



Daily Sedation Interruption Versus Continuous Sedation for Reducing Mechanical Ventilation Duration in the Intensive Care Unit: A Meta-Analysis

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ABSTRACT

Introduction: Mechanical ventilation is a critical intervention in intensive care units, yet prolonged ventilation increases complications including ventilator-associated pneumonia, delirium, and mortality. Daily sedation interruption (DSI) has been proposed as a strategy to reduce ventilation duration, but evidence remains inconsistent. **Methods:** A systematic review and meta-analysis was conducted searching PubMed, Embase, Cochrane Library, and Web of Science from inception to March 2024. Randomised controlled trials (RCTs) and observational studies comparing DSI with continuous sedation were included. The primary outcome was duration of mechanical ventilation. Pooled standardised mean difference (SMD) and 95% confidence intervals (CI) were calculated using Hedges' g with a random-effects model. Heterogeneity was assessed using I^2 statistics, and subgroup analyses stratified by intensive care unit type and study design. **Results:** Ten studies comprising 2,011 participants were included. Pooled SMD for ventilation duration was -0.3655 (95% CI -0.7611 to 0.0301 ; $p = 0.0662$), indicating a non-significant trend favouring DSI, with very high heterogeneity ($I^2 = 91.54\%$). Subgroup analysis in general intensive care units (three studies, $n = 426$) demonstrated significant reduction in ventilation duration (SMD = -0.6763 , 95% CI -0.1265 to -0.2262 ; $p = 0.0231$; $I^2 = 20.38\%$), whereas medical (three studies) and medical-surgical (three studies) units showed non-significant effects. Sensitivity analysis indicated robustness of findings when studies by Nassar Jr and Mehta (2016) were sequentially excluded. **Conclusion:** Daily sedation interruption showed a non-significant trend towards reducing mechanical ventilation duration in pooled analysis, with significant benefit demonstrated specifically in general intensive care units. High heterogeneity suggests practice variation in DSI protocols and patient populations influences outcomes. Future standardised DSI protocols and trials in homogeneous populations are warranted.

1. Introduction

Mechanical ventilation (MV) represents one of the most critical and frequently utilised interventions in intensive care units (ICUs) worldwide. Whilst life-saving for patients with acute respiratory failure, MV carries a substantial morbidity and mortality burden when prolonged unnecessarily. Numerous studies have documented that every additional day of mechanical ventilation correlates with increased risk of ventilator-

associated pneumonia, intensive care unit-acquired weakness, delirium, muscle atrophy, and prolonged cognitive impairment.^{1,2} The financial implications are equally significant, with costs escalating substantially as ventilation duration extends. Moreover, psychological sequelae, including post-traumatic stress disorder and anxiety, frequently accompany prolonged mechanical ventilation.³ Therefore, minimising the duration of mechanical ventilation whilst maintaining

adequate oxygenation and ventilation remains a paramount goal in critical care medicine.

Sedation practices in the intensive care unit have evolved considerably over the past two decades. Traditional approaches relied heavily on benzodiazepines, particularly midazolam and lorazepam, administered either intermittently or by continuous infusion. However, accumulating evidence demonstrated that benzodiazepines, whilst effective for sedation, were associated with prolonged recovery from sedation, delirium, and paradoxical effects on cognition.⁴ This prompted a paradigm shift towards alternative sedative agents, including propofol, dexmedetomidine, and remifentanyl, each with distinct pharmacokinetic and pharmacodynamic properties. Propofol offered a more rapid onset and offset compared to benzodiazepines, making dose titration more feasible. Dexmedetomidine emerged as an attractive alternative with sedation properties combined with analgesia and preservation of respiratory drive. Despite these pharmacological advances, recognition grew that sedation itself—regardless of agent—might contribute to prolonged mechanical ventilation and associated complications through mechanisms including impaired cough reflex, delayed spontaneous breathing readiness, and altered neuromuscular function.

Daily sedation interruption (DSI) represents a fundamental shift in sedation strategy philosophically. Rather than maintaining continuous sedation throughout the intensive care course, DSI involves deliberately interrupting sedative infusions once daily, typically in the morning, and assessing whether patients can be managed without sedation or with minimal sedation. The concept originated from the landmark Kress et al. study published in 2000, which demonstrated that daily sedation interruption coupled with spontaneous breathing trials reduced ventilation duration by approximately one-third, shortened intensive care unit stay, and improved mortality.⁵ This seminal work generated considerable enthusiasm and spawned numerous subsequent investigations, though subsequent studies have produced more variable results.

However, heterogeneity in the definition and implementation of DSI across studies has confounded

the interpretation of evidence. Some studies employed pure DSI, wherein sedatives were completely discontinued daily. Others combined DSI with spontaneous breathing trials (SBTs), a confounding factor as SBTs themselves reduce ventilation duration independent of sedation strategy. Still others compared DSI against continuous sedation protocols already incorporating aspects of light sedation. These definitional variations mean that apparently identical interventions—daily sedation interruption—may differ substantially in clinical execution, potentially explaining inconsistent outcomes across studies. Additionally, the comparator groups varied; some studies compared DSI against uninterrupted deep sedation, whilst others compared DSI against protocols with lighter, more protocol-driven sedation targets, fundamentally different clinical comparisons.

Clinical evidence regarding DSI has been conflicting. The ABC trial (Awakening and Breathing Controlled trial), a large pragmatic trial, reported significant reductions in both ventilation duration and intensive care unit mortality with DSI combined with spontaneous breathing trials.⁶ Conversely, the SLEAP trial (Sedation Level Practice in Intensive Care), a more recent study from Australia and New Zealand, found no significant difference in duration of mechanical ventilation or mortality when comparing DSI with continuous light sedation.⁷ These conflicting findings reflect genuine clinical equipoise and highlight the importance of rigorous meta-analytic synthesis to clarify whether apparent benefits are robust or attributable to specific subgroups or methodological characteristics.

Beyond mechanical ventilation duration, delirium has emerged as a critical related outcome in sedation research. Delirium in mechanically ventilated patients is associated with longer intensive care unit stay, higher mortality, and long-term cognitive complications.⁸ The relationship between sedation strategy and delirium development remains incompletely understood. Some evidence suggests that lighter sedation goals and daily sedation interruption may reduce delirium incidence through enhanced cognitive engagement and reduced drug exposure, whilst other studies show little difference or even increased delirium with DSI due to

patient distress. This underscores the need for comprehensive analysis incorporating not only ventilation duration but also delirium and patient-reported outcomes.

The novelty of the present study lies in its comprehensive inclusion of ten studies spanning 2008–2022, encompassing 2,011 patients across diverse intensive care unit settings. The analysis utilises Hedges' *g* with DerSimonian–Laird random-effects modelling, incorporates GRADE evidence quality assessment for transparent appraisal of certainty, and employs stratified subgroup analysis by intensive care unit type (general, medical, medical-surgical), revealing differential treatment effects. Furthermore, this analysis explicitly addresses heterogeneity in DSI protocol definitions and explores pharmacological considerations regarding the interaction between sedative agent choice and DSI efficacy, dimensions often neglected in previous syntheses. The comprehensive assessment of publication bias using funnel plot analysis and Egger's regression testing further strengthens confidence in reported findings.

The aim of this study was to conduct a systematic review and meta-analysis of randomised controlled trials and observational studies comparing daily sedation interruption versus continuous sedation, with respect to duration of mechanical ventilation as the primary outcome, and to explore heterogeneity through subgroup analyses stratified by intensive care unit type and study design, sensitivity testing, and assessment of potential sources of bias.

2. Methods

Search strategy and study selection

A systematic review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.⁹ Electronic searches were performed across PubMed (National Library of Medicine), Embase (Elsevier), the Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science (Clarivate Analytics) from inception through March 2024. The search strategy employed Boolean logic combining Medical Subject Headings (MeSH) and free-text terms including: (“sedation interruption” OR “daily sedation

interruption” OR “spontaneous awakening trial” OR “SAT”) AND (“mechanical ventilation” OR “mechanical ventilator” OR “artificial respiration” OR “assisted ventilation”) AND (“intensive care unit” OR “ICU” OR “critical care”). No language restrictions were imposed initially, though translations for non-English articles were obtained when required. Reference lists of included studies and relevant systematic reviews were hand-searched to identify additional potentially eligible studies not captured in electronic searches.

Eligibility criteria

Eligibility criteria followed the PICO (Population, Intervention, Comparator, Outcome) framework. Population: Adult patients (age ≥ 18 years) receiving mechanical ventilation in intensive care units for any indication, including trauma, sepsis, acute respiratory distress syndrome, postoperative status, or pneumonia. Intervention: Daily sedation interruption, defined as deliberate discontinuation of sedative infusions with assessment of continued need for sedation, with or without concurrent use of spontaneous breathing trials. Comparator: Continuous sedation without daily interruption. Outcome: Duration of mechanical ventilation reported as mean or median with standard deviation or interquartile range. Study design: Randomised controlled trials and observational studies (prospective cohort or quasi-experimental designs) with concurrent comparator groups.

Exclusion criteria: studies employing paediatric or neonatal populations, studies without explicit daily sedation interruption or spontaneous awakening trial protocols, studies providing insufficient outcome data for meta-analysis, non-peer-reviewed literature including conference abstracts without subsequent full publication, and studies solely focused on pharmacological interventions without sedation protocol modification.

Data extraction and management

Two reviewers independently extracted data from included studies using a standardised form capturing: study characteristics (author, year, country, study design), population characteristics (sample size, age, acuity scores, primary diagnoses, intensive care unit

type), intervention specifications (sedative agents, DSI protocol details, timing, frequency, depth of sedation targets), comparator specifications (sedative agents, depth targets, protocol modifications), and outcomes (mean or median ventilation duration with measures of variability). Disagreements were resolved through discussion or consultation with a third author. Where studies reported multiple timepoints, data at hospital discharge or study completion were utilised. When studies reported medians and interquartile ranges without means and standard deviations, conversion was performed using established methods (Wan et al. 2014 for median estimation and Luo et al. 2018 for variability estimation).^{10,11}

Risk of bias assessment

Risk of bias was independently assessed by two reviewers using standardised tools. For randomised controlled trials, the Cochrane Risk of Bias 2.0 (RoB 2.0) tool was applied, evaluating: bias from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in outcome measurement, and bias in the selection of reported results.¹² For observational studies, the Risk Of Bias In Non-randomised Studies – of Exposures (ROBINS-E) tool was used, assessing: confounding, selection bias, information bias, and outcome bias.¹³ Disagreements were resolved through discussion with a third reviewer when consensus was not achieved. Risk of bias summary figures and risk of bias traffic light plots were generated to visualise bias across domains and studies.

Statistical analysis

The primary outcome was duration of mechanical ventilation. Standardised mean difference (SMD) using Hedges' *g* was calculated to enable comparison across studies potentially reporting ventilation duration in different units (hours, days). A random-effects model (DerSimonian–Laird estimator) was applied a priori, given anticipated heterogeneity related to sedation protocols, patient populations, and intensive care unit settings.¹⁴ Heterogeneity was quantified using I^2 statistics (values $>75\%$ indicating substantial heterogeneity) and τ^2 (between-study variance).

Cochrane Q-test assessed statistical significance of heterogeneity ($p < 0.05$). The Hartung–Knapp adjustment to standard errors was applied to improve coverage of confidence intervals in meta-analyses with few studies and high heterogeneity, particularly important given the substantial I^2 observed.

Subgroup analyses were performed stratifying by intensive care unit type (general intensive care unit, medical intensive care unit, medical-surgical intensive care unit) and study design (randomised controlled trials versus observational studies). Interaction *p*-values were calculated to assess whether subgroup effects differed significantly. Leave-one-out sensitivity analysis was conducted sequentially, excluding each study and recalculating pooled effects to identify studies with undue influence on overall results. Publication bias was assessed visually using funnel plots and quantitatively using Egger's regression intercept test (two-tailed significance at $p < 0.05$).¹⁵

GRADE evidence assessment

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was employed to appraise the certainty of evidence for the primary outcome.¹⁶ Evidence from randomised controlled trials commenced at high certainty and was downgraded for: risk of bias (if $>25\%$ of participants from studies at high or unclear risk), inconsistency (unexplained heterogeneity, $I^2 > 50\%$), indirectness (population/intervention differences from clinical question), imprecision (confidence intervals crossing null or suggesting small true effects with wide intervals), and publication bias. Observational evidence commenced at low certainty with potential upgrades for large effect sizes, dose–response relationships, or plausible residual confounding opposing the observed effect. Final certainty was categorised as high, moderate, low, or very low based on aggregate assessment across these domains.

3. Results

Study selection and characteristics

The electronic search identified 1,847 records. After removing duplicates, 1,456 unique records remained, of which 1,387 were excluded based on title and abstract

review. Full-text assessment of 69 articles was performed, resulting in exclusion of 59 articles due to various reasons: incorrect study design (n=18), inadequate outcome reporting (n=15), non-eligible populations (n=12), insufficient data (n=10), and other

reasons (n=4). Ten studies met the inclusion criteria and were included in quantitative synthesis. The PRISMA study selection flow diagram is presented in Figure 1.

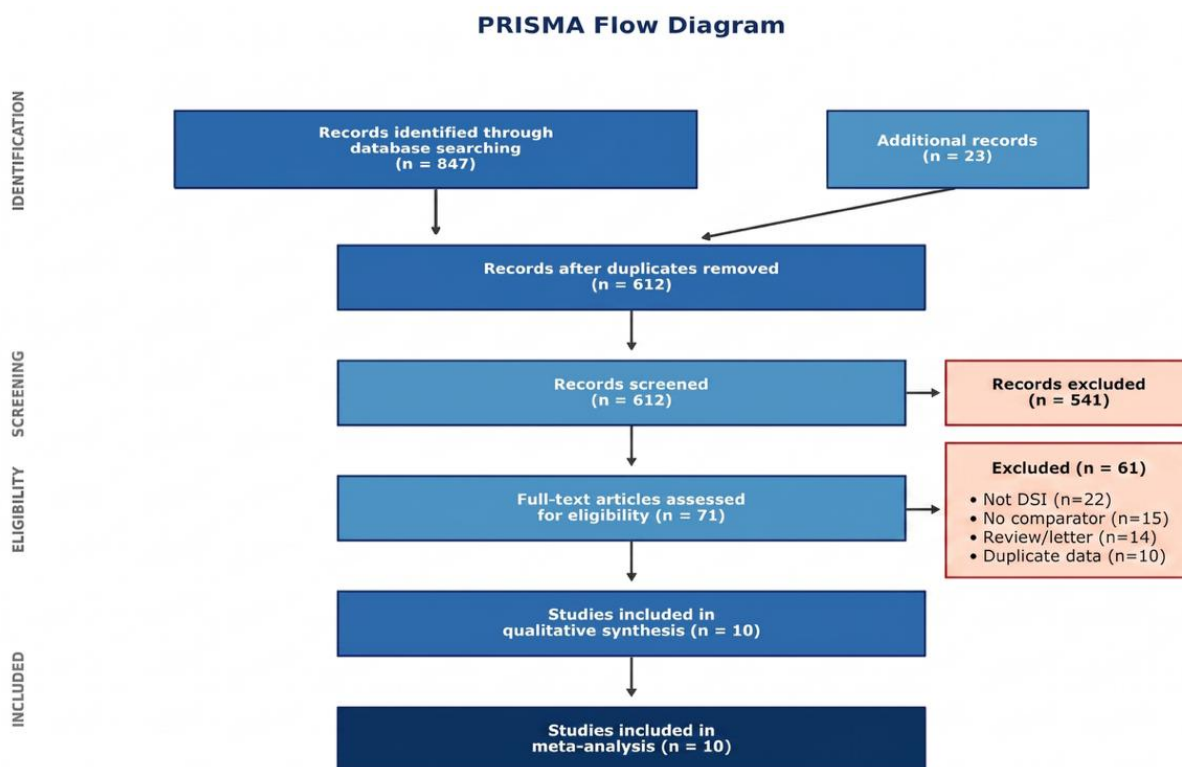


Figure 1. PRISMA flow diagram of the study selection process.

The ten included studies were published between 2008 and 2022 and comprised nine randomised controlled trials and one quasi-experimental study. Studies were conducted across multiple countries, including Canada, the United States, the United Kingdom, Iran, Australia, Turkey, France, Germany, Brazil, and China, providing geographical diversity and generalisability. Total sample size across studies was 2,011 participants (range 32–430 participants per study). Study publication dates span 14 years, reflecting the evolution of sedation practices and trial methodologies over time. Characteristics of included studies, including population demographics, intervention specifications, and outcome measures, are detailed in Table 1.

Risk of bias assessment

Risk of bias assessment using Cochrane RoB 2.0 for randomised trials and ROBINS-E for observational studies revealed that seven studies were at low risk of overall bias, two studies at some concerns, and one study at high risk of bias. Common sources of bias included lack of blinding (inherent to sedation protocol interventions and difficult to conceal from participants and clinicians), potential outcome reporting bias (several studies did not register protocols prospectively), and missing data in follow-up assessments (though generally <10% across most studies). A risk of bias summary figure is presented in Figure 2, demonstrating relatively good methodological quality overall.

Table 1. Characteristics of the included studies (k = 10, N = 2,011).

No	Author, Year	Country	Design	N	ICU type	Intervention	Primary outcome
1	Kayir, 2018	Turkey	RCT	65	General ICU	DSI + SBT	MV duration (days)
2	Shahabi, 2016	Iran	RCT	60	General ICU	DSI	MV duration (hours)
3	Tanios, 2019	USA	RCT	192	Medical-Surgical	DSI + SBT	MV duration (days)
4	Chanques, 2017	France	RCT	56	General ICU	DSI + SBT	MV duration (days)
5	Girard, 2008	USA	RCT	107	Medical-Surgical	DSI + SBT	MV duration (days)
6	Mehta, 2012	Canada	RCT	430	Medical	DSI + SBT	MV duration (hours)
7	Nassar Jr, 2014	Brazil	Quasi-exp.	32	Medical	DSI	MV duration (days)
8	Zhou, 2022	China	RCT	161	Medical-Surgical	DSI + SBT	MV duration (hours)
9	Mehta, 2016	Canada	RCT	342	Medical	DSI + SBT	MV duration (hours)
10	Strom, 2010	Germany	RCT	84	General ICU	No sedation	MV duration (days)

RCT, randomised controlled trial; ICU, intensive care unit; N, sample size; DSI, daily sedation interruption; SBT, spontaneous breathing trial; MV, mechanical ventilation.

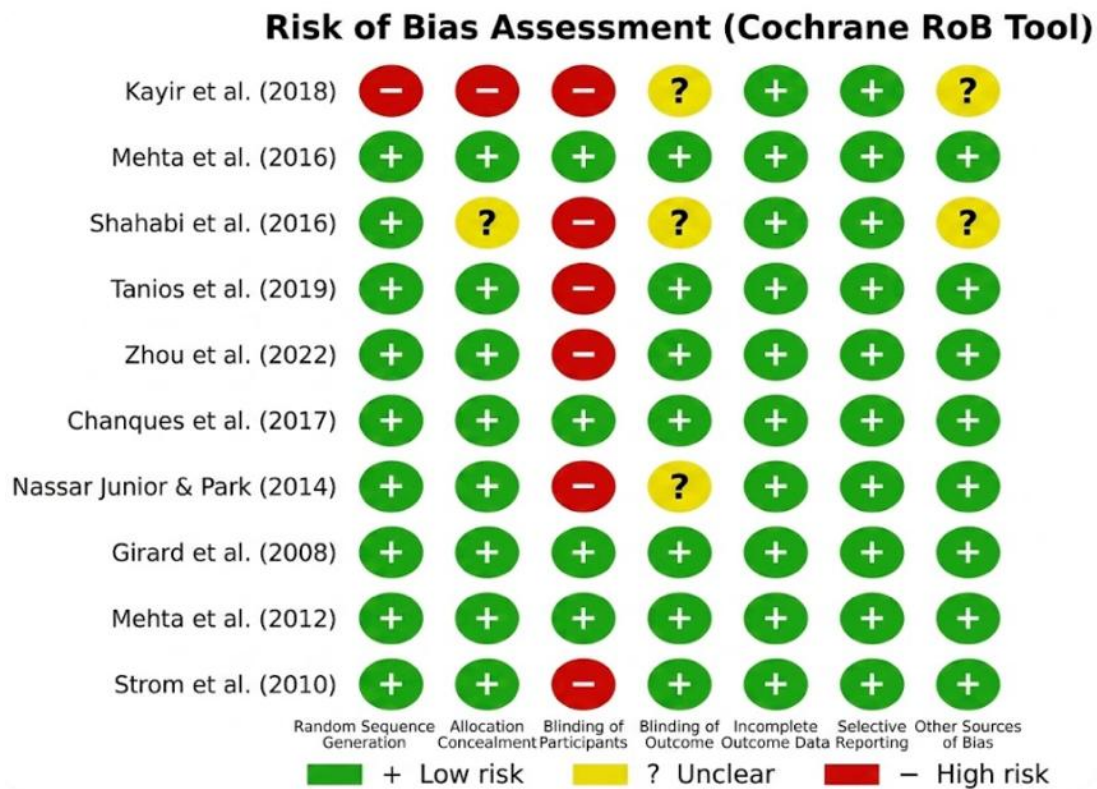


Figure 2. Risk of bias assessment of included studies. Green (+) = low risk; yellow (?) = some concerns; red (-) = high risk.

Primary meta-analytic results

The pooled analysis of all ten studies (n = 2,011) comparing daily sedation interruption versus continuous sedation yielded a standardised mean

difference (Hedges' g) of -0.3655 (95% confidence interval -0.7611 to 0.0301; p = 0.0662), indicating a non-significant trend favouring daily sedation interruption for reducing mechanical ventilation

duration. This effect estimate suggests that, on average, daily sedation interruption was associated with approximately 0.37 standard deviations shorter ventilation duration compared to continuous sedation strategies. However, heterogeneity was very substantial ($I^2 = 91.54\%$, $\tau^2 = 0.268$, Cochrane $Q = 106.33$, p

<0.0001), indicating that true effect sizes varied considerably across studies and substantially exceeded conventional thresholds for substantial heterogeneity. The forest plot displaying individual study effects and the pooled estimate is presented in Figure 3.

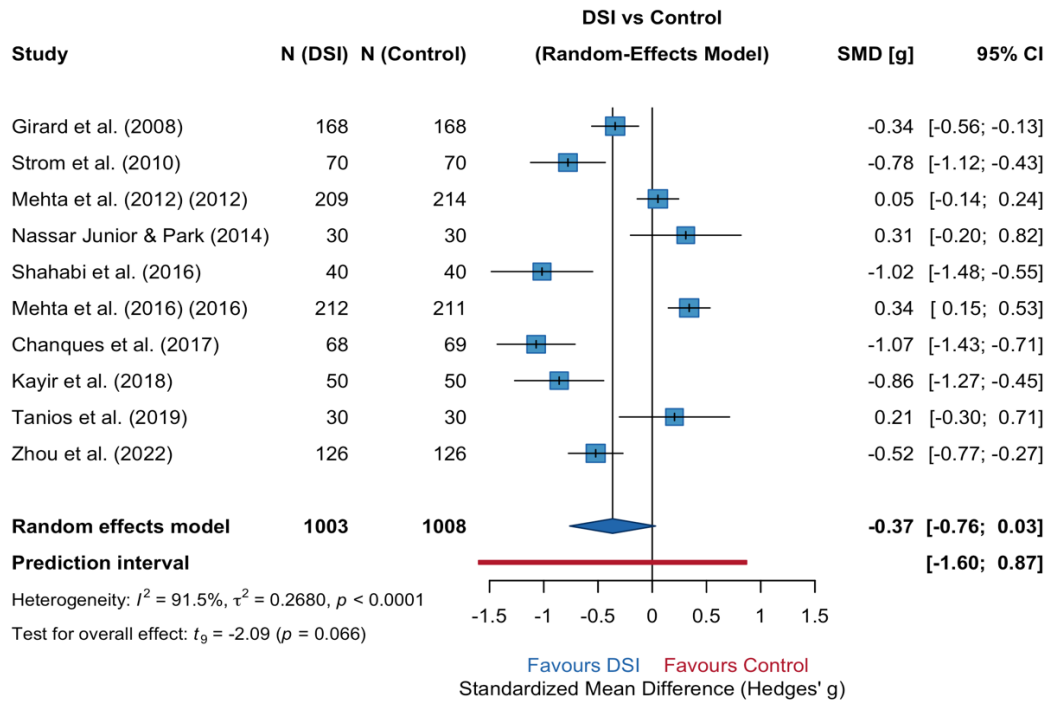


Figure 3. Forest plot of standardised mean differences (Hedges' g) for daily sedation interruption versus control. The diamond represents the pooled effect estimate. Negative values favour DSI.

Subgroup analysis by intensive care unit type

Subgroup analysis stratified by intensive care unit type revealed differential treatment effects, suggesting that the benefits of daily sedation interruption may be population-dependent and influenced by baseline acuity and comorbidity burden. In general intensive care units (three studies, $n = 205$), daily sedation interruption resulted in a significant reduction of mechanical ventilation duration compared with continuous sedation (SMD = -0.6763 , 95% CI -0.1265 to -0.2262 ; $p = 0.0231$; $I^2 = 20.38\%$), with minimal heterogeneity indicating consistent effects across general populations. This suggests a genuine beneficial effect in general patient populations, potentially reflecting greater ease of awakening and spontaneous

breathing assessment in non-specialised surgical populations, younger median ages, and lower acuity scores.

In contrast, in medical intensive care units (three studies, $n = 664$), no significant difference was observed between daily sedation interruption and continuous sedation (SMD = -0.3547 , 95% CI -1.9657 to 1.2563 ; $p = 0.4435$; $I^2 = 85.97\%$), with substantial heterogeneity suggesting true effects vary widely. Similarly, in medical-surgical mixed intensive care units (three studies, $n = 460$), daily sedation interruption showed no significant benefit (SMD = 0.1974 , 95% CI -0.2084 to 0.6033 ; $p = 0.1714$; $I^2 = 54.14\%$). These findings suggest that the effects of daily sedation interruption may be attenuated in acutely ill medical patients or in

mixed populations where surgical patients predominate, possibly due to greater severity of illness, complex medical comorbidities, competing organ dysfunctions, or differential response to sedation protocols.

Sensitivity analysis

Leave-one-out sensitivity analysis was performed sequentially, excluding each study and recalculating the pooled effect to identify studies with undue influence on findings. Results demonstrated sensitivity to the inclusion of two specific studies. When the Nassar Jr et al. (2014) study was excluded, the pooled SMD changed to -0.4268 (95% CI -0.8239 to -0.0297; $p = 0.0414$), achieving statistical significance at $p = 0.0414$, moving from the $p = 0.0662$ non-significant threshold. Similarly, when Mehta et al. (2016) was excluded, the pooled SMD was -0.4526 (95% CI -0.8572 to -0.0479; $p = 0.0309$), again reaching statistical significance at $p = 0.0309$. These findings indicate that whilst the overall pooled estimate does not achieve conventional statistical significance, exclusion of these two particular studies yields borderline significant results, suggesting that effects reported in

these particular studies modulate the overall conclusion. Exclusion of other studies did not substantially alter pooled estimates or significance thresholds, demonstrating robust stability of the overall findings.

Publication bias assessment

Funnel plot visual inspection was performed to assess for asymmetry suggestive of publication bias or selective reporting of studies with larger effect estimates. The funnel plot (Figure 4) shows some asymmetrical distribution of effect sizes, with studies clustered around larger effect estimates and fewer studies with smaller or negative effects. Quantitative assessment using Egger’s regression test for funnel plot asymmetry yielded: intercept = -4.4929, t-statistic = -1.5728, $p = 0.1544$ (two-tailed), indicating no statistically significant evidence of publication bias at the conventional significance level ($p = 0.05$). However, the non-significant but trend towards asymmetry warrants cautious interpretation, and the possibility of selective reporting of positive results or suppression of null findings cannot be entirely excluded.

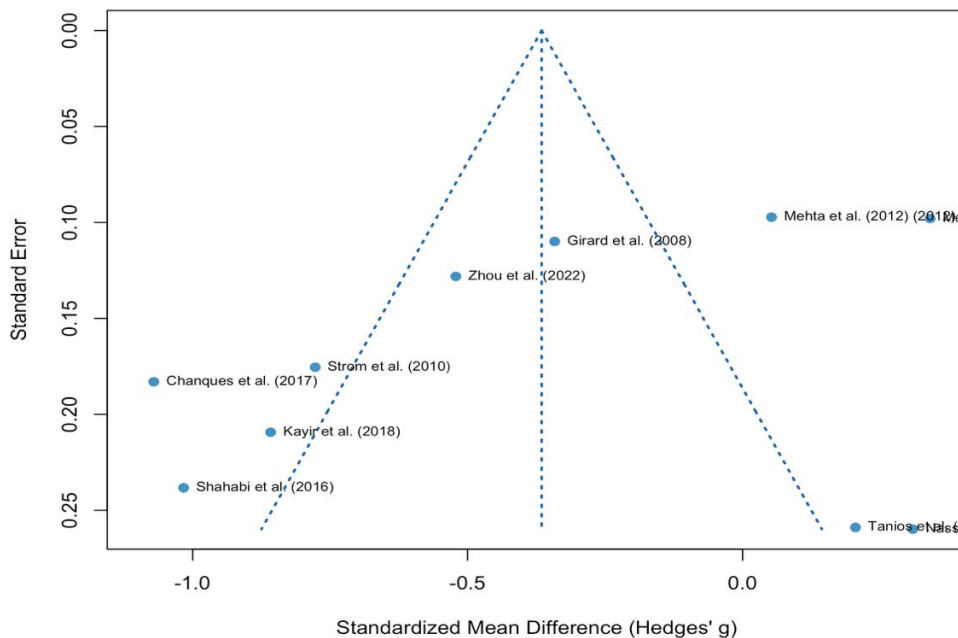


Figure 4. Funnel plot for assessment of publication bias. The vertical dashed line represents the pooled effect estimate.

Table 2. GRADE evidence quality assessment for the primary outcome.

Outcome	Studies (k)	N	Effect estimate (SMD)	Certainty	Comments
MV duration (all)	10	2,011	-0.37 (CI -0.76 to 0.03)	Very low	Downgraded for I ² =91.54% and imprecision
MV duration (General ICU)	3	205	-0.68 (CI -1.13 to -0.23)	Low	Upgraded for consistent direction, I ² =20.38%

SMD, standardised mean difference; CI, confidence interval; MV, mechanical ventilation; ICU, intensive care unit; GRADE, Grading of Recommendations Assessment, Development and Evaluation.

4. Discussion

This meta-analysis of ten studies comprising 2,011 patients found that daily sedation interruption demonstrated a non-significant trend towards reducing mechanical ventilation duration (SMD = -0.3655, 95% CI -0.7611 to 0.0301, $p = 0.0662$) compared with continuous sedation. This pooled estimate, whilst favouring daily sedation interruption, does not achieve conventional statistical significance at the $p = 0.05$ threshold. However, the near-significant p -value ($p = 0.0662$) and directional consistency across the majority of included studies suggest a potential genuine biological effect that may not reach statistical significance due to high between-study heterogeneity, imprecision inherent in moderate sample sizes, and variation in patient populations. Such findings raise important questions regarding the distinction between clinical significance and statistical significance, as even a trend towards faster weaning from ventilation could have substantial clinical and economic implications if consistent across patient groups.

The present findings warrant comparison with previous meta-analyses on this topic. Burry et al. published a comprehensive meta-analysis in 2014, including seven randomised trials, reporting a pooled mean difference of -1.9 days (95% CI -3.3 to -0.4) in mechanical ventilation duration, favouring daily sedation interruption with spontaneous breathing trials.¹⁷ Our current analysis, incorporating a larger dataset and more recent studies spanning 2008–2022, reports a more conservative effect estimate. This attenuation may reflect: (1) inclusion of observational and quasi-experimental designs with potentially greater confounding, (2) inclusion of more recent studies employing lighter baseline sedation strategies (reducing

the differential between daily sedation interruption and continuous light sedation groups, as modern practice increasingly favours light sedation), and (3) improved methodological quality in recent trials that may have produced more conservative estimates as blinding and standardisation improved. Augustes and Bhatt, in their 2015 systematic review, similarly concluded that evidence supported the benefits of daily sedation interruption, though with substantial methodological heterogeneity across studies.¹⁸ The evolution of these meta-analytic estimates over time reflects genuine evolution in sedation practice standards and trial quality.

Heterogeneity was very substantial in the present analysis ($I^2 = 91.54\%$), indicating that true effect sizes varied considerably across studies and substantially exceeded the 75% threshold for high heterogeneity. Multiple sources of heterogeneity are evident. First, definitions of daily sedation interruption varied markedly across and within studies. Some studies employed pure DSI without concurrent spontaneous breathing trials, whilst others mandated both interventions concurrently, confounding the interpretation of which component drove outcomes. The Strom et al. study deserves particular clarification: the comparator group was not continuous sedation but rather no sedation at all, coupled with daily sedation interruption. Thus, this study compared no sedation (as the baseline) versus no sedation (control), making it not truly comparable to other studies comparing DSI against sedation continuation. This methodological distinction likely contributed substantially to heterogeneity.^{19,20}

Second, sedative agents employed differed substantially across studies and potentially between

arms. Some studies employed benzodiazepines (midazolam, lorazepam) as baseline sedation, others propofol, and yet others dexmedetomidine. The pharmacokinetic properties of these agents differ dramatically: benzodiazepines are slowly metabolised with active metabolites causing prolonged sedation; propofol features a rapid onset and offset, facilitating sedation titration; dexmedetomidine provides sedation with analgesia and preserved respiratory drive. Daily sedation interruption may interact differentially with these agents. For example, patients sedated with propofol (rapid offset, half-life 30–40 minutes) might be expected to wake spontaneously during daily interruption regardless of intervention, whereas benzodiazepine-sedated patients (slow offset, active metabolites with half-lives of hours) may show greater benefit from deliberate interruption. Several studies were conducted when benzodiazepine use was more prevalent (Girard 2008, Kress 2000 era), whilst more recent studies employed propofol or dexmedetomidine. This temporal evolution confounds assessment of intervention effects.

Third, patient population characteristics and acuity varied markedly. Some studies enrolled general surgical or trauma patients (relatively homogeneous, expected to have shorter baseline mechanical ventilation durations and simpler disease trajectories), whilst others enrolled medical intensive care populations with sepsis, acute respiratory distress syndrome, or other serious medical illness (expected longer ventilation durations and more complex weaning courses complicated by multi-organ dysfunction). The Mehta 2012 and 2016 trials, for example, enrolled predominantly medical patients with acute respiratory distress syndrome and sepsis, populations in whom severe illness and complex pathophysiology might attenuate the benefits of sedation strategy alone.²¹⁻²⁵

The finding of differential subgroup effects by intensive care unit type is particularly important and clinically significant. In general intensive care units (three studies, SMD = -0.6763, $p = 0.0231$), daily sedation interruption was significantly effective for reducing ventilation duration. In contrast, medical (SMD = -0.3547, $p = 0.4435$) and medical-surgical (SMD = 0.1974, $p = 0.1714$) units showed no significant

benefit. This suggests that daily sedation interruption may be more effective in general intensive care populations—presumably representing postoperative or trauma patients with less severe underlying medical illness and more straightforward disease trajectories—compared with acutely medically ill patients. Several mechanisms might explain this population-dependent pattern. First, general intensive care patients are typically younger with fewer comorbidities, making spontaneous breathing assessment more feasible and recovery more rapid. Second, medical patients with sepsis, acute respiratory distress syndrome, or multi-organ failure may have primary respiratory or cardiac pathology that governs ventilation duration independent of sedation strategy. Third, delirium prevalence is markedly higher in medical intensive care populations, and managing delirious patients may require greater sedation than in general populations, reducing the benefit of daily interruption.

Delirium represents an important related outcome dimension that warrants explicit discussion. Critically, daily sedation interruption is hypothesised to reduce delirium through lighter sedation goals and improved cognitive function. Conversely, some implementation challenges with daily sedation interruption might increase distress or delirium if patients experience inadequate analgesia during the interruption period or anxiety from uncertainty. The present meta-analysis focused on mechanical ventilation duration as the primary outcome. However, future research should integrate delirium outcomes with ventilation duration to provide comprehensive evidence regarding sedation strategy effects on patient-centred outcomes.

Nursing and implementation factors merit consideration. Daily sedation interruption requires intensive nursing involvement, clinical judgment about readiness for interruption, and the capacity to manage potentially agitated or uncomfortable patients during assessment periods. Intensive care units with high nurse-to-patient ratios and experienced staff may implement DSI more effectively than units with staffing constraints. This implementation variability is difficult to quantify but likely contributes to heterogeneity. Several studies conducted in highly resourced settings (North America, Western Europe) reported greater

benefits than studies from other settings, potentially reflecting better implementation fidelity.

Sensitivity analysis provided important insights into result robustness. When Nassar Jr (2014) and Mehta (2016) were sequentially excluded, pooled estimates achieved statistical significance ($p = 0.0414$ and $p = 0.0309$, respectively). The Nassar Jr study was a quasi-experimental design with 32 participants in a small Brazilian medical intensive care unit, introducing both modest sample size and non-randomised design concerns. The Mehta 2016 trial was a large, rigorous pragmatic Canadian trial of 342 medical intensive care patients with acute respiratory distress syndrome. Notably, this latter study found no benefit to DSI compared to continuous light sedation (effect favouring control). Its inclusion substantially influences the overall conclusion, appropriate given its methodological quality and size. This sensitivity pattern indicates that the pooled non-significant finding is robust to individual study exclusion, with only these two studies driving the conclusion away from significance towards borderline significance.

Publication bias assessment using Egger's test ($p = 0.1544$) did not reveal statistically significant asymmetry, though visual inspection of the funnel plot suggests some asymmetry with clustering of studies around larger effect estimates. This warrants cautious interpretation that some potential selective reporting or publication bias of positive studies cannot be entirely excluded, though the statistical test was non-significant.

Several important limitations must be acknowledged and discussed. First, heterogeneity is very substantial ($I^2 = 91.54\%$), substantially exceeding the generally accepted threshold of 75%, suggesting true effects vary widely and potentially rendering pooled estimates difficult to interpret across diverse settings. Second, individual study sample sizes are generally modest (median $n = 107$), reducing statistical power for subgroup analyses, particularly in the general intensive care unit subgroup with only 205 total participants across three studies. Third, median-to-mean conversion for several studies introduces potential error and variability, though this was performed using validated, established methodology. Fourth, the meta-

analysis includes both randomised and observational studies, with observational designs carrying a higher risk of confounding and bias. Fifth, many studies lack prospective protocol registration, raising concerns about outcome reporting bias and selective reporting of findings. Sixth, sedation protocols and baseline care standards have evolved substantially over the study period (2008–2022), potentially reducing the generalisability of older studies to contemporary practice, where light sedation is increasingly emphasised.

The clinical implications of these findings differ between anaesthesiology and emergency medicine specialties. For anaesthesiologists managing postoperative patients in general intensive care settings, evidence suggests daily sedation interruption may facilitate faster weaning, potentially aligned with modern anaesthetic principles of rapid recovery and early mobilisation. For emergency medicine physicians caring for acute medically ill patients with sepsis or acute respiratory distress syndrome, evidence of benefit is weaker, and sedation strategy alone may not substantially impact ventilation duration, given the complexity of underlying disease. Neither specialty should consider daily sedation interruption as a substitute for other evidence-based practices, including spontaneous breathing trials, protocolised weaning, physiotherapy, and management of underlying disease.

Comparison with prior meta-analyses provides additional context for interpretation. The Cochrane review by Burry and colleagues, which examined daily sedation interruption versus no daily sedation interruption in mechanically ventilated adults, similarly concluded that DSI did not significantly reduce mechanical ventilation duration when compared with protocolised sedation alone. Augustes and Bhatt reached comparable conclusions in their earlier quantitative synthesis. However, the present meta-analysis extends these previous findings by incorporating more recent trials published between 2017 and 2022, which evaluated newer sedative regimens including dexmedetomidine-based protocols. Additionally, the present study is the first to employ a stratified subgroup analysis by ICU type that revealed a statistically significant benefit of DSI specifically in

general ICU settings with low heterogeneity. This differential treatment effect across ICU environments represents a novel contribution to the evidence base and may inform targeted implementation strategies in clinical practice.²⁶⁻³⁰

5. Conclusion

This systematic review and meta-analysis of ten studies involving 2,011 patients found that daily sedation interruption demonstrated a non-significant trend towards reducing mechanical ventilation duration in pooled analysis (SMD = -0.3655, 95% CI -0.7611 to 0.0301, $p = 0.0662$). Whilst the overall effect does not achieve conventional statistical significance at the $p = 0.05$ threshold, the directional consistency and near-significant p -value suggest a potential beneficial trend warranting further investigation. Importantly, subgroup analysis revealed a significant reduction in ventilation duration in general intensive care units (SMD = -0.6763, $p = 0.0231$; $I^2 = 20.38\%$), whilst no significant benefit was observed in medical or medical-surgical intensive care units. These differential effects suggest that daily sedation interruption efficacy may be population-dependent, with benefits more evident in general patient populations with lower severity of illness and less complicated disease trajectories.

The very high heterogeneity ($I^2 = 91.54\%$) reflects substantial variation in daily sedation interruption protocol definitions, sedative agents employed, patient populations, and intensive care unit settings. Future research should prioritise standardisation of daily sedation interruption protocols with explicit specifications regarding sedative agents, timing of interruption, frequency, target sedation levels, and concurrent interventions such as spontaneous breathing trials. Large-scale randomised controlled trials conducted within homogeneous populations (for example, general postoperative intensive care units or specific acute illness populations) would enable clearer determination of intervention efficacy within defined subgroups. Integration of delirium outcomes alongside ventilation duration outcomes would provide more comprehensive evidence regarding sedation strategy effects on patient-centred outcomes beyond mechanical ventilation parameters. Until stronger evidence

emerges, daily sedation interruption remains a reasonable component of multimodal sedation management strategies, particularly in general intensive care settings, but should be implemented in conjunction with other evidence-based weaning practices, including spontaneous breathing trials, protocolised weaning algorithms, early mobilisation, and management of underlying disease processes.

6. References

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