

SYSTEMATIC REVIEW AND META-ANALYSIS

Daily Sedation Interruption Versus Continuous Sedation and the Duration of Mechanical Ventilation in Critically Ill Adults: A Systematic Review and Meta-Analysis

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ABSTRACT

Background. Daily sedation interruption (DSI) aims to limit sedative accumulation in mechanically ventilated adults. Trials have conflicted. Implementation studies have not been synthesized with randomized data.

Objective. To compare DSI with continuous sedation without scheduled interruption for ventilation duration and clinical outcomes in critically ill adults.

Methods. PubMed, Europe PMC and Scopus were searched, with citation searching. Randomized trials, concurrent cohorts and before–after studies were eligible. Standardized mean differences (SMDs) were pooled with random-effects models (DerSimonian–Laird, Hartung–Knapp). Risk of bias was assessed with RoB 2 and ROBINS-I, and certainty with GRADE.

Results. Twenty-three studies were included (12 randomized trials, one cohort, 10 before–after studies), and 10 (2,297 patients) were pooled for the primary outcome, in which DSI did not significantly shorten ventilation (SMD –0.11, 95% confidence interval [CI] –0.49 to 0.28; I^2 89.1%; 95% prediction interval –1.13 to 0.92; ratio of means 0.88, 0.66 to 1.17). The SMD was 0.05 (–0.42 to 0.53) in randomized trials ($p=0.16$ versus non-randomized studies) and 0.00 (–0.71 to 0.70) against protocolized sedation. Point estimates for mortality (risk ratio 0.85, 0.54 to 1.33, randomized trials) and tracheostomy (0.64, 0.40 to 1.00) favored DSI, but the intervals included no effect. Self-extubation, reintubation, delirium and length of stay did not differ. Certainty was very low for ventilation duration and low for mortality.

Conclusion. DSI did not consistently shorten mechanical ventilation compared with continuous sedation. Randomized trials showed no effect. A possible benefit in intensive care units (ICUs) without protocolized light sedation rests mainly on non-randomized evidence.

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1. Introduction

Ventilation duration tracked closely with outcome in a large international cohort of 481 intensive care units (ICUs) in 50 countries: only 65% of patients ventilated for at least two days were successfully weaned by day 90, and higher sedation scores were independently associated with delayed initiation of weaning and with weaning failure.¹ Extubation failure was among the strongest predictors of death in a national multicenter cohort in Argentina,² and the incidence of ventilator-associated pneumonia (VAP) varied widely across European ICUs.³ Indonesian cohorts showed the same burden. Prolonged ventilation after open-heart surgery was independently associated with in-hospital mortality,⁴ and more than three-quarters of the patients who developed VAP in a tertiary referral hospital died in hospital.⁵ The harm did not stop at discharge. Post-intensive care syndrome

affected more than half of survivors in a nationwide cohort,⁶ muscle weakness persisted at one year,⁷ and recovery of quality of life and cognition was slower after delirium.⁸

Sedation practice is modifiable, and deeper sedation was associated with longer ventilation and worse outcomes in these cohorts. Early deep sedation was associated with fewer ventilator-free days and higher mortality in a dual-center cohort,⁹ and with delayed extubation after adjustment in a multicenter Korean cohort.¹⁰ Persistently deep sedation trajectories were linked to longer ICU stay and higher hospital mortality,¹¹ and medication-induced deep sedation to loss of independent living.¹² Days of deep sedation were associated with ICU amnesia. Delusional memories were associated with later post-traumatic stress symptoms,¹³ although sedation intensity during the first day was not independently associated with psychological impairment at three months.¹⁴ Deep sedation often began

before ICU admission. In a national cohort of more than 72,000 air-transported patients, 88% were deeply sedated.¹⁵

Daily sedation interruption (DSI) was proposed to prevent drug accumulation. Continuous sedative infusions were stopped once a day until the patient was awake. The same practice has been described as a spontaneous awakening trial, a sedation hold, a sedation vacation or a daily wake-up, and in this review these terms were treated as synonyms and the abbreviation DSI is used throughout. The rationale was strongest for long-acting agents. Midazolam and its active metabolite accumulate during prolonged infusion, so the time to awakening lengthens with the duration of sedation. In the landmark single-center trial, DSI shortened ventilation and ICU stay.¹⁶ Paired with a spontaneous breathing trial (SBT), it also improved ventilator-free days and one-year survival.¹⁷ Later trials were less consistent. Adding DSI to nurse-led protocolized sedation did not change the time to extubation,¹⁸ and one trial was stopped early because ventilation was longer with DSI than with a nursing-implemented sedation algorithm.¹⁹ The most recent focused guideline update addressed the choice of sedative and recommended dexmedetomidine over propofol, rather than DSI.²⁰ Audits showed wide variation in the use of DSI and sedation protocols across countries, including low- and middle-income settings.^{21–23}

Three recent syntheses addressed DSI. The updated Cochrane review pooled randomized trials in adults and children, with protocolized, usual-care and analgesia-first or no-sedation comparators,²⁴ a meta-analysis of 45 randomized trials found large benefits that were moderated by illness severity,²⁵ and a network meta-analysis ranked DSI and protocolized sedation similarly for ventilator-free days.²⁶ None of them integrated the before–after implementation studies through which DSI has been introduced into routine care. None examined whether the effect depended on how long patients were ventilated under the comparator strategy. None reported prediction intervals for the effect expected in a new ICU. Here, continuous sedation denoted a continuous sedative infusion without a scheduled daily interruption, whether it was titrated at the clinicians' discretion (usual care) or by a nurse-led protocol to a light sedation target (protocolized sedation). The distinction matters for ICUs in which continuous benzodiazepine infusions without a sedation protocol remain common.

This systematic review and meta-analysis addressed one question. In critically ill adults receiving invasive mechanical ventilation (population), did daily interruption of continuous sedative infusions (intervention), compared with continuous sedation without scheduled daily interruption (comparator), shorten the duration of mechanical ventilation (primary outcome)? Did it also affect mortality, length of stay and safety outcomes (secondary outcomes), in randomized and non-randomized comparative studies?

2. Methods

2.1. Protocol, registration and reporting

The review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.²⁷ A protocol specifying the review question, eligibility criteria, outcomes, data items and analysis plan was prepared

before screening began. One amendment was made before data synthesis: because only eight studies (seven randomized trials and one concurrent cohort) reported the duration of ventilation in a form suitable for pooling, before–after implementation studies were added to the eligible designs, and the analysis restricted to randomized trials was designated the principal sensitivity analysis. The protocol was not registered in a public registry. [Author query: add a repository where the protocol text can be inspected, or state the date of the internal protocol.]

2.2. Eligibility criteria

Eligibility was defined by population, intervention, comparator, outcomes and study design. The population was adults (16 years or older) receiving invasive mechanical ventilation and continuous intravenous sedation in any ICU. The intervention was a protocol of daily interruption of all continuous sedative infusions, with or without opioid infusions, until the patient was awake or showed predefined signs of intolerance. Nurse-led and physician-led protocols were eligible, whether or not DSI was paired with an SBT.

The comparator was continuous sedation without scheduled daily interruption, either usual care with titration at the clinicians' discretion or protocolized sedation with continuous infusions titrated to a target. Studies were excluded when the comparator was intermittent bolus sedation, analgesia without sedative infusion or a no-sedation strategy, or when daily interruption was applied in both groups. Differences in co-interventions, including the sedation-depth target, did not lead to exclusion but were recorded and examined in sensitivity analyses.

The primary outcome was the duration of mechanical ventilation in days, as defined by the authors. Secondary outcomes were ICU and hospital length of stay, ventilator-free days to day 28, all-cause mortality, self-extubation or unplanned extubation, reintubation, tracheostomy, VAP and delirium. Randomized controlled trials, concurrent cohort studies and before–after implementation studies comparing consecutive cohorts treated before and after the introduction of a DSI protocol were eligible. Reviews, case reports, editorials, conference abstracts without a full publication, pediatric studies and reports in journals not indexed in MEDLINE, Scopus or Web of Science were excluded. There was no language restriction.

2.3. Information sources and search strategy

PubMed/MEDLINE, Europe PMC and Scopus were searched from inception to [Author query: date of the last search]. Two concept blocks were combined: DSI and its synonyms (including sedation interruption, sedation vacation, sedation hold, spontaneous awakening trial, wake-up test, daily arousal and sedation break), and the context of mechanical ventilation, critical illness or sedation. The PubMed string was: ("daily sedation interruption"[tiab] OR "daily interruption"[tiab] OR "sedation interruption"[tiab] OR "interruption of sedation"[tiab] OR "interruption of sedative"[tiab] OR "interrupting sedation"[tiab] OR "interrupted sedation"[tiab] OR "sedative interruption"[tiab] OR "sedation vacation"[tiab] OR "sedation hold"[tiab] OR "sedative hold"[tiab] OR "spontaneous awakening"[tiab] OR "awakening trial"[tiab] OR "daily awakening"[tiab] OR "awakening and breathing"[tiab] OR "wake-up test"[tiab] OR "wake up test"[tiab] OR "daily wake"[tiab] OR "sedation stop"[tiab] OR "stopping

sedation"[tiab] OR "sedation cessation"[tiab] OR "cessation of sedation"[tiab] OR "discontinuation of sedation"[tiab] OR "sedation discontinuation"[tiab] OR "sedation break*"[tiab] OR "daily arousal*"[tiab] OR "arousal therapy"[tiab] OR "awakening therapy"[tiab] OR "daily awaken*"[tiab] OR "wake-up call*"[tiab] OR "wake up call*"[tiab]) AND ("Respiration, Artificial"[Mesh] OR "Ventilator Weaning"[Mesh] OR "Intensive Care Units"[Mesh] OR "Critical Illness"[Mesh] OR "Critical Care"[Mesh] OR "Hypnotics and Sedatives"[Mesh] OR "Conscious Sedation"[Mesh] OR "Deep Sedation"[Mesh] OR "mechanical ventilat*"[tiab] OR "mechanically ventilated"[tiab] OR ventilat*[tiab] OR "intensive care"[tiab] OR ICU[tiab] OR ICUs[tiab] OR "critically ill"[tiab] OR "critical care"[tiab] OR intubated[tiab] OR sedat*[tiab]) NOT ("Animals"[Mesh] NOT "Humans"[Mesh]).

The same terms were translated into the syntax of Europe PMC (title and abstract fields, restricted to MEDLINE, PubMed Central, Agricola and Chinese Biological Abstracts sources) and Scopus (title, abstract and keyword fields, journal articles). Forward and backward citation searching of the landmark trial, of the included studies and of earlier systematic reviews was carried out through OpenAlex citation records. The complete strategies for every source are provided in Supplementary Table S1.

2.4. Study selection

Records were merged and de-duplicated on PubMed identifier, digital object identifier and normalized title. Titles and abstracts were screened against the eligibility criteria, and potentially eligible reports were assessed in full. One reviewer screened records and assessed full texts with a standardized form. A second reviewer verified every inclusion and exclusion decision, and disagreements were resolved by discussion. Reasons for full-text exclusion were recorded (Supplementary Table S2).

2.5. Data collection and data items

A standardized form recorded the design, country, setting, type of ICU, numbers of patients in each group, age, sex, illness severity, the DSI protocol, the comparator strategy, pairing with an SBT, the predominant sedative, the sedation target, the definition of ventilation duration, follow-up, and every primary and secondary outcome in the format reported. Values were extracted exactly as printed; medians were not treated as means, and no missing value was imputed. The second reviewer checked each value against the corresponding table or sentence of the source report.

Effect sizes were oriented so that DSI was always the experimental group. In one trial, daily interruption was the control arm of the original comparison, and the direction of its effect sizes was reversed accordingly.²⁸ Mortality was taken at the short-term time point closest to hospital discharge or day 28; ICU mortality was used when no later short-term time point was reported.

Because the duration of ventilation is right-skewed, many studies reported medians. When a median with interquartile range was reported, the mean was estimated with the method of Luo and colleagues (Equation 1) and the standard deviation with the method of Wan and colleagues (Equation 2), in which q_1 and q_3 denote the quartiles, m the median, n the group size and Φ^{-1} the standard normal quantile function.²⁹

$$\bar{x} \approx w \frac{q_1 + q_3}{2} + (1 - w)m, \quad (1)$$

$$w = 0.7 + \frac{0.39}{n}$$

$$s \approx \frac{q_3 - q_1}{2\Phi^{-1}\left(\frac{0.75n - 0.125}{n + 0.25}\right)} \quad (2)$$

When a median was reported with its 95% confidence interval (CI), the standard deviation was derived from the standard error of the median (Equation 3), where L_m and U_m are the limits of the interval. Means with standard errors or CIs were converted to standard deviations with the usual identities, and medians without any measure of dispersion were summarized narratively. Conversions from medians can underestimate within-study standard errors,³⁰ so a quantile-estimation approach was applied as a sensitivity analysis.

$$s \approx \frac{\sqrt{n}}{\sqrt{2}} \times \frac{U_m - L_m}{2 \times 1.96} \quad (3)$$

2.6. Risk of bias assessment

Randomized trials were assessed with the revised Cochrane risk-of-bias tool (RoB 2) for the duration of ventilation. Its five domains were the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result. Written decision rules for each domain were agreed before the assessment, because implementation guidance improves the reliability of RoB 2.³¹

Non-randomized studies were assessed with ROBINS-I across confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes and selection of the reported result. Secular trends, co-interventions introduced with the protocol and baseline imbalance were considered under confounding. The original rating scale was applied without modification, and non-randomized studies were analysed separately from randomized trials, as recommended after a methodological review found frequent misapplication of the tool.³²

2.7. Synthesis and statistical analysis

The primary effect measure was the standardized mean difference (SMD), calculated as Hedges' g with the small-sample correction J (Equation 4). In Equation 4, $\bar{x}$, s and n are the mean, standard deviation and size of the DSI (subscript 1) and comparator (subscript 2) groups. The sampling variance of g was calculated with Equation 5, and negative values indicate shorter ventilation with DSI.

$$g_i = J \times \frac{\bar{x}_1 - \bar{x}_2}{s_p}, \quad (4)$$

$$s_p = \sqrt{\frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{n_1 + n_2 - 2}},$$

$$J = 1 - \frac{3}{4(n_1 + n_2) - 9}$$

$$v_i = \frac{n_1 + n_2}{n_1 n_2} + \frac{g_i^2}{2(n_1 + n_2)} \quad (5)$$

Effect sizes were pooled with a random-effects model. The between-study variance τ^2 was estimated with the DerSimonian-Laird method (Equation 6), and each study was weighted by the inverse of the sum of its within-study and the between-study variance (Equation 7). The CI of the pooled estimate used the Hartung-Knapp adjustment with a t distribution on $k-1$ degrees of freedom and the DerSimonian-Laird τ^2 (Equation 8), because this

adjustment maintains coverage better than Wald-type intervals when few studies are pooled.^{33,34}

$$\tau^2 = \max \left\{ 0, \frac{Q - (k-1)}{\sum_i w_i - \frac{\sum_i w_i^2}{\sum_i w_i}} \right\}, \quad (6)$$

$$w_i = \frac{1}{v_i}$$

$$\hat{\mu} = \frac{\sum_i w_i^* g_i}{\sum_i w_i^*}, \quad (7)$$

$$w_i^* = \frac{1}{v_i + \tau^2}$$

$$\hat{\mu} \pm t_{k-1, 0.975} \sqrt{\frac{\sum_i w_i^* (g_i - \hat{\mu})^2}{(k-1) \sum_i w_i^*}} \quad (8)$$

Heterogeneity was quantified with Cochran's Q and I^2 (Equation 9), in which $\hat{\mu}_{FE}$ denotes the common-effect (inverse-variance) estimate. The 95% prediction interval was calculated to describe the range of effects expected in a new setting (Equation 10).³⁵

$$Q = \sum_i w_i (g_i - \hat{\mu}_{FE})^2, \quad (9)$$

$$I^2 = \max \left\{ 0, \frac{Q - (k-1)}{Q} \right\} \times 100\%$$

$$\hat{\mu} \pm t_{k-2, 0.975} \sqrt{\tau^2 + SE^2(\hat{\mu})} \quad (10)$$

The SMD expresses differences in standard-deviation units that depend on the spread of each study population. The ratio of means (ROM) was therefore calculated as a complementary measure on the log scale (Equation 11) and back-transformed for presentation as a relative change in the duration of ventilation.³⁶

$$\ln(\text{ROM}) = \ln \left(\frac{\bar{x}_1}{\bar{x}_2} \right), \quad (11)$$

$$\text{Var}(\ln(\text{ROM})) = \frac{s_1^2}{n_1 \bar{x}_1^2} + \frac{s_2^2}{n_2 \bar{x}_2^2}$$

Randomized and non-randomized studies were pooled together in the primary analysis and separately by design, because pooling bodies of evidence from both designs can modify conclusions even when the direction of effect is concordant.³⁷ Pre-specified subgroup analyses compared randomization, study design, comparator strategy (protocolized sedation versus usual care), predominant sedative (benzodiazepine-based versus other), pairing with an SBT, region and overall risk of bias. Within each subgroup, the DerSimonian–Laird estimator was used with Hartung–Knapp intervals, or with Wald-type intervals when fewer than three studies were available, and subgroups were compared with random-effects tests for subgroup differences.

Random-effects meta-regression (restricted maximum likelihood with the Hartung–Knapp adjustment; Equation 12) examined the mean duration of ventilation in the comparator arm, publication year and the logarithm of sample size. Because the comparator-arm mean also enters the effect size, this analysis was considered exploratory.

$$g_i = \beta_0 + \beta_1 x_i + u_i + \varepsilon_i, \quad (12)$$

$$u_i \sim N(0, \tau_{\text{res}}^2)$$

Sensitivity analyses varied the model: the restricted maximum likelihood estimator, Wald-type intervals and a common-effect model. They varied the evidence base:

randomized trials only, trials with each type of comparator, and studies at low or moderate risk of bias. They excluded before–after studies, studies with abstract-level data, the trial in which the standard deviation was derived from the CI of the median, and the trial in which the two arms had different sedation-depth targets. Finally, the quantile-estimation conversion was applied, and leave-one-out analysis was performed.

Small-study effects were examined with a funnel plot, the Egger regression test (Equation 13) and the trim-and-fill method, because 10 studies were available.

$$\frac{g_i}{\sqrt{v_i}} = \beta_0 + \beta_1 \frac{1}{\sqrt{v_i}} + \varepsilon_i \quad (13)$$

Continuous secondary outcomes were pooled as SMDs and ROMs (length of stay) or mean differences (ventilator-free days), and binary outcomes as risk ratios (RRs) with Mantel–Haenszel weights within a random-effects model. Hartung–Knapp intervals were used when at least three studies were pooled and Wald-type intervals when only two were available. Analyses were performed in R 4.5.3 with the meta (8.2.1) and metafor (4.8.0) packages, and two-sided $p < 0.05$ indicated statistical significance.

2.8. Certainty of evidence and ethics

Certainty of evidence was rated with the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. The rating was based on the randomized trials for each outcome, because the non-randomized studies were all at serious risk of bias and would have started at low certainty; the combined estimate is shown alongside for the primary outcome. Risk of bias, inconsistency, indirectness, imprecision and publication bias were considered. The prediction interval was used to judge inconsistency and imprecision together, so that the same uncertainty was not penalized twice.³⁸ Ethical approval was not required because only published aggregate data were analysed.

3. Results

3.1. Study selection

The database searches identified 1,961 records (PubMed 693, Europe PMC 659, Scopus 609). After removal of 1,137 duplicates, 824 records were screened. Of these, 793 were excluded on title and abstract, mainly because they were reviews, editorials or case reports, did not evaluate a daily interruption protocol, concerned children or intraoperative wake-up tests, or compared DSI with a no-sedation strategy. Full texts were sought for 31 reports. Five could not be retrieved, and 26 were assessed for eligibility. Three reports were excluded: two because the comparator was intermittent bolus sedation and one because daily interruption was not the core of the intervention. Citation searching identified 2,836 additional records, of which six were sought and four assessed. All four were published in journals not indexed in MEDLINE, Scopus or Web of Science. In total, 23 studies were included, as illustrated in Figure 1.

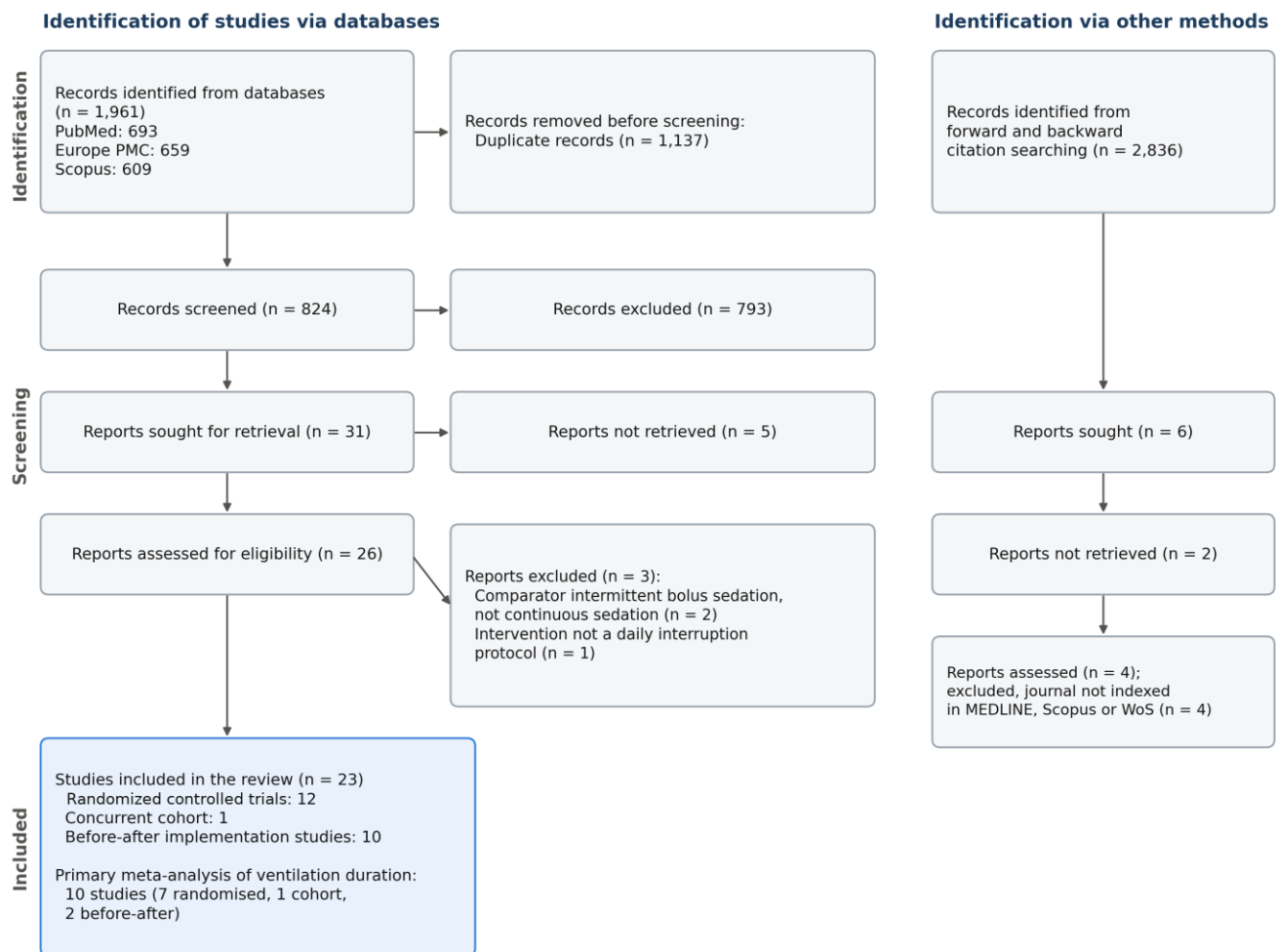


Figure 1. PRISMA 2020 flow diagram of the identification, screening and inclusion of studies. MEDLINE, Medical Literature Analysis and Retrieval System Online; WoS, Web of Science.

3.2. Characteriztics of the included studies

The 23 studies comprised 12 randomized controlled trials, one concurrent cohort study and 10 before–after implementation studies. They were conducted in 9 countries. In total, 14 were from North America and five from middle-income countries (Turkey, China and Iran), and none was from Indonesia or a low-income country. Among the trials, six compared DSI with protocolized sedation and six with usual care; all before–after studies compared a DSI protocol with pre-implementation practice. DSI was paired with an SBT in 10 studies. The predominant sedative was benzodiazepine-based in six

studies, a combination of agents in six, and propofol with dexmedetomidine in one. It was not reported in 10, mostly before–after studies. The study populations were drawn from mixed or medical-surgical ICUs in 16 studies, medical ICUs in four, and one each from cardiac, burn and trauma-dominated units. The trials that reported group sizes analysed between 50 and 423 patients, and only three analysed more than 100. The before–after studies ranged from 56 patients to 5,164 ventilation episodes. Where reported, the mean or median age in the trials ranged from about 40 to 69 years. The main characteriztics are detailed in Table 1.

Table 1. Characteristics of the included studies.

Study	Country	Setting	n	Comparator	With SBT	Main sedative	Duration of ventilation, days (DSI vs comparator)	Risk of bias
Randomized controlled trials								
Kress 2000 ¹⁶	USA	Single-center medical ICU	68/60	Usual care	No	Midazolam or propofol	Median 4.9 (2.5–8.6) vs 7.3 (3.4–16.1)	Some concerns
Girard 2008 ¹⁷	USA	Four tertiary centers (ABC trial)	167/168	Usual care	Yes	Mixed	Not reported; ventilator-free days 14.7 (SE 0.9) vs 11.6 (SE 0.9)	Low
Mehta 2008 ³⁹	Canada	Three university medical-surgical ICUs (pilot)	65 (total)	Protocolized sedation	No	Benzodiazepine and opioid	Median 10.5 vs 8 (no dispersion)	Some concerns
de Wit 2008 ¹⁹	USA	Single-center closed medical ICU	36/38	Protocolized sedation	Yes	Mixed	Median 6.7 (95% CI 4.1–10.4) vs 3.9 (2.9–4.9)	High
Anifantaki 2009 ⁴⁰	Greece	Single-center medical-surgical ICU	97 (total)	Usual care	No	Mixed infusions	Median 8.7 vs 7.7 (no dispersion)	Some concerns
Yilmaz 2010 ⁴¹	Turkey	Single-center general (mixed) adult ICU	25/25	Protocolized sedation	No	Midazolam	Mean 6.66 ± 5.22 vs 9.52 ± 6.07	Some concerns
Weisbrodt 2011 ⁴²	Australia	Two level-3 mixed ICUs (double-blind pilot)	26/24	Usual care	No	Midazolam, fentanyl	Median 8 (3.6–14.5) vs 8.4 (4.4–14.3)	Some concerns
Guo 2012 ⁴³	China	Single-center ICU (four-arm trial)	30/30	Usual care	No	NR	No difference (values not reported)	Some concerns
Mehta 2012 ¹⁸	Canada, USA	16 tertiary medical and surgical ICUs (SLEAP)	214/209	Protocolized sedation	No	Benzodiazepine and opioid	Median 7 (4–13) vs 7 (3–12)	Low
Shahabi 2016 ⁴⁴	Iran	Critical care units of one university hospital	40/40	Usual care	No	Mixed	Not reported (VAP outcome)	High
Guo 2018 ²⁸	China	Single-center ICU	40/40	Protocolized sedation	No	Propofol, dexmedetomidine	Mean 7.8 ± 2.7 vs 5.6 ± 1.9	Some concerns
Tanios 2019 ⁴⁵	USA	Single-center medical-surgical ICU (three-arm pilot)	31/28	Protocolized sedation	No	Midazolam, fentanyl	Median 4 (2–7) vs 5 (2–8)	Low
Concurrent cohort study								
Kayir 2018 ⁴⁶	Turkey	Single-center anesthesiology ICU (retrospective, concurrent groups)	50/50	Protocolized sedation	No	Mainly midazolam	Mean 4.02 ± 3.71 vs 8.1 ± 4.9	Serious
Before–after implementation studies								
Kher 2013 ⁴⁷	USA	Two 10-bed medical ICUs (QI)	32/33	Pre-implementation care	Yes	Mixed infusions	No difference ($p=0.75$)	Serious
Jones 2014 ⁴⁸	USA	ICU performance-improvement project	NR	Pre-implementation care	Yes	NR	Median 2.7 vs 3.8 (no dispersion)	Serious
Khan 2014 ⁴⁹	USA	22-bed mixed medical-surgical ICU (QI)	440/262	Pre-implementation care	Yes	NR	Median 5 vs 4 (no dispersion)	Serious
Klompas 2015 ⁵⁰	USA	20 ICUs (12 collaborative, 8 surveillance-only)	3425/1739	Concurrent and pre-implementation care	Yes	NR	Decreased within collaborative units (episode level)	Serious
Ackriyo 2016 ⁵¹	USA	Adult ICUs of an urban academic center (QI)	NR	Pre-implementation care	No	NR	No significant change	Serious
Lee 2017 ⁵²	USA	Burn ICU	136/171	Pre-implementation care	Yes	NR	Fewer ventilator days after implementation ($p<0.05$)	Serious
Kallet 2018 ⁵³	USA	Level-1 trauma center ICU, ARDS survivors	656/397	Pre-implementation care	Yes	NR	Median 9 (4–17) vs 14 (6–29)	Serious
Ferraioli 2019 ⁵⁴	United Kingdom	10-bed district general ICU/HDU (QI)	NR	Pre-implementation care	Yes	NR	Median 5 vs 7 (no dispersion)	Serious
Ketcham 2022 ⁵⁵	USA	Cardiac ICU (nurse-driven SAT protocol)	27/29	Pre-implementation care	No	NR	Median 3.8 vs 4.7 (no dispersion)	Serious
Nitta 2026 ⁵⁶	Japan	Advanced emergency and critical care center	122/158	Pre-implementation care	Yes	NR	Median 6 (4–11) vs 6 (4–10)	Serious

Notes: Duration of mechanical ventilation in days as reported (DSI vs comparator). Mehta 2012 reported time to successful extubation, Tanios 2019 the duration of the first intubation, Kallet 2018 the duration in survivors and Nitta 2026 the duration in patients extubated by protocol. n, patients in the DSI and comparator groups (total randomized when group sizes were not reported); SBT, DSI paired with a spontaneous breathing trial. Risk of bias: RoB 2 for randomized trials (low, some concerns, high); ROBINS-I for non-randomized studies (low, moderate, serious, critical). ARDS, acute respiratory distress syndrome; CI, confidence interval; DSI, daily sedation interruption; HDU, high-dependency unit; ICU, intensive care unit; NR, not reported; QI, quality improvement; SAT, spontaneous awakening trial; SBT, spontaneous breathing trial; SE, standard error; VAP, ventilator-associated pneumonia.

Sixteen studies reported the duration of ventilation, and 10 provided data suitable for standardization: three reported means and standard deviations, six medians with interquartile ranges and one a median with its 95% CI. Definitions differed. SLEAP [Author query: expand SLEAP] reported time to successful extubation,¹⁸ one trial reported the duration of the first intubation,⁴⁵ one before–after study included only survivors,⁵³ and another included only

patients extubated by protocol.⁵⁶ The six studies that reported medians without dispersion showed no consistent direction: the medians were shorter with DSI in three before–after studies^{48,54,55} and longer with DSI in two trials and one before–after study.^{39,40,49} Seven studies gave no summary of ventilation duration. The Awakening and Breathing Controlled trial reported more ventilator-free days with paired DSI and SBT,¹⁷ two before–after studies

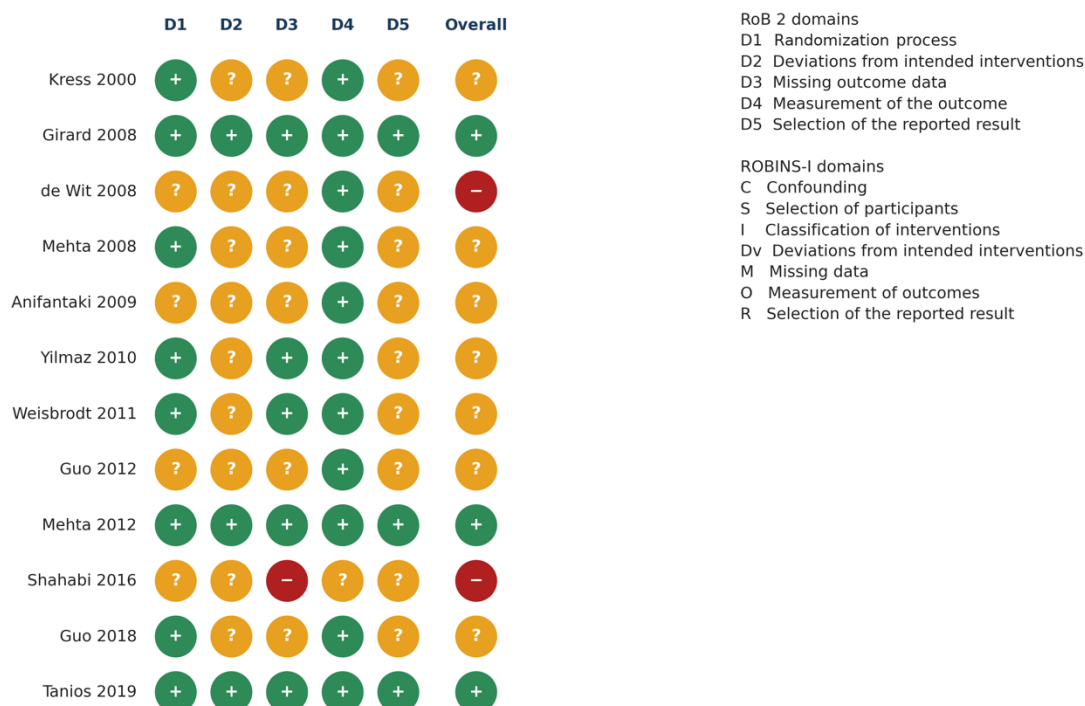
reported shorter ventilation after implementation,^{50,52} and three reported no difference.^{43,47,51} The remaining trial reported only VAP.⁴⁴

3.3. Risk of bias

Among the 12 randomized trials, three were at low risk of bias, seven raised some concerns and two were at high risk. Concerns arose most often from deviations from intended interventions (nine trials), mainly unblinded delivery with ad hoc interruptions in the comparator arm. Selection of the reported result was the other frequent concern (nine

trials), mainly in reports available only as abstracts. Missing outcome data raised concerns in seven trials because of post-randomization exclusions. In contrast, outcome measurement was at low risk in 11 because the duration of ventilation is objective. All 11 non-randomized studies were at serious risk of bias, chiefly because of confounding by secular trends and by co-interventions introduced with the protocol. The domain-level judgments for each study are illustrated in Figure 2.

A. Randomized trials (RoB 2)



B. Non-randomized studies (ROBINS-I)

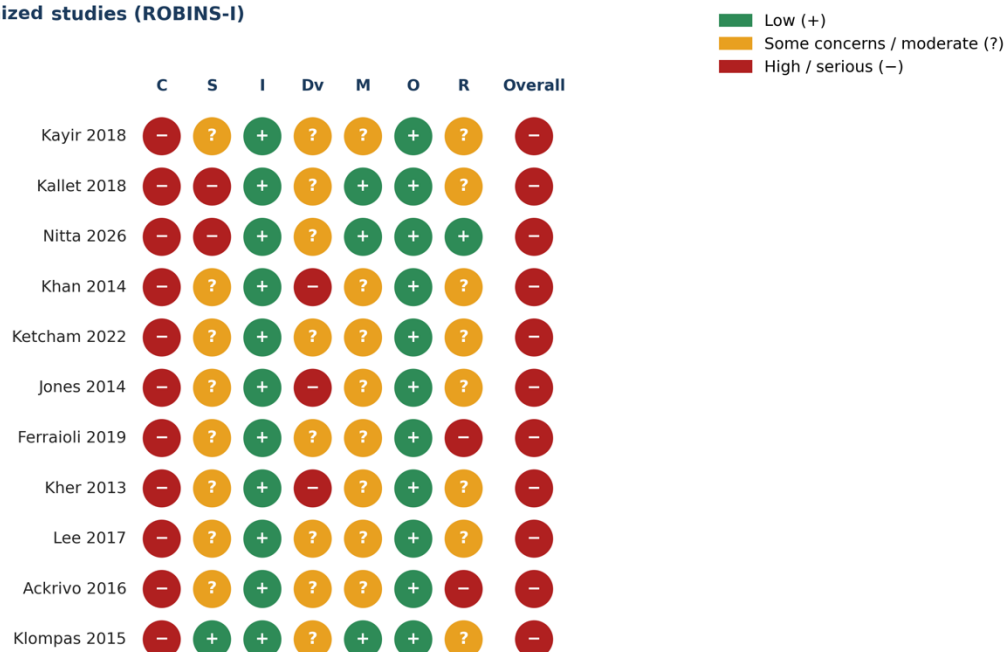
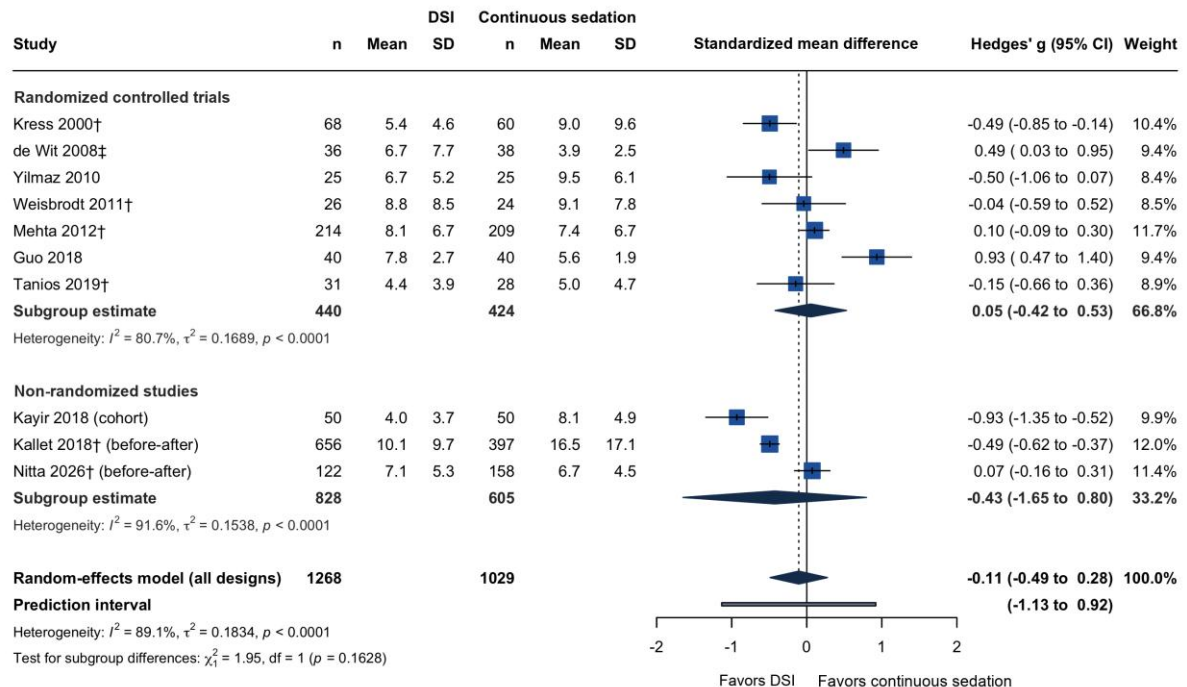


Figure 2. Risk-of-bias judgments for the duration of mechanical ventilation. (A) Randomized trials assessed with the revised Cochrane risk-of-bias tool (RoB 2); (B) non-randomized studies assessed with ROBINS-I. +, low risk; ?, some concerns (RoB 2) or moderate risk (ROBINS-I); –, high (RoB 2) or serious (ROBINS-I) risk.

3.4. Synthesis of results

In the primary meta-analysis of 10 studies (2,297 patients; 1,268 DSI and 1,029 comparator), DSI did not significantly shorten the duration of mechanical ventilation (SMD -0.11 (95% CI -0.49 to 0.28); $p=0.54$). Heterogeneity was considerable (I^2 89.1%, 95% CI 82.1% to 93.4%; τ^2 0.183; Q 82.9, df 9, $p<0.001$). The 95% prediction interval ranged

from -1.13 to 0.92 . In the seven randomized trials, the SMD was 0.05 (-0.42 to 0.53), and in the three non-randomized studies -0.43 (-1.65 to 0.80) ($p=0.16$ for the difference), as illustrated in Figure 3. Study estimates ranged from -0.93 to 0.93 . The CIs of Kress 2000¹⁶, Kayir 2018⁴⁶ and Kallet 2018⁵³ lay entirely below zero, whereas those of de Wit 2008¹⁹ and Guo 2018²⁸ lay entirely above zero.



† mean and SD estimated from median and interquartile range; ‡ SD estimated from the 95% CI of the median. Non-randomised studies: one concurrent cohort and two before-after implementation studies.

Figure 3. Forest plot of the standardized mean difference (Hedges' g) in the duration of mechanical ventilation between daily sedation interruption (DSI) and continuous sedation, grouped by randomization. Squares are study estimates (size proportional to random-effects weight) with 95% confidence intervals (CIs); diamonds are random-effects pooled estimates (DerSimonian-Laird, Hartung-Knapp), and the bar is the 95% prediction interval. Negative values favor DSI. Means and standard deviations marked † were estimated from medians and interquartile ranges, and the standard deviation marked ‡ from the 95% CI of the median.

Expressed as a ratio of means, ventilation was 12% shorter with DSI (ROM 0.88 (0.66 to 1.17); $p=0.35$; 95% prediction interval 0.35 to 2.20). This is a modest change. For a comparator-arm duration of 7.7 days, the median across the included studies, this corresponded to about 0.9 days less ventilation, with a CI from 2.6 days less to 1.3 days more. In the randomized trials the ROM was 1.00 (0.71 to 1.41). That corresponds to no difference, with a CI from 2.2 days less to 3.2 days more (Supplementary Figure S1).

The secondary outcomes are detailed in Table 2. Mortality was assessed in hospital in Kress 2000¹⁶ and de Wit 2008¹⁹, at 28 days in Girard 2008¹⁷ and Tanios 2019⁴⁵, and in the ICU in Yilmaz 2010⁴¹, Weisbrodt 2011⁴² and Kayir 2018⁴⁶. It was 25.7% with DSI and 31.7% with continuous sedation across seven studies (RR 0.82 (0.54 to 1.23); I^2 31.5%). The RR was 0.85 (0.54 to 1.33) in the six randomized trials. Tracheostomy was performed in 43/297 (14.5%) versus 63/290 (21.7%) of patients (RR 0.64 (0.40 to 1.00); $p=0.051$; I^2 0.0%).

Table 2. Secondary outcomes.

Outcome	Studies and measure	k	Participants	Events (DSI vs comparator)	Estimate (95% CI)	I^2 (%)
Continuous outcomes						
ICU length of stay	All designs (SMD)	11	2,632	—	-0.08 (-0.48 to 0.31)	87.1
	Randomized trials (SMD)	8	1,199	—	0.09 (-0.42 to 0.59)	86.6
	All designs (ROM)	11	2,632	—	0.91 (0.73 to 1.15)	91.4
Hospital length of stay	All designs (SMD)	7	1,114	—	0.01 (-0.34 to 0.35)	69.5

Outcome	Studies and measure	k	Participants	Events (DSI vs comparator)	Estimate (95% CI)	I ² (%)
Ventilator-free days to day 28	Randomized trials (SMD)	5	734	—	0.07 (−0.51 to 0.65)	78.7
	All designs (ROM)	7	1,114	—	1.03 (0.77 to 1.36)	78.8
	Randomized trials (MD, days)	4	518	—	−0.73 (−9.58 to 8.12)	82.6
Binary outcomes						
Mortality	All designs	7	811	104/404 vs 129/407	0.82 (0.54 to 1.23)	31.5
	Randomized trials	6	711	101/354 vs 122/357	0.85 (0.54 to 1.33)	35.7
Tracheostomy	Randomized trials	4	587	43/297 vs 63/290	0.64 (0.40 to 1.00)	0.0
Self-extubation or unplanned extubation	Randomized trials	4	943	29/480 vs 22/463	1.20 (0.32 to 4.55)	45.9
Reintubation	All designs	5	696	53/352 vs 58/344	0.91 (0.31 to 2.69)	63.0
	Randomized trials	4	596	51/302 vs 47/294	1.10 (0.44 to 2.75)	47.7
Ventilator-associated pneumonia	All designs	3	260	32/130 vs 47/130	0.69 (0.05 to 10.36)	86.2
Delirium	Randomized trials	2	160	27/80 vs 28/80	1.07 (0.25 to 4.57)	88.9
	Randomized trials	3	838	257/421 vs 242/417	1.07 (0.65 to 1.75)	49.3

Notes: Random-effects models (DerSimonian–Laird) with Hartung–Knapp confidence intervals when $k \geq 3$ and Wald-type intervals when $k = 2$; risk ratios from Mantel–Haenszel weighting within the random-effects framework. SMD < 0, ROM < 1, MD > 0 for ventilator-free days and RR < 1 favor DSI. Events are DSI vs comparator. Mortality was in-hospital in Kress 2000 and de Wit 2008, at 28 days in Girard 2008 and Tanios 2019, and in the ICU in Yilmaz 2010, Weisbrodt 2011 and Kayir 2018. CI, confidence interval; DSI, daily sedation interruption; ICU, intensive care unit; MD, mean difference; ROM, ratio of means; RR, risk ratio; SMD, standardized mean difference (Hedges' g).

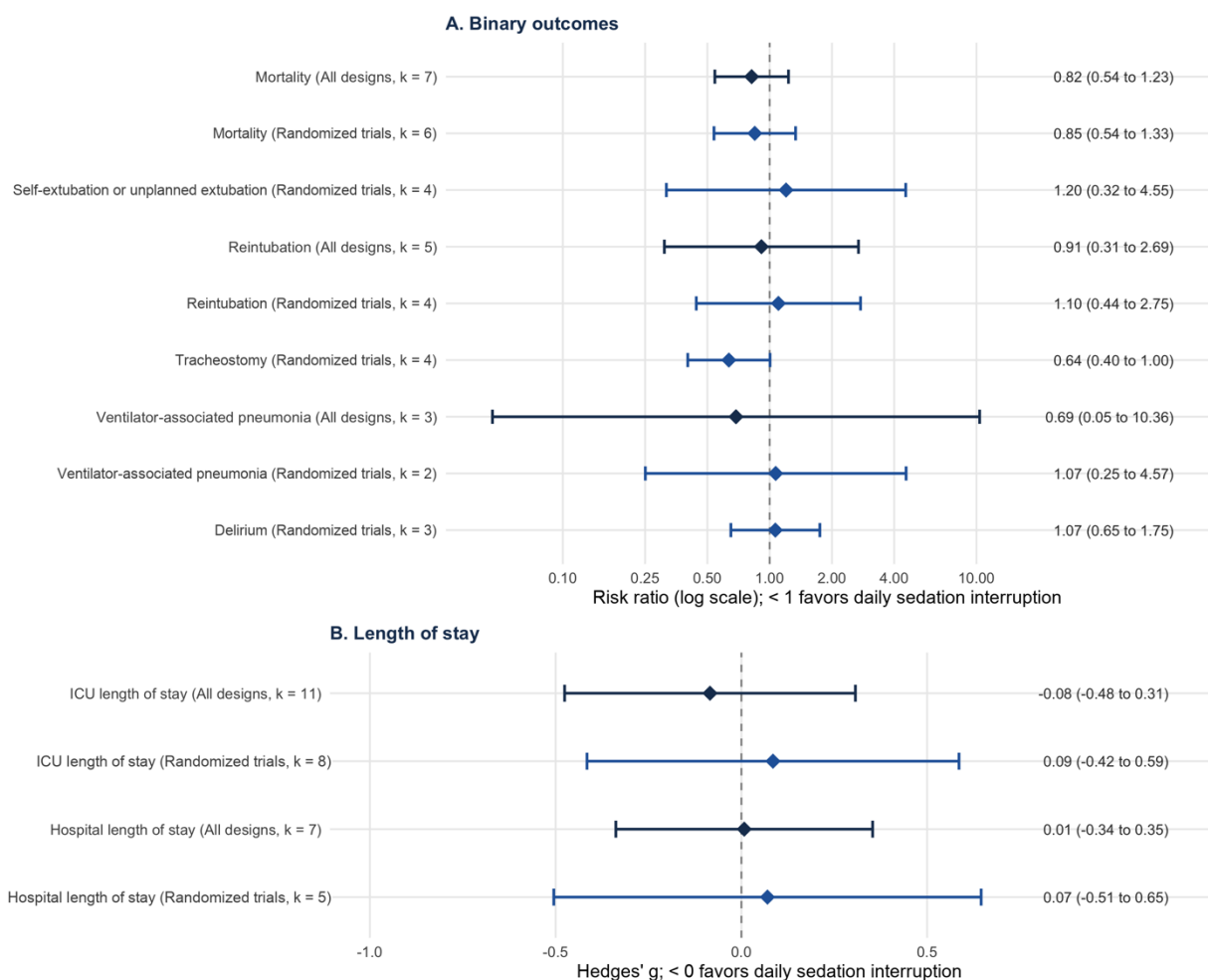


Figure 4. Pooled estimates for the secondary outcomes in all designs (dark) and in randomized trials only (blue); outcomes reported only by randomized trials are shown once. (A) Risk ratios for binary outcomes (log scale); (B) standardized mean differences for length of stay. Bars are 95% confidence intervals; values below 1 (A) or 0 (B) favor daily sedation interruption. k , number of studies.

3.5. Heterogeneity, subgroup, sensitivity analyses and small-study effects

The pooled estimate was robust to the choice of estimator (restricted maximum likelihood -0.11 (−0.49 to 0.28)) and to the conversion of medians (-0.08 (−0.47 to 0.32)), as detailed in Table 3. The common-effect model gave a statistically significant reduction (-0.22 (−0.31 to -0.14)). It was not appropriate given the heterogeneity.

Excluding the trial with different sedation-depth targets gave -0.21 (−0.54 to 0.11), and excluding the trial with the standard deviation derived from the CI of the median gave -0.17 (−0.57 to 0.23). Excluding before–after studies (-0.07 (−0.57 to 0.42)), studies with abstract-level data (-0.22 (−0.65 to 0.21)) or studies at high or serious risk of bias (-0.02 (−0.57 to 0.53)) did not change the conclusion. In leave-one-out analysis the pooled SMD ranged from -0.21 (omitting Guo 2018²⁸) to -0.02 , and no omission

produced a statistically significant result (Supplementary Figure S2).

Table 3. Sensitivity analyses of the duration of mechanical ventilation.

Analysis	<i>k</i>	Estimate (95% CI)	<i>I</i> ² (%)	<i>p</i>
Primary analysis				
DerSimonian–Laird, Hartung–Knapp (primary)	10	−0.11 (−0.49 to 0.28)	89.1	<i>p</i> =0.54
Statistical model				
Restricted maximum likelihood, Hartung–Knapp	10	−0.11 (−0.49 to 0.28)	89.1	<i>p</i> =0.55
DerSimonian–Laird, Wald-type interval	10	−0.11 (−0.40 to 0.19)	89.1	<i>p</i> =0.48
Common-effect (inverse variance) model	10	−0.22 (−0.31 to −0.14)	NA	<i>p</i> <0.001
Study design and comparator				
Randomized trials only	7	0.05 (−0.42 to 0.53)	80.7	<i>p</i> =0.79
Excluding before–after studies	8	−0.07 (−0.57 to 0.42)	86.3	<i>p</i> =0.74
Randomized trials with protocolized comparator	5	0.19 (−0.48 to 0.86)	79.6	<i>p</i> =0.47
Randomized trials with usual-care comparator	2	−0.32 (−0.75 to 0.11)	45.2	<i>p</i> =0.15
Data source, conversion and risk of bias				
Excluding de Wit 2008 (SD from 95% CI of the median)	9	−0.17 (−0.57 to 0.23)	89.1	<i>p</i> =0.36
Excluding Guo 2018 (different sedation-depth targets)	9	−0.21 (−0.54 to 0.11)	86.2	<i>p</i> =0.17
Excluding studies with abstract-level data	7	−0.22 (−0.65 to 0.21)	79.7	<i>p</i> =0.26
Excluding high or serious risk of bias	6	−0.02 (−0.57 to 0.53)	81.8	<i>p</i> =0.94
Quantile-estimation conversion of medians	10	−0.08 (−0.47 to 0.32)	91.1	<i>p</i> =0.67
Alternative effect measure (ratio of means)				
All designs	10	0.88 (0.66 to 1.17)	91.7	<i>p</i> =0.35
Randomized trials only	7	1.00 (0.71 to 1.41)	81.4	<i>p</i> =0.99

Notes: Estimates are SMDs (Hedges' *g*) except for the ratio-of-means rows (ROM<1 indicates shorter ventilation with DSI). The common-effect model does not estimate between-study variance (*I*² not applicable). Abstract-level data: Mehta 2012, Guo 2018 and Kallet 2018. CI, confidence interval; DSI, daily sedation interruption; ROM, ratio of means; SD, standard deviation; SMD, standardized mean difference.

Subgroup analyses are detailed in Table 4. Randomized and non-randomized studies did not differ significantly (*p*=0.16). When the non-randomized studies were split into the single cohort and the two before–after studies, the three-level test was significant (*p*=0.002). This test rested on a subgroup containing one study and was interpreted with caution. Among the randomized trials, the SMD was 0.19 (−0.48 to 0.86) against protocolized sedation and −0.32 (−0.75 to 0.11) against usual care.

Across all designs, the subgroup estimates were 0.00 (−0.71 to 0.70) for protocolized comparators and −0.26 (−0.74 to 0.23) for usual care (*p*=0.42). The estimates were −0.29 (−0.82 to 0.24) for benzodiazepine-based and 0.07 (−0.69 to 0.84) for other sedation (*p*=0.28). With and without a paired SBT, the estimates were −0.01 (−1.23 to 1.20) and −0.15 (−0.70 to 0.40) (*p*=0.70). Region and risk of bias did not modify the effect.

Table 4. Subgroup analyses and meta-regression of the duration of mechanical ventilation.

Subgroup or moderator	<i>k</i>	SMD (95% CI)	<i>I</i> ² (%)	<i>p</i> for difference
Study design				
Randomized trials	7	0.05 (−0.42 to 0.53)	80.7	<i>p</i> =0.002
Concurrent cohort †	1	−0.93 (−1.35 to −0.52)	NA	
Before–after studies †	2	−0.22 (−0.77 to 0.33)	94.2	
Randomization				
Randomized	7	0.05 (−0.42 to 0.53)	80.7	<i>p</i> =0.16
Non-randomized	3	−0.43 (−1.65 to 0.80)	91.6	
Comparator strategy				
Protocolized sedation	6	0.00 (−0.71 to 0.70)	88.5	<i>p</i> =0.42
Usual care (concurrent or historical)	4	−0.26 (−0.74 to 0.23)	84.2	
Predominant sedative				
Benzodiazepine-based	5	−0.29 (−0.82 to 0.24)	81.7	<i>p</i> =0.28
Other, mixed or not reported	5	0.07 (−0.69 to 0.84)	93.1	
Paired spontaneous breathing trial				
Interruption paired with SBT	3	−0.01 (−1.23 to 1.20)	93.2	<i>p</i> =0.70
Interruption without paired SBT	7	−0.15 (−0.70 to 0.40)	86.9	
Region				
North America	5	−0.13 (−0.64 to 0.38)	89.7	<i>p</i> =0.91
Other regions	5	−0.09 (−0.96 to 0.78)	89.5	
Risk of bias				
Low risk of bias †	2	0.07 (−0.11 to 0.25)	0.0	<i>p</i> =0.37
Some concerns, high or serious	8	−0.13 (−0.64 to 0.37)	89.8	
Meta-regression (slope per unit, 95% CI)				
Comparator-arm mean duration of ventilation (per day)	10	−0.081 (−0.180 to 0.018)	<i>R</i> ² 26	<i>p</i> =0.095
Publication year (per year)	10	0.008 (−0.051 to 0.067)	<i>R</i> ² 0	<i>p</i> =0.76
Log sample size (per log unit)	10	−0.078 (−0.491 to 0.335)	<i>R</i> ² 0	<i>p</i> =0.67

Notes: Subgroup estimates are SMDs (Hedges' *g*) from separate random-effects models with Hartung–Knapp intervals; † Wald-type interval because fewer than three studies were available. *p* values are from random-effects tests for subgroup differences. Meta-regression: restricted maximum likelihood with the Hartung–Knapp adjustment; *R*² (%), shown in the *I*² column, is the proportion of between-study variance explained. CI, confidence interval; SBT, spontaneous breathing trial; SMD, standardized mean difference.

In exploratory meta-regression, a longer mean duration of ventilation in the comparator arm was associated with a larger reduction with DSI, but the CI included no association (slope -0.081 SMD per day, 95% CI -0.180 to 0.018 ; $p=0.095$; R^2 26%), as illustrated in Figure 5. Publication year ($p=0.76$) and sample size ($p=0.67$) were not associated with the effect.

The funnel plot showed no clear asymmetry, as illustrated in Figure 6. The Egger test was not significant (intercept 1.87 , $t=0.98$, $df=8$; $p=0.36$). Trim-and-fill imputed two studies on the side favoring DSI, giving an adjusted SMD of -0.30 (-0.72 to 0.13).

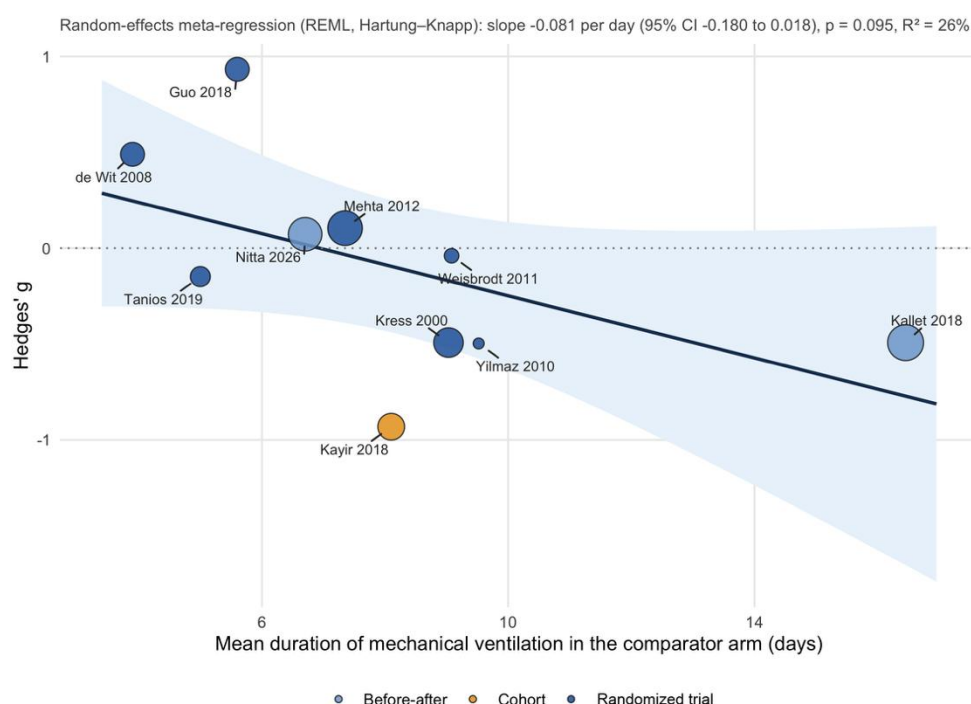


Figure 5. Random-effects meta-regression of the standardized mean difference in the duration of ventilation on the mean duration of ventilation in the comparator arm. Circle size is proportional to study weight; the line is the fitted regression with its 95% confidence band; colors indicate study design.

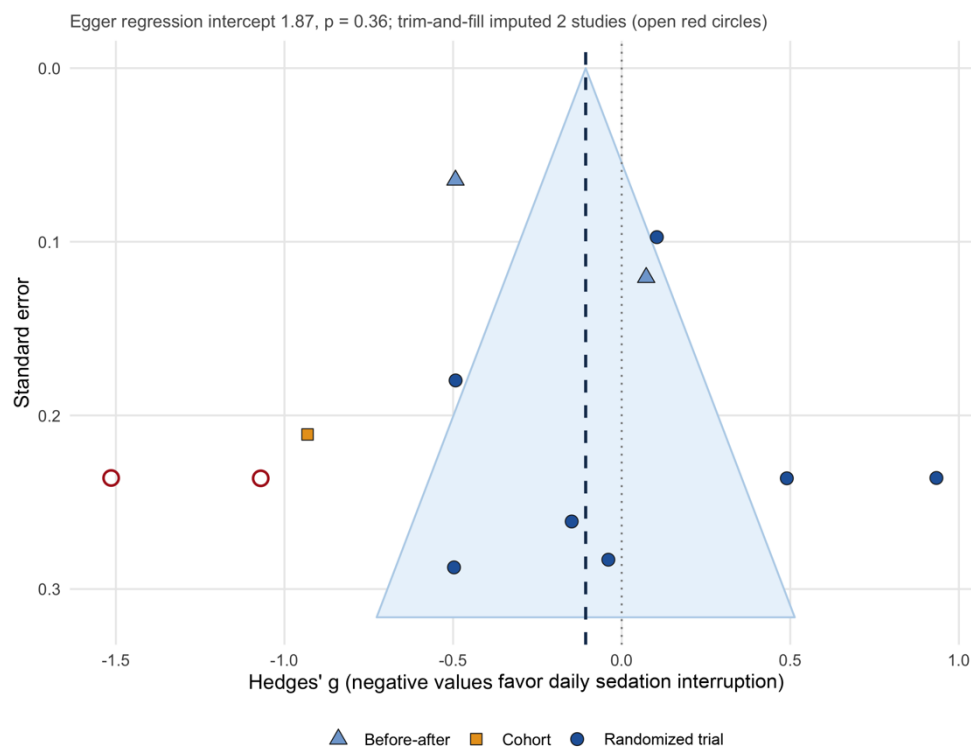


Figure 6. Funnel plot of the standardized mean differences against their standard errors. The dashed line is the pooled estimate, the dotted line marks no effect and the shaded area is the pseudo 95% confidence region; marker shapes indicate study design, and open red circles are studies imputed by trim-and-fill.

3.6. Certainty of the evidence

The certainty of evidence from randomized trials was very low for the duration of ventilation, downgraded for risk of

bias, inconsistency and imprecision. It was low for mortality and tracheostomy (risk of bias and imprecision) and for delirium (inconsistency and imprecision), and very

low for length of stay, ventilator-free days, self-extubation, reintubation and VAP. The judgments and absolute effects are summarized in Table 5.

Table 5. Summary of findings and certainty of evidence (GRADE).

Outcome	Studies (participants)	Relative effect (95% CI)	Absolute or alternative effect (95% CI)	Certainty	Reasons
Duration of mechanical ventilation	7 RCTs (864)	SMD 0.05 (−0.42 to 0.53)	ROM 1.00 (0.71 to 1.41); all designs ROM 0.88 (0.66 to 1.17)	Very low	Downgraded for risk of bias (serious), inconsistency (serious), imprecision (serious). Five of seven trials at some concerns or high risk; $I^2 = 80.7\%$ with effects in opposite directions; CI spans a moderate reduction and a moderate increase; Egger test not significant.
Mortality	6 RCTs (711)	RR 0.85 (0.54 to 1.33)	342 per 1,000 with continuous sedation; 52 fewer per 1,000 (158 fewer to 114 more)	Low	Downgraded for risk of bias (serious), imprecision (serious). Most weight from trials at some concerns or high risk; CI includes a 33% relative increase and a 46% reduction.
Tracheostomy	4 RCTs (587)	RR 0.64 (0.40 to 1.00)	217 per 1,000 with continuous sedation; 79 fewer per 1,000 (130 fewer to 1 more)	Low	Downgraded for risk of bias (serious), imprecision (serious). Consistent direction ($I^2 = 0\%$) but upper confidence limit reaches 1.00 with 106 events.
Self-extubation or unplanned extubation	4 RCTs (943)	RR 1.20 (0.32 to 4.55)	48 per 1,000 with continuous sedation; 10 more per 1,000 (32 fewer to 169 more)	Very low	Downgraded for inconsistency (serious), imprecision (very serious). Most weight from low-risk trials, but the two largest trials pointed in opposite directions; few events (51); CI from 68% reduction to 4.5-fold increase.
Reintubation	4 RCTs (596)	RR 1.10 (0.44 to 2.75)	160 per 1,000 with continuous sedation; 16 more per 1,000 (89 fewer to 280 more)	Very low	Downgraded for risk of bias (serious), imprecision (very serious). Few events; very wide CI.
Ventilator-associated pneumonia	2 RCTs (160)	RR 1.07 (0.25 to 4.57)	350 per 1,000 with continuous sedation; 24 more per 1,000 (262 fewer to 650 more)	Very low	Downgraded for risk of bias (very serious), inconsistency (serious), imprecision (serious). Two small trials at high or some-concern risk with opposite effects.
Delirium	3 RCTs (838)	RR 1.07 (0.65 to 1.75)	580 per 1,000 with continuous sedation; 38 more per 1,000 (203 fewer to 435 more)	Low	Downgraded for inconsistency (serious), imprecision (serious). Two of three trials at low risk; moderate heterogeneity; CI compatible with benefit and harm.
ICU length of stay	8 RCTs (1,199)	SMD 0.09 (−0.42 to 0.59)	All designs ROM 0.91 (0.73 to 1.15)	Very low	Downgraded for risk of bias (serious), inconsistency (serious), imprecision (serious). Substantial heterogeneity; CI crosses no effect in both directions.
Hospital length of stay	5 RCTs (734)	SMD 0.07 (−0.51 to 0.65)	All designs ROM 1.03 (0.77 to 1.36)	Very low	Downgraded for risk of bias (serious), inconsistency (serious), imprecision (serious). Substantial heterogeneity; wide CI.
Ventilator-free days to day 28	4 RCTs (518)	MD −0.73 (−9.58 to 8.12) days	—	Very low	Downgraded for risk of bias (serious), inconsistency (serious), imprecision (very serious). Two trials contribute converted medians; $I^2 = 82.6\%$; CI spans 9 days in either direction.

Notes: Certainty was rated for the randomized evidence; starting level high. Absolute effects apply the pooled RR to the event rate in the comparator arms of the randomized trials (upper limits truncated at 100% risk). CI, confidence interval; ICU, intensive care unit; MD, mean difference; RCT, randomized controlled trial; ROM, ratio of means; RR, risk ratio; SMD, standardized mean difference.

4. Discussion

4.1. Summary of main findings

DSI did not significantly shorten mechanical ventilation compared with continuous sedation without scheduled interruption, and the certainty of this evidence was very low. The randomized trials showed no effect. Their ROM was 1.00 (0.71 to 1.41). The prediction interval (−1.13 to 0.92) indicated that the effect in a new ICU could range from a large reduction to a moderate increase, and the apparent benefit was concentrated in the non-randomized studies and in comparisons with usual care. DSI was not associated with a detectable increase in self-extubation, reintubation or delirium overall, although the intervals were wide (for example, self-extubation RR 1.20, 0.32 to 4.55; very low certainty), and the point estimates for mortality and tracheostomy favored DSI without statistical significance.

4.2. Comparison with previous reviews and primary studies

The updated Cochrane review pooled 18 trials for the duration of ventilation and reported a 14% relative reduction with low certainty and similar heterogeneity ($I^2 = 88\%$), together with probable reductions in mortality and tracheostomy.²⁴ The point estimate of the present review across all designs (ROM 0.88 (0.66 to 1.17)) was almost identical, but its interval was wider. Four differences may explain this. First, the Cochrane review included pediatric trials and analgesia-first or no-sedation comparators, whereas the present review was restricted to adults and to comparators that maintained continuous sedation; trials in which DSI was the control arm for a no-sedation strategy were therefore excluded. Second, Hartung–Knapp intervals were used here, and these are appropriately wider when few heterogeneous studies are pooled.³³ Third, trials reporting only medians without dispersion were summarized narratively rather than pooled. Fourth, the Cochrane mortality estimate rested on 18 trials and 725 deaths, whereas the present randomized mortality analysis included six trials and 223 deaths, which explains its wider interval despite a similar point estimate.

The meta-analysis of 45 trials reported significant reductions in ventilation, ICU stay, tracheostomy and VAP.²⁵ It drew on Chinese-language databases, and study quality was a significant moderator of the effect. The present review included only reports in indexed journals and found no benefit in the two trials at low risk of bias that could be pooled (0.07 (−0.11 to 0.25)). The network meta-analysis of nurse-implementable strategies estimated that DSI and protocolized sedation each added about 2.6 ventilator-free days compared with usual care, with no meaningful difference between them.²⁶ That pattern fits the comparator dependence seen here.

The primary trials show the same gradient. The benefits in the original trial and in the Awakening and Breathing Controlled trial were obtained against usual care,^{16,17} whereas trials that added DSI to protocolized light sedation found no difference or longer ventilation.^{18,19,45} In SLEAP, the largest of these, DSI was associated with higher daily doses of midazolam and fentanyl and with a higher nurse-rated workload.¹⁸ A small trial with a protocolized comparator reported shorter ventilation with DSI in a Turkish ICU.⁴¹ A double-blind pilot trial against usual care found no difference. Adherence to interruption was low in both arms.⁴²

One Chinese trial deserves specific comment. Its DSI arm targeted a deeper sedation level than the light-sedation comparator, so it tested interruption combined with deeper sedation rather than interruption alone, and it showed the largest effect against DSI.²⁸ It met the eligibility criteria, because the comparator was a continuous infusion without scheduled interruption, and it was retained as pre-specified. Without it, the pooled SMD was −0.21 (−0.54 to 0.11). The conclusion did not change.

The non-randomized evidence was more favorable but less reliable. A retrospective cohort in a Turkish anesthesiology ICU found shorter ventilation with DSI,⁴⁶ and the large before–after study of survivors of acute respiratory distress syndrome found shorter ventilation after SBT and conservative sedation protocols were introduced over a long period of secular change.⁵³ A recent Japanese study that used inverse probability weighting found no difference after nurse-led DSI was incorporated into an extubation protocol.⁵⁶ Other implementation projects reported lighter sedation or better adherence to DSI, but their effects on ventilation were inconsistent.^{48,49,54,55} The trials that reported medians without dispersion showed no consistent direction.^{39,40}

The safety findings agreed with the Cochrane review, which found little or no difference in accidental removal of the endotracheal tube.²⁴ Context still matters. The excess of self-extubations with DSI in the Awakening and Breathing Controlled trial shows that the risk depends on the setting.¹⁷ Outside trials, self-extubation accounted for most unplanned extubations in French ICUs and was not associated with higher mortality than planned extubation,⁵⁷ whereas reintubation after self-extubation was associated with higher mortality and nosocomial pneumonia.⁵⁸ The lower tracheostomy rate with DSI matched the Cochrane estimate,²⁴ although the timing of tracheostomy did not change the time to discontinuation of sedation or ventilation in a recent cohort.⁵⁹

4.3. Interpretation of the pooled findings

This review adds three findings to the existing syntheses. First, it integrated randomized and implementation evidence while keeping them analytically separate, and the

impression of benefit from routine-care implementation was not reproduced in randomized comparisons. Second, the effect appeared to depend on the comparator. Against protocolized sedation the pooled SMD was 0.00 (−0.71 to 0.70), close to zero, whereas the comparison with usual care favored DSI. The test for this difference was not significant ($p=0.42$), so the pattern is compatible with, but does not establish, effect modification by the comparator.

Third, the exploratory meta-regression suggested that any benefit of DSI may be larger where ventilation under the comparator strategy is longer (an SMD 0.081 lower per additional day). The association was imprecise, was based on 10 studies and is vulnerable to regression to the mean, because the comparator-arm mean is part of the effect size. It should be treated as a hypothesis. Taken together, the findings suggest that DSI is best viewed as one of several strategies to avoid oversedation. Where sedation is already light and protocolized, interruption appears to add little. Where continuous infusions are titrated without a target and patients remain ventilated for long periods, a daily interruption may be a simple safeguard, although this has not been tested in randomized trials in such settings.

4.4. Implications for practice and policy

Two practical messages follow. In ICUs that already deliver nurse-led protocolized light sedation, the evidence does not support adding a mandatory daily interruption to shorten ventilation, and it may increase sedative and opioid exposure and nursing workload.¹⁸ In ICUs in which continuous benzodiazepine infusions are titrated without a protocol, a DSI protocol paired with an SBT is a reasonable first step towards lighter sedation. It should be introduced with a validated sedation scale, clear criteria for failing the interruption, adequate nurse staffing during the awakening and a policy on physical restraint. This recommendation for low- and middle-income settings is an extrapolation. None of the included studies came from Indonesia or a low-income country.

The choice of sedative modifies the value of interruption. Accumulation is greatest with prolonged midazolam infusions, and non-benzodiazepine sedation was associated with more ventilator-free days in surgical and trauma patients.⁶⁰ ICUs staffed by advanced practice providers used fewer benzodiazepines and more propofol, and early propofol was associated with shorter time to extubation.⁶¹ Early goal-directed sedation with dexmedetomidine was associated with less delirium.⁶² Where propofol or dexmedetomidine is available and affordable, moving away from continuous benzodiazepines may matter as much as interrupting them. Where midazolam remains the default [Author query: cite a source for midazolam as the default sedative in Indonesian ICUs], a daily interruption is one safeguard against accumulation.

Staff knowledge and attitudes determine whether DSI is delivered safely. In a large survey, nurses' knowledge of DSI was insufficient, and fear of self-removal of tubes and catheters was the most common barrier.⁶³ Qualitative work identified the absence of interprofessional rounds and limited nursing capacity to manage an awakening patient as key barriers,⁶⁴ and staff perceived extubation as often later than ideal, citing staffing, communication and sedation-weaning practices.⁶⁵ Even after successful implementation, clinicians kept unresolved concerns that may limit sustainment.⁶⁶

Organizational context matters most in resource-limited settings. Implementation of the ABCDEF bundle was low across all income groups in a survey of 54 countries, and a protocol was a common facilitator.⁶⁷ In Vietnam, sedation assessment and awakening trials were limited by staffing shortages and unclear professional roles,²³ and leadership, staff buy-in and workflow integration were the main determinants of bundle compliance in a multicenter survey.⁶⁸ Monitoring and feedback can sustain practice. Risk-adjusted digital quality measures for awakening and breathing trials were deployed across a large health system,⁶⁹ routine electronic data identified missed bundle elements,⁷⁰ and higher bundle compliance was associated with better functional outcomes at one year.⁷¹ Champion-based education alone increased compliance with DSI only modestly,⁷² whereas nurse-led targeted sedation-analgesia management was associated with shorter ventilation.⁷³

Concerns about safety should not be dismissed, but they can be managed. In a recent trial, self-extubation was similarly frequent with low-use and high-use physical restraint strategies,⁷⁴ so routine restraint is not required to make awakening safe. Monitoring of self-extubation and reintubation should accompany any implementation program.

4.5. Strengths

The review used a comprehensive search with citation searching and no language restriction, and it extracted every value in its reported format. It kept randomized and non-randomized evidence separate in subgroup, sensitivity and GRADE assessments. It applied conservative random-effects methods with Hartung–Knapp intervals and prediction intervals, and it reported a ratio of means, translated into days, alongside the SMD to aid clinical interpretation. Pre-specified sensitivity analyses addressed data conversion, risk of bias, the comparator and design. The comparator was classified explicitly for every study. The extracted dataset, the conversion code and every analysis script are supplied, so that each estimate can be reproduced from the values reported in the primary studies.

4.6. Limitations

The limitations of the evidence were considerable. Only seven randomized trials contributed to the primary analysis, most were small, and five raised some concerns or were at high risk of bias. Data for 12 studies, including three in the primary analysis, were available only at abstract level. Medians were converted to means, which assumes a distribution that may not hold for highly skewed durations.^{29,30} Conversion tends to underestimate within-study variance, so it may inflate heterogeneity rather than bias the direction of effect, and the quantile-estimation analysis gave a similar result. The ratio of means used the same converted means, however, and is not independent of this assumption.

Outcome definitions differed, and two before–after studies analysed only survivors or only patients extubated by protocol. Such analyses are biased if DSI affects mortality, although excluding before–after studies did not change the result. Mortality was measured at different time points. All non-randomized studies were at serious risk of bias from secular trends and co-interventions. Ventilator-free days were analysed as a mean difference that partly relied on converted medians, although the optimal analysis of this composite is debated.^{75,76} With 10 heterogeneous studies, the Egger test had limited power, and for SMDs the

standard error depends partly on the effect size, which can create artifactual asymmetry; trim-and-fill imputed studies on the side favoring DSI, so small-study effects, if present, would not explain the absence of a pooled effect. The prediction interval is itself imprecise when few studies are pooled.³⁵ Sedative and opioid doses were not analysed.

The review process also had limitations. Embase, CENTRAL, CINAHL, Web of Science, trial registries and Chinese-language databases were not searched directly, although Europe PMC covers Chinese Biological Abstracts and citation searching was extensive. Reports in non-indexed journals were excluded, and authors were not contacted for missing data. A second reviewer verified selection and extraction rather than performing them independently in duplicate. The protocol was not registered. Before–after studies were added to the eligible designs after the initial search; this amendment was made before data synthesis, and the randomized-trial analysis was reported with equal prominence.

4.7. Recommendations for future research

Future trials should compare DSI with protocolized light sedation in ICUs where protocolized sedation is not yet established, particularly in low- and middle-income countries such as Indonesia, where midazolam infusions remain common [Author query: source, see Section 4.4]. With a standard deviation of 5.2 days, the median of the included studies, detecting a one-day difference in the duration of ventilation would require about 425 patients per group (two-sided α 0.05, 80% power). A cluster-randomized design would require more. Trials should report the duration of ventilation as a mean with standard deviation, or with the full five-number summary, so that future syntheses do not depend on conversions, and they should report sedative doses, adherence to interruption and time to extubation analysed with death as a competing event or with hierarchical approaches,^{76,77} together with long-term outcomes such as post-intensive care syndrome.⁶ Implementation studies should use concurrent controls or interrupted time-series designs. Trials of sedative choice should report whether daily interruption was used,^{78,79} because the effect of an interruption may differ for shorter-acting agents such as propofol and dexmedetomidine, whose dose–response relationships and effects on the stress response are still being characterized.^{80,81}

5. Conclusion

In critically ill adults receiving mechanical ventilation, DSI did not consistently shorten the duration of ventilation compared with continuous sedation without scheduled interruption (SMD -0.11 , 95% CI -0.49 to 0.28 ; very low certainty). Randomized trials showed no effect. A benefit in settings without protocolized light sedation remains possible, but it rests mainly on non-randomized evidence. DSI was not associated with detectably more self-extubation, reintubation or delirium (very low to low certainty; wide intervals). Point estimates for mortality and tracheostomy favored DSI, though not significantly (low certainty).

6. Declarations

Ethical approval and consent to participate. Not applicable. This review analysed published aggregate data only and involved no contact with human participants.

Consent for publication. Not applicable; no individually identifiable patient data are presented.

Availability of data and materials. The extraction workbook, the search strategies for every source, the list of excluded reports with reasons and the R and Python scripts that reproduce every analysis and figure are provided as supplementary material and are available from the corresponding author on reasonable request.

Artificial intelligence (AI) use statement. The authors declare that no generative artificial intelligence tools were used in the design, analysis, or writing of this manuscript.

Author contribution statement. I.I.S.H.: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. A.Y.A.: Validation, Investigation, Writing – review & editing. Both authors approved the final manuscript.

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7. References

- Pham T, Heunks L, Bellani G, et al. Weaning from mechanical ventilation in intensive care units across 50 countries (WEAN SAFE): a multicentre, prospective, observational cohort study. *Lancet Respir Med.* 2023;11(5):465–76. doi:10.1016/S2213-2600(22)00449-0
- Plotnikow GA, Gogniat E, Accoce M, et al. Epidemiology of mechanical ventilation in Argentina. The EpVAr multicenter observational study. *Med Intensiva (Engl Ed).* 2022;46(7):372–82. doi:10.1016/j.medine.2022.05.002
- Jackson H, Hernandez Padilla AC, Vincent LEM, et al. Perpetual observational study of the clinical and microbiological epidemiology of ventilator-associated pneumonia in Europe. *Crit Care.* 2026;30(1):112. doi:10.1186/s13054-025-05753-5
- Virsty J, Kurniawan MB, Halimi RA, et al. Prolonged mechanical ventilation and in-hospital mortality following open-heart surgery: a retrospective cohort study. *Cardiol Res.* 2026;17(5):526–33. doi:10.14740/cr2269
- Turbawaty DK, Dewa A, Indrati AR, et al. Neutrophil-to-lymphocyte ratio and systemic inflammatory response index as predictors of in-hospital mortality in ventilator-associated pneumonia patients. *Infect Drug Resist.* 2026;19:1–8. doi:10.2147/IDR.S572622
- Oh TK, Song IA. Post-intensive care syndrome after critical illness: incidence and predictors in a nationwide cohort. *Anaesthesia.* 2026;81(6):810–8. doi:10.1111/anae.70131
- Wu MS, Chiu KL, Chiba Y, et al. One-year trajectories of peripheral and inspiratory muscle strength in critical illness survivors: the impact of ICU-acquired weakness. *Respir Med.* 2026;259:108884. doi:10.1016/j.rmed.2026.108884
- Zhong M, Wang X, Feng S, et al. Longitudinal trajectories of health-related quality of life and cognitive function in ICU survivors with versus without delirium: a 6-month follow-up study. *Gen Hosp Psychiatry.* 2026;103:118–27. doi:10.1016/j.genhosppsych.2026.09.016
- Stephens RJ, Evans EM, Pajor MJ, et al. A dual-center cohort study on the association between early deep sedation and clinical outcomes in mechanically ventilated patients during the COVID-19 pandemic: the COVID-SED study. *Crit Care.* 2022;26(1):179. doi:10.1186/s13054-022-04042-9
- Hyun DG, Ahn JH, Gil HY, et al. The profile of early sedation depth and clinical outcomes of mechanically ventilated patients in Korea. *J Korean Med Sci.* 2023;38(19):e141. doi:10.3346/jkms.2023.38.e141
- Hyun DG, Ahn JH, Gil HY, et al. Longitudinal trajectories of sedation level and clinical outcomes in patients who are mechanically ventilated based on a group-based trajectory model: a prospective, multicentre, longitudinal and observational study in Korea. *BMJ Open.* 2023;13(6):e072628. doi:10.1136/bmjopen-2023-072628
- Wongtangman K, Borngaesser F, Rudolph MI, et al. Association of medication-induced deep sedation and emotional distress during mechanical ventilation with loss of independent living: an observational cohort study. *Lancet Respir Med.* 2026;14(1):49–59. doi:10.1016/S2213-2600(25)00264-4
- Kookan RWJ, Tilburgs B, Slooter AJC, et al. Determinants of ICU memories and the impact on the development and trajectory of post-traumatic stress symptoms: a multicenter longitudinal cohort study. *Intensive Care Med.* 2025;51(11):2021–30. doi:10.1007/s00134-025-08132-4
- Iwatani M, Morimoto M. Early sedation intensity and psychological outcomes in critically ill adults. *Nurs Crit Care.* 2026;31(3):e70500. doi:10.1111/nicc.70500
- Moy HP, Olvera D, Nayman BD, et al. The AIR-SED study: a multicenter cohort study of sedation practices, deep sedation, and coma among mechanically ventilated air transport patients. *Crit Care Explor.* 2021;3(12):e0597. doi:10.1097/CCE.0000000000000597
- Kress JP, Pohlman AS, O'Connor MF, et al. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med.* 2000;342(20):1471–7. doi:10.1056/NEJM200005183422002
- Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet.* 2008;371(9607):126–34. doi:10.1016/S0140-6736(08)60105-1
- Mehta S, Burry L, Cook D, et al. Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. *JAMA.* 2012;308(19):1985–92. doi:10.1001/jama.2012.13872
- de Wit M, Gennings C, Jenvey WJ, et al. Randomized trial comparing daily interruption of sedation and nursing-implemented sedation algorithm in medical intensive care unit patients. *Crit Care.* 2008;12(3):R70. doi:10.1186/cc6908
- Lewis K, Balas MC, Stollings JL, et al. A focused update to the clinical practice guidelines for the prevention and management of pain, anxiety, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med.* 2025;53(3):e711–27. doi:10.1097/CCM.00000000000006574
- Mehta S, Bensemmane S, Heybati K, et al. Characteristics and reported practices of ICUs participating in the Sedation, Analgesia and Delirium Management International Study: variability in site-level management of mechanically ventilated adults. *Crit Care Explor.* 2026;8(9):e1479. doi:10.1097/CCE.0000000000001479
- Thomson WR, Puthucherry Z, Stavrinou P, et al. Delivery of evidence-based critical care practices across the United Kingdom: a UK-wide multi-site service evaluation in adult units. *J Intensive Care Soc.* 2025;26(2):137–45. doi:10.1177/17511437241293917
- Phuoc AL, Hoang VT, Trung TN, et al. A rapid evaluation of quality of sedation and ventilation care processes for critically ill patients in Vietnam. *PLoS One.* 2026;21(4):e0339157. doi:10.1371/journal.pone.0339157
- Rose L, Williamson DR, McCullagh IJ, et al. Daily sedation interruption versus no daily sedation interruption for critically ill adults and children requiring invasive mechanical ventilation. *Cochrane Database Syst Rev.* 2026;10(10):CD009176. doi:10.1002/14651858.CD009176.pub3
- Chen TJ, Chung YW, Chen PY, et al. Effects of daily sedation interruption in intensive care unit patients undergoing mechanical ventilation: a meta-analysis of randomized controlled trials. *Int J Nurs Pract.* 2022;28(2):e12948. doi:10.1111/ijn.12948
- Zhang L, Zhou J, Liu X, et al. Comparative effectiveness and clinical credibility of nurse-implementable sedation strategies for mechanically ventilated adults in intensive care: a systematic review and network meta-analysis. *Front Med (Lausanne).* 2026;13:1830570. doi:10.3389/fmed.2026.1830570
- Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021;372:n71. doi:10.1136/bmj.n71
- Guo K, Zhang H, Peng S. [Comparison of two schemes of daily arousal and comfort analgesia and sedation in patients on mechanical ventilation in intensive care unit]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue.* 2018;30(10):950–2. PMID: 30439315. [In Chinese]
- Shi J, Luo D, Wan X, et al. Detecting the skewness of data from the five-number summary and its application in meta-analysis. *Stat Methods Med Res.* 2023;32(7):1338–60. doi:10.1177/09622802231172043
- McGrath S, Katzenschlager S, Zimmer AJ, et al. Standard error estimation in meta-analysis of studies reporting medians. *Stat Methods Med Res.* 2023;32(2):373–88. doi:10.1177/09622802221139233
- Minozzi S, Dwan K, Borrelli F, et al. Reliability of the revised Cochrane risk-of-bias tool for randomised trials (RoB2) improved with the use of implementation instruction. *J Clin Epidemiol.* 2022;141:99–105. doi:10.1016/j.jclinepi.2021.09.021
- Igelström E, Campbell M, Craig P, et al. Cochrane's risk of bias tool for non-randomized studies (ROBINS-I) is frequently misapplied: a methodological systematic review. *J Clin Epidemiol.* 2021;140:22–32. doi:10.1016/j.jclinepi.2021.08.022
- Weber F, Knapp G, Glass A, et al. Interval estimation of the overall treatment effect in random-effects meta-analyses: recommendations from a simulation study comparing frequentist, Bayesian, and bootstrap methods. *Res Synth Methods.* 2021;12(3):291–315. doi:10.1002/jrsm.1471
- Duan Y, Mathew T, Alemayehu D, et al. Novel approaches for random-effects meta-analysis of a small number of studies under normality. *Res Synth Methods.* 2025;16(6):922–36. doi:10.1017/rsm.2025.10022
- Mátrai P, Kóti T, Sipos Z, et al. Assessing the properties of the prediction interval in random-effects meta-analysis. *Res Synth Methods.* 2026;17(3):517–37. doi:10.1017/rsm.2025.10055
- Igelmann JB, Pauly M, Viechtbauer W. Back-transformations in random-effects meta-analysis-impact and interpretation. *Res Synth Methods.* Epub 2026 May 15. doi:10.1017/rsm.2026.10096
- Bröckelmann N, Stadelmaier J, Harms L, et al. An empirical evaluation of the impact scenario of pooling bodies of evidence from

- randomized controlled trials and cohort studies in medical research. *BMC Med.* 2022;20(1):355. doi:10.1186/s12916-022-02559-y
38. Murad MH, Morgan RL, Falck-Ytter Y, et al. Simultaneous evaluation of the imprecision and inconsistency domains of GRADE can be performed using prediction intervals. *J Clin Epidemiol.* 2024;175:111543. doi:10.1016/j.jclinepi.2024.111543
 39. Mehta S, Burry L, Martinez-Motta JC, et al. A randomized trial of daily awakening in critically ill patients managed with a sedation protocol: a pilot trial. *Crit Care Med.* 2008;36(7):2092-9. doi:10.1097/CCM.0b013e31817bfb85
 40. Anifantaki S, Prinianakis G, Vitsaksaki E, et al. Daily interruption of sedative infusions in an adult medical-surgical intensive care unit: randomized controlled trial. *J Adv Nurs.* 2009;65(5):1054-60. doi:10.1111/j.1365-2648.2009.04967.x
 41. Yilmaz C, Kelebek Girgin N, Özdemir N, et al. The effect of nursing-implemented sedation on the duration of mechanical ventilation in the ICU. *Ulus Trauma Acil Cerrahi Derg.* 2010;16(6):521-6. PMID: 21153945.
 42. Weisbrodt L, McKinley S, Marshall AP, et al. Daily interruption of sedation in patients receiving mechanical ventilation. *Am J Crit Care.* 2011;20(4):e90-8. doi:10.4037/ajcc2011415
 43. Guo JY, Deng Q, Guo XS, et al. [Sedation with stimulative circadian rhythm in mechanically ventilation patients in intensive care unit]. *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue.* 2012;24(7):402-6. PMID: 22748455. [In Chinese]
 44. Shahabi M, Yousefi H, Yazdannik AR, et al. The effect of daily sedation interruption protocol on early incidence of ventilator-associated pneumonia among patients hospitalized in critical care units receiving mechanical ventilation. *Iran J Nurs Midwifery Res.* 2016;21(5):541-6. doi:10.4103/1735-9066.193420
 45. Tanios M, Nguyen HM, Park H, et al. Analgesia-first sedation in critically ill adults: a U.S. pilot, randomized controlled trial. *J Crit Care.* 2019;53:107-13. doi:10.1016/j.jcrc.2019.06.008
 46. Kayir S, Ulusoy H, Dogan G. The effect of daily sedation-weaning application on morbidity and mortality in intensive care unit patients. *Cureus.* 2018;10(1):e2062. doi:10.7759/cureus.2062
 47. Kher S, Roberts RJ, Garpestad E, et al. Development, implementation, and evaluation of an institutional daily awakening and spontaneous breathing trial protocol: a quality improvement project. *J Intensive Care Med.* 2013;28(3):189-97. doi:10.1177/0885066612444255
 48. Jones K, Newhouse R, Johnson K, et al. Achieving quality health outcomes through the implementation of a spontaneous awakening and spontaneous breathing trial protocol. *AACN Adv Crit Care.* 2014;25(1):33-42. doi:10.1097/NCL.000000000000011
 49. Khan BA, Fadel WF, Tricker JL, et al. Effectiveness of implementing a Wake Up and Breathe program on sedation and delirium in the ICU. *Crit Care Med.* 2014;42(12):e791-5. doi:10.1097/CCM.0000000000000660
 50. Klompas M, Anderson D, Trick W, et al. The preventability of ventilator-associated events. The CDC Prevention Epicenters Wake Up and Breathe Collaborative. *Am J Respir Crit Care Med.* 2015;191(3):292-301. doi:10.1164/rccm.201407-13940C
 51. Akrivo J, Horbowicz KJ, Mordino J, et al. Successful implementation of an automated sedation vacation process in intensive care units. *Am J Med Qual.* 2016;31(5):463-9. doi:10.1177/1062860615593340
 52. Lee YL, Sims KD, Butts CC, et al. The combination of SAT and SBT protocols may help reduce the incidence of ventilator-associated pneumonia in the burn intensive care unit. *J Burn Care Res.* 2017;38(2):e574-9. doi:10.1097/BCR.0000000000000451
 53. Kallet RH, Zhuo H, Yip V, et al. Spontaneous breathing trials and conservative sedation practices reduce mechanical ventilation duration in subjects with ARDS. *Respir Care.* 2018;63(1):1-10. doi:10.4187/respcare.05270
 54. Ferraioli D, Ferguson L, Carberry M. Quality improvement project aimed at improving the reliability of spontaneous awakening trials in a district general intensive care unit. *BMJ Open Qual.* 2019;8(2):e000518. doi:10.1136/bmjoc.2018-000518
 55. Ketcham SW, Adie SK, Brummel K, et al. Implementation of a nurse-driven spontaneous awakening trial protocol in a cardiac intensive care unit. *Crit Care Nurse.* 2022;42(2):56-61. doi:10.4037/ccn2022114
 56. Nitta K, Imamura H, Kamijo H, et al. Successful implementation of a nurse-led daily spontaneous awakening trial within a modified extubation protocol: a before-and-after study. *Cureus.* 2026;18(4):e108008. doi:10.7759/cureus.108008
 57. Guillemin J, Rieu B, Huet O, et al. Prospective multi-center evaluation of the incidence of unplanned extubation and its outcomes in French intensive care units. The Safe-ICU study. *Anaesth Crit Care Pain Med.* 2024;43(5):101411. doi:10.1016/j.accpm.2024.101411
 58. Trenchat L, Galerneau LM, Ruckly S, et al. Self-extubation in critically ill patients: from the French OUTCOMEREA network. *Crit Care.* 2025;29(1):286. doi:10.1186/s13054-025-05472-x
 59. Buglione A, Colella C, Pepe E, et al. Early (≤ 10 days) vs. late (> 10 days) tracheostomy in the intensive care unit: impact on discontinuation of sedation and mechanical ventilation. *Life (Basel).* 2026;16(6):891. doi:10.3390/life16060891
 60. VanOtterloo T, Ryan-Hummel K, Attridge R, et al. Effect of non-benzodiazepine versus benzodiazepine sedation on days alive and free of mechanical ventilation in the surgical/trauma intensive care unit. *Ann Pharmacother.* Epub 2026 Apr 6. doi:10.1177/10600280261433047
 61. Shah J, Dzierba AL, Muir J, et al. Sedation practices and associated clinical outcomes among adult ICU patients managed by advanced practice providers versus resident physicians. *J Crit Care.* 2026;91:155252. doi:10.1016/j.jcrc.2025.155252
 62. Sun X, Chen T, Wei L, et al. Early goal-directed sedation with dexmedetomidine is associated with lower delirium rate in mechanically ventilated patients. *BMC Anesthesiol.* 2026;26(1):130. doi:10.1186/s12871-026-03651-z
 63. Hu L, Du X, Zhang P, et al. Knowledge, attitudes, and practices of ICU nurses regarding daily sedation interruption: a cross-sectional study. *Front Med (Lausanne).* 2026;13:1822534. doi:10.3389/fmed.2026.1822534
 64. Graham ND, Graham ID, Vanderspauk-Wright B, et al. Factors influencing nurses' use of sedation interruptions in a critical care unit: a descriptive qualitative study. *IBI Evid Implement.* 2024;22(3):316-29. doi:10.1097/XEB.0000000000000415
 65. Rankin BP, Xu D, Doucet K. Ventilator liberation: evaluating staff perceptions of practice and policy adherence. *Am J Crit Care.* 2025;34(5):372-9. doi:10.4037/ajcc2025622
 66. Knighton AJ, Kean J, Peltan ID, et al. Normalizing daily awakening and breathing coordination at 15 heterogeneous ICUs: a multicenter post-implementation survey. *Implement Sci Commun.* 2025;6(1):91. doi:10.1186/s43058-025-00770-5
 67. Haruna J, Unoki T, Liu K, et al. Factors associated with ABCDEF bundle implementation for critically ill patients: an international cross-sectional survey in 54 countries. *SAGE Open Med.* 2025;13:20503121241312944. doi:10.1177/20503121241312944
 68. Gurnani PK, Setliff EL, Abu-Sultaneh S, et al. Barriers and facilitators to ICU Liberation Bundle implementation and compliance. *Crit Care Explor.* 2026;8(6):e1431. doi:10.1097/CCE.0000000000001431
 69. Horvat CM, Klug J, Li R, et al. Early use of a risk-adjusted mechanical ventilation digital quality measure bundle in a large health system. *Crit Care Med.* 2025;53(8):e1630-40. doi:10.1097/CCM.00000000000006740
 70. Blatter C, Exl MT, Musy SN, et al. Non-adherence to ABCDEF bundle as indicator of missed care in the intensive care unit: a retrospective longitudinal study using routine data. *Int J Nurs Stud.* 2026;183:105646. doi:10.1016/j.ijnurstu.2026.105646
 71. Boehm LM, Mart MF, LaNoue M, et al. Association between ABCDE bundle compliance and long-term outcomes: a secondary longitudinal analysis. *Intensive Care Med.* 2026;52(3):466-75. doi:10.1007/s00134-026-08346-0
 72. Rozsa RH, Lecznar CM, Matzke CM. Practice patterns in spontaneous awakening and breathing trials in the intensive care unit. *Crit Care Nurse.* 2025;45(6):14-21. doi:10.4037/ccn2025653
 73. Li X, Zhang H, Zhang H, et al. Association of nurse-led targeted sedation-analgesia management with ventilation duration and sedation quality in mechanically ventilated patients. *PLoS One.* 2026;21(7):e0353344. doi:10.1371/journal.pone.0353344
 74. Sonnevile R, Couffignal C, Sigaud F, et al. Restrictive vs liberal physical restraint strategies in critically ill patients: the R2D2-ICU randomized clinical trial. *JAMA.* 2026;335(14):1232-42. doi:10.1001/jama.2026.2897
 75. Serpa Neto A, Bailey M, Shehabi Y, et al. Alternative approaches to analyzing ventilator-free days, mortality and duration of ventilation in critical care research. *Crit Care Sci.* 2024;36:e20240246en. doi:10.62675/2965-2774.20240246-en
 76. Renard Triché L, Jabaudon M, Molinari N, et al. What is the optimal approach to analyse ventilator-free days? A simulation study. *Crit Care.* 2025;29(1):251. doi:10.1186/s13054-025-05474-9
 77. Zhou Y, Ma J, Chen H, et al. Hierarchical ventilator-free days with win method in acute respiratory distress syndrome treatment. *Thorax.* Epub 2026 Mar 18. doi:10.1136/thorax-2025-224263
 78. Hughes CG, Mailloux PT, Devlin JW, et al. Dexmedetomidine or propofol for sedation in mechanically ventilated adults with sepsis. *N Engl J Med.* 2021;384(15):1424-36. doi:10.1056/NEJMoa2024922
 79. Walsh TS, Parker RA, Aitken LM, et al. Dexmedetomidine- or clonidine-based sedation compared with propofol in critically ill patients: the A2B randomized clinical trial. *JAMA.* 2025;334(1):32-45. doi:10.1001/jama.2025.7200
 80. Shehabi Y, Serpa Neto A, Bellomo R, et al. Dexmedetomidine and propofol sedation in critically ill patients and dose-associated 90-day mortality: a secondary cohort analysis of a randomized controlled trial (SPICE III). *Am J Respir Crit Care Med.* 2023;207(7):876-86. doi:10.1164/rccm.202206-12080C
 81. Moore JPR, Shehabi Y, Reade MC, et al. Stress response during early sedation with dexmedetomidine compared with usual-care in ventilated critically ill patients. *Crit Care.* 2022;26(1):359. doi:10.1186/s13054-022-04237-0