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REVIEW ARTICLE

# Outcomes of dexmedetomidine *versus* propofol sedation in critically ill adults requiring mechanical ventilation: a systematic review and meta-analysis of randomised controlled trials

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## Abstract

**Background:** Guidelines have recommended the use of dexmedetomidine or propofol for sedation after cardiac surgery, and propofol monotherapy for other patients. Further outcome data are required for these drugs.
**Methods:** This systematic review and meta-analysis was prospectively registered on PROSPERO. The primary outcome was ICU length of stay. Secondary outcomes included duration of mechanical ventilation, ICU delirium, all-cause mortality, and haemodynamic effects. Intensive care patients were analysed separately as cardiac surgical, medical/noncardiac surgical, those with sepsis, and patients in neurocritical care. Subgroup analyses based on age and dosage were conducted.
**Results:** Forty-one trials ($N$=3948) were included. Dexmedetomidine did not significantly affect ICU length of stay across any ICU patient subtype when compared with propofol, but it reduced the duration of mechanical ventilation (mean difference −0.67 h; 95% confidence interval: −1.31 to −0.03 h; $P$=0.041; low certainty) and the risk of ICU delirium (risk ratio 0.49; 95% confidence interval: 0.29–0.87; $P$=0.019; high certainty) across cardiac surgical patients. Dexmedetomidine was also associated with a greater risk of bradycardia across a variety of ICU patients. Subgroup analyses revealed that age might affect the incidence of haemodynamic side-effects and mortality among cardiac surgical and medical/other surgical patients.
**Conclusion:** Dexmedetomidine did not significantly impact ICU length of stay compared with propofol, but it significantly reduced the duration of mechanical ventilation and the risk of delirium in cardiac surgical patients. It also significantly increased the risk of bradycardia across ICU patient subsets.

**Keywords:** critical illness; dexmedetomidine; ICU sedation; meta-analysis; propofol

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### Editor's key points

- Dexmedetomidine and propofol are recommended for sedation after surgery, but there is a paucity of evidence in patients with septicaemia or neurological injury.
- In this meta-analysis, the authors demonstrate that dexmedetomidine slightly reduces the duration of mechanical ventilation and risk of delirium in cardiac surgical patients but increases the risk of bradycardia in the broader ICU population, with age possibly affecting its impact on mortality and haemodynamic stability.
- Larger trials are needed in ICU sub-populations outside cardiac surgery.

Adult patients in the ICU often require continuous infusion sedatives to facilitate their tolerance of mechanical ventilation (MV).[1] Propofol is a sedative-hypnotic anaesthetic agent that is commonly used for sedation.[2–4] While it is utilised because of its rapid onset and short duration of action, it possesses a significant adverse event profile. Specifically, hypotension is of concern, especially for patients with underlying cardiovascular conditions.[2,5] However, dexmedetomidine functions as a centrally acting, alpha-2 adrenergic receptor agonist.[1] Dexmedetomidine sedation has been associated with improved patient rousability, greater preservation of cognitive performance, and reduced risk of respiratory depression with minimal effect on central ventilatory drive.[1] However, its use may lead to a dose-dependent biphasic blood pressure response, with lower doses leading to a decrease in mean arterial pressure and heart rates and higher doses being associated with hypertension.[3]

Past reviews have demonstrated a significant reduction in delirium among a combination of adult ICU patients receiving dexmedetomidine *vs* propofol sedation.[6,7] Although dexmedetomidine was shown to significantly shorten ICU length of stay (LOS) in one review,[7] another review that included trials with patients ≥60 yr old found no significant differences between the two sedatives.[8] Moreover, both of these trials analysed different ICU patient types in combination, limiting the applicability of these findings to specific ICU patients. In addition, dexmedetomidine sedation has been associated with adverse events including bradycardia, hypertension, and hypotension.[9,10] A previous meta-analysis[11] aimed to clarify the role of these sedatives in post-cardiac surgical sedation, however, its findings were hampered by its problematic methodology and inclusion criteria, as highlighted by a letter to the editor.[12] Although the 2018 *Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU* (PADIS) guidelines recommended the use of propofol over benzodiazepines for sedation among cardiac surgical ICU patients,[13] there were insufficient data on the efficacy of dexmedetomidine *vs* propofol in this population. In medical/noncardiac surgical patients, the use of either propofol or dexmedetomidine over benzodiazepines is recommended,[13] although there were no specific recommendations as to whether propofol or dexmedetomidine is preferential over the other. The impact of age, sedative dosage, and illness severity scores on treatment effects, especially given the biphasic blood pressure response for dexmedetomidine and unique presentation of critical illness in older adults, has not been described in prior reviews.[13]

Because of the aforementioned limitations and inconsistencies across prior reviews, and the recent publication of larger randomised trials across different ICU patient subtypes, this systematic review and meta-analysis aims to further elucidate whether dexmedetomidine, when compared with propofol, impacts ICU LOS and the duration of MV in critically ill adults. We also aim to investigate adverse effects, including the incidence and duration of ICU delirium, mortality, hypertension, hypotension, bradycardia, and tachycardia. Furthermore, this review will analyse outcomes across cardiac surgical, medical/other surgical, ICU sepsis, and neurocritical care patients separately while also investigating the impact of age and sedative dosage across each ICU type.

## Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020[14] guideline (see Supplementary Table S1 for the checklist) and the Cochrane Handbook[15] to complete this systematic review and meta-analysis. This review was prospectively registered on PROSPERO (CRD42021253050).

### Eligibility criteria

The inclusion criteria consisted of RCTs, comparing dexmedetomidine or propofol sedation in which critically ill adults required MV, and reported at least one of the following outcomes: ICU LOS, duration of MV, incidence/duration of ICU delirium, all-cause mortality, tachycardia, bradycardia, hypertension, or hypotension. The primary outcome of this review was ICU LOS. Delirium was assessed using validated screening tools such as CAM-ICU across the trials. Blood pressure and heart rate-related adverse events were defined by individual investigators, with hypotension typically representing a systolic blood pressure of ≤90 mm Hg and a mean arterial pressure of ≤60 mm Hg and bradycardia as a heart rate of ≤50–60 beats $min^{-1}$. We excluded non-randomised trials, reviews, those including patients receiving noninvasive ventilation, and other drugs of comparison such as benzodiazepines.

### Literature search and selection

Systematic literature searches were conducted by a health sciences librarian up to May 16, 2021, in MEDLINE, EMBASE, CINAHL, CENTRAL, Web of Science, and Scopus (Supplementary Tables S2–S7). We also hand-searched the references of past relevant trials. Screening was conducted independently and in duplicate by four reviewers (KH, FZ, SA, JD). Relevant data were extracted in duplicate using prespecified extraction sheets. All disagreements were resolved through consensus.

### Risk of bias and certainty of evidence

We assessed the risk of bias in duplicate using the revised Cochrane risk of bias tool for randomised trials (RoB-2).[16] The quality of evidence for each outcome was determined using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework.[17] The summary of

findings tables were generated using GRADEpro.[18] All disagreements were resolved through consensus.

### Statistical analysis

We conducted random-effects meta-analyses using the *meta* 4.18 library in R 3.6.3.[19] Each ICU subtype was analysed separately. Because of the underlying clinical heterogeneity of the included patients within each ICU subtype, we cannot assume that they share the same effect from the interventions. Therefore, random-effect was chosen to account for this variability and minimise the risk of false-positive findings. Pooled risk ratios (RRs) were calculated for dichotomous outcomes, and pooled mean differences (MDs) were calculated for continuous outcomes with 95% confidence intervals (CIs). The Mantel–Haenszel and inverse variance methods were used for estimating study weight.[20] Heterogeneity was assessed using Cochran's Q with a threshold of $P_Q<0.10$ as recommended by Cochrane guidelines.[20] Heterogeneity was further quantified using $I^2$, with an $I^2$ of 25–75% interpreted as moderate, and $I^2>75\%$ as high. We conducted sensitivity analyses by excluding trials with high risk of bias, as planned *a priori*. The results of the meta-analyses were displayed as forest plots.

### Missing data

Thirteen authors were contacted for missing data and four responded. For data presented only in graphical form, we estimated the numerical values by counting pixels using WebPlotDigitizer (https://automeris.io/WebPlotDigitizer/). For trials reporting median and range, inter-quartile range, or both without author response, we imputed the mean and standard deviation using methods following tests for normality.[21–24] Results from trials that had no response and could not be quantified by pixel counting, or could not be imputed because of skewness, were described narratively.

### Subgroup analysis and meta-regression

As previous studies have suggested a dose-dependent blood pressure response in patients receiving dexmedetomidine sedation with lower doses leading to a decrease in mean arterial pressure and heart rates and higher doses being associated with hypertension,[3] we conducted a predefined subgroup analysis by sedative dosage. High dosages were defined as >0.7 μg $kg^{-1}$ $h^{-1}$ for dexmedetomidine and ≥5 mg $kg^{-1}$ $h^{-1}$ for propofol.[25–27] Furthermore, because prior trials including older adults have suggested different treatment effects—especially for ICU LOS and duration of MV—when compared with the general adult population,[7,8] we also conducted a predefined subgroup analysis on trials with a mean/median patient age of ≥65 and <65 yr. We conducted predefined meta-regressions on the mean/median Acute Physiology And Chronic Health Evaluation (APACHE) II scores for all outcomes and the duration of follow-up for mortality. Lastly, meta-regression on the duration of dexmedetomidine and propofol infusion was undertaken as a *post hoc* analysis.

### Publication bias

Funnel plots were used to assess publication bias. Egger's regression test was used if >10 trials were analysed to ensure sufficient power. If significant publication bias was detected either by Egger's test or visual inspection, trim-and-fill was utilised to estimate the effect of the bias if >10 trials are included.[15,28,29]

## Results

### Screening

We identified 4060 citations from systematic literature searches and seven from hand searches. Of these, 58 full texts were reviewed, 41 trials.[30–50,51–70] (*N*=3948 patients) met the inclusion criteria, and data from 38 trials (*N*=3825 patients) were included in the meta-analysis. The PRISMA 2020 flow diagram can be found in Fig 1.

### Characteristics of included trials

The characteristics of the included trials are tabulated in Supplementary Table S8. Across all trials (*N*=3948 patients), the mean age ranged from 34.56 to 83.10 yr and 32.08% of the patients were female (1182/3684). Twelve trials reported mean/median APACHE II scores, with mean scores varying from 12.29 to 22 (seven trials) and median values of 15–29 (five trials). Fifteen trials enrolled cardiac surgical patients only, 16 focused on medical and noncardiac surgical patients, five enrolled patients with sepsis, three included patients from neurocritical care, and two enrolled a combination of patients.

### Risk of bias

Overall, 20 trials were rated to have a high risk of bias, 20 had some concerns, and one[40] had a low risk of bias (Fig 2; Supplementary Table S9). The primary concerns of internal validity were deviations from intended interventions, the lack of reporting of allocation concealment, and the risk of selective reporting.

### Cardiac surgical ICU patients

The results of quantitative synthesis for cardiac surgical ICU patients are tabulated in Supplementary Table S10.

#### *ICU length of stay*

Ten studies[31,32,34,35,45,48,51,54,62,63] (*N*=769 patients) reported ICU LOS, with two[32,62] (*N*=303 patients) presenting skewed, non-significant results. Across the eight[31,34,35,45,48,51,54,63] (*N*=466 patients), dexmedetomidine was not associated with a significant reduction in ICU LOS when compared with propofol sedation (MD −8.94 h; 95% CI: −22.40 to 4.52 h; P=0.1603; very low certainty; Fig 3) with moderate and significant heterogeneity ($I^2$=72%; $P_Q$=0.001). Subgroup and sensitivity analyses were not statistically significant (Supplementary Figs S1–S3).

#### *Duration of mechanical ventilation*

Ten trials[31,32,34,35,38,43,46,48,51,54] (*N*=969 patients) investigated the duration of MV, and two[32,38] (*N*=478 patients) presented skewed, non-significant results. Among the eight[31,34,35,43,46,48,51,54] (*N*=491 patients) that were analysed, patients receiving dexmedetomidine had a significantly shorter duration of MV (MD −0.67 h; 95% CI: −1.31 to −0.03 h; P=0.041; low certainty; Fig 4) with moderate and significant

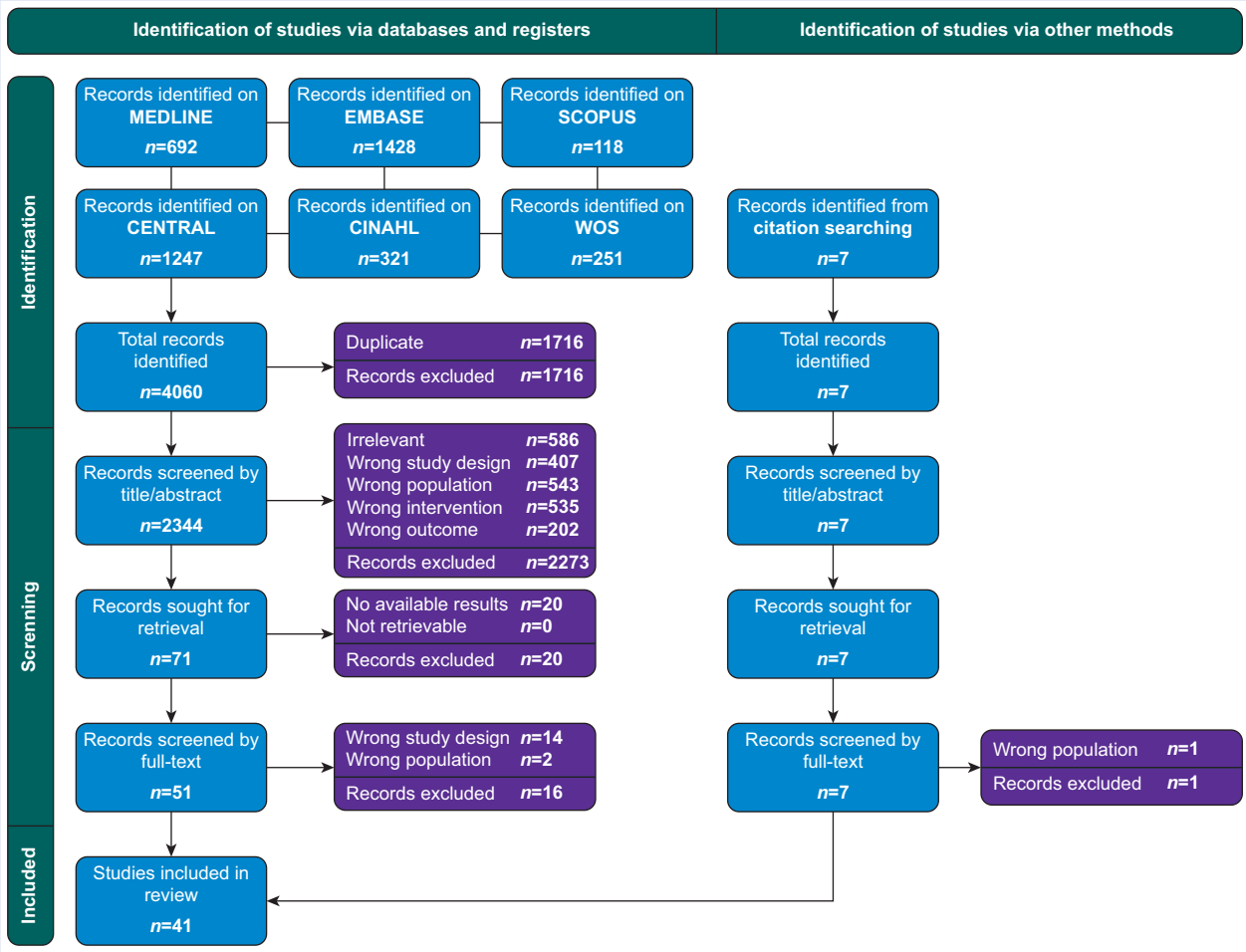


Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. CENTRAL, Cochrane Central Register of Controlled Trials; CINAHL, Cumulative Index of Nursing and Allied Health Literature; EMBASE, Excerpta Medica Database; MEDLINE, Medical Literature Analysis and Retrieval System Online; WOS, Web of Science.

heterogeneity ($I^2$=43%; $P_Q$=0.090). Subgroup analyses and meta-regressions were not significant (Supplementary Figs S4–S7). After the exclusion of trials with a high risk of bias, the effect size was no longer significant, and heterogeneity was low (Supplementary Fig. S8).

### *Incidence and duration of delirium*

Ten trials[31,32,35,45,46,48,62,63,67,69] (N=801 patients) reported the incidence of ICU delirium. Patients receiving dexmedetomidine sedation had a significantly lower risk of developing delirium when compared with those receiving propofol (RR

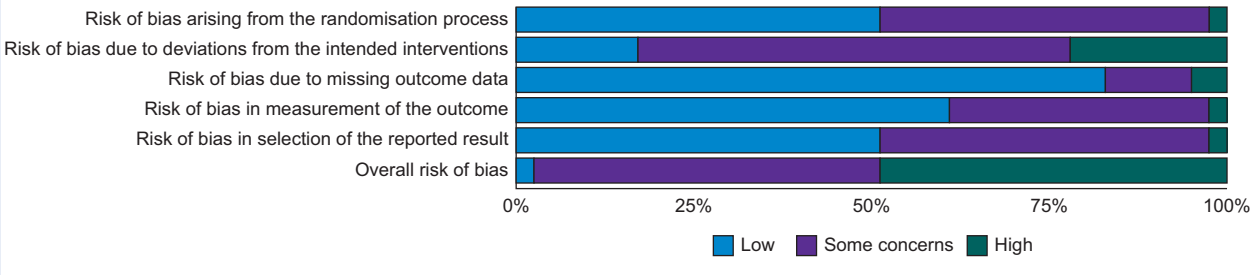


Fig 2. Risk of bias (RoB) summary graph.

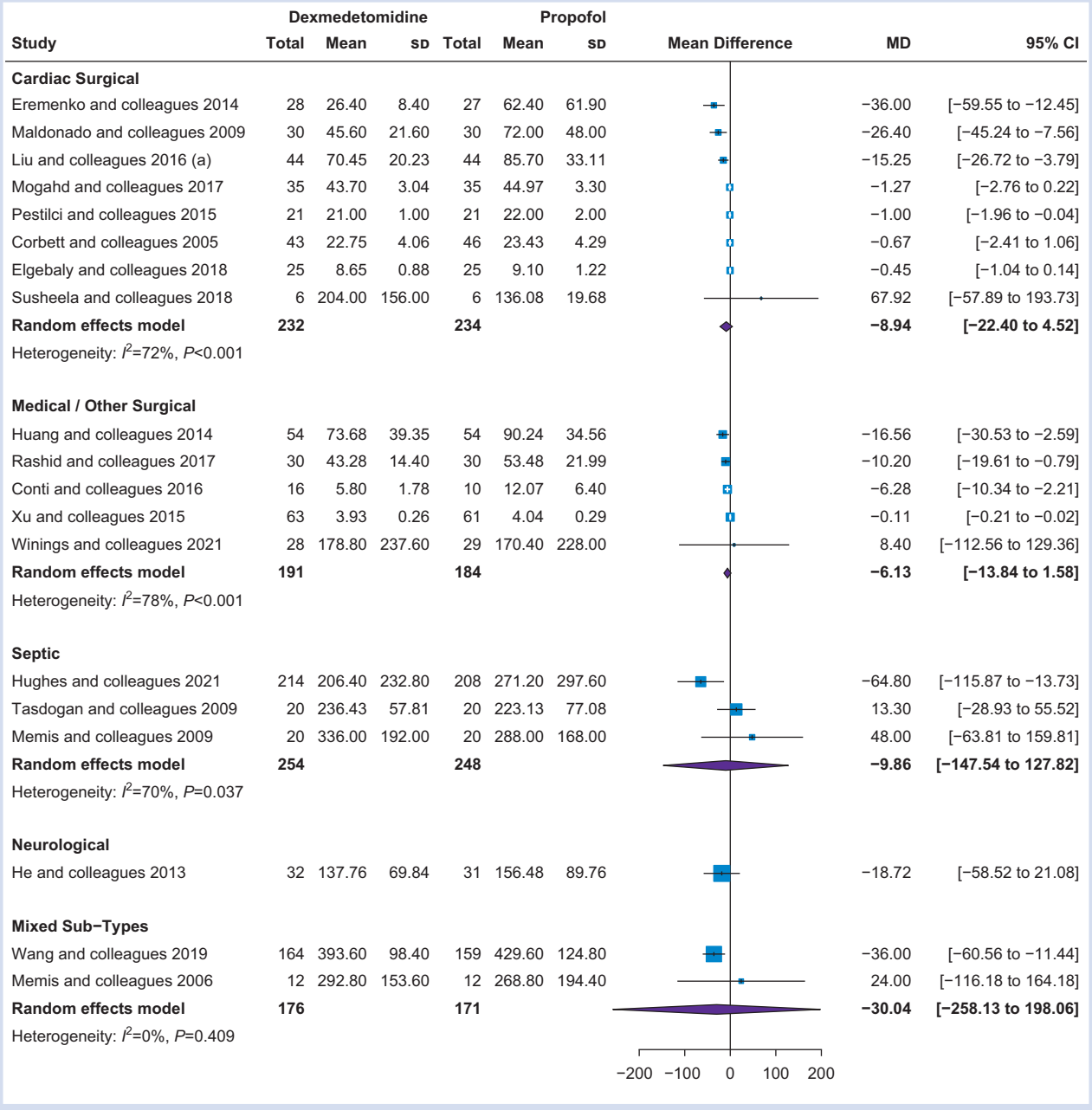


Fig 3. ICU length of stay (LOS) forest plot. All data are presented in hours unless otherwise specified. CI, confidence interval; MD, mean difference; SD, standard deviation.

0.50; 95% CI: 0.29–0.87; P=0.019; high certainty; Fig 5) with low heterogeneity ($I^2$=21%; $P_Q$=0.251). Subgroup and sensitivity analyses were not significant (Supplementary Figs S9–S11). Publication bias was not detected ($P_{Egger}$=0.280, Supplementary Fig. S12).

Four trials[32,48,62,63] ($N$=369 patients) reported the duration of ICU delirium with one[63] reporting means without variance. Across the three analysed trials[32,48,62] ($N$=363 patients), no significant difference was found (Supplementary Figs S13–S16).

### *Mortality*

Four trials[31,45,48,62] ($N$=364 patients) investigated all-cause mortality and found no significant difference between dexmedetomidine compared with propofol (RR 0.73; 95% CI: 0.12–4.35; P=0.618; very low certainty; Supplementary Fig. S17; Supplementary Table S15) with low heterogeneity ($I^2$=0%; $P_Q$=0.718). Subgroup analyses did not significantly impact the findings (Supplementary Figs S18 and S19). None of the trials had a high risk of bias.

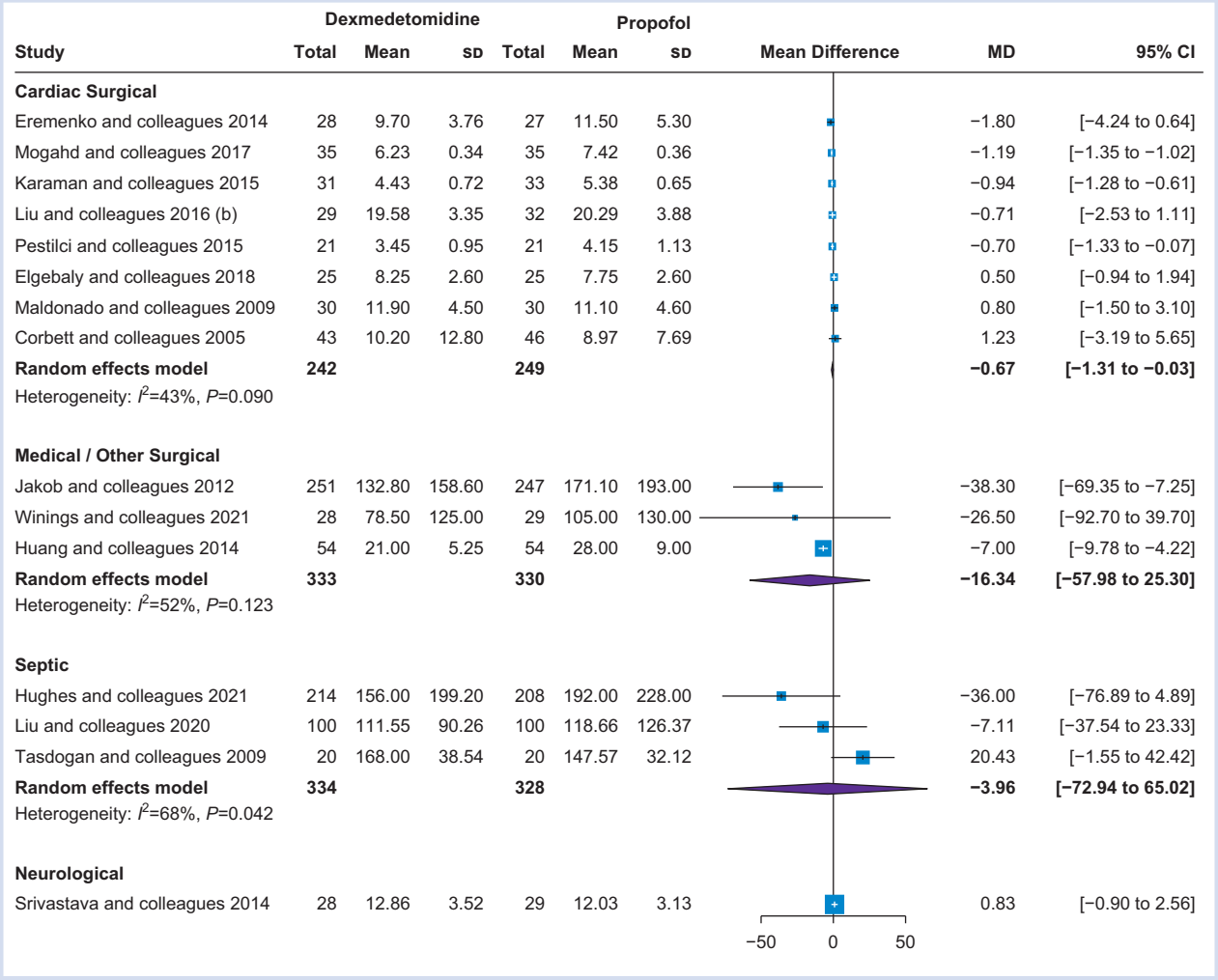


Fig 4. Duration of mechanical ventilation (MV) forest plot. All data are presented in hours unless otherwise specified. CI, confidence interval; MD, mean difference; SD, standard deviation.

### *Hemodynamic effects*

Eight trials[35,38,43,45,46,54,62,67] ($N$=785 patients) reported the incidence of bradycardia, three trials[38,43,54] ($N$=401 patients) reported the incidence of tachycardia, 11 trials[31,35,38,42,43,45,46,54,62,63,67] ($N$=944 patients) reported the incidence of hypotension, and three trials[38,42,54] ($N$=395 patients) reported the incidence of hypertension. Dexmedetomidine was significantly associated with a reduction in the risk of bradycardia compared with propofol (RR 2.33; 95% CI: 1.40–3.90; $P$=0.006; moderate certainty; Supplementary Fig. S20) with low heterogeneity ($I^2$=0%; $P_Q$=0.894). There were no significant differences across other haemodynamic parameters. Detailed results are summarised in Supplementary Results S1.

## Medical/other surgical ICU patients

The results of quantitative synthesis for medical/other surgical ICU patients are tabulated in Supplementary Table S11.

### *ICU length of stay*

Nine trials[30,39,41,44,55,57,65,69,70] ($N$=1031 patients) investigated the ICU LOS, with four[41,44,57,65] ($N$=656 patients) presenting skewed, non-significant results. Across the five[30,39,55,69,70] ($N$=375 patients) that were quantitatively analysed, dexmedetomidine did not significantly alter the ICU LOS when compared with propofol (MD −6.13 h; 95% CI: −13.84 to 1.58 h; $P$=0.092; very low certainty; Fig 3) with high and significant heterogeneity ($I^2$=78%; $P_Q$=0.001). Subgroup analyses were not significant (Supplementary Figs S34 and S35). However, the subgroup analysis based on dosage decreased the heterogeneity ($I^2$=0%; $P_Q$=0.69).

### *Duration of mechanical ventilation*

Six trials[30,39,41,44,65,69] ($N$=782 patients) reported the duration of MV, with three[30,44,65] ($N$=119 patients) presenting skewed, non-significant results. Three trials[39,41,69] ($N$=663 patients) were included in the meta-analysis and no significant

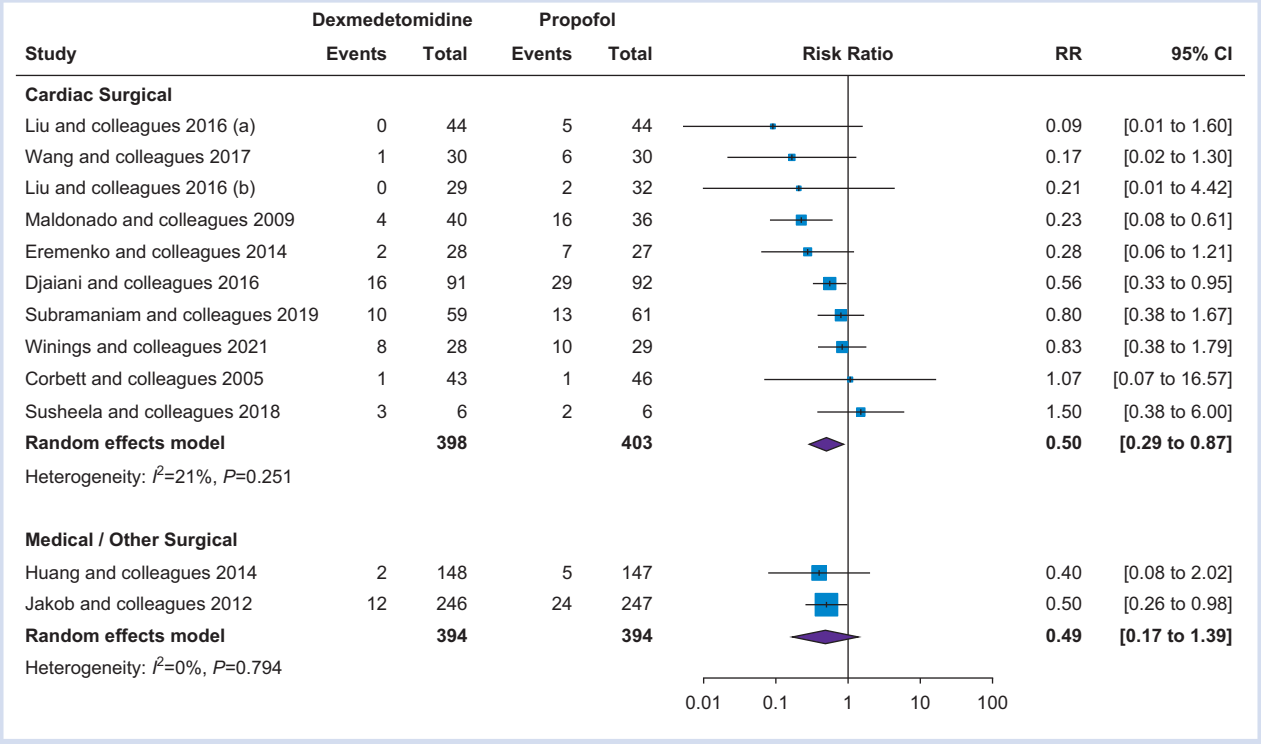


Fig 5. Incidence of ICU delirium forest plot. CI, confidence interval; RR, risk ratio.

difference was noted (MD −16.34 h; 95% CI: −57.34 to 25.30 h; $P$=0.233; very low certainty; Fig 4) with moderate heterogeneity ($I^2$=52%; $P_Q$=0.123). Subgroup analysis based on age was not significant ($P$=0.825; Supplementary Fig. S36). No significant interactions between dosage subgroups were found ($P$=0.056; Supplementary Fig. S37), however, one study[41] which administered low-dose propofol and high-dose dexmedetomidine found a significant reduction in the duration of MV across patients receiving dexmedetomidine *vs* propofol, whereas other subgroups were not significant (Supplementary Figs S36 and S37).

### *Incidence and duration of delirium*

Two[39,41] trials ($N$=788 patients) investigated the incidence of delirium and found no significant difference between dexmedetomidine *vs* propofol sedation (RR 0.49; 95% CI: 0.17–1.39; $P$=0.073; low certainty; Fig 5) with low heterogeneity ($I^2$=0%; $P_Q$=0.794). Both trials had a mean/median patient age of ≥65 yr (Supplementary Fig. S38). One[41] trial which administered low-dose propofol and high-dose dexmedetomidine found a significant reduction in the risk of delirium across those receiving dexmedetomidine *vs* propofol; however, other subgroups were not significant (Supplementary Figs S38 and S39). None of the trials reported the duration of delirium.

### *Mortality*

Six trials[30,41,44,52,66,69] ($N$=742 patients) reported all-cause mortality and no significant difference between the two sedatives was found (RR 0.81; 95% CI: 0.60–1.09; $P$=0.123; low certainty; Supplementary Fig. S17) with low heterogeneity ($I^2$=0%; $P_Q$=0.896). Subgroup analysis based on age revealed a significant interaction ($P$=0.015), and a significant effect size among the <65 yr subgroup (Supplementary Fig. S40). Other subgroup analyses were not significant (Supplementary Figs S41–S43).

### *Haemodynamic effects*

Nine trials[30,33,39,41,53,60,66,69,70] ($N$=1008 patients) reported the incidence of bradycardia, three trials[41,60,70] ($N$=677 patients) reported the incidence of tachycardia, seven trials[33,39,41,60,66,69,70] ($N$=922 patients) reported the incidence of hypotension, and four trials[39,41,55,70] ($N$=785 patients) reported the incidence of hypertension. Dexmedetomidine was only significantly associated with a greater risk of developing bradycardia when compared with propofol (RR 2.18; 95% CI: 1.06–4.49; $P$=0.038; low certainty; Supplementary Fig. S20) with low heterogeneity ($I^2$=0%; $P_Q$=0.456). Detailed results are summarised in Supplementary Results S2.

## ICU patients with sepsis

The results of quantitative synthesis for septic ICU patients are tabulated in Supplementary Table S12.

### *ICU length of stay*

Five trials[40,47,50,59,64] ($N$=738 patients) reported the ICU LOS with two[47,59] ($N$=236 patients) presenting skewed data. Three[40,50,64] ($N$=502 patients) were analysed and no significant differences were found (MD −9.86 h; 95% CI: −147.54 to 127.82 h; $P$=0.787; very low certainty; Fig 3). There was moderate and

significant heterogeneity ($I^2$=70%; $P_Q$=0.037). Subgroup and sensitivity analyses were not conducted. Meta-regression on APACHE II scores did not reveal any significant correlation (*P*=0.313; Supplementary Fig. S57).

### *Duration of mechanical ventilation*

Four trials[40,47,59,64] (*N*=698 patients) investigated the duration of MV with one[59] (*N*=36 patients) reporting skewed, non-significant results. Across the three analysed trials[40,47,64] (*N*=662), dexmedetomidine did not significantly impact the duration of MV when compared with propofol (MD −3.96 h; 95% CI: −72.94 to 65.02 h; *P*=0.828; very low certainty; Fig 4). There was moderate and significant heterogeneity ($I^2$=68%; $P_Q$=0.042). Subgroup analysis based on dosage was not significant, however, it reduced heterogeneity ($I^2$=19%; $P_Q$=0.27; Supplementary Fig. S58). Meta-regression did not demonstrate a significant correlation with APACHE II scores (*P*=0.427; Supplementary Fig. S59).

### *Incidence and duration of delirium*

None of the trials reported the incidence or duration of delirium.

### *Mortality*

Five trials[40,47,50,59,64] (*N*=738 patients) investigated all-cause mortality and did not identify a significant difference between dexmedetomidine *vs* propofol sedation (RR 0.97; 95% CI: 0.82–1.15; *P*=0.662; moderate certainty; Supplementary Fig. S17). There was low heterogeneity ($I^2$=0%; $P_Q$=0.908). All trials had a mean/median patient age of <65 yr. Subgroup analysis based on low doses of both sedatives did not yield a significant effect size (Supplementary Fig. S60). Meta-regression did not demonstrate significant correlations with the duration of follow-up (*P*=0.825; Supplementary Fig. S61), APACHE II scores (*P*=0.500; Supplementary Fig. S62), or the duration of dexmedetomidine, and propofol infusions (*P*=0.898 and *P*=0.752, respectively, Supplementary Figs S60–S64). None of the trials were rated as high risk of bias.

### *Haemodynamic effects*

Hughes and colleagues[40] (*N*=422 patients) found a greater risk of bradycardia among patients receiving dexmedetomidine when compared with propofol sedation (RR 1.62; 95% CI: 1.14–2.29; *P*=0.007; moderate certainty; Supplementary Fig. S20). There were no significant differences across other hemodynamic parameters.[40,50,64] Detailed results are summarised in Supplementary Results S3.

## Neurocritical care and mixed ICU patients

No significant differences were found across any of the outcomes.[36,37,68,61,49] Detailed results are summarised in Supplementary Results S4 and S5.

## Skewed data and quality of evidence

Findings of studies with skewed data are tabulated in Supplementary Table S13. The summary of findings and GRADE evaluation for each ICU type is tabulated in Supplementary Tables S14–S18.

# Discussion

This study of 41 trials, of which 38 were analysed, serves as the largest and most comprehensive meta-analysis on the efficacy and safety of dexmedetomidine *vs* propofol sedation in critically ill patients receiving MV. Dexmedetomidine led to a significant reduction in the duration of MV and the risk of ICU delirium across cardiac surgical patients, however, this was not significant across other patient types. Moreover, cardiac surgical, medical/other surgical, and septic ICU patients who were sedated with dexmedetomidine had a greater risk of bradycardia when compared with propofol. Subgroup analyses also revealed that age could alter treatment effects across outcomes including the incidence of bradycardia in cardiac surgical, and hypertension, mortality, tachycardia for medical/other surgical patients. Meta-regression identified a potential correlation between APACHE II scores and the treatment effect with respect to the incidence of hypotension across medical/other surgical patients. There were no significant differences in ICU LOS, all-cause mortality, tachycardia, hypertension, and hypotension across different ICU types.

## Comparison with existing evidence

Dexmedetomidine sedation has been associated with easier patient rousability and preservation of cognitive performance.[3] Additionally, respiratory depression is less common after dexmedetomidine administration *vs* other sedatives.[3] The 2018 PADIS guidelines suggest the use of propofol or dexmedetomidine for the sedation of cardiac surgical patients, and either propofol or dexmedetomidine for medical/other surgical patients.[13] However, it is unclear whether one sedative should be used over another. Whereas past trials have investigated the role of dexmedetomidine sedation, many of these have compared dexmedetomidine with placebo, benzodiazepines, or a combination of drugs rather than with propofol.[71,72] There is also a paucity of evidence on patients with septicaemia and neurological injury who require MV. Furthermore, the impact of age and sedative dosage has not been extensively studied.

A previous review reported a decrease in ICU LOS[7]; however, they analysed all ICU patient types in combination. Given the heterogeneity in the presentation and management of patients with critical illness, the combination of all patient types could have resulted in a significant finding which may not be clinically applicable. Additionally, a review on adults ≥60 yr old, which also analysed all ICU types in combination, did not find a significant reduction in ICU LOS.[8] This may be attributable to factors including a limited sample size or the potential impact of older age on treatment effects. In our study, we did not find a significant difference in the ICU LOS across any specific ICU type, or subgroup interactions with age or dosage. However, more well-designed trials are required to improve the certainty of these findings.

Additionally, existing evidence[7] suggests no significant difference in the duration of MV across a combination of ICU patients. Our analyses across specific ICU patient types also found no significant difference. However, across cardiac surgical patients, dexmedetomidine reduced the duration of MV. This finding aligns with the shorter elimination half-life of dexmedetomidine, and its lower impact on ventilatory drive, when compared with propofol.[3] Additionally, we hypothesise that noncardiac surgical patients may have other underlying comorbidities that may influence their duration of MV beyond

the action of the sedatives. Furthermore, the finding may also be attributed to our larger sample size and analysis across a specific type of ICU patients, which resulted in greater precision than in prior studies.

Furthermore, a recent meta-analysis[11] on cardiac surgical patients did not find a significant reduction in the incidence of delirium, however, two of the included trials administered the intervention as adjuncts, intraoperatively, or both. The exclusion of these two trials identified a significant reduction in ICU delirium across patients receiving dexmedetomidine *vs* propofol. Previous reviews[7,8] have also concluded that dexmedetomidine sedation could decrease the incidence of ICU delirium when compared with propofol. Our meta-analysis, based on high certainty of evidence, demonstrated this significant reduction in the risk of ICU delirium across cardiac surgical patients receiving dexmedetomidine.

The cardiovascular adverse events associated with dexmedetomidine sedation must also be considered. The increase in the risk of bradycardia across cardiac surgical patients is consistent with the review by Abowali and colleagues.[11] This significant finding was also noted across medical/other surgical patients and those with sepsis. Our meta-analysis identified significant subgroup interactions based on age in cardiac surgical patients with the significant effect size being maintained across the <65 yr subgroup only. The impact of age should continue to be investigated in future trials and meta-analyses. Moreover, past reviews[7,11] have also found no significant differences in all-cause mortality and tachycardia. However, contrary to our findings, Xia and colleagues[7] noted a significant increase in hypertension. This may be as a result of their analysis of different ICU patients in combination, and increased sample size and decreased heterogeneity across cardiac surgical patients in our review. Additionally, consistent with our results, two previous systematic reviews did not find a significant difference in hypotension.[7,8] However, a more recent review on cardiac surgical patients[11] reported an increase in the odds of this adverse event. Our non-significant finding, with moderate certainty, could be attributable to our inclusion of seven non-English trials on cardiac surgical patients which reduces the risk of publication and language bias while increasing the sample size. We identified a correlation between the treatment effect and APACHE II scores among medical/other surgical patients, however, this must be interpreted with caution because of the risk of overfitting. The impact of illness severity scores should continue to be investigated in future reviews and trials.

### Strengths and limitations

Our review analysed more trials with a larger sample size of patients, providing a more representative and up-to-date estimate of treatment effects compared with previous meta-analyses. In addition, we analysed each ICU type separately while also conducting comprehensive, *a priori* subgroup analyses to explain possible sources of heterogeneity to ensure the applicability of our findings. Furthermore, the significant age group interactions could serve as an area of future investigation. The certainty of evidence for each finding was also determined using GRADE, with the incidence of delirium across cardiac surgical patients being rated as high certainty. Our meta-analysis also provides a comprehensive summary of patients with septicaemia and neurological injury.

Despite the inclusion of additional trials, the number of patients in many of our subgroup analyses and meta-regressions were limited, making it difficult to detect significant treatment effects within subgroups or significant covariate correlations. There was a particularly limited number of trials for those with sepsis and patients in neurocritical care units. Many trials, especially those including cardiac surgical and medical/other surgical patients, did not report illness severity scores such as SOFA or APACHE II. Additionally, while *post hoc* analysis of the duration of sedative infusion did not yield significant results, many trials did not report exact infusion times and therefore further investigation may be warranted. Furthermore, the meta-analysis for multiple outcomes had fewer than 10 trials, and therefore, Egger's test was not warranted because of insufficient power. However, we attempted to minimise publication bias through a comprehensive search without language restrictions. Lastly, numerous trials were classified as high risk of bias. We attempted to minimise the impact of this by conducting sensitivity analyses in which high risk of bias trials were excluded.

### Conclusions

Our meta-analysis provides up-to-date evidence on the efficacy and safety of dexmedetomidine *vs* propofol in critically ill, mechanically ventilated ICU patients. Dexmedetomidine significantly reduces the duration of mechanical ventilation and the risk of delirium across cardiac surgical ICU patients. However, it increases the risk of bradycardia in cardiac surgical, medical/other surgical, and ICU patients with sepsis. Age could also alter treatment effects across various outcomes. Given that the strongest evidence is limited to cardiac surgical patients, larger clinical trials are needed to improve the certainty of these findings and provide further insight into specific age groups and dosages.

## Authors' contributions

Contributed to the conception and design of the study, acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, final approval of the version to be submitted, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: all authors.

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## Declarations of interest

The authors declare that they have no conflicts of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2022.06.020.

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