least one acute (e.g. ICU or in-hospital delirium, hallucinations, psychomotor, or neurological recovery) or long-term (e.g. post-hospital discharge cognitive function and ICU memories) cognitive or psychiatric (e.g. anxiety, depression, and PTSD) outcomes; and (iii) were published as case series, retrospective, and prospective studies between January 1970 and December 2021. We excluded studies using halothane and nitrous oxide, as these agents are infrequently used in critical care settings, abstracts, case reports, paediatric, and non-English-language studies.

Study selection

Two reviewers (SC and AS) used Covidence software to screen the titles and abstracts of articles identified by the search strategy and applied eligibility criteria to select articles for full-text review. Two reviewers then read full-text articles selected in the previous step and applied eligibility criteria to select articles for final data extraction. Disagreements between

reviewers were resolved by discussion; consensus; and, when necessary, adjudication by a third reviewer (MS).

Data extraction

Two reviewers (SC and AS) independently performed data extraction. For each study, we extracted the following variables: (i) *study characteristics*: study design, study size, country, setting (i.e. type of ICU), and stated objective; (ii) *patient characteristics*: patient sex, admission diagnosis, and study eligibility criteria; (iii) *secondary clinical outcomes*: ICU length of stay, hospital length of stay, and in-hospital mortality; (iv) *sedation characteristics*: sedation targets and their measurement, inhaled anaesthetic or i.v. sedative used, target sedative dose, and anti-psychotic drug use; and (v) *cognitive and psychiatric outcomes*: reported values (e.g. delirium rates), instruments used to measure these outcomes, and timing when these outcomes were assessed.

Quality assessment and risk of bias

Risk of bias and study quality were assessed by two independent reviewers (SC and AS). Case series were appraised using the Joanna Briggs Institute (JBI) 2017 Critical Appraisal, cohort studies by the Newcastle–Ottawa, and RCTs by the Cochrane risk-of-bias tools. Discrepancies were resolved by a third reviewer (MS).

Data reporting and meta-analysis

Quantitative data were summarised using median (interquartile range) or mean (standard deviation) for continuous variables and frequency (percentage) for categorical variables.

The only consistently reported outcome amenable to meta-analysis was incidence of delirium. We performed meta-analysis of RCTs reporting incidence of delirium using random-effects model in Review Manager 5.3 (Cochrane Collaboration, Oxford, UK). Heterogeneity was assessed *via* calculation of the I^2 statistic, where values >50% indicated moderate heterogeneity.

Results

Study selection

Our search strategy produced 1856 total records. After the removal of 347 duplicates, 1509 studies were included for title and abstract screening. Of these, 1368 studies were excluded, leaving 141 studies for full-text assessment (Fig. 1). Of the 141 studies included for full-text assessment, 26 were review articles, and of these five were determined to be potentially relevant to the outcome(s) of interest in our systematic review. The references within these review articles were also screened for inclusion in our study. After full-text assessment along with cross-referencing of relevant review articles, 13 studies met our inclusion criteria and were included in data extraction.

Study characteristics

We identified four distinct groups *a priori*[24] of critically ill adults who were sedated with inhaled anaesthetics and assessed for neurocognitive or psychiatric outcomes. These groups included cardiac arrest survivors (n=828), postoperative noncardiac (n=235), postoperative cardiac (n=170), or mixed medical–surgical patients (n=448; Table 1).

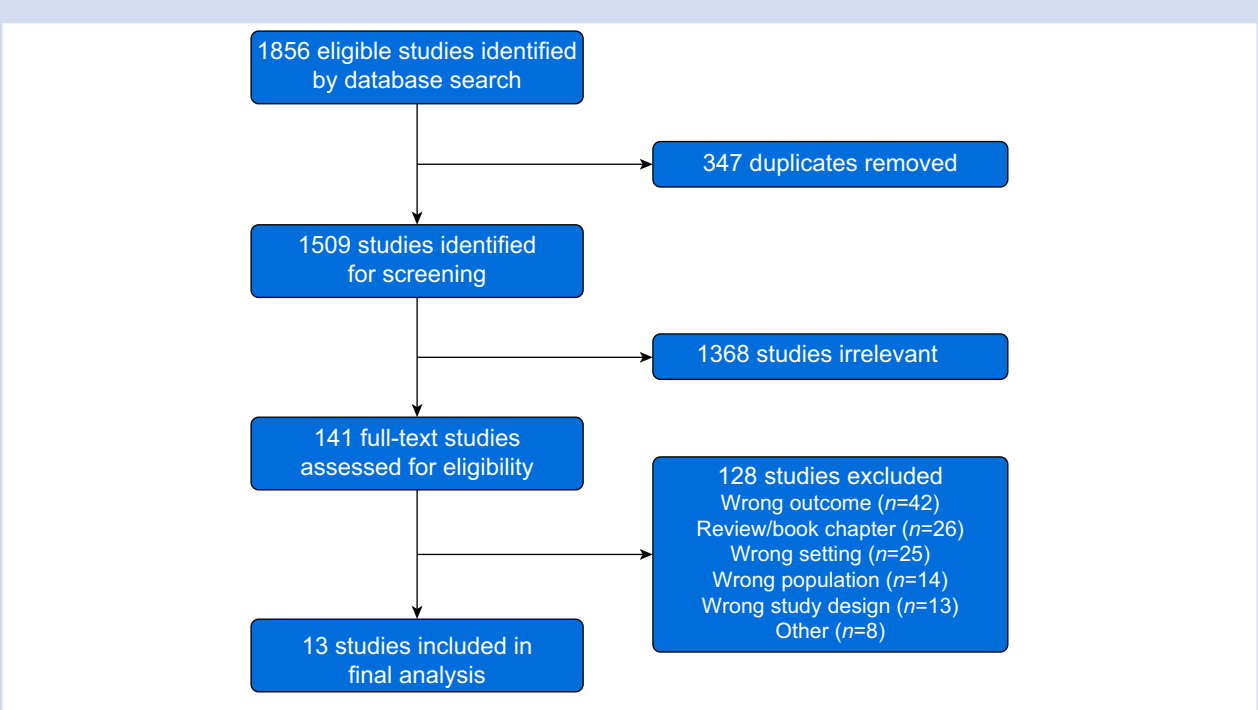

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

Table 1 Characteristics of included studies. NA, not applicable; NR, not reported. *Data presented as permitted range, or median (IQR), mean [SD], or mean (range) when reported. †Median (IQR), mean [SD], or mean (range). IQR, inter-quartile range; LOS, length of stay; MAC, minimum alveolar concentration; SD, standard deviation.

Reference	*n*	Design	Agent	Age (years)	Percentage of female (%)	MAC or end-tidal percentage concentration (%)*	Duration of sedation (h)†	ICU LOS (days)	Mortality (%)
Cardiac arrest survivors	828								
Foudraine and colleagues[25] (2021)	170	Retrospective cohort	Sevoflurane	65.5 (62.5–68.5)	28	0.5	34.3 (25.8–55.5)	6.5 (4.7–22.4)	40
			Midazolam or propofol	65.4 (62.5–68.3)	29	NA	NR	8.1 (6.7–11.6)	44.7
Staudacher and colleagues[26] (2018)	214	Retrospective cohort	Isoflurane	66.6 (62.5–70.7)	14	0.5–1.0	46.5 (37.0–59.5)	11.1 (8.6–13.5)	36
			Propofol	66.0 (63.9–68)	32	NA	NR	9.8 (8.9–10.8)	29.2
Krannich and colleagues[27] (2017)	432	Retrospective cohort	Isoflurane	62.3 (59.6–65.0)	24	0.5–1.5	NR	8.5 (4.2–16.0)	NR
			Midazolam or propofol	61.9 (58.9–64.8)	26	NA	NR	13.0 (6–26.7)	NR
Hellström and colleagues[28] (2014)	12	Retrospective case series	Isoflurane	NR	17	0.8 [0.1]	31.0 [12.0]	NR	50
Postoperative (noncardiac)	235								
Jung and colleagues[29] (2020)	49	Retrospective cohort	Sevoflurane	62 (54.5–70.5)	28	0.7 (95% CI: 0.6–0.8)	12.9 [6.5]	2 (2–2)	NR
			Propofol	61 (57–65)	29	NA	62.8 [86.44]	2 (2–2)	NR
Röhm and colleagues[30] (2009)	130	Single-blinded RCT	Sevoflurane	67 [10]	28	0.5–1.0	9.2 [4.3]	1.3 [0.9]	2
			Propofol	67 [8]	27	NA	9.3 [4.7]	1.61 [1.91]	3.28
Meiser and colleagues[31] (2003)	56	Single-blinded RCT	Desflurane	65 (37–83)	32	3.5 [0.5]	6.1 [1.8]	NR	NR
			Propofol	59.9 (33–73)	39	NA	6.02 [1.48]	NR	NR
Postoperative (cardiac)	170								
Hellström and colleagues[32] (2012)	100	Single-blinded RCT	Isoflurane	65 [8]	24	0.8 [0.18]	2.7 (2.1–3.2)	0.9 (0.8–1.0)	3
			Propofol	66 [11]	16	NA	3.08 (2.11–4.05)	0.91 (0.83 –0.99)	4.3
Röhm and colleagues[33] (2008)	70	Single-blinded RCT	Isoflurane	64.6 [8.6]	20	0.8 (NR)	8.1 [3.1]	1.2 [0.6]	2.85
			Midazolam	66.4 [8.0]	28	NA	8.4 [4.2]	1.65 [1.48]	2.85
Mixed medical –surgical	448								
Meiser and colleagues[34] (2021)	301	Open-label RCT	Isoflurane	56.0 (45.5–67.0)	31	0.5 [0.2]	NR; maximum 54	NR	23
			Propofol	64.3 [12.9]	35	NA	NR; maximum 54	NR	20
	60	Single-blinded RCT	Isoflurane	61.00 (56.0 –71.0)	24	Daily median 0.2–0.4	114.0 (68.7 –189.3)	15.8 (10.9 –27.2)	58

Continued

Table 1 Continued

Reference	n	Design	Agent	Age (years)	Percentage of female (%)	MAC or end-tidal percentage concentration (%)*	Duration of sedation (h)†	ICU LOS (days)	Mortality (%)
Jerath and colleagues[35] (2020)			Propofol or midazolam	56.0 (45.5–67.0)	42	NA	88.0 (41.3–117.0)	12.8 (7.3–18.1)	36.9
Mesnil and colleagues[1] (2011)	47	Single-blinded RCT	Sevoflurane Propofol or midazolam	52 (33–64) Propofol: 54 (45–63); midazolam: 55 (31–61)	47 Propofol: 35; midazolam: 28	0.50 NA	50 (39–71) Propofol: 57 (35–89); midazolam: 50 (38–71)	10 (5–16) Propofol: 12 (7–19); midazolam: 12 (9–17)	NR NR
Sackey and colleagues[36] (2008)	40	Prospective follow-up after RCT	Isoflurane Midazolam	58 (39–80) 57 (19–80)	55 45	NR NA	44.2 [31.3] 61.3 [33.4]	6.7 [5.2] 7.85 [6.99]	5 10

Individual studies ranged in sample size from 12 to 432 patients (Table 1). Of the 13 included studies, four retrospective cohort studies (n=828) examined cardiac arrest survivors. Three studies (n=235) assessed postoperative noncardiac patients, two of which were RCTs and the third a retrospective cohort study. Two RCTs (n=170) evaluated postoperative cardiac surgery patients. Four studies (n=448) were in a mixed medical–surgical population, three of which were RCTs and one a prospective cohort follow-up after an RCT.

Participant and intervention characteristics

The median age of patients was 62 yr (range: 52–67 yr), the percentage of female patients was 35% (range: 14–55%), the duration of sedation was 31 h (range: 6–114 h), the ICU length of stay was 7.85 days (range: 0.9–15.8 days), and mortality was 20% (range: 2–58%) amongst studies reporting these characteristics. The most frequently used intervention was isoflurane, in eight of 13 studies (62%). Sevoflurane was used in four of 13 studies (31%) and desflurane in one of 13 studies (7%). In terms of i.v. drugs, six of 13 studies (46%) compared inhaled anaesthetics with propofol only, whereas two of 13 studies (15%) used only midazolam. The remaining five of 13 studies (39%) used either midazolam or propofol at the discretion of the study investigators. The one case series did not have an active i.v. comparator.[28]

Acute (ICU or in-hospital) cognitive outcomes

Outcomes

The most frequently reported outcome was delirium, which was reported in eight of 13 studies (62%; n=1034) (three mixed medical–surgical, two post-cardiac arrest, two postoperative noncardiac, and one postoperative cardiac; Table 2). Amongst eight studies, one retrospective study in post-cardiac arrest survivors[25] reported a significantly lower incidence of delirium in patients who received isoflurane compared with propofol sedation (16% *vs* 37%; P<0.009), whereas the rest of the studies showed no difference in delirium between sedation arms. A meta-analysis of the five available RCTs showed no difference in the incidence of delirium between inhaled and i.v. sedation (Fig. 2). One RCT in mixed medical–surgical patients[1] showed higher proportion of patients experiencing hallucination with i.v. than inhaled sedatives (propofol 28.6%, midazolam 35.7%, and sevoflurane 0%; P=0.04). One RCT assessing psychomotor recovery in postoperative noncardiac patients, patients randomised to desflurane, recalled significantly more words 1, 5, and 10 min after they were able to state their birthdate correctly, but there was no difference in two other psychometric tests compared with propofol.[31] The sole retrospective study in cardiac arrest survivors comparing inhaled and i.v. sedation showed no difference in neurological recovery between sedation arms.[27]

Instruments

Delirium was assessed using the Confusion Assessment Method for the ICU (CAM-ICU) in four of eight studies (50%; n=580), blinded chart review of healthcare professional documentation in one study (12%; n=40),[36] and three studies (38%; n=414) did not report the method of assessment. For the meta-analysis on delirium outcomes, only two of five studies (40%; n=180) used CAM-ICU, whereas the remainder were based on healthcare provider assessments without clearly

Table 2 Description of outcomes studied. CAM-ICU, Confusion Assessment Method for the ICU; DSST, digit symbol substitution test; GCS, *Glasgow Coma Scale*; HADS, Hospital Anxiety and Depression Scale; IES, Impact of Event Scale; NA, not applicable; NR, not reported; NS, reported as not statistically significant. *Statistically significant.

Reference	*n*	Inhaled anaesthetic	I.V. comparator	Outcome(s) assessed	Timing assessment	Tool(s) used	Frequency of assessment	Score or incidence (%) (volatile)	Score or incidence (%) (i.v.)	Reported *P*-value
Cardiac arrest survivors	828									
Foudraine and colleagues[25] (2021)	170	Sevoflurane	Midazolam or propofol	Delirium	First 14 days of ICU stay	CAM-ICU	NR	16.1%	37.3%	0.009*
Staudacher and colleagues[26] (2018)	214	Isoflurane	Propofol	Delirium	NR	NR	NR	41.7%	35.4%	0.569
Krannich and colleagues[27] (2017)	432	Isoflurane	Midazolam or propofol	Neurological recovery	At ICU discharge	Cerebral performance category	Once	44.5%	46.4%	0.599
Hellström and colleagues[28] (2014)	12	Isoflurane	None	Neurological recovery	>72 h after rewarming	Glasgow Coma Scale	Once	Average GCS 8.3	NA	NA
Postoperative (noncardiac)	235									
Jung and colleagues[29] (2020)	49	Sevoflurane	Propofol	Delirium	Until ICU discharge	CAM-ICU	NR	0%	0%	NA
Röhm and colleagues[30] (2009)	130	Sevoflurane	Propofol	Delirium	Within 24 h of extubation	NR	NR	7.8%	11.5%	NR
Meiser and colleagues[31] (2003)	56	Desflurane	Propofol	Psychomotor recovery	During ICU stay	DSST	60 and 120 min after extubation	14 (60 min); 18 (120 min)	14 (60 min); 19 (120 min)	NR
						Trieger dot test	30 and 60 min after extubation	16 (60 min); 22 (120 min)	20 (60 min); 21 (120 min)	NR
						Five-word recall	Once, after patient stated birthdate correctly after extubation	2.0 (1 min); 1.6 (5 min); 0.6 (10 min)	1.2 (1 min); 0.9 (5 min); 0.6 (10 min)	<0.05*
Postoperative (cardiac)	170									
Hellström and colleagues[32] (2012)	100	Isoflurane	Propofol	Memories	On the day of hospital discharge	ICU memory tool	Once	20.5% (delusions); 84.1% (factual); 54.5% (feelings)	20.5% (delusions); 84.1% (factual); 54.5% (feelings)	0.47; 1.00; 0.67
Röhm and colleagues[33] (2008)	70	Isoflurane	Midazolam	Delirium	During ICU stay	NR	NR	11.4%	14.3%	NS
Mixed medical–surgical	448									
Meiser and colleagues[34] (2021)	301	Isoflurane	Propofol	Delirium	Up to 7 days after ICU admission	CAM-ICU	NR	5%	5%	NS

Continued

Table 2 Continued

Reference	n	Inhaled anaesthetic	I.V. comparator	Outcome(s) assessed	Timing assessment	Tool(s) used	Frequency of assessment	Score or incidence (%) (volatile)	Score or incidence (%) (i.v.)	Reported P-value
Jerath and colleagues[35] (2020)	60	Isoflurane	Propofol or midazolam	Delirium	For 72 h post-extubation	CAM-ICU	Every 12 h	'The proportion of CAM-ICU positive patients post-extubation demonstrated a similar trend'		NA
				Long-term cognitive dysfunction	3 months after ICU discharge	Telephone Interview for Cognitive Status	Once	67%	78%	NS
Mesnil and colleagues[1] (2011)	47	Sevoflurane	Propofol or midazolam	Hallucinations	After discontinuation of sedation in the ICU	Review of provider assessments	NR	0%	35.7% (midazolam); 28.6% (propofol)	0.04*
Sackey and colleagues[36] (2008)	40	Isoflurane	Midazolam	Delirium	At the time of terminated sedation or 96 h after initiation of sedation for up to 4 days	Review of provider assessments	Each assessment documented by a nurse, physician, or physiotherapy notes	22.3%	16.67%	1.0
				Memories	6 months after ICU discharge	ICU memory tool	Once	20% (delusions); 50% (factual); 50% (feelings)	66.7% (delusions); 66.7% (factual); 50% (feelings)	0.06; 0.6; 1.0
				Anxiety and depression	6 months after ICU discharge	HADS	Once	60%	33%	0.6
				PTSD	6 months after ICU discharge	IES	Once	60%	33%	0.6

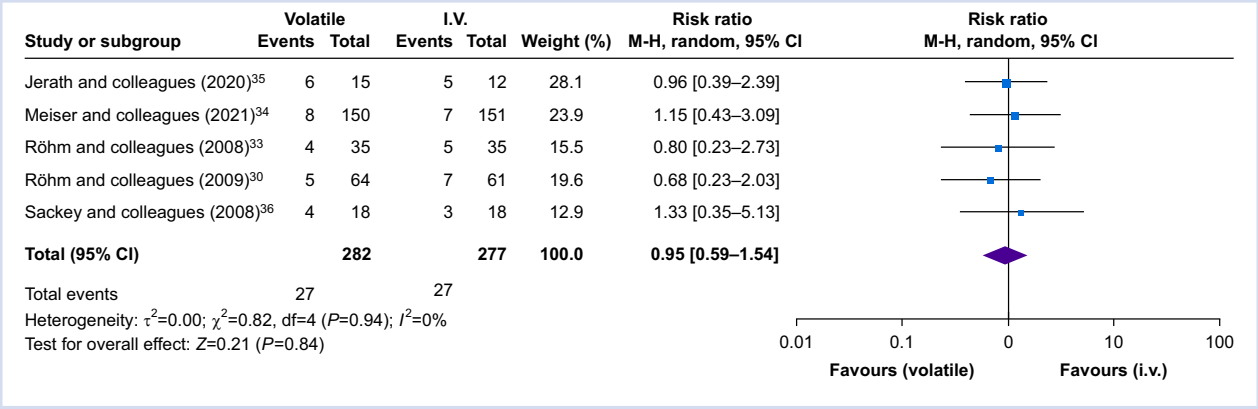

Fig 2. Effect of inhaled volatile anaesthetics on delirium incidence compared with intravenous anaesthesia in critically ill adults. CI, confidence interval.

describing use of a validated tool in their articles. Of note, the three of five studies that did not report use of a validated tool to ascertain ICU delirium were published before the publication of Pain, Agitation, and Delirium[37] and Pain, Agitation, Delirium, Immobility, and Sleep[38] guidelines that recommended use of validated ICU delirium assessment tools, and the event (delirium) rate in these studies was not different from the two of five studies that used CAM-ICU tool. Hallucinations were assessed by reviewing healthcare professional documentation.[1] Psychomotor recovery was assessed using digital substitution subtraction, Trieger dot, and five-word memory tests.[31] Neurological recovery post-cardiac arrest was assessed using Cerebral Performance Scale or Glasgow Coma Scale.[27,28] See Table 3 for brief description and performance characteristics of these instruments.

Timing of assessments

Delirium was assessed whilst the patient was in the ICU in seven of eight studies (88%; *n*=820), with one study (12%; *n*=214) not explicitly stating the timing of delirium assessments.[26] The frequency of delirium assessments was only reported in two studies (25%; *n*=100). Hallucinations were assessed after discontinuation of sedation in the ICU. Psychomotor recovery was assessed in the ICU at pre-defined time intervals within 2 h of extubation.[31] Neurological recovery was assessed in the ICU at least 72 h after rewarming from therapeutic hypothermia or at ICU discharge.[27,28]

Long-term (post-hospital discharge) cognitive outcomes

Outcomes

Only one study (*n*=60) assessed long-term cognitive dysfunction and did not find any difference between inhaled and i.v. sedation groups.[35] Two studies (*n*=140) assessed ICU memories in mixed medical–surgical and postoperative cardiac patients.[32,36] In both studies, there were no differences in memories of feelings, factual events, or delusions from the ICU between the two sedation groups, although in one study fewer patients had memories of ICU hallucinations or delusions, but this result was not statistically significant (P=0.06).[36]

Instruments

The only study assessing long-term cognitive dysfunction used the Telephone Interview for Cognitive Status (TICS).[35 43] This instrument is a global mental status test that can either be administered over the telephone or face to face. A score below 26 (of possible 41) is considered cognitive impairment. ICU memories were assessed using the ICU memory tool.[44] This tool assessed 14 specific memories from the ICU during the recovery period analysed in three groups (delusional, factual, and memories of specific feelings). See Table 3 for brief description and performance characteristics of these instruments.

Timing of assessments

Long-term cognitive dysfunction was assessed at 3 months after ICU discharge.[35] ICU memories were assessed on the day of discharge[32] or 6 months[36] after hospital discharge.

Psychiatric outcomes

Outcomes

Only one study assessed anxiety, depression, and PTSD with no difference in outcomes between inhaled and i.v. sedation groups.[36]

Instruments

Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS) tool, whereas PTSD was assessed using the Impact of Event Scale tool. These tools are questionnaires based on the patient's reported symptoms.

Timing of assessments

Psychiatric outcomes were assessed at 6 months after ICU discharge in this one study.

Study quality assessment

The study quality performed for each study is summarised in the Supplementary material. The included RCTs

Table 3 Description of cognitive and psychiatric tools. CAM-ICU, Confusion Assessment Method for the ICU; CI, confidence interval; DSST, digit symbol substitution test; HADS, Hospital Anxiety and Depression Scale; IES, Impact of Event Scale; NA, not applicable; NR, not reported; PTSD, post-traumatic stress disorder; TICS, Telephone Interview for Cognitive Status.

Reference	*n*	Inhaled anaesthetic	I.V. comparator	Outcome(s) assessed	Tool(s) used	Tool description	Test validity (if applicable)	Reference
Cardiac arrest survivors	828							
Foudraine and colleagues[25] (2021)	170	Sevoflurane	Midazolam or propofol	Delirium	CAM-ICU	Clinical assessment for delirium validated for mechanically ventilated, non-verbal patients	Sensitivity: 84% (95% CI: 77–88%); specificity: 95% (95% CI: 91–97%)	Boney and colleagues[40] (2022)
Staudacher and colleagues[26] (2018)	214	Isoflurane	Propofol	Delirium	NR	NR	—	—
Krannich and colleagues[27] (2017)	432	Isoflurane	Midazolam or propofol	Neurological recovery	Cerebral performance category	Standardised descriptor of neurological functional status	NA	NA
Hellström and colleagues[28] (2014)	12	Isoflurane	None	Neurological recovery	Glasgow Coma Scale	Standardised assessment of level of consciousness	NA	NA
Postoperative (noncardiac)	235							
Jung and colleagues[29] (2020)	49	Sevoflurane	Propofol	Delirium	CAM-ICU	Clinical assessment for delirium validated for mechanically ventilated, non-verbal patients	Sensitivity: 84% (95% CI: 77–88%); specificity: 95% (95% CI: 91–97%)	Boney and colleagues[40] (2022)
Röhm and colleagues[30] (2009)	130	Sevoflurane	Propofol	Delirium	NR	NR	NA	NA
Meiser and colleagues[31] (2003)	56	Desflurane	Propofol	Psychomotor recovery	DSST	The DSST is a paper-and-pencil cognitive test presented on a single sheet of paper that requires a subject to match symbols to numbers according to a key	Cohen's effect size (*d*-test statistic) for Alzheimer's disease: −1.76 (sensitivity of 81%)	Morandi and colleagues[41] (2012)
					Trieger dot test	A paper-and-pencil test with a variable number of dots that requires the subject to connect the dots to form a figure	NA	NA
					Five-word memory test	Subjects are provided with five words and asked to recall them at various time points	NA	NA
Postoperative (cardiac)	170							
Hellström and colleagues[32] (2012)	100	Isoflurane	Propofol	Memories	ICU memory tool	Assessment of 14 specific memories from the ICU during the recovery period analysed in three groups (delusional, factual, and memories of specific feelings)	Internal consistency (*α*): 0.86	Hellström and colleagues[32] (2012)

Continued

Table 3 Continued

Reference	n	Inhaled anaesthetic	I.V. comparator	Outcome(s) assessed	Tool(s) used	Tool description	Test validity (if applicable)	Reference
Röhm and colleagues[33] (2008)	70	Isoflurane	Midazolam	Delirium	NR	NR	NA	NA
Mixed medical −surgical	448							
Meiser and colleagues[34] (2021)	301	Isoflurane	Propofol	Delirium	CAM-ICU	Clinical assessment for delirium validated for mechanically ventilated, non-verbal patients	Sensitivity: 84% (95% CI: 77 −88%); specificity: 95% (95% CI: 91 −97%)	Boney and colleagues[40] (2022)
Jerath and colleagues[35] (2020)	60	Isoflurane	Propofol or midazolam	Delirium	CAM-ICU	Clinical assessment for delirium validated for mechanically ventilated, non-verbal patients	Sensitivity: 84% (95% CI: 77 −88%); specificity: 95% (95% CI: 91 −97%)	Boney and colleagues[40] (2022)
				Long-term cognitive dysfunction	TICS	The TICS is a global mental status test that can either be administered over the telephone or face to face. A score below 26 (of possible 41) is considered cognitive impairment.	Sensitivity: 69.0%; specificity: 71.4%	Jerath and colleagues[35] (2020)
Mesnil and colleagues[1] (2011)	47	Sevoflurane	Propofol or midazolam	Hallucinations	Review of provider assessments	—	—	—
Sackey and colleagues[36] (2008)	40	Isoflurane	Midazolam	Delirium	Review of provider assessments	—	—	—
				Memories	ICU memory tool	Assessment of 14 specific memories from the ICU during the recovery period analysed in three groups (delusional, factual, and memories of specific feelings)	Internal consistency (α): 0.86	Hellström and colleagues[32] (2012)
				Anxiety and depression	HADS	A self-administered measure with 14 items in total that ask the client to reflect on their mood in the past week	Sensitivity: 82.0%; specificity: 77.0% (for a combined score of 11)	Wood and colleagues[39] (2018)
				PTSD	IES	A 17-point self-assessment tool that screens for PTSD by measuring the patient's response to a specific traumatic event	Sensitivity: 91%; specificity: 72% (for a cutoff score of 27)	Geissbühler and colleagues[42] (2021)

demonstrated five independent outcomes with a low risk of bias,[31] both delirium and long-term cognitive dysfunction outcomes.[32,34,35] Five outcomes had some concerns (delirium, anxiety, depression, and PTSD[36]; delirium[30,33]) and two outcomes had high risk of bias (delirium outcome[36]; hallucination outcome[1]) (Supplementary Table S1). Of the four observational studies, two were of good quality[27,29] and two were of fair quality,[25,35] as evaluated by the Newcastle–Ottawa Scale (Supplementary Table S2). One case series was deemed of sufficient quality to be included for analysis by the JBI Critical Appraisal tool (Supplementary Table S3).

Discussion

Our systematic review and meta-analysis aimed to summarise existing evidence regarding acute and long-term cognitive and psychiatric outcomes in adult critically ill patients receiving inhaled anaesthetic *vs* i.v. sedation. We identified 13 studies that enrolled more than a thousand patients from the following subgroups: cardiac arrest survivors, postoperative noncardiac, postoperative cardiac, or mixed medical–surgical patients. Most patients received either isoflurane or sevoflurane. Incidence of ICU delirium was the most common reported acute cognitive outcome, with available evidence showing no difference amongst patients receiving inhaled or i.v. sedatives, although we have low certainty in this result given methodological limitations of existing evidence. Only one RCT assessed long-term cognition at 3 months after hospital discharge using the TICS instrument and showed no difference between patients randomised to inhaled or i.v. sedatives. Similarly, only one study assessed psychiatric outcomes at 6 months and showed no difference between inhaled and i.v. sedatives. Instruments used to assess cognitive and psychiatric outcomes were heterogeneous across studies, making it challenging to compare results between studies. The strengths of this review include that it adhered to the PRISMA guidelines, was registered in PROSPERO (ID: CRD42021236455), and its protocol was peer reviewed and published with incorporation of reviewer suggestions regarding search strategy and relevant outcomes.[24]

Limitations of existing evidence

Our certainty in the results of this systematic review is tempered by the limitations of the available evidence. First, although we included 13 studies enrolling more than a thousand patients, there was paucity of RCTs, and individual studies amenable to meta-analysis had small sample sizes.

Second, some of the included studies did not use validated and up-to-date instruments to assess cognitive and psychiatric outcomes. For example, delirium was assessed using the validated CAM-ICU tool in only two of the five trials included in our meta-analysis, although this was likely because the remaining three studies were published before the Pain, Agitation, and Delirium[37] and Pain, Agitation, Delirium, Immobility, and Sleep[38] guidelines recommending use of validated tools to assess ICU delirium. For psychiatric outcomes, the use of outdated instruments (e.g. HADS for anxiety and depression) may inaccurately measure the burden of psychiatric morbidity in this patient population.

Third, reporting of outcomes was incomplete. For example, although some studies reported delirium incidence, they did not report on delirium duration or the competing effects of ICU mortality and coma (both of which preclude delirium assessment). Delirium- and coma-free days would likely be a more informative assessment of delirium burden in future studies. For long-term cognition, the use of TICS instrument,[45] an 11-item questionnaire that is modelled after the Mini-Mental State Examination (MMSE),[46] limited the assessment of cognition to global cognitive score and did not allow assessment of cognitive impairment across different domains that are commonly affected in critically illness survivors.[12,47] Furthermore, similar to MMSE, this cognitive impairment screening tool may be prone to ceiling effect, which may prevent detection of cognitive impairment in critical illness survivors.[12]

Finally, the timing of cognitive and psychiatric assessments varied across studies. Given that cognitive dysfunction in critically ill patients varies across time during ICU and hospital and may persist for up to 2 yr after hospital discharge,[12] future studies should define standard time points for routine assessment of these outcomes across the trajectory of critical illness and recovery.

Why is it important to measure cognitive and psychiatric outcomes in ICU sedation studies?

Cognitive function and psychiatric health are important patient-centred outcomes that impact patient recovery from critical illness. Long-term cognitive dysfunction occurs in up to 80% of ICU survivors, is severe (comparable with Alzheimer's or moderate traumatic brain injury), affects patients across the age span, and can last beyond 2 yr after hospital discharge.[12,14] Acute cognitive dysfunction (e.g. delirium) is associated with longer duration of ventilation, ICU and hospital length of stay, and hospital mortality.[13] Given that delirium is an independent predictor of long-term cognitive dysfunction[14] and because sedation-associated delirium is the most common delirium phenotype (>60% patients[18]), optimising sedation may reduce delirium and improve long-term cognition in critical illness survivors. Although inhaled anaesthetics have favourable pharmacokinetic properties that may reduce ICU delirium by shortening sedation exposure,[48] the evidence summarised in the current meta-analysis does not support this hypothesis. However, given heterogeneity of study designs, patient populations, and instruments used to assess cognitive and psychiatric outcomes, further research is needed to better understand the impact of inhaled anaesthetics on cognitive and psychiatric outcomes. Given that sedation is one of the most common interventions delivered in the ICU and because cognitive vitality is an important patient-centred outcome, advancing our understanding regarding impact of inhaled anaesthetics on cognitive and psychiatric outcomes in critically ill patients is important for informing future practice.

Future directions

Cognitive and psychiatric function are important patient-centred outcomes that impact patient's recovery from critical illness. ICU delirium is associated with longer duration of ventilation, ICU and hospital length of stay, and hospital mortality,[13] and is an independent predictor of long-term cognitive dysfunction that affects up to 80% of critical illness survivors.[14] Optimising ICU sedation may improve these outcomes, as sedation-associated delirium is the most common ICU delirium phenotype (>60% patients[18]). Inhaled anaesthetics have favourable pharmacokinetic properties that may

reduce ICU delirium by shortening sedation exposure,[48] but whether their use improves cognitive and psychiatric outcomes remains unclear and should be explored in future studies that address limitations of existing evidence identified in this systematic review.

First, future studies should use rigorous study design (e.g. multicentre RCTs with prospective cohort follow-up studies) that incorporates routine measurement of cognitive and psychiatric outcomes at regular time intervals that, similar to other critical care cohorts,[49] extend at least to 12 months beyond hospital discharge. Given the high attrition rate attributable to mortality and loss to follow-up (ranging between 31% and 45%) in longitudinal cohorts of critically ill patients,[50] larger sample sizes and patient retention strategies will ensure that future studies are powered to assess differences in long-term cognitive and psychiatric outcomes.[51] However, the cost and effort associated with carrying out further studies on larger populations need to be weighed heavily, given the lack of signal for any difference between sedation strategies for our outcomes of interest identified in this systematic review.

Second, future studies should utilise validated, comprehensive, and contemporary instruments for assessment of outcomes, such as the CAM-ICU or Intensive Care Delirium Screening Checklist for assessment of ICU delirium.[38] Assessment of long-term cognitive outcomes would benefit from the use of neurocognitive batteries that assess cognition across multiple domains (e.g. Repeatable Battery for the Assessment of Neuropsychological Status [RBANS]) and avoid ceiling effects commonly seen with simple screening tools, such as MMSE.[12,14] Cognitive instruments that can be delivered remotely *via* telephone (e.g. the virtual version of RBANS[39,52]) or web-based interfaces may facilitate patient retention in follow-up cohorts. Psychiatric assessments should use modern instruments, such as Patient Health Questionnaire, Generalized Anxiety Disorder, and PTSD Checklist for DSM-5, for assessment of depression, anxiety, and PTSD, respectively, given that they have better sensitivity and specificity than older tools, such as HADS and Impact of Event Scale.[5–39, 43–55] Standardised reporting of core outcomes related to cognition and psychiatric outcomes in the postoperative population has gained interest,[40,56] and a similar approach should be adapted to the critical care population.

Third, to account for competing outcomes of death and coma and better quantify the burden of ICU delirium, assessment of delirium should expand beyond measurement of delirium incidence and include computation of composite outcomes, such as days alive and free from delirium and coma.

Fourth, cognitive and psychiatric assessments should occur at standard time intervals (e.g. during ICU stay, at hospital discharge, and at 3–12 months after hospital discharge) to allow assessment of cognitive and psychiatric recovery in individual patients and enable comparison of outcomes across studies.

Finally, future RCTs comparing i.v. and inhaled sedatives should explore whether guiding sedation using bedside depth of sedation monitors (e.g. bispectral index or sub-hairline, full-scalp, or high-density electroencephalography) may improve cognitive or psychiatric outcomes by both shortening the duration of sedative exposure and ensuring appropriate depth of sedation for each patient that minimises delusions, hallucinations, bad memories, and delirium.[41]

Limitations of this systematic review and meta-analysis

The main limitation of this review related to the heterogeneity of included studies in terms of study designs, sample size, cognitive and psychiatric outcomes assessed, instruments used for outcomes assessment, and timing of assessments. Due to this heterogeneity, we could only meta-analyse randomised controlled studies reporting incidence of delirium, although the low quality of some of the included studies and described heterogeneity lowered the certainty in the observed results. We also considered meta-regression to explore the effect of key predictor variables (e.g. age, severity of illness, etc.) on delirium outcome. However, given limited number (k=5) of primary studies, we elected not to perform meta-regression to avoid the risk of overfitting.[42] Future meta-analyses may consider meta-regression once more primary studies are completed (suggest more than 10 studies).[57] Despite these limitations, our comprehensive search and systematic approach enabled us to identify and describe existing heterogeneity and issue recommendations on how to improve future studies in this emerging field.

Conclusions

There are limited studies comparing the effects of i.v. and inhaled sedatives on cognitive and psychiatric outcomes in critically ill adults. Although available evidence suggests similar incidence of ICU delirium in adult patients receiving inhaled or i.v. sedatives, we have low certainty in this result because of heterogeneity and paucity of high-quality studies. Future research should include well-designed studies that apply validated, comprehensive, and contemporary instruments at standardised time intervals to compare cognitive and psychiatric outcomes across the continuum of critical illness in patients receiving i.v. *vs* inhaled sedatives.

Authors' contributions

Review concept/design: SC, AJ, KG, DW, CF, MS
Data acquisition/extraction: SC, AJ, KG, AS, DW, CF, MS
Drafting and revision of paper: all authors
Final approval of paper: all authors

Acknowledgements

The authors wish to thank the London Health Sciences Centre clinical librarian, Alla Iansavitchene, for her assistance with performing the literature search.

Declarations of interest

The authors have no interests to declare related to the production of this paper. MS and AJ have an ongoing clinical trial examining the effects of inhaled anaesthetics on cognitive outcomes in critically ill adults.

Funding

Canadian Institute of Health Research (Covid-19 Rapid Research Grant # 447612) to AJ, MS, CM, and BHC; Government of Ontario (Covid-19 Rapid Research Fund # C-055-2421758) to

AJ, MS, CM, and BHC; Alternative Funding Plan, Ministry of Ontario to AJ and BHC; Merit Award, Department of Anesthesiology and Pain Medicine, University of Toronto to AJ and BHC

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2023.05.004.

References

1. Mesnil M, Capdevila X, Bringuier S, et al. Long-term sedation in intensive care unit: a randomized comparison between inhaled sevoflurane and intravenous propofol or midazolam. *Intensive Care Med* 2011; **37**: 933–41
2. Jabaudon M, Boucher P, Imhoff E, et al. Sevoflurane for sedation in acute respiratory distress syndrome. A randomized controlled pilot study. *Am J Respir Crit Care Med* 2017; **195**: 792–800
3. Jerath A, Panckhurst J, Parotto M, et al. Safety and efficacy of inhaled anaesthetic agents compared with standard intravenous midazolam/propofol sedation in ventilated critical care patients: a meta-analysis and systematic review of prospective trials. *Anesth Analg* 2017; **124**: 1190–9
4. Kanji S, Burry L, Williamson D, et al. Therapeutic alternatives and strategies for drug conservation in the intensive care unit during times of drug shortage: a report of the Ontario COVID-19 ICU Drug Task Force. *Can J Anaesth* 2020; **67**: 1405–16
5. Jerath A, Ferguson ND, Cuthbertson B. Inhalational inhaled-based sedation for COVID-19 pneumonia and ARDS. *Intensive Care Med* 2020; **46**: 1563–6
6. Flinspach AN, Zacharowski K, Ioanna D, Adam EH. Volatile isoflurane in critically ill coronavirus disease 2019 patients—a case series and systematic review. *Crit Care Explor* 2020; **2**, e0256
7. Hanidziar D, Bittner EA. Sedation of mechanically ventilated COVID-19 patients: challenges and special considerations. *Anesth Analg* 2020; **131**: e40–1
8. Calvin CM, Batty GD, Der G, et al. Childhood intelligence in relation to major causes of death in 68-year follow-up: prospective population study. *BMJ* 2017; **357**: j2708
9. Deary IJ, Strand S, Smith P, Fernandes C. Intelligence and educational achievement. *Intelligence* 2017; **35**: 13–21
10. Gale CR, Batty GD, Tynelius P, Deary IJ, Rasmussen F. Intelligence in early adulthood and subsequent hospitalisation and admission rates for the whole range of mental disorders: longitudinal study of 1,049,663 men. *Epidemiology* 2010; **21**: 70–7
11. Kuncel NR, Hezlett SA. Fact and fiction in cognitive ability testing for admissions and hiring decisions. *Curr Dir Psychol Sci* 2010; **19**: 339–45
12. Honarmand K, Lalli RS, Priestap F, et al. Natural history of cognitive impairment in critical illness survivors: a systematic review. *Am J Respir Crit Care Med* 2020; **202**: 193–201
13. Wilcox ME, Girard TD, Hough CL. Delirium and long term cognition in critically ill patients. *BMJ* 2021; **373**: n1007
14. Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. *N Engl J Med* 2013; **369**: 1306–16
15. Kotfis K, Marra A, Ely EW. ICU delirium—a diagnostic and therapeutic challenge in the intensive care unit. *Anaesthesiol Intensive Ther* 2018; **50**: 160–7
16. Müller A, von Hofen-Hohloch J, Mende M, et al. Long-term cognitive impairment after ICU treatment: a prospective longitudinal cohort study (Cog-I-CU). *Sci Rep* 2020; **10**, 15518
17. Sakusic A, O'Horo JC, Dziadzko M, et al. Potentially modifiable risk factors for long-term cognitive impairment after critical illness: a systematic review. *Mayo Clin Proc* 2018; **93**: 68–82
18. Girard TD, Thompson JL, Pandharipande PP, et al. Clinical phenotypes of delirium during critical illness and severity of subsequent long-term cognitive impairment: a prospective cohort study. *Lancet Respir Med* 2018; **6**: 213–22
19. Wade DM, Howell DC, Weinman JA, et al. Investigating risk factors for psychological morbidity three months after intensive care: a prospective cohort study. *Crit Care* 2012; **16**: R192
20. Rabiee A, Nikayin S, Hashem MD, et al. Depressive symptoms after critical illness: a systematic review and meta-analysis. *Crit Care Med* 2016; **44**: 1744–53
21. Nikayin S, Rabiee A, Hashem MD, et al. Anxiety symptoms in survivors of critical illness: a systematic review and meta-analysis. *Gen Hosp Psychiatry* 2016; **43**: 23–9
22. Righy C, Rosa RG, da Silva RTA, et al. Prevalence of posttraumatic stress disorder symptoms in adult critical care survivors: a systematic review and meta-analysis. *Crit Care* 2019; **23**: 1–13
23. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol* 2009; **62**: e1–34
24. Cuninghame S, Gorsky K, Francoeur C, et al. Effect of sedation with inhaled anaesthetics on cognitive and psychiatric outcomes in critically ill adults: a systematic review protocol. *BMJ Open* 2022; **12**, e052893
25. Foudraine NA, Algargoush A, van Osch FH, Bos AT. A multimodal sevoflurane-based sedation regimen in combination with targeted temperature management in post-cardiac arrest patients reduces the incidence of delirium: an observational propensity score-matched study. *Resuscitation* 2021; **159**: 158–64
26. Staudacher DL, Hamilton SK, Duerschmied D, et al. Isoflurane or propofol sedation in patients with targeted temperature management after cardiopulmonary resuscitation: a single center study. *J Crit Care* 2018; **45**: 40–4
27. Krannich A, Leithner C, Engels M, et al. Isoflurane sedation on the ICU in cardiac arrest patients treated with targeted temperature management: an observational propensity-matched study. *Crit Care Med* 2017; **45**: e384–90
28. Hellström J, Öwall A, Martling CR, Sackey PV. Inhaled isoflurane sedation during therapeutic hypothermia after cardiac arrest: a case series. *Crit Care Med* 2014; **42**: e161–6
29. Jung S, Na S, Kim HB, Joo HH, Kim J. Inhalation sedation for postoperative patients in the intensive care unit: initial sevoflurane concentration and comparison of opioid use with propofol sedation. *Acute Crit Care* 2020; **35**: 197–204
30. Röhm KD, Mengistu A, Boldt J, Mayer J, Beck G, Piper SN. Renal integrity in sevoflurane sedation in the intensive care unit with the anesthetic-conserving device: a comparison with intravenous propofol sedation. *Anesth Analg* 2009; **108**: 1848–54
31. Meiser A, Sirtl C, Bellgardt M, et al. Desflurane compared with propofol for postoperative sedation in the intensive care unit. *Br J Anaesth* 2003; **90**: 273–80

32. Hellström J, Öwall A, Sackey PV. Wake-up times following sedation with sevoflurane versus propofol after cardiac surgery. *Scand Cardiovasc J* 2012; **46**: 262–8
33. Röhm KD, Wolf MW, Schöllhorn T, Schellhaass A, Boldt J, Piper SN. Short-term sevoflurane sedation using the Anaesthetic Conserving Device after cardiothoracic surgery. *Intensive Care Med* 2008; **34**: 1683–9
34. Meiser A, Volk T, Wallenborn J, et al. Inhaled isoflurane via the anaesthetic conserving device versus propofol for sedation of invasively ventilated patients in intensive care units in Germany and Slovenia: an open-label, phase 3, randomised controlled, non-inferiority trial. *Lancet Respir Med* 2021; **11**: 1231–40
35. Jerath A, Wong K, Wasowicz M, et al. Use of inhaled volatile anesthetics for longer term critical care sedation: pilot randomized controlled trial. *Crit Care Explor* 2020; **2**, e0281
36. Sackey PV, Martling CR, Carlswärd C, Ö Sundin, Radell PJ. Short-and long-term follow-up of intensive care unit patients after sedation with isoflurane and midazolam—a pilot study. *Crit Care Med* 2008; **36**: 801–6
37. 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
38. Devlin JW, Skrobik Y, Gélinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med* 2018; **46**: e825–73
39. Wood MD, Maslove DM, Muscedere J, Scott SH, Boyd JG. Canadian Critical Care Trials Group. Robotic technology provides objective and quantifiable metrics of neurocognitive functioning in survivors of critical illness: a feasibility study. *J Crit Care* 2018; **48**: 228–36
40. Boney O, Moonesinghe SR, Myles PS, et al. Core Outcome Measures for Perioperative and Anaesthetic Care (COMPAC): a modified Delphi process to develop a core outcome set for trials in perioperative care and anaesthesia. *Br J Anaesth* 2022; **128**: 174–85
41. Morandi A, Rogers BP, Gunther ML, et al. The relationship between delirium duration, white matter integrity, and cognitive impairment in intensive care unit survivors as determined by diffusion tensor imaging. *Crit Care Med* 2012; **40**: 2182–9
42. Geissbühler M, Hincapié CA, Aghlmandi S, Zwahlen M, Jüni P, da Costa BR. Most published meta-regression analyses based on aggregate data suffer from methodological pitfalls: a meta-epidemiological study. *BMC Med Res Methodol* 2021; **21**: 1–9
43. Knopman DS, Roberts RO, Geda YE, et al. Validation of the telephone interview for cognitive status-modified in subjects with normal cognition, mild cognitive impairment, or dementia. *Neuroepidemiology* 2010; **34**: 34–42
44. Jones C, Humphris G, Griffiths RD. Preliminary validation of the ICUM tool: a tool for assessing memory of the intensive care experience. *Clin Intensive Care* 2000; **11**: 251–5
45. Brandt J, Spencer M, Folstein M. The telephone interview for cognitive status. *Neuropsychiatry Neuropsychol Behav Neurol* 1988; **1**: 111–7
46. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; **12**: 189–98
47. Honarmand K, Malik S, Wild C, et al. Feasibility of a web-based neurocognitive battery for assessing cognitive function in critical illness survivors. *PLoS One* 2019; **14**, e0215203
48. Jerath A, Parotto M, Wasowicz M, Ferguson ND. Volatile anesthetics. Is a new player emerging in critical care sedation? *Am J Respir Crit Care Med* 2016; **193**: 1202–12
49. Herridge MS, Tansey CM, Matté A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med* 2011; **364**: 1293–304
50. Khan JM, Wood MD, Lee KF, et al. Delirium, cerebral perfusion, and high-frequency vital-sign monitoring in the critically ill. The CONFOCAL-2 feasibility study. *Ann Am Thorac Soc* 2021; **18**: 112–21
51. Bower P, Brueton V, Gamble C, et al. Interventions to improve recruitment and retention in clinical trials: a survey and workshop to assess current practice and future priorities. *Trials* 2014; **15**: 399
52. Galusha-Glasscock JM, Horton DK, Weiner MF, Cullum CM. Video teleconference administration of the repeatable battery for the assessment of neuropsychological status. *Arch Clin Neuropsychol* 2016; **31**: 8–11
53. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med* 2006; **166**: 1092–7
54. Mitchell AJ, Meader N, Symonds P. Diagnostic validity of the Hospital Anxiety and Depression Scale (HADS) in cancer and palliative settings: a meta-analysis. *J Affect Disord* 2010; **126**: 335–48
55. Levis B, Benedetti A, Thombs BD. Accuracy of Patient Health Questionnaire-9 (PHQ-9) for screening to detect major depression: individual participant data meta-analysis. *BMJ* 2019; **365**: I1476
56. Evered L, Silbert B, Knopman DS, et al. Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery—2018. *Anesthesiology* 2018; **129**: 872–9
57. The Cochrane Collaboration. Cochrane handbook for systematic reviews of interventions. Available from https://training.cochrane.org/handbook/current (accessed 16 April 2023).

Handling editor: Jonathan Hardman