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Review

Processed electroencephalogram-guided anesthesia and its impact on postoperative delirium and perioperative efficiency: A systematic review and meta-analysis

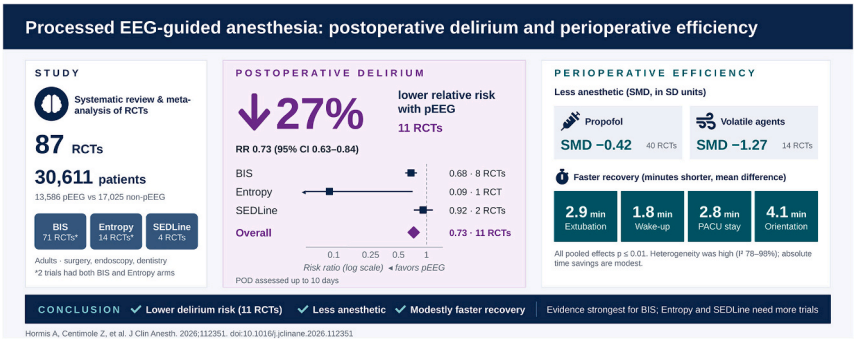
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HIGHLIGHTS

- Brain monitoring versus conventional practice to guide anesthesia.
- Depth of anesthesia monitoring reduced the amount of anesthetics used.
- Lower risk of postoperative delirium with processed electroencephalogram brain monitoring.
- First meta-analysis to compare different processed electroencephalograms.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Processed electroencephalography (pEEG) provides quantitative indices for monitoring anesthetic depth and is recommended in international guidelines. Prior meta-analyses have assessed EEG-guided anesthesia but none have evaluated available evidence stratified by pEEG technology.

Methods: We performed a systematic literature review and meta-analysis of randomized controlled trials in adults undergoing surgical, endoscopic, or dental procedures comparing pEEG-guided with non-pEEG-guided anesthesia. Primary outcomes were anesthetic drug use (TIVA and volatile agents) and postoperative delirium (POD ≤10 days). Secondary outcomes were extubation time, wake-up time, time to orientation, and post-anesthesia care unit (PACU) length of stay. Searches (PubMed Central, MEDLINE) were conducted on 11 April 2025; the

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protocol was registered in PROSPERO (CRD420251067170). Random-effects models produced standardized mean differences (SMD), mean differences (MD), and risk ratios (RR) with 95% confidence interval (CI).
Results: Eighty-seven RCTs (30,611 patients; 13,586 pEEG; 17,025 non-pEEG) were included. pEEG significantly reduced propofol use (SMD −0.42, 95% CI −0.74 to −0.10; $p = 0.01$) and volatile anesthetic use (SMD −1.27, 95% CI −1.88 to −0.66; $p < 0.01$). The risk of POD decreased by 27% (RR 0.73, 95% CI 0.63 to 0.84; $p < 0.01$). Efficiency outcomes favored pEEG: extubation time (MD −2.90 min, 95% CI −3.64 to −2.16; $p < 0.01$), wake-up time (MD −1.83 min, 95% CI −2.42 to −1.25; $p < 0.01$), time to orientation (MD −4.11 min, 95% CI −6.99 to −1.23; $p < 0.01$), and PACU length of stay (MD −2.81 min, 95% CI −4.66 to −0.96; $p < 0.01$). Subgroup analyses suggested benefits were most consistently observed for BIS; estimates for Entropy and SEDLine were less precise due to fewer studies. Heterogeneity was substantial for several outcomes.
Conclusions: Across 87 RCTs, pEEG-guided monitoring utilizing multiple device types improved perioperative efficiency and reduced POD compared with not using pEEG. Evidence is strongest for BIS; further well-reported trials are needed to delineate device-specific effects.

1. Background

General anesthesia renders a patient unconscious by suppressing cerebral activity, therefore, achieving and maintaining the appropriate depth of anesthesia is essential. Patient monitoring supports the fine balance between avoiding intraoperative awareness and excessive drug exposure causing brain toxicity and cardiovascular collapse. Exposure to unnecessarily high anesthetic concentrations can contribute to perioperative neurocognitive disorders (PND), with postoperative delirium (POD) representing an acute subtype of PND [1,2]. Patients who develop POD often experience longer hospital stays and require more resource-intensive care [3,4].

Traditional clinical signs provide only indirect estimates of the depth of anesthesia, whereas processed electroencephalography (pEEG) offers real-time brain-derived information through a simplification of the visualized waveform EEG into a numerical index generated by device-specific algorithms [5]. Several pEEG monitors use distinct proprietary signal-processing approaches to guide anesthetic titration [5]. Although pEEG-guided anesthesia has been associated with reduced anesthetic exposure and improved postoperative outcomes including POD [6–8], benefits are still being debated and it remains unclear whether benefits differ across individual devices [9].

This systematic literature review and meta-analysis summarizes evidence for pEEG devices that convert EEG signals into simplified indices for anesthesia guidance and identifies device-specific evidence gaps.

2. Methods

This SLR assesses whether pEEG devices improve procedure efficiency and patient outcomes compared with non-pEEG-guided anesthesia care. The primary outcomes were anesthetic drug use for both TIVA and anesthetic gases (procedure efficiency) and POD within 10 days post-surgery (patient outcomes). Follow-up periods for POD varied across studies; therefore, a 10-day cutoff was used to maximize study inclusion. Secondary procedure efficiency outcomes were time to extubation, wake-up time, time to orientation, and post-anesthesia care unit (PACU) length of stay.

We registered the SLR protocol in the PROSPERO database (CRD420251067170) on 4 June 2025 prior to initiating data extraction as is accepted by PROSPERO eligibility criteria. The SLR was performed by two independent reviewers using PICO Portal (Version 3.0, PICO Portal Inc., Florida; Available from: https://picoportal.org‘). The SLR followed the registered protocol with three deviations, and reporting adheres to the PRISMA reporting checklist [10].

2.1. Search strategy

The search strategy was limited to MEDLINE and PubMed Central as prespecified in the PROSPERO protocol with the search performed on 11 April 2025. The full search strings were applied as documented in the PROSPERO protocol (CRD420251067170). Searches were restricted to randomized controlled trials (RCTs) in humans that compared pEEG devices versus non-pEEG-guided anesthesia care. The pEEG technologies considered were BIS, Conox, Entropy, Narcotrend, and SEDLine. Search strings included specific device names and pEEG terminology; therefore, studies that did not reference device names or processed EEG terminology in searchable fields may not have been retrieved.

2.2. Eligibility criteria

Studies were included if they met all of the following criteria:

- Reported on original research from RCT data,
- Included adult patients undergoing surgical, endoscopic, or dental procedures with moderate to deep sedation or anesthesia,
- Compared pEEG device with non-pEEG-guided anesthesia care where the anesthetic dose was adjusted to maintain device-specific index ranges in the intervention arm,
- Reported at least on a primary or secondary outcome of interest.

Non-pEEG-guided anesthesia care usually included clinical assessment of the patient's vital signs, the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale, and/or end-tidal anesthetic-agent concentration, as well as when the surgical and anesthesia teams were blinded to information and alarms provided by pEEG devices.

We excluded studies that did not meet the inclusion criteria: e.g., non-RCTs or mild sedation, extended deep sedation in intensive care, or if required data were not presented, e.g., level of sedation was not specified, the pEEG device name was not reported, or a mix of pEEG devices was used.

2.3. Screening and study selection

Literature deduplication, screening, and risk of bias assessment were performed using the PICO Portal platform (https://picoportal.org). The platform ensures that reviewers worked independently and were blinded to each other's decisions. We independently screened titles and abstracts to remove studies meeting exclusion criteria. Studies passing the initial screen were reviewed in full-text form against the selection criteria. If there were any disagreements between reviewers, we resolved them using a third independent reviewer. We performed the review process in line with PRISMA requirements and provide the PRISMA diagram in Fig. 1 [11].

2.4. Available pEEG technologies

There are more than ten devices on the market for the commercial monitoring of brain function [5]. The following technologies were identified in the title and abstracts of RCTs but only those devices with sufficient data were included in the meta-analysis: Bispectral™ (BIS™) Monitoring System (BIS; Medtronic, Minneapolis,MN, USA), CONOX® (Conox; Fresenius Kabi, Bad Homburg, Germany), ENTROPY®

(Entropy; GE Healthcare, Chicago, IL, USA), Narcotrend® (Narcotrend; MT MonitorTechnik, Hannover, Germany), SEDLine® (SEDLine; Masimo, Irvine, CA, USA).

2.5. Data extraction

Data were extracted from studies meeting the inclusion criteria at full-text review. Initially, extracted data were basic study details, including device used and patient population size. To ensure that sufficient data were available for analysis, we only extracted further data on pEEG technologies that were reported in at least ten different studies or if there were > 500 patients monitored with the technology. Final pEEG technologies included for analysis were BIS, Entropy, and SEDLine.

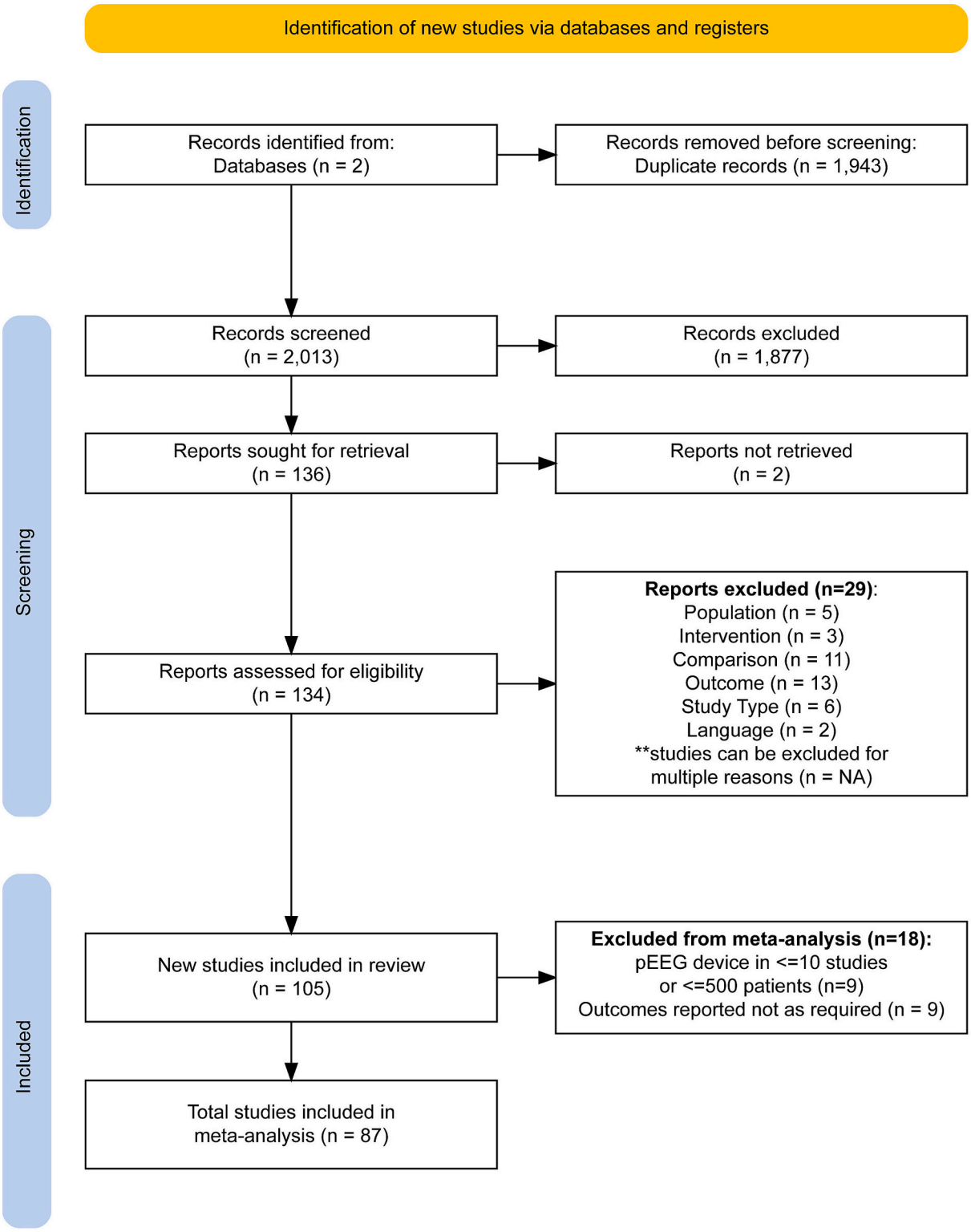


Fig. 1. PRISMA diagram.
Note: Studies may be excluded for more than one reason during full-text screening.

Data extraction used a pre-piloted Microsoft Excel form. Extracted data included study design, country, population size, procedure, depth of sedation, type of sedation (gas or TIVA), and anesthetics used, as well as details regarding the intervention and comparison and the primary and secondary outcomes of interest. For TIVA, total use of the drug was extracted; separately reported induction and maintenance were not considered. If a study reported TIVA and anesthetic gas use using different metrics, the data most normalized (by weight and/or time) were extracted.

Data were extracted by one researcher, with cross-reference to the original source documented in Citavi (Lumivero, Denver, Colorado, USA) reference and knowledge management. Extracted data were independently checked and verified by a second reviewer. Disagreements were settled through discussion and consensus including a third independent reviewer.

2.6. Risk of bias assessment

We assessed risk of bias using the ROBUST-RCT tool [12], which evaluates random sequence allocation, allocation concealment, blinding of participants, healthcare providers, and outcome assessors, and outcome data not included in the analysis. One reviewer conducted initial assessments that were independently checked by a second reviewer. Disagreements were adjudicated by a third reviewer.

2.7. Data synthesis

Meta-analyses compared procedure efficiency and neurocognitive outcomes between pEEG and non-pEEG-guided anesthesia care for monitoring depth of anesthesia. Continuous outcomes that were reported in different units (TIVA use, anesthetic gas use) were synthesized as standardized mean difference (SMD) ± 95% confidence interval (CI). Use of anesthesia is reported in different units, such as mg, mg/kg, or mg/kg/min. The use of SMD enables synthesis of similar data that is measured using different units by expressing the effect size in units of standard deviations (SDs). The units of time outcomes were unified to minutes and then the data were synthesized as mean differences (MD) ± 95% CI. SMDs were calculated using Hedges' g.

We calculated the SMD and MD from means and SDs using exact formulas. If studies did not report the mean and SD, we estimated them from the median and range or interquartile range using the methods described by Wan et al. [13]. The SD was estimated from ranges (range divided by 4) or calculated from the 95% CI as per Cochrane Handbook [14]. Categorical outcomes were synthesized as risk ratios (RR) ± 95% CI and calculated from the number of events and the population size. RRs were pooled on the natural logarithmic scale and back-transformed for presentation.

The meta-analysis results are shown in forest plots. A p-value <0.05 was considered statistically significant. Data synthesis, meta-analysis, and generation of forest plots were performed in Stata version 18.5 (StataCorp SS1.1). We anticipated substantial heterogeneity between studies; therefore, all meta-analyses were performed using a random-effects model. Eligibility of studies for inclusion in data synthesis was confirmed by reviewing extracted study characteristics. Heterogeneity was evaluated using I^2, with $I^2 \geq 50\%$ indicating substantial heterogeneity. The DerSimonian and Laird method was used to estimate between-study variance.

For studies with multiple pEEG intervention arms and a shared control arm (indicated by an asterisk in the forest plots), the shared control group was split evenly between comparisons following the Cochrane-recommended approach for multi-arm studies [15]. This adjustment prevented double counting of control participants while allowing all eligible intervention arms to be retained in the analysis.

2.7.1. Subgroup analyses

To differentiate between care options, identify evidence gaps, and to explore potential sources of heterogeneity, we conducted subgroup analyses by pEEG device type (BIS, SEDLine, Entropy had sufficient data to be included) and by type of anesthetic gas (desflurane, sevoflurane, isoflurane).

2.7.2. Sensitivity analyses

The large ENGAGES and ENGAGES-CANADA trials [16,17] were not included in our search because their intervention description did not match the search criteria: (1) device names were not specified in the titles or abstracts and (2) both studies primarily used waveform EEG to limit periods of burst suppression rather than maintaining pEEG indices such as the BIS index, patient-state index (PSI), or State Entropy (SE) index within a certain range, removing them from the scope of the primary analysis. The original ENGAGES trial used BIS and the later ENGAGES-CANADA trial used a mix of devices [16,17]. Although they did not meet the inclusion criteria of the original research question, they are important trials in the field of EEG-guided monitoring. Most importantly, they are null trials as they report no effect on POD. Therefore, the authors considered it important to include both trials in a post hoc sensitivity analysis of the POD outcome to present a more complete picture of available evidence and because there are limited studies reporting on POD. Furthermore, both ENGAGES trials have POD as their primary outcome.

A second post hoc analysis for the POD outcome was also performed where results from Kunst et al. were excluded due to the intervention including both BIS and cerebral oxygen saturation monitoring with INVOS™ (INVOS; Medtronic, Minneapolis,MN, USA) [18]. Although cerebral monitoring is separate from pEEG monitoring, it may have also affected the POD outcome.

2.8. Reporting bias assessment

For each outcome, we used contour-enhanced funnel plots to assess reporting bias from included studies. Asymmetric funnel plots can be an indication for reporting or publication bias. Because random-effects models do not allow plotting of the 95% CIs in funnel plots, these intervals are not shown. Reporting bias and small study effects were further assessed using the Egger's regression test, the Begg's rank correlation test and where appropriate, the trim-and-fill method was applied as a sensitivity analysis to evaluate the potential impact of potentially missing studies.

2.9. Deviations from the protocol

We considered three deviations from the protocol as necessary: (1) POD was considered for 10 days instead of 5 days post-surgery because five papers reporting POD for follow-up periods up to 7 or 10 days (see Supplementary Table 3 for a summary of POD studies including follow-up period and testing method); (2) we included length of PACU stay as an outcome post hoc as it is another hospital resource and reflects efficiency; and (3) we performed a *post-hoc* sensitivity analysis to assess the impact of excluding the well-known ENGAGES trials that were missed by the search strategy.

3. Results

3.1. Study selection

We identified 2012 unique articles on PubMed, of which 105 met all selection criteria (Fig. 1). Of these, 18 studies were excluded from the quantitative analysis (Supplementary Table 1). Narcotrend was used in eight studies for only 366 patients and therefore all cohorts using Narcotrend were excluded from the data synthesis as per protocol. Five of the Narcotrend studies were excluded but three were retained because they also reported on the use of BIS in a multi-arm comparison. Nine studies were excluded because their data were not reported in a format

suitable for the meta-analysis, three studies reported only induction but not maintenance of anesthesia for propofol use, and one study used two pEEG devices in the intervention group simultaneously. For the final meta-analysis, we included the remaining 87 studies, comprising 30,611 patients (13,586 monitored with pEEG and 17,025 with non-pEEG-guided anesthesia care).

3.2. Study characteristics

Study characteristics of the included studies are provided in Supplementary Table 2. Subgroup categories for pEEG device type were: BIS (81 cohorts; 71 studies; 11,782 patients), Entropy (15 cohorts; 14 studies; 849 patients), and SEDLine (4 cohorts; 4 studies; 955 patients). Two studies reported outcomes separately for BIS and Entropy [19,20]. 13 studies included multiple intervention arms: BIS and Entropy [19,20], two separate BIS cohorts [21–30], and two Entropy cohorts [31]. Only those multi-arm cohorts sharing a single control cohort were adjusted as described in the data synthesis.

Most included studies evaluated surgical procedures (69 studies), followed by endoscopic (14 studies), dental procedures (2 studies), and other procedural sedation (2 studies). Included participants had procedures performed under general anesthesia (69 studies), while deep and moderate sedation were each reported in 8 and 10 studies, respectively. Studies with extended periods of sedation in intensive care were not included.

3.3. Synthesis of results

All outcomes are summarized in Table 1. Please note that the sum of studies per outcome do not always add up independently to the total number of studies because some studies report results for multiple devices or for multiple patient cohorts that were included separately. Reporting bias per outcome are summarized in Supplementary Table 4 and Supplementary Figs. 5 to 12. Many funnel plots showed asymmetry, which may reflect heterogeneity across procedure types (surgical, dental, and endoscopic) and variation in sedation depth (general anesthesia, deep and moderate sedation).

3.3.1. Propofol use

Total propofol use during TIVA was reported by 40 studies (43 pEEG cohorts), which compared non-pEEG-guided anesthesia care to BIS (35 cohorts), Entropy (6 cohorts), and SEDLine (2 cohorts). Overall, pEEG monitoring significantly reduced total propofol use (SMD -0.42 [95% CI -0.74; −0.10], $p = 0.01$) (Fig. 2). In the subgroup analysis, a statistically significant reduction was observed only for BIS (SMD −0.44, [95% CI -0.83; −0.06], $p = 0.02$). Reductions were observed for Entropy and SEDLine and were in line with overall results but the difference was not statistically significant (SMD -0.44 [95% CI -0.88; −0.00], $p = 0.05$) for Entropy (although right on the border of significance) or (SMD -0.08 [95% CI -0.18; 0.01], $p = 0.09$) SEDLine. Entropy and SEDLine would need additional studies to confirm their impact on TIVA use. The heterogeneity was substantial ($I^2 = 98.38\%$).

3.3.2. Anesthetic gas use

Anesthetic gas use was reported in 14 studies (17 pEEG cohorts). The 10 studies comparing non-pEEG-guided anesthesia care to BIS used sevoflurane (8 cohorts) or desflurane (4 cohorts), whereas the five cohorts with Entropy all used sevoflurane (Fig. 3). The use of pEEG significantly reduced anesthetic gas use overall by SMD -1.27 (95% CI -1.88 to −0.66, $p < 0.001$). In the subgroup analyses, BIS use significantly reduced desflurane volume (SMD -1.06 [95% CI -1.74; −0.37], $p < 0.001$) and sevoflurane volume (SMD -1.41 [95% CI -2.52; −0.29], $p = 0.01$). Entropy was associated with a significant reduction in sevoflurane volume (SMD -1.24 [95% CI -2.38; − 0.09], $p = 0.03$). The outcome showed substantial heterogeneity ($I^2 = 94.58\%$). Further studies are required to make conclusive statements about all combinations of volatile agent and pEEG device.

3.3.3. POD

Eleven studies reported POD outcomes, comparing non-pEEG-guided

Table 1
Outcome effects and subgroup analysis by device comparing pEEG to non-pEEG-guided anesthesia care.

Outcome	Subgroup	Number of studies (cohorts*)	Data synthesis methods	Pooled effect	Heterogeneity	*p*-value
Propofol use	Total**	40 (43)	SMD [95% CI]	-0.42 [−0.74; −0.10]	98.38%	0.01
	BIS	33 (35)		-0.44 [−0.83; −0.06]	98.08%	0.02
	Entropy	6		-0.44 [−0.88; −0.00]	90.60%	0.05
	SEDLine	2		-0.08 [−0.18; 0.01]	0.00%	0.09
Gas use	Total**	14 (17)	SMD [95% CI]	-1.27 [−1.88; −0.66]	94.58%	<0.01
	BIS, desflurane	4		-1.06 [−1.74; −0.37]	80.43%	<0.01
	BIS, sevoflurane	8		-1.41 [−2.52; −0.29]	96.14%	0.01
	Entropy, sevoflurane	5		-1.24 [−2.38; −0.09]	95.46%	0.03
POD	Total	11	RR [95% CI]	0.73 [0.63; 0.84]	11.08%	<0.01
	BIS	8		0.68 [0.59; 0.79]	0.00%	<0.01
	Entropy	1		0.09 [0.01; 0.71]	n/a	0.02
	SEDLine	2		0.92 [0.73; 1.17]	0.00%	0.51
Extubation time, min	Total**	32 (42)	MD [95% CI]	−2.90 [−3.64; −2.16]	78.39%	<0.01
	BIS	26 (34)		−2.85 [−3.61; −2.08]	76.39%	<0.01
	Entropy	6 (7)		−15.71 [−39.43; 8.00]	99.85%	0.19
	SEDLine	1		0.50 [−2.72; 3.72]	n/a	0.76
Wake-up time, min	Total**	40 (48)	MD [95% CI]	−1.83 [−2.42; −1.25]	90.19%	<0.01
	BIS	34 (39)		−1.90 [−2.57; −1.22]	92.09%	<0.01
	Entropy	8 (9)		−1.65 [−2.78; −0.52]	67.62%	<0.01
Time to orientation, min	Total	17 (22)	MD [95% CI]	−4.11 [−6.99; −1.23]	97.45%	<0.01
	BIS	16 (21)		−3.34 [−5.85; −0.83]	96.47%	0.01
	Entropy	1		−19.20 [−22.66; −15.74]	n/a	<0.01
PACU length of stay, min	Total	23 (26)	MD [95% CI]	−2.81 [−4.66; −0.96]	79.34%	<0.01
	BIS	18 (21)		−3.28 [−5.52; −1.04]	84.13%	<0.01
	Entropy	4		10.12 [−18.54; 38.79]	96.88%	0.49
	SEDLine	1		0.00 [−2.96; 2.96]	n/a	1.00

* Please note that due to multi-arm studies, we report the number of patient cohorts using pEEG separately only when this number deviates from the number of studies.

** The number of studies by device does not add up to the total number of studies because of multi-arm studies reporting on more than one pEEG device. pEEG, processed electroencephalograpy/electroencephalogram; POD, postoperative delirium.

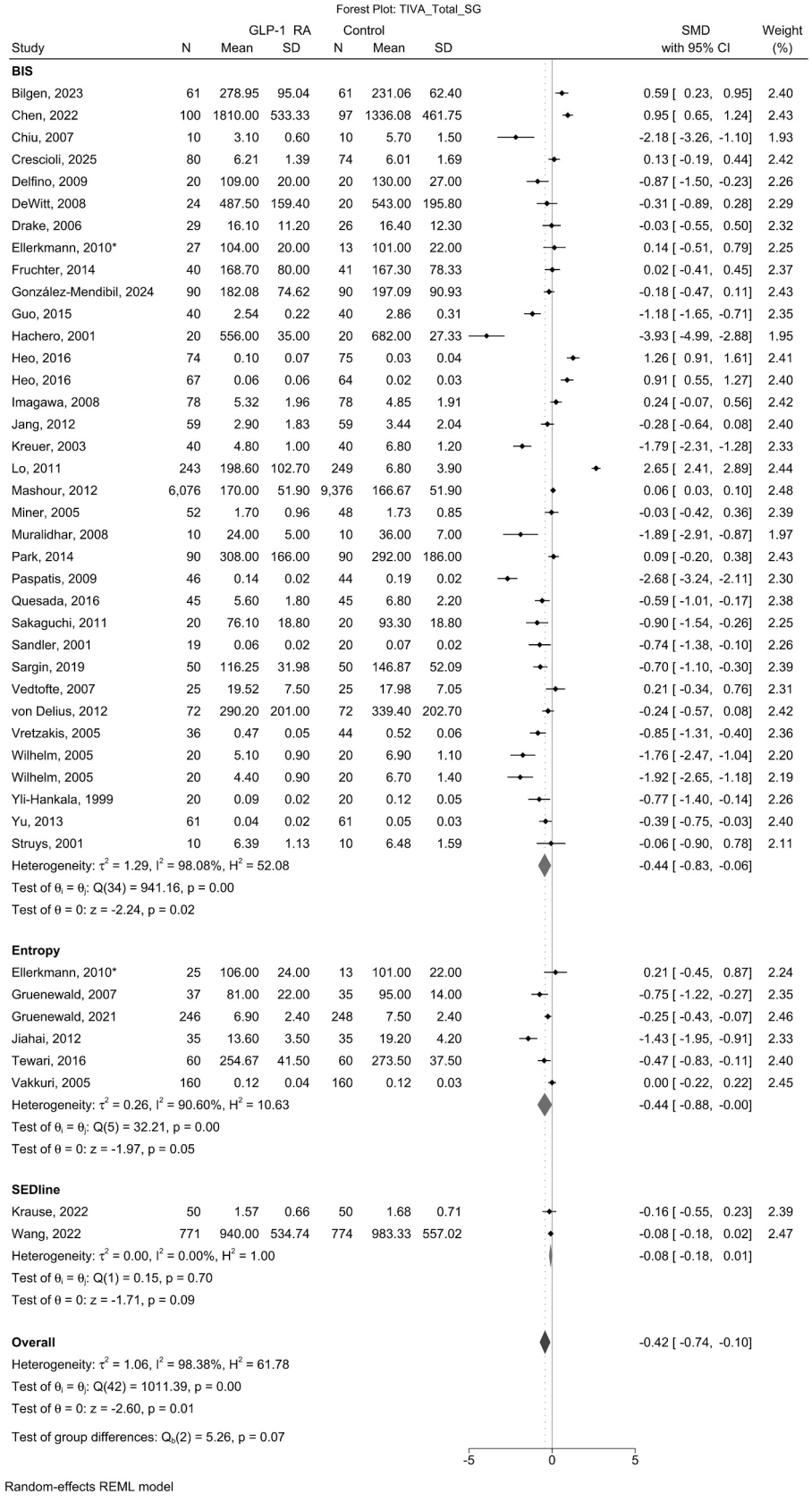


Fig. 2. Standardized mean difference in total propofol use between pEEG and non-EEG-guided anesthesia care by pEEG device.
Note: Pooled estimates of total propofol use for the use of pEEG to monitor depth of anesthesia compared with non-pEEG-guided anesthesia care and subgroup analysis by pEEG device. Data extracted from references [19,22,24,29,30,32–61] for BIS, [19,62–66] for Entropy, and [67,68] for SEDLine. pEEG, processed encephalogram. *Studies marked with an asterisk had shared control arms and adjustments for double counting were applied as specified in the methods. Other studies listed twice had independent cohorts.

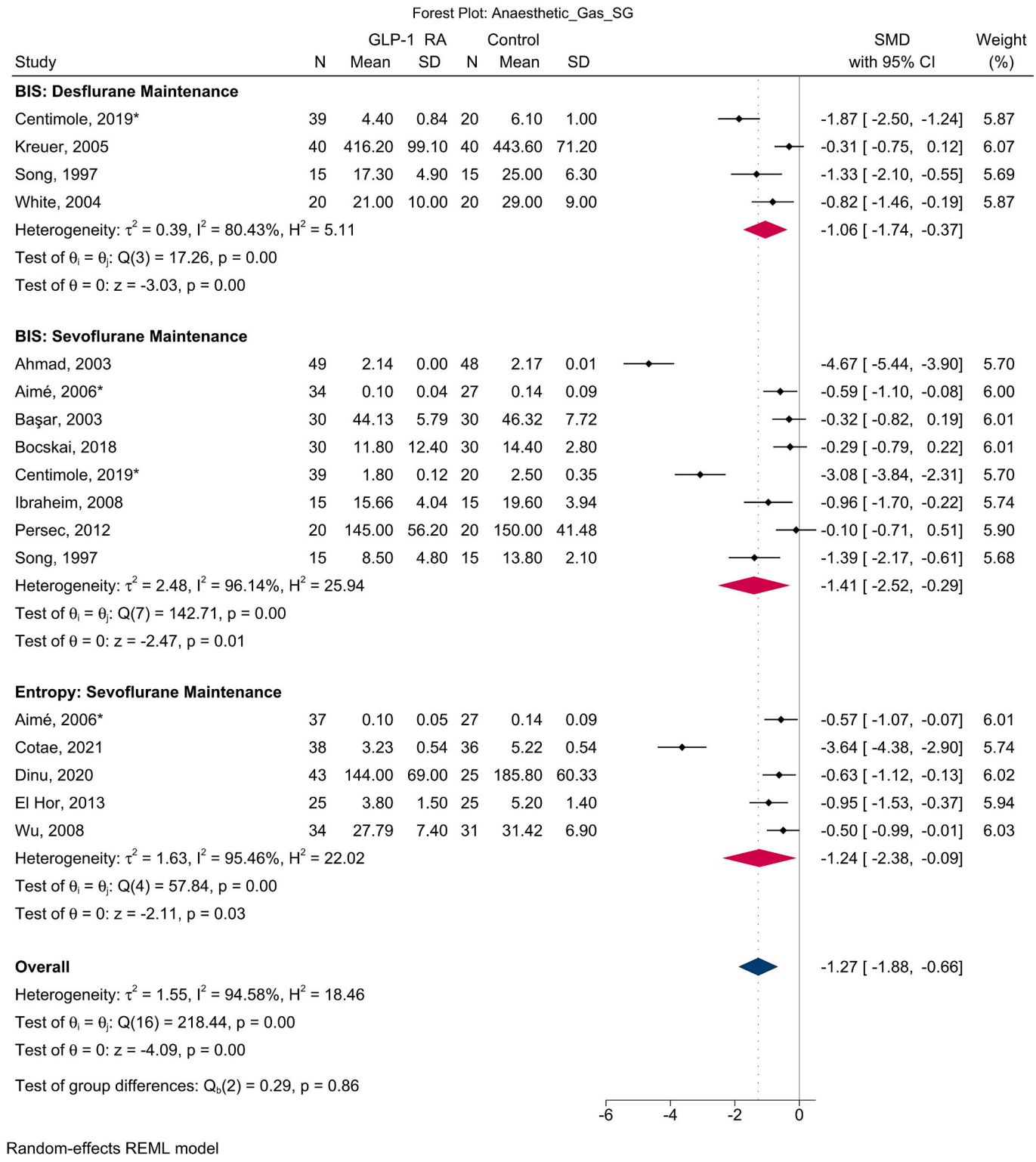


Fig. 3. Standardized mean difference in anesthetic gas use between pEEG and non-pEEG-guided anesthesia by pEEG device and anesthetic gas.
Note: Pooled estimates of anesthetic gas use for the use of pEEG to monitor depth of anesthesia compared with non-pEEG-guided anesthesia care and subgroup analysis by pEEG device and anesthetic gas used. Data extracted from references [27,69–71] for the use of desflurane with BIS, [20,21,27,69,72–75] for the use of sevoflurane with BIS, and [20,76–79] for the use of sevoflurane with Entropy. pEEG, processed encephalogram. *Studies marked with an asterisk had shared control arms and adjustments for double counting were applied as specified in the methods. Other studies listed twice had independent cohorts.

anesthesia care with BIS (8 cohorts), Entropy (1 cohort) and SEDLine (2 cohorts). The risk of POD was significantly reduced by 27% (RR 0.73 [95% CI 0.63; 0.84], $p < 0.001$) (Fig. 4). In the subgroup analysis, BIS significantly reduced the POD risk by 32% (RR 0.68 [95% CI 0.59; 0.79], $p < 0.001$). Entropy significantly reduced the risk to RR 0.09 (95% CI 0.01; 0.71, $p = 0.02$); however, this was based on a single study. SEDLine did not significantly affect the POD risk (RR 0.92 [95% CI 0.73; 1.17], $p = 0.51$). The outcome showed low heterogeneity ($I^2 = 11.08\%$) with

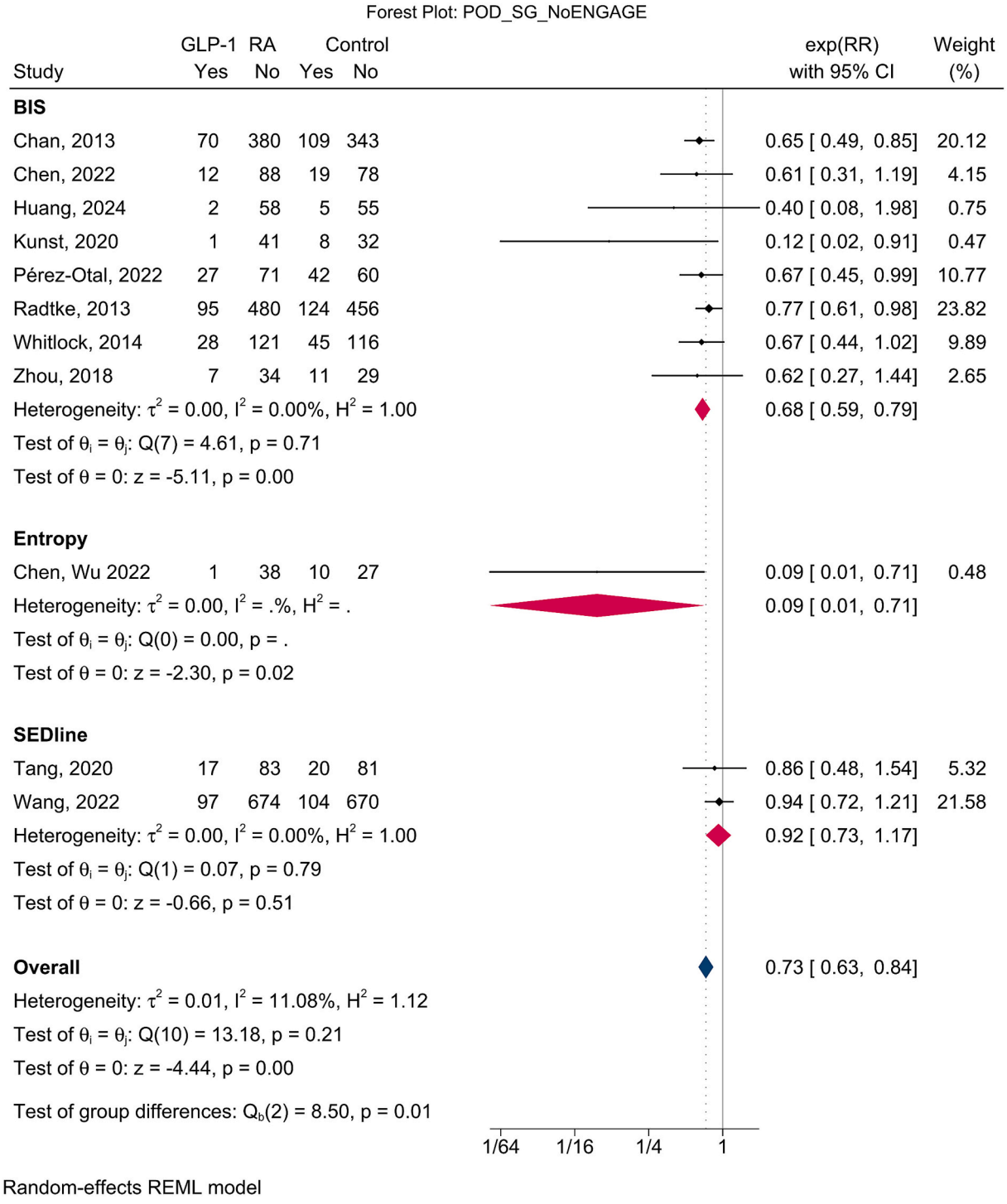


Fig. 4. Risk ratio for POD between pEEG and non-pEEG-guided anesthesia care by pEEG device.
Note: Pooled estimates of perioperative delirium for the use of pEEG to monitor depth of anesthesia compared with non-pEEG-guided anesthesia care and subgroup analysis by pEEG device. Data extracted from references [18,32,80–85] for BIS, [86] for Entropy, and [67,87] for SEDLine. pEEG, processed encephalogram; POD, postoperative delirium. pEEG, processed encephalogram.

no heterogeneity for BIS alone ($I^2 = 0.00\%$). Further studies are required to make conclusive statements about Entropy and SEDLine.

Details of all POD studies are summarized in Supplementary Table 3. Follow-up ranged from 1 to 10 days, delirium assessments varied, all types of surgeries were included, and anesthetic techniques were heterogeneous.

3.3.4. *Extubation time*

Extubation time was reported in 32 studies (42 pEEG cohorts), showing a mean reduction of −2.90 min (95% CI -3.64; −2.16, $p < 0.01$) with pEEG monitoring (Fig. 5). In the BIS subgroup (34 cohorts), extubation time was significantly reduced by −2.85 min (95% CI -3.61; −2.08, $p < 0.01$). Neither the Entropy subgroup comprising seven cohorts (−15.71 [95% CI -39.43; 8.00], $p = 0.19$) nor the SEDLine subgroup of a single cohort (0.50 [95% CI -2.72; 3.72], $p = 0.76$) showed a

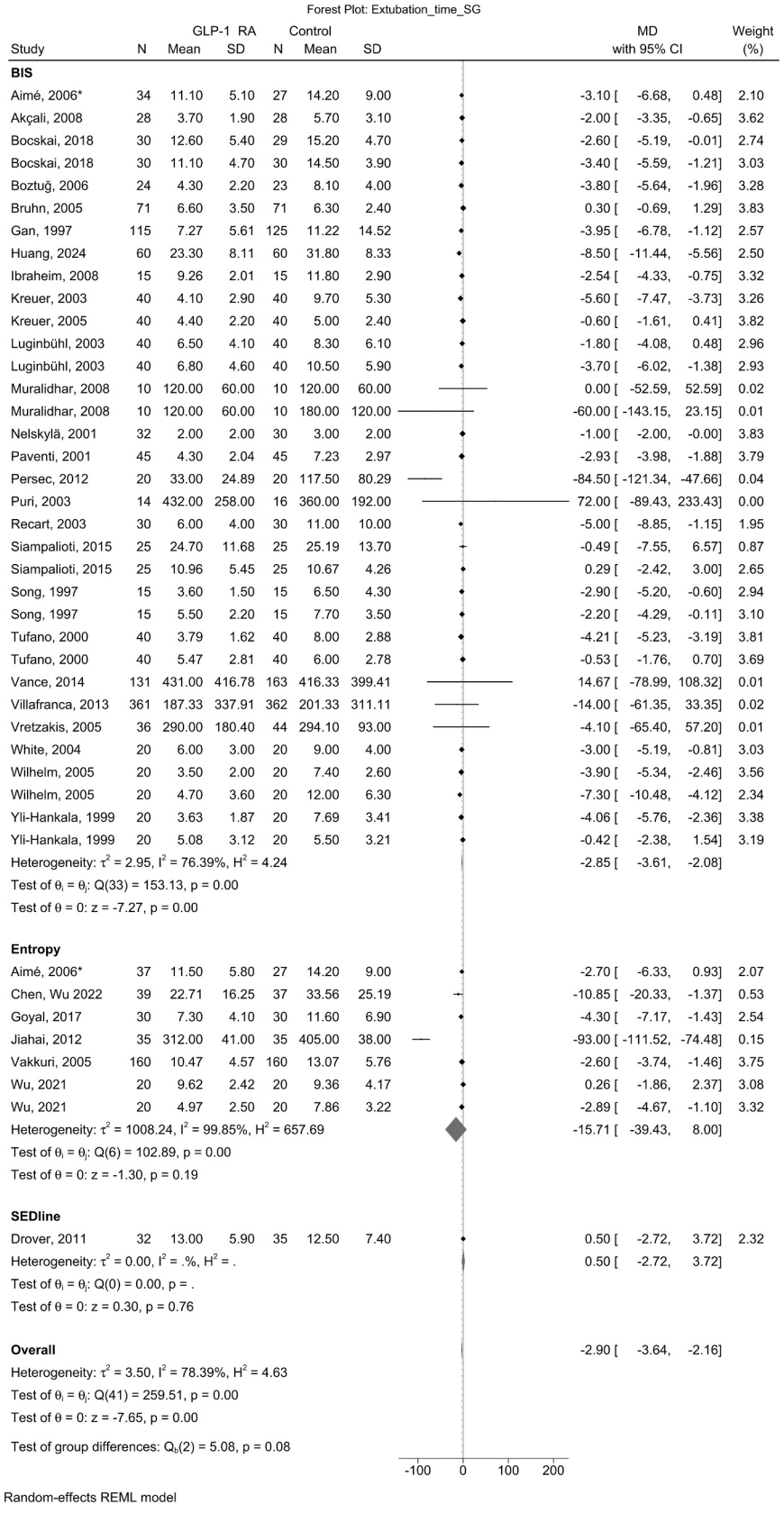


Fig. 5. Mean difference in extubation time between pEEG and non-pEEG-guided anesthesia care according to pEEG device subgroups.
Note: Pooled estimates of extubation time [min] for the use of pEEG to monitor depth of anesthesia compared with non-pEEG-guided anesthesia care and subgroup analysis by pEEG device. Data extracted from references [20,21,23,24,26–30,46,59,70,71,74,75,80,88–97] for BIS, [20,31,64,66,86,98] for Entropy, and 60 for SEDLine. pEEG, processed encephalogram. *Studies marked with an asterisk had shared control arms and adjustments for double counting were applied as specified in the methods. Other studies listed twice had independent cohorts.

significant difference compared to standard practice. The outcome showed substantial heterogeneity ($I^2 = 78.39\%$).

3.3.5. Wake-up time

Wake-up time was reported in 40 studies (48 pEEG cohorts) comparing pEEG monitoring with non-pEEG-guided anesthesia care (BIS in 39 cohorts, Entropy in 9 cohorts). Overall, pEEG monitoring reduced wake-up time by −1.83 min (95% CI -2.42; −1.25, $p < 0.001$) (Supplementary Fig. 1). Both subgroups also showed significant reductions: BIS with −1.90 min [95% CI -2.57; −1.22], $p < 0.001$) and Entropy with −1.65 min (95% CI -2.78; −0.52, $p < 0.001$). Heterogeneity was substantial ($I^2 = 90.19\%$).

3.3.6. Time to orientation

Seventeen studies reported time to orientation (22 pEEG cohorts). Using pEEG significantly reduced time to orientation by an average − 4.11 min (95% CI -6.99; −1.23, $p < 0.001$) (Supplementary Fig. 2). Patients needed −3.34 min (95% CI -5.85; −0.83, $p = 0.01$) minutes less time to return to orientation in the BIS subgroup (21 cohorts). The single cohort reporting time to orientation for Entropy also showed a significant reduction by −19.20 min (95% CI -22.66; −15.74, $p < 0.001$). The outcome showed substantial heterogeneity ($I^2 = 97.45\%$). Further studies are required to make conclusive statements about Entropy and SEDLine.

3.3.7. PACU length of stay

Twenty-three studies reported PACU length of stay (26 pEEG cohorts): BIS (21 cohorts), Entropy (4 cohorts), and SEDLine (1 cohort). The use of pEEG significantly reduced length of PACU stay by −2.81 min (95% CI -4.66; −0.96, $p < 0.001$) (Supplementary Fig. 3). The PACU stay was also significantly reduced by −3.28 min (95% CI -5.52; −1.04, $p < 0.001$) in the BIS subgroup, but not in the Entropy subgroup (10.12 min [95% CI -18.54; 38.79], $p = 0.49$) or the SEDLine subgroup (0.00 min [95% CI -2.96; 2.96], $p = 1.00$). The outcome showed substantial heterogeneity ($I^2 = 79.34\%$). Further studies are required to make conclusive statements about Entropy and SEDLine.

3.4. Risk of bias

Risk of bias results are summarized in Supplementary Fig. 4 with study-level assessments provided in Supplementary Table 5. Although all studies were RCTs, approximately one-third did not report sufficient detail on randomization and sequence generation, making adequacy difficult to judge. Most studies lacked detailed descriptions of allocation concealment, resulting in a probably high or high risk of bias for 81% of studies in this category.

In device studies, it is inherently difficult or even impossible to leave healthcare providers and, to a lesser extent, patients and outcome assessors unaware of intervention assignment, inevitably increasing the risk of bias. However, whether the patients are aware of the assigned intervention or not is unlikely to introduce much bias here, as the outcomes assessed in this meta-analysis were mainly collected perioperatively while the patient was sedated or anesthetized. Roughly two-thirds of the studies made attempts to blind the outcome assessors. Follow-up completeness was high, with few missing data due to the short timing of perioperative outcomes.

3.5. Sensitivity analyses

To assess the impact of the two well-known ENGAGES trials on the POD outcome, we performed a sensitivity analysis that included results from the ENGAGES and ENGAGES-CANADA trials [16,17]. The effect size was slightly reduced but still significant (Supplementary Fig. 14): 0.79 [95% CI 0.68; 0.93, $p < 0.001$]. This means that a significant reduction in POD is observed despite including these two large null trials.

Moreover, heterogeneity increased substantially when including the ENGAGES trials from 11.08% to 49.97% overall and from 0.00% to 54.97% for BIS. This indicates that the ENGAGES trials deviate from the other trials reporting on POD. In particular, all other included studies maintained the device-specific pEEG index within the recommended range, whereas both ENGAGES trials primarily used waveform EEG to limit periods of burst suppression (Supplementary Table 3), which sets them apart from the others.

A second sensitivity analysis was performed by removing Kunst et al. (2020) from the POD outcome where both BIS and INVOS were used in the intervention arm [18]. Removal of this study had a negligible impact on the overall POD estimate, changing the pooled risk ratio from 0.73 (95% CI 0.63–0.84) in the base-case analysis to 0.74 (95% CI 0.64–0.84). Similarly, in the BIS subgroup analysis, the pooled risk ratio changed only marginally from 0.68 (95% CI 0.59–0.79) to 0.69 (95% CI 0.60–0.80). These findings further support the robustness of the observed association between pEEG-guided anesthesia and reduced POD.

4. Discussion

In this meta-analysis of 87 RCTs, pEEG-guided monitoring was associated with significant improvements in perioperative efficiency compared with non-pEEG-guided anesthesia care. The meta-analysis yielded significant reductions in anesthetic consumption and perioperative recovery times when using pEEG. Additionally, pEEG monitoring was associated with a significantly lower risk of developing POD, an acute manifestation within the spectrum of PND. These findings support the use of pEEG as a tool to optimize anesthetic delivery and improve cognition-related patient outcomes.

The 27% reduction in POD risk (RR 0.73) is the most clinically consequential finding of this meta-analysis, and its interpretation is strengthened by the lower heterogeneity across studies — in marked contrast to the efficiency outcomes, where substantial heterogeneity limits generalizability. This finding is consistent with established mechanisms: pEEG guidance reduces the depth and duration of anesthesia, thereby limiting exposure to burst suppression, which has been independently associated with a ~ 50% increase in POD odds ratio in a recent meta-analysis of 6435 patients [99]. POD is not merely an acute inconvenience; it extends hospitalization, increases rates of discharge to rehabilitation facilities, and is associated with substantial downstream cognitive and functional decline and loss of independence [100–103]. It should be noted that preoperative risk, surgeries, and anesthetic techniques were varied (Supplementary Table 3) but these factors did not seem to affect heterogeneity for POD because it was very low in this outcome and reduced to 0% in the BIS subgroup.

Both the ENGAGES trial [16] and ENGAGES-CANADA trial [17] are important studies that have generated substantial discussion in the literature [104–108], with both reporting that POD was unchanged by EEG-guided anesthesia. Neither study met the selection criteria as they primarily used waveform EEG to guide anesthesia. In addition, the ENGAGES-CANADA protocol indicated that more than one pEEG technology could be used during the intervention [109]. Older meta-analyses including the ENGAGES trial had reported that there was no significant effect on POD, which was largely driven by the ENGAGES trial [110,111]. In a subgroup analysis, Sumner et al. reported a significant reduction in POD among studies that adhered to manufacturers' and published guidelines for maintaining pEEG indices within recommended target ranges [110]. Several more studies have been published since then [18,32,67,80,81,86,87]. When considering the current data, POD remained significantly reduced even when including both ENGAGES and ENGAGES-CANADA trials in the sensitivity analysis. Moreover, heterogeneity was substantially increased from low (11%) to moderate (50%) when adding the ENGAGES and ENGAGES-CANADA trials to the base-case analysis. For the BIS subgroup, the heterogeneity increase was even more pronounced, increasing from 0% to 55%.

Although note that the ENGAGES-CANADA trial reported using a mix of devices including BIS [17]. Taken together, these findings suggest that the effects of EEG-guided anesthesia may vary across clinical settings. Monitoring technologies are particularly difficult to evaluate because clinical benefit depends not only on the monitor itself but also on how clinicians act on the information provided. Because direct comparisons are lacking, it cannot be determined whether pEEG index-guided anesthesia is more effective than waveform-guided EEG approaches. Further well-designed trials are required to understand the differences in outcomes.

Although the observed time savings were modest, they may become clinically meaningful when applied across large procedural volumes. Whether these gains translate into operational benefits depends on local recovery pathways.

Beyond resource efficiency, reductions in anesthetic gas use also have environmental implications. Volatile anesthetics are potent greenhouse gases, and in 2019, they accounted for approximately 2% of the total carbon footprint of the National Health Service in England [112]. Among volatile agents, desflurane has by far the greatest greenhouse gas emissions, followed by isoflurane and then sevoflurane [113,114]. Propofol, by contrast, has substantially lower greenhouse emissions, by approximately four orders of magnitude [113]. Propofol, however, introduces a separate environmental concern, as propofol is aquatoxic, non-biodegradable, and contributes substantially to pharmaceutical waste streams [115]. Reducing any anesthetic consumption where clinically feasible may therefore offer environmental co-benefits.

4.1. Limitations

This review has several limitations. First, anesthetic dosing regimens are interdependent: propofol requirements are influenced by concomitant opioid administration and other agents commonly used in balanced anesthesia. Our analyses treated total propofol consumption as the primary proxy for the depth of anesthesia, implicitly assuming that comedication patterns were similar between groups; dedicated trials would be required to isolate the magnitude of any opioid-interaction effects.

Second, there were limitations in the available evidence base, particularly for non-BIS devices. Entropy and SEDLine were represented by fewer studies, limiting precision and potentially underpowering subgroup comparisons. Devices with even smaller evidence bases (e.g., Narcotrend, Conox) were excluded from quantitative synthesis by design (threshold of $\geq$10 studies or $\geq$ 500 patients), which may limit generalizability to all pEEG devices. Although searching additional databases may have identified further studies, comparison with previous POD meta-analyses that searched EMBASE and the Cochrane Central Register of Controlled Trials suggests that only one small study (Jildenstål 2012; $n = 16$ per arm) using a device not included for analysis was missed [110,111].

Third, outcome measurement heterogeneity was present. POD assessment methods, patient selection (often older adults), and observation windows (from 1 to 10 days) varied across trials, which can affect event detection and comparability. For efficiency outcomes, time metrics and workflow practices differ by setting, which likely contributed to the substantial statistical heterogeneity observed (high I^2 values in several analyses). For anesthetic consumption, units and reporting formats varied; while SMD enabled synthesis across units, SMDs are less directly interpretable than raw units.

Fourth, estimation of missing means and SDs may have introduced uncertainty.

Fifth, risk of bias assessments identified frequent concerns regarding allocation concealment and blinding of providers in device trials, which are inherently difficult. Although most outcomes were perioperative and less susceptible to bias from lack of patient blinding, residual bias cannot be excluded.

Sixth, reporting and publication bias are possible, as suggested by asymmetry in several funnel plots; however, asymmetry may also reflect true heterogeneity across procedure types and anesthesia modalities. Although a risk of bias assessment was included, a full critical appraisal such as a GRADE assessment was not performed.

Finally, review-level constraints may influence findings. The search strategy excluded studies not meeting prespecified reporting requirements (e.g., device not named or not mentioned in the abstract), and we analyzed only RCTs in adult populations. We also expanded the POD window to 10 days post hoc and added PACU length of stay as a post hoc efficiency outcome. Sensitivity analysis for the POD did not change the direction or significance of the POD effect, but residual selection effects cannot be completely ruled out.

The limited evidence base for Entropy, SEDLine, and other devices compared with BIS restricts confidence in device-specific subgroup estimates and highlights the need for additional device-specific RCTs.

5. Conclusion

Evidence from RCTs evaluating pEEG-guided depth-of-anesthesia monitoring suggests improvements in perioperative efficiency—reducing anesthetic consumption and shortening recovery intervals—and a lower risk of POD compared with non-pEEG-guided anesthesia care. The most robust evidence base is for BIS, with a few studies available for Entropy and SEDLine but often with inconclusive results. While heterogeneity and reporting limitations warrant cautious interpretation, these findings support pEEG-guided monitoring as a strategy to enhance outcomes and resource efficiency, and they motivate additional device-specific RCTs.

Use of generative AI

During the preparation of this work, the authors used Microsoft 365 Copilot to support language editing for clarity and consistency. The authors reviewed and edited the output as needed and take full responsibility for the content of the published article.

CRediT authorship contribution statement

Anil Hormis: Writing – review & editing, Writing – original draft, Validation, Investigation. **Zohn Centimole:** Writing – review & editing, Writing – original draft, Validation, Investigation. **Sita J. Saunders:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Youssef Ahmed:** Writing – review & editing, Software, Methodology, Formal analysis. **Juliane Hafermann:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Rhodri Saunders:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Funding acquisition, Conceptualization. **Jonas Villinger:** Writing – review & editing, Resources, Project administration, Investigation, Funding acquisition, Conceptualization. **Vanessa Moll:** Writing – review & editing, Writing – original draft, Validation, Investigation.

Ethical approval

Ethical approval is not required as this meta-analysis only uses aggregate data from published studies that already obtained informed consent where required.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinane.2026.112351.

Data availability

The data and code used for all analyses are available from the authors upon reasonable request.

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