



Effect of processed electroencephalography-guided anesthesia on postoperative delirium: an updated systematic review and meta-analysis

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Background: Postoperative delirium (POD) is a common complication following surgery, associated with extended hospital stays, cognitive decline, and increased mortality, yet effective pharmacological prevention remains elusive. Processed electroencephalography (p-EEG) guided general anesthesia is designed to reduce excessive neural suppression linked to POD development. However, conflicting evidence exists due to variations in devices and regional practices.

Methods: We systematically searched Medline, Embase, and the Cochrane Central Register of Controlled Trials from database inception to January 2025, randomized controlled trial (RCT) comparing p-EEG guided general anesthesia with standard care in adult surgical patients. Statistical analysis employed random-effects models calculated risk ratios (RR) and mean differences (MD) with 95% confidence intervals (CIs). The primary outcome was POD incidence.

Results: Twelve RCTs involving 4523 surgical patients were included. p-EEG guided general anesthesia reduced the incidence of POD compared with control group (RR 0.81, 95% CI 0.69–0.95, $I^2 = 46\%$), with pronounced benefits in elderly patients (≥ 60 years, RR 0.83, 95% CI 0.69–0.99) and non-cardiac surgeries (RR 0.78, 95% CI 0.64–0.95). Regional heterogeneity was significant: European and East Asian/Australasian trials demonstrated efficacy, whereas North American studies showed no benefit. In addition, p-EEG guided general anesthesia reduced postoperative cognitive dysfunction (RR 0.66, 95% CI 0.49–0.89), shortened hospital stays (MD –0.90 days, 95% CI –1.60 to –0.20), and lowered vasopressor requirements (RR 0.73, 95% CI 0.64–0.83). Mortality did not differ between groups.

Conclusion: p-EEG guided general anesthesia demonstrates reduces POD incidence and associated complications, especially in elderly patients and non-cardiac surgeries. However, the effectiveness may vary due to differences in practice, anesthetic protocols, and cultural factors. Our findings support the implementation of tailored neuromonitoring in high-risk populations.

Keywords: anesthesia monitoring, electroencephalography, meta-analysis, neuromonitoring, postoperative delirium

Introduction

Postoperative delirium (POD), a clinically significant neuropsychiatric syndrome occurring postoperatively^[1,2], appears as sudden mental confusion marked by poor focus, disordered thoughts, and changes in awareness^[3,4]. Associated with longer hospital stays, worsening brain function, and more medical complications^[1,5,6], occurring in 5%–10% of general surgery patients but exceeding 50% in high-risk groups such as cardiac surgery patients^[7–10]. The exact biological causes remain unclear.

Current theories involve interactions between neuroinflammatory pathways, neurotransmitter imbalances, and potentially exacerbated neurodegenerative processes^[2,7,11–15]. Although risk stratification tools exist, effective pharmacological prevention remains elusive, positioning anesthetic management optimization as a critical preventive strategy.

Traditional hemodynamic-based depth-of-anesthesia (DOA) monitoring risks anesthetic overdose. This may cause burst suppression electroencephalography (EEG) patterns (manifesting as thalamocortical discharges) linked to neuronal injury through tau phosphorylation and synaptic dysfunction^[16–18]. These injury mechanisms may underlie POD pathogenesis^[19–21], motivating research into neuromonitoring-based prevention approaches. Processed electroencephalography (p-EEG) systems aim to optimize cerebral activity during anesthesia^[17,22,23], yet their efficacy in preventing POD shows inconsistent evidence. The ENGAGES trial found no delirium reduction with BIS monitoring^[24], whereas the BALANCED substudy demonstrated significant risk reduction (RR 0.58, 95% CI 0.38–0.88) using shallow

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anesthesia protocols^[25]. Meta-analyses show borderline statistical significance (OR 0.78, 95% CI 0.60–1.00)^[26]. This contrasts with recent trials such as ENGAGES-Canada, which confirmed no significant effects^[27]. These discrepancies reflect methodological differences across studies and diverse patient populations.

Given this clinical uncertainty, we conducted a systematic review and meta-analysis to examine p-EEG's role in preventing POD. Our rigorous methodology enabled evidence-based recommendations for intraoperative neuromonitoring strategies.

Methods

We conducted this comprehensive systematic review and meta-analysis in strict accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines^[28] (Supplemental Digital Content Table S1, available at: <http://links.lww.com/JS9/E696>) and the Assessing the Methodological Quality of Systematic Reviews guidelines^[29] (Supplemental Digital Content Table S2, available at: <http://links.lww.com/JS9/E696>). The study protocol was prospectively registered with PROSPERO before commencing data collection to enhance methodological transparency and minimize reporting bias. This study was conducted and reported in accordance with the Transparency In The reporting of Artificial Intelligence – the TITAN guideline criteria for transparent and artificial intelligence^[30] (Supplemental Digital Content Table S3, available at: <http://links.lww.com/JS9/E696>).

Search strategy

We conducted a comprehensive literature search across databases: MEDLINE (PubMed), Embase (Ovid), and the Cochrane Central Register of Controlled Trials. The search encompassed all relevant literature available up to January 2025. Furthermore, we examined reference lists from both included studies and relevant systematic reviews to identify additional eligible trials, with detailed search strategies provided in Supplemental Digital Content Materials, available at: <http://links.lww.com/JS9/E696>.

Eligibility criteria

The included trials enrolled adult patients aged 18 years or older undergoing surgery with general anesthesia. The intervention group received anesthesia management guided by p-EEG monitoring, using proprietary DOA indices, p-EEG waveforms, or derived indices were also considered, such as burst suppression ratio, spectral edge frequency 95%, and electromyographic activity. The control group received standard anesthesia care either without EEG guidance or with sham monitoring, where clinicians remained blinded to all EEG parameters except essential device functionality indicators like signal quality indices. Only peer-reviewed randomized controlled trials (RCTs) published in English that reported POD incidence were eligible for inclusion. We excluded involving pediatric populations or animal subjects, using neuraxial anesthesia with sedation or regional block-based analgesia. Studies on delirium in long term intensive care unit (ICU) settings were excluded to avoid confounding from critical care-related cognitive dysfunction. The CAM-ICU tool was allowed for early postoperative assessments in post-anesthesia care units or transitional care units, consistent with its validation for rapid detection in non-prolonged critical

HIGHLIGHTS

- Processed electroencephalography (EEG)-guided anesthesia significantly reduces postoperative delirium (POD) risk in elderly non-cardiac surgery patients, proving particularly valuable for high-risk populations.
- Geographic variations occurred: European and East Asian/Australasian trials reduced POD significantly, unlike North American studies, possibly due to differing anesthetic protocols.
- Beyond reducing delirium, EEG guidance decreases cognitive deficits, shortens hospital stays, and lowers vasopressor requirements, underscoring its broader role in enhancing perioperative outcomes and resource efficiency.

care contexts. All the retained trials ensured that the delirium evaluation reflected the acute effects of surgery and anesthesia rather than the factors acquired during ICU stay.

Study selection and data extraction

Two investigators (L.C. and Q.C.) independent conducted titles and abstracts for initial screening based on predefined eligibility criteria. We assessed potentially eligible article through dual independent full-text reviews, and a third investigator (H.L.) was involved in a consensus discussion to resolve discrepancies. Data collection was conducted by one reviewer (Y.Y.X.) and independently cross-checked for accuracy by two reviewers (L.C. and Q.C.). We collected the following (1) study characteristics (authors, publication year, country, sample size), (2) participant demographics (clinical background, surgical procedure), (3) interventions/comparisons (monitoring devices), and (4) outcome measures (assessment method, frequency, follow-up period). When data were missing, we contacted the corresponding authors to request the necessary information.

Study outcomes

The primary outcome was the incidence of POD (a positive diagnosis was made when at least one assessment met the criteria). Delirium was assessed using the established Confusion Assessment Method (CAM) or CAM-ICU^[31,32]. Secondary outcomes included postoperative cognitive dysfunction (POCD). POCD was defined in an individual when the reliable change index score was < -1.96 on ≥ 2 tests, the combined Z score was < -1.96 , or both. Other secondary outcomes were hospital length of stay (LOS), which was the total days from surgery to discharge; mortality, referring to postoperative all-cause mortality; end-tidal volatile anesthetic concentrations (ETAC), expressed as age-adjusted minimum alveolar concentration (MAC) multiples; and intraoperative adverse events such as hypotension requiring inotrope or vasopressors, which meant the intraoperative administration of any inotrope or vasoactive agent.

Risk of bias and evidence certainty assessment

Two investigators (L.C. and Y.Y.X.) independent evaluated the risk of bias for each included RCTs assessed using the Cochrane risk-of-bias tool 2.0 (RoB 2.0)^[33]. The RoB 2.0 tool

systematically evaluates five critical domains: risk of bias arising from the randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain received one of three ratings: “low risk,” “moderate concern,” or “high risk” based on predefined signaling questions and algorithmic decision rules outlined in the ROB 2.0 handbook. The overall certainty of evidence was appraised through the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework, which evaluating key dimensions including risk of bias, inconsistency, indirectness, imprecision, and publication bias. Using the GRADE framework, we categorized evidence quality into four levels: high, moderate, low, or very low^[34]. To minimize assessment bias, two investigators performed all evaluations independently using standardized forms. Discrepancies in domain judgments or GRADE evaluations were resolved through repeated review of original studies followed by adjudication with the third author (H.L.) until consensus was achieved.

Statistical analysis

All analyses were performed with R statistical software (version 4.4.1) with the meta and metafor packages^[35]. We used a random-effects model with inverse-variance weighting to determine the combined effect sizes and address potential research discrepancies. DerSimonian–Laird estimator was used for the meta-analysis^[36]. Dichotomous outcomes were pooled as risk ratios (RRs) and continuous outcomes as mean differences (MD), both with 95% confidence intervals (CIs). When studies reported continuous data as medians with interquartile ranges, we converted the medians and interquartile ranges to means and standard deviations using validated transformation methods^[37]. We used I^2 and τ^2 statistics to assess heterogeneity^[38] and supplemented it with visual inspection of L’Abbe plots. Specifically, we calculated the 95% prediction interval (PI) to show the extent of between study heterogeneity. The L’Abbe plot displays outcome event incidence in intervention (y-axis) and control (x-axis) groups. Specifically, homogeneous studies align along a straight line, while deviations suggest potential heterogeneity sources. We assessed publication bias across studies by visually inspecting funnel plots for asymmetry and using Egger’s test for the primary outcome. We conducted a trial sequential analysis (TSA) for primary outcomes, using TSA, version 0.9.5.10 to test the certainty of the results in by minimizing the random error by calculating the required sample size, adjusting the thresholds for the cumulative statistical significance by the α -spending method (O’Brien–Fleming boundaries), and testing for futility with a type-1 error of 5.0% and a power of 80.0% set as the futility boundaries.

Subgroup and sensitivity analysis

We prespecified subgroup analyses to examine potential effect modifiers of p-EEG-guided general anesthesia on POD incidence:

Age stratification: Elderly (≥ 60 years) versus younger adults (< 60 years)

Surgical category: Cardiac (with cardiopulmonary bypass) versus non-cardiac procedures

Anesthetic protocol: Total intravenous anesthetic (based on propofol) versus volatile anesthetic

These stratification approaches helped evaluate whether the intervention effects varied across clinically relevant patient subgroups.

Beyond subgroup analyses, we used two complementary approaches to assess result robustness. We did leave-one-out cross-validation by systematically excluding individual studies to evaluate their influence on the overall results. Additionally, we categorized the analysis based on study quality, comparing outcomes between trials with low risk of bias and those with some concerns or high risk of bias for our primary outcome. This rigorous approach offered robust evidence supporting the reliability of our conclusions.

Results

Literature screening

Our comprehensive literature search initially identified 1438 potentially relevant records from electronic databases. We first removed 672 duplicate entries and excluded 614 clearly irrelevant records during preliminary screening. Then, two independent researchers evaluated the remaining 152 articles at the abstract level. Subsequently, detailed full-text assessments were performed on 53 studies that appeared to meet eligibility criteria. Ultimately, our rigorous selection process yielded 12 high-quality RCTs encompassing a total of 4523 participants that satisfied all predefined inclusion requirements^[24,25,27,39–47] (Fig. 1 and Table 1).

Study characteristics

Among the 12 studies, including three cardiac surgery trials ($n = 1680$)^[27,43,46] and nine non-cardiac surgery trials ($n = 2843$)^[24,25,39–42,44,45,47], with no studies reporting neurosurgical populations. Geographically, four trials originated from China^[39,40,45,47], four from North America^[24,27,44,46], three from Europe^[41–43], and one multinational trial spanned Australia, China, and the United States^[25]. Eight of the twelve studies employed single-center designs^[24,40,41,43–47], while four utilized multicenter methodologies^[25,27,39,42]. p-EEG-guided general anesthesia protocols exhibited notable heterogeneity in monitoring devices and implementation strategies. Most studies ($n = 7$) employed the Bispectral Index (BIS®; Covidien, Boulder, CO, USA) for DOA monitoring^[24,25,39,40,42,46,47]. Other devices included the SedLine® EEG monitor (Masimo Corporation, Irvine, CA) in two studies^[44,45], which incorporated Patient State Index, spectral edge frequency (SEF95%), density spectral array, and real-time EEG waveform analysis, the A-line monitor (Danmeter A/S, Odense, Denmark) targeting mid-latency auditory evoked potentials in one study^[41], the Narcotrend® system (Hannover, Germany) maintaining a Narcotrend Index between 37 and 64 in one study^[43], and the BIS monitor or SedLine® monitor or NeuroSENSE® monitor in one study^[27]. Control group strategies varied significantly across trials. Ten studies adopted a blinded EEG monitoring approach^[24,27,39–45,47], where clinicians were restricted from accessing EEG-derived parameters except signal quality indices. One trial compared light (BIS target 50) and deep (BIS target 35) general anesthesia regimens^[25], while another involving open-heart surgery utilized ETAC-guided alerts (thresholds: <0.7 or >1.3 age-adjusted MAC)^[46]. Seven studies used combined intravenous and volatile

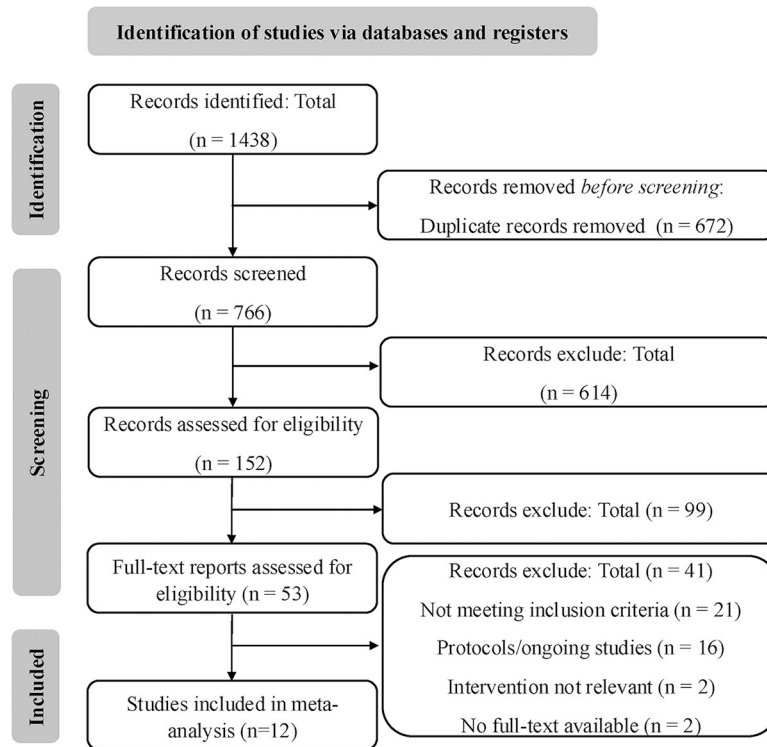


Figure 1. PRISMA flowchart of the included studies.

anesthetic regimens^[24,25,27,39,41,43,44], typically pairing propofol with sevoflurane or desflurane. Three studies maintained anesthesia exclusively via intravenous propofol infusions^[40,45,47]. One trial permitted either total intravenous anesthesia (TIVA) with propofol or volatile agents based on clinician preference^[42]. Notably, a single study in open heart surgery employed ETAC-guided volatile anesthesia^[46]. ROB 2.0 evaluation revealed a high risk of bias in two RCTs^[41,47] and some concerns in two others^[40,43]. The remaining eight trials demonstrated a robust risk of bias with low risk of bias^[24,25,27,39,42,44–46] (Fig. 2). Variability in assessment methodologies across studies compromised the reliability of POD outcome evidence. This methodological heterogeneity contributed to the overall GRADE evaluation indicating limited confidence in the conclusion that p-EEG monitoring effectively reduces POD incidence (Table 2).

Primary outcome: POD

All included studies used validated diagnostic tools (3D-CAM, CAM-ICU, or CAM)^[24,25,27,39–47] to assess POD. Evaluations were performed once or twice daily during follow-up periods lasting 1–10 days postoperatively. Reported delirium incidence varied substantially across trials, reflecting differences in surgical populations and assessment protocols. Pooled analysis showed p-EEG guided anesthesia reduced delirium risk by 16% (RR 0.81, 95% CI 0.69–0.95, 95% PI 0.52–1.24), with incidence rates of 15.0% (562/3743) versus 17.9% (676/3778) compared to conventional care. (Fig. 3 and Table 2), and moderate heterogeneity ($I^2 = 46\%$) (L'Abbe plot; Supplemental Digital Content Figure S1, available at: <http://links.lww.com/JS9/E696>). However, the PIs encompassed values either side of the null effect, thus suggesting that p-EEG guided general anesthesia may not

significantly reduce POD in similar future studies. TSA showed that the curve crossed the conventional significance threshold but not the TSA boundary, and the accrued information size did not reach the required information size. These findings suggest that the meta-analysis may have produced a false positive result, and additional trials are required to confirm the efficacy of the treatment (Supplemental Digital Content Figure S2, available at: <http://links.lww.com/JS9/E696>).

Five studies additionally reported delirium duration or severity using standardized scales (Memorial Delirium Assessment Scale)^[24,27,41,44,46]. No studies identified significant intergroup differences. Our comprehensive analysis found no significant effect modification by surgical category (cardiac vs. non-cardiac procedures) on the association between p-EEG monitored anesthesia and POD risk (P for interaction = 0.56; Supplemental Digital Content Figure S3, available at: <http://links.lww.com/JS9/E696>). The treatment effect remained consistent regardless of patient age stratification (≥ 60 years vs. < 60 years; P for interaction = 0.51; Supplemental Digital Content Figure S4, available at: <http://links.lww.com/JS9/E696>) or anesthetic maintenance regimen (propofol-based intravenous anesthesia vs. volatile agent maintenance vs. TIVA; P for interaction = 0.58; Supplemental Digital Content Figure S5, available at: <http://links.lww.com/JS9/E696>).

Our exploratory analysis of regional subgroups revealed significant heterogeneity (P for interaction = 0.002; Supplemental Digital Content Figure S6, available at: <http://links.lww.com/JS9/E696>). Trials conducted in Europe (RR 0.79, 95% CI 0.63–0.99) and East Asia/Australia (RR 0.65, 95% CI 0.54–0.79) demonstrated significant reductions in POD incidence with p-EEG-guided general anesthesia. In contrast, North American trials showed no evidence of benefit (RR 1.01, 95% CI 0.87–1.16).

Table 1
Study characteristics of included randomized controlled trials

Study	Country	Number of sites	No. patients randomized	Age (year)	Enrolment criteria	Type of p-EEG monitor	Control group	Delirium assessment method	Delirium follow-up	Delirium screens per day	Primary outcome
Chan <i>et al</i> 2013	China	2	921	≥60 yr	Elective major surgery expected to last ≥2 h	BIS-guided (40–60)	BIS blinded	CAM	1 day	1	POCD at 3 months after surgery
Chen <i>et al</i> 2022	China	1	220	>18 yr	Laparoscopic gastrointestinal surgery >2 h	BIS-guided (40–60)	BIS blinded	CAM	7 days	NR	Incidence of DNR on 7th day and 1-month, PND at 6th month and 1 yr, POD from 1st–7th day
ENGAGES-Canada 2024	Canada	4	1140	≥60 yr	Cardiac surgical procedure with CPB	EEG waveforms and derived parameters	Blinded except the signal quality index	CAM, CAM-ICU, or chart review	5 days	1	Delirium incidence during postoperative days 1–5
Evered <i>et al</i> 2021	Australia, China, USA	8	547	≥60 yr	Major noncardiac surgery with expected duration >2 h	BIS guided-target 50	BIS guided-target 35	3D-CAM or CAM-ICU	5 days or discharge	2	Presence of POD on any of the 10 assessments
Jlidenatal <i>et al</i> 2012	Sweden	1	32	40–94 yr	Major ENT surgery	AEP, A-line; AAI between 15 and 25	AAI blinded	CAM	1 day	1	Postoperative cognitive dysfunction or inflammatory response
Radtke <i>et al</i> 2013	Germany	2	1277	≥60 yr	Elective surgery expected to last 60 min or more	Bilateral BIS, guided target 40–60	Blinded except the signal quality index	DSM IV	7 days	2	Postoperative delirium
Sponholz <i>et al</i> 2020	Germany	1	252	≥18 yr	Elective cardiac surgery with CPB ≤180 min or elective OPCAB	Narcorent, NT guided target 37–64	NT blinded	CAM-ICU	NR	NR	Intraoperative norepinephrine requirement following anesthetic drug administration
Tang <i>et al</i> 2020	USA	1	223	≥65 yr	Major elective noncardiac surgery	Sedline, PSI >35	Sedline blinded	CAM	3 days	1	EEG suppression
Wang <i>et al</i> 2020	China	1	1560	≥50 yr	Elective laparoscopic surgery	Sedline, PSI between 25 and 50	Sedline blinded	CAM, CAM-ICU	5 days	2	The incidence of POD on each of postoperative days 1–5
Whitlock <i>et al</i> 2014	USA	1	337	≥18 yr	Major cardiac and/or thoracic	BIS, guided-target 40–60	ETAC guided target 0.7–1.3	CAM-ICU	10 days or ICU discharge	2	Postoperative delirium
ENGAGES 2019	USA	1	1232	≥60 yr	Major surgery with general anesthesia	BIS, guided target >40	BIS blinded	CAM, CAM-ICU	5 days	1	Postoperative delirium
Zhou <i>et al</i> 2018	China	1	89	65–75	Elderly patients with colon carcinoma	BIS, guided-target 40–60	BIS blinded	CAM	5 days	1	The assessments of alerting, orienting, and executive control functions as determined by the ANT

AAI, A-line APX index; AEP, auditory evoked potential; ANT, Attention Network Test; BIS, bispectral index; CAM, confusion assessment method; CFQ, cognitive failure questionnaire; CNTAB, included a Motor Screening Test, two tests of visual memory (pattern recognition memory and spatial recognition memory) and a test of attention (choice reaction time); CPB, cardiopulmonary bypass; DNR, delayed neurocognitive recovery; DSM IV, Diagnostic and Statistical Manual of Mental Disorders; MMSE, mini-mental state examination; PND, postoperative neurocognitive disorder.

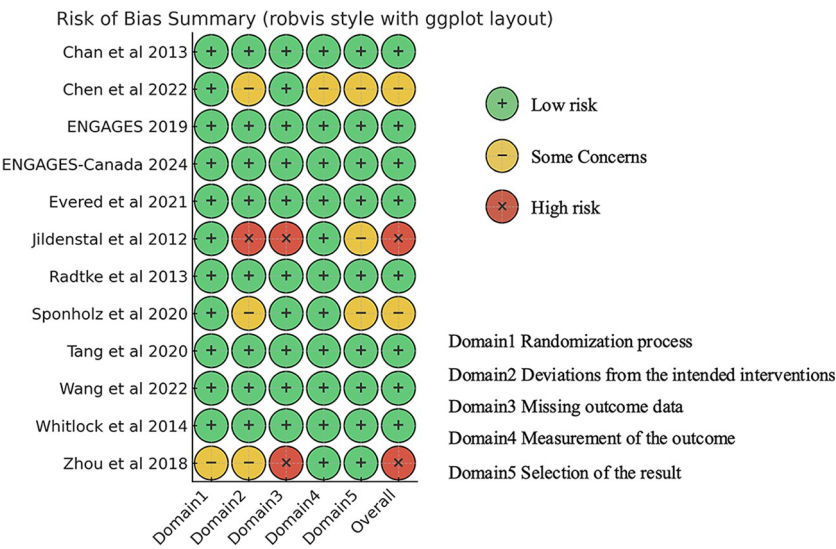


Figure 2. Rob2 risk of bias assessment for primary outcome.

The robustness of primary outcome findings was substantiated through sensitivity analyses. No significant variation in effect direction or magnitude was observed when comparing studies with low versus some concerns/high risk of bias (P for interaction = 0.54; Supplemental Digital Content Figure S7, available at: <http://links.lww.com/JS9/E696>). Exclusion of the ENGAGES trial eliminated statistical heterogeneity (I^2 decreasing from 46% to 0%) and strengthened the treatment effect (RR 0.76, 95% CI 0.66–0.88). Exclusion of any other single study maintained both statistical significance (RR range: 0.76–0.84) and heterogeneity levels (I^2 range: 37%–51%), confirming no disproportionate influence from any individual trial (Supplemental Digital Content Figure S8, available at: <http://links.lww.com/JS9/E696>). Funnel plot analysis of the primary outcome revealed asymmetry, suggesting potential publication

bias (Supplemental Digital Content Figure S9, available at: <http://links.lww.com/JS9/E696>). While funnel plot asymmetry suggested potential publication bias, Egger’s test showed no significant small-study effects (intercept = -1.16 , $P = 0.152$), though interpretation remains cautious given methodological heterogeneity and limited studies.

Secondary outcomes

Four studies evaluated neurocognitive outcomes with follow-up periods ranging from 1 month to 1 year postoperatively^[39–42]. Compared to conventional management, p-EEG guided anesthesia showed a 35% relative reduction in POCD risk (RR 0.66, 95% CI 0.49–0.89; Supplemental Digital Content Figure S10, available at: <http://links.lww.com/JS9/E696> and Table 2), with

Table 2
GRADE score for significant outcomes reported in the manuscript

Outcome	RCT	p-EEG	Controls	RR or MD (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty	Comment
POD	12	3743	3778	0.82 (0.69–0.95)	Serious	Serious	No	No	No	⊕ ⊕ ⊕ ⊕ Low	Increased risk of bias, Inconsistency among studies
POCD	4	1094	1105	0.66 (0.49–0.89)	Serious	Serious	No	No	No	⊕ ⊕ ⊕ ⊕ Low	Increased risk of bias, Inconsistency among studies
Hospital LOS	8	3464	3504	−0.90 (−1.60 to −0.20)	No	Serious	No	Serious	No	⊕ ⊕ ⊕ ⊕ Low	Inconsistency among studies, Imprecision with wide CI and high I^2
Vasopressor require	4	844	850	0.73 (0.64–0.83)	Serious	No	No	No	No	⊕ ⊕ ⊕ ⊕ Moderate	Increased risk of bias
Mortality	4	2052	2062	0.55 (0.23–1.31)	No	Serious	No	Serious	No	⊕ ⊕ ⊕ ⊕ Low	Inconsistency among studies, Imprecision with wide CI and high I^2

CI, confidence intervals; LOS, length of stay; MD, mean difference; POCD, postoperative cognitive dysfunction; POD, postoperative delirium; RCT, randomized controlled trials; RR, risk ratios.

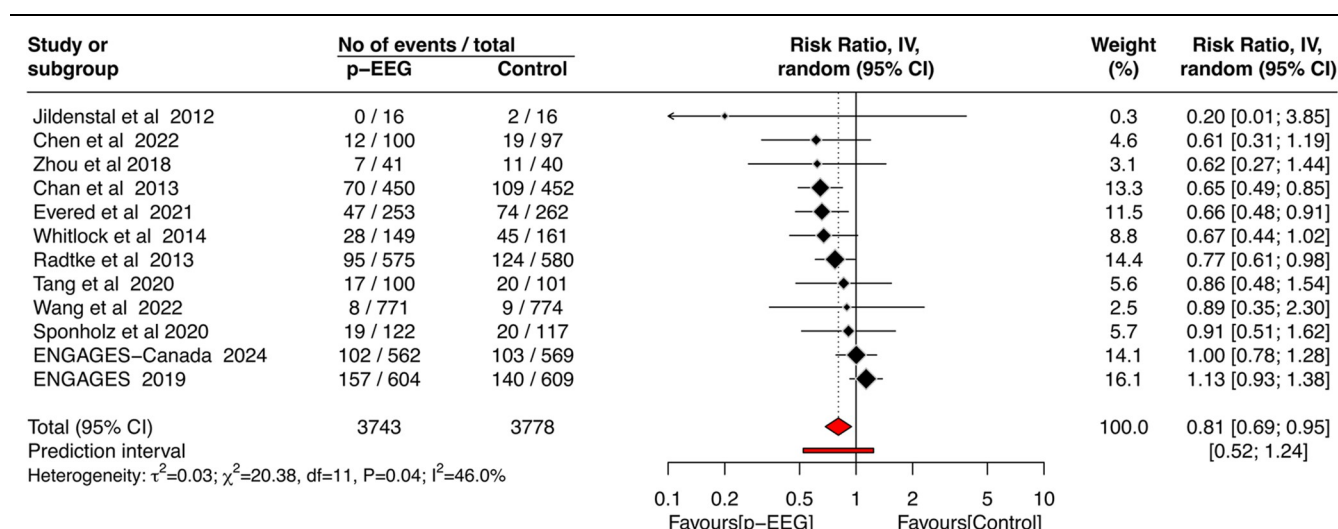


Figure 3. Forest plot for postoperative delirium. Analysis with random-effects model. p-EEG, processed electroencephalography; CI, confidence interval; IV, inverse-variance.

moderate heterogeneity across trials ($I^2 = 33\%$). Heterogeneity stemmed from differing assessment tools (Montreal Cognitive Assessment or Mini-Mental State Examination) and different follow-up periods.

Eight RCTs ($n = 6968$) reported hospital LOS, with mean durations between 5.6 and 15.9 days^[24,25,27,39,40,42,45,46]. Our pooled analysis revealed that p-EEG guided anesthesia or lighter p-EEG targets significantly reduced LOS compared to conventional care showing an MD of -0.90 days (95% CI -1.60 to -0.20) despite substantial between-study heterogeneity ($I^2 = 85\%$) (Supplemental Digital Content Figure S11, available at: <http://links.lww.com/JS9/E696> and Table 2), indicating protocol-specific or population-specific variability in effect sizes.

Six trials reported intraoperative inotrope or vasopressor requirements^[24,25,39-41,47], with four providing quantitative data for pooled analysis^[25,39,40,47]. First, ENGAGES trial demonstrated a significant reduction in phenylephrine dose with p-EEG guided (MD -0.63 mg, 95% CI -1.22 to -0.03)^[24]. Another study observed significantly lower ephedrine requirements in the intervention group (2.4 ± 1.2 vs. 10 ± 17.5 mg, $P < 0.005$)^[41]. Finally, pooled analysis of four studies^[25,39,40,47] showed p-EEG guided reduction in inotrope or vasopressor requirements (RR 0.73, 95% CI 0.64–0.83, $I^2 = 44.1\%$) (Supplemental Digital Content Figures S12, available at: <http://links.lww.com/JS9/E696> and Table 2).

Postoperative mortality was evaluated in four RCTs^[24,40,42,45]. Among these trials, the pooled analysis showed no statistically significant difference in mortality between p-EEG guided anesthesia and standard care (RR 0.55, 95% CI 0.23–1.31, $I^2 = 67\%$) (Supplemental Digital Content Figure S13, available at: <http://links.lww.com/JS9/E696>, and Table 2). While the point estimate suggested a numerical reduction in mortality risk with EEG guidance, the wide CI crossing the null value (RR = 1) precluded definitive conclusions about benefit or harm.

Among five studies reporting ETAC^[24,25,27,39,41], four used MAC multiples^[24,25,27,39] while one specifically measured desflurane^[41], all studies showed reduced ETAC with p-EEG

guided versus conventional practice. Due to high heterogeneity ($I^2 = 98\%$) and methodological variability in concentration measurements, we adopted narrative synthesis instead of quantitative meta-analysis. Given these limitations in quantitative synthesis, we omitted forest plot generation for this outcome.

Discussion

This meta-analysis demonstrates that p-EEG guided general anesthesia reduces POD incidence, particularly in elderly patients (≥ 65 years) and non-cardiac surgeries. However, efficacy varied by region. European and East Asian/Australasian cohorts showed significant reductions, whereas North American trials reported neutral effects. Secondary benefits include reduced intraoperative vasopressor requirements, shorter hospital stays, and decreased risk of POCD. The study demonstrated no mortality benefit. However, methodological differences in EEG algorithms and perioperative management prevent definitive conclusions, emphasizing the need for standardization. The difference between Sumner *et al*^[26] and Sun *et al*^[48] mainly reflects whether ENGAGES-Canada^[27] was included and how the ENGAGES trial^[24] was analyzed. Crucially, when adherence to EEG targets was achieved in non-cardiac surgeries and elderly populations, pooled effects consistently favored intervention. Differences in practice across regions further explain why North American trials couldn't reproduce the benefits seen in other areas. The current study and Sumner *et al*^[26] included high-risk populations. In addition, the sensitivity analysis for Sun *et al*^[48] showed a shift to positive results after excluding the ENGAGES study^[24], which suggests that the ENGAGES data had a great impact on their conclusions. The subgroup analysis of Sumner *et al*^[26] showed a significant effect in studies that followed device guidelines, which suggests the importance of implementation quality. ENGAGES-Canada^[27] reduced EEG suppression time but not delirium, supporting the view that delirium mechanisms are complex, and EEG alone is insufficient. The current study added three new trials^[27,37,42], including ENGAGES-Canada^[27], with a larger

sample size and subgroup analyses to strengthen the conclusion of a benefit of non-cardiac surgery in the elderly, and sensitivity analyses to demonstrate the robustness of the results.

p-EEG monitoring aims to mitigate anesthesia-induced neural suppression through real-time cerebral activity tracking. Extended EEG suppression during surgery, especially burst suppression (indicating deep anesthesia), shows a clear dose-response relationship with POD risk^[18,19]. When suppression ratios exceed 50%, indicating significant cortical network disruption, every extra minute of suppression raises delirium risk by 3.8 percentage points in elderly patients^[49]. Deep anesthesia (BIS <40) decreases cerebral oxygen metabolism by 30%–40% and may disrupt glymphatic neurotoxin clearance^[50]. However, clinical implementation challenges persist, retrospective studies establish a critical burst suppression threshold (>4.4 minutes) for elevated POD risk, beyond which prolonged suppression shows no additional risk increase^[51]. The ENGAGES trial achieved reduced median suppression times (7 vs. 13 minutes). However, neither group reached subthreshold levels, potentially explaining the null delirium outcomes^[24]. These findings highlight both the need for strict suppression duration targets (<4.5 minutes) to optimize efficacy and the value of comprehensive evidence synthesis despite trial discrepancies^[52]. While the ENGAGES-Canada trial^[27] achieved a 64% reduction in EEG suppression time, delirium rates remained nearly identical (18.15% with EEG guidance versus 18.10% without), highlighting delirium's complex pathophysiology. Technical limitations, such as automated BIS algorithms underestimating suppression duration by 42% versus raw EEG analysis, further challenge device-dependent protocols^[53]. Cardiac surgery-related delirium arises from combined stressors like hemodynamic instability and hypoperfusion. This requires comprehensive risk assessment combining EEG biomarkers (frontal alpha power, connectivity patterns) with systemic physiological measures^[19].

Variability in intraoperative medications complicates assessment of p-EEG's neuroprotective effects. While historical studies implicated benzodiazepines in POD, recent large-scale trials – including the B-Free trial ($n = 20\,000$ cardiac patients) and a cohort study of 5000 elderly non-cardiac patients both showed no significant association between midazolam use and POD risk^[54,55]. In contrast, anticholinergic drug burden demonstrates a consistent dose-dependent delirium risk^[56], necessitating vigilant pharmacologic oversight. Anesthetic agents further complicate EEG interpretation, while propofol enhances gamma activity (30–45 Hz) and elevates BIS values by 5–10 units, volatile anesthetics primarily induce delta oscillations (1–4 Hz). This divergence underscores anesthetic-specific EEG target optimization, as BIS shows stronger correlation with cerebral metabolism during propofol anesthesia ($r = 0.82$) compared with sevoflurane ($r = 0.65$)^[57,58]. Vasopressor heterogeneity also obscures outcomes – phenylephrine associates with higher delirium risk than ephedrine^[59]. Implementing standardized pharmacologic protocols are imperative to isolate p-EEG's neuroprotective efficacy.

Commercial EEG monitoring systems employ proprietary algorithms to generate DOA indices (e.g. BIS, entropy), introducing significant inter-device variability in detecting burst suppression, filtering artifacts, and interpreting anesthetic-specific EEG patterns^[60]. These indices (dimensionless, 0–100 scales) exhibit critical limitations^[61,62], most notably, they often fail to account for age-related EEG changes (e.g. attenuated alpha power [8–13 Hz]

and delta dominance [1–4 Hz] in elderly patients)^[63], leading to inaccuracies in vulnerable populations. Comparative analyses of five DOA monitors revealed contradictory recommendations in two-thirds of cases, with one-third overestimating hypnotic depth relative to raw EEG findings^[60]. These inconsistencies reveal the limitations of processed indices and underscore why raw EEG interpretation is needed, which directly visualizes cortical oscillations (e.g. alpha-delta coherence) and quantifies burst suppression – key electrophysiological biomarkers linked to POD risk^[64,65]. Despite being technically demanding, raw EEG analysis outperforms index-guided protocols for delirium prevention. This superiority probably stems from its capacity for age-adjusted spectral analysis and reduced algorithmic bias and suppress algorithmic biases inherent to commercial systems. While our findings support p-EEG's utility in high-risk populations, optimizing its neuroprotective potential requires targeted innovation. We propose three priority directions for p-EEG guided anesthesia to prevent delirium more effectively. First, combine machine learning with preoperative brain scans to identify patients at high risk of anesthesia-related cognitive complications. Second, create combined treatment plans that involve EEG monitoring during surgery and cognitive rehabilitation after surgery, including virtual reality therapies. Third, standardize EEG interpretation by setting consistent brain activity thresholds, training clinicians to read raw EEG data, and using EEG measurements to guide medication choices. Future research should determine whether EEG-based pain monitoring reduces brain inflammation that may cause delirium.

Limitations

There are three main limitations that need to be considered when interpreting these findings. First, commercial DOA indices have two key limitations: they are affected by signal artifacts and pharmacological variability. Consequently, their reliability as standalone hypnotic depth measures is limited. Ironically, overreliance on these metrics may increase the risk of intraoperative awareness. Second, methodological variability – particularly inconsistent reporting of continuous variables – and clinical heterogeneity, including diverse delirium assessments and surgical cohorts, compromise both data synthesis and generalizability. Furthermore, the high statistical heterogeneity suggests that the effect reliability might be overestimated. Third, the limited sample sizes precluded stratified analyses of either device-specific protocols or vasopressor strategies, which consequently restricted our ability to examine hemodynamic-EEG interactions.

Conclusions

p-EEG guided general anesthesia reduces POD incidence, particularly in elderly patients and non-cardiac surgeries. However, efficacy differed regionally because of differences in anesthetic protocols and delirium assessment rigor. Crucially, reduced intraoperative anesthetic exposure (lower ETAC/MAC, shorter burst suppression) may mediate POD reduction. Implementation requires standardized EEG monitoring parameters to address device heterogeneity. Future trials should validate whether raw EEG monitoring, in terms of effectiveness and accuracy, outperforms processed indices for delirium prevention.

Ethical approval

This meta-analysis synthesized data exclusively from previously published studies. As no original human/animal participants were directly involved, no new primary data were collected, and all included studies had obtained their own ethical approvals, institutional ethics committee clearance was not required for this secondary analysis.

Consent

This meta-analysis is a secondary synthesis of aggregated data from previously published studies. Since no original patient-level data, identifiable personal information, or clinical images were collected or analyzed in this research, individual patient consent is not applicable.

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Author contributions

Study concept and design: L.C., Q.C., Y.Y.X., and Z.X.W.; acquisition of data: Y.Y.X., F.C., Z.J.Z., and M.Y.; analysis and interpretation: L.C. and Q.C.; draft the manuscript and preliminary revise: L.C., Q.C., and G.Y.Y.; analyses and reviewed the manuscript: G.Y.Y. and Q.C.; study supervision and final approval: G.Y.Y. and H.L. All authors read and approved the final manuscript.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

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Data availability statement

The datasets used and/or analyzed in this study are available from the corresponding author upon reasonable request.

References

- [1] Oh ES, Fong TG, Hsieh TT, Inouye SK. Delirium in older persons: advances in diagnosis and treatment. *JAMA* 2017;318:1161–74.

- [2] Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet* 2014;383:911–22.
- [3] Alexander SK, Needham E. Diagnosis of delirium: a practical approach. *Pract Neurol* 2023;23:192–99.
- [4] Hughes CG, Boncyk CS, Culley DJ, *et al.* American society for enhanced recovery and perioperative quality initiative joint consensus statement on postoperative delirium prevention. *Anesth Analg* 2020;130:1572–90.
- [5] Inouye SK, Marcantonio ER, Kosar CM, *et al.* The short-term and long-term relationship between delirium and cognitive trajectory in older surgical patients. *Alzheimers Dement* 2016;12:766–75.
- [6] Scholz AF, Oldroyd C, McCarthy K, Quinn TJ, Hewitt J. Systematic review and meta-analysis of risk factors for postoperative delirium among older patients undergoing gastrointestinal surgery. *Br J Surg* 2016;103:e21–e28.
- [7] Jin Z, Hu J, Ma D. Postoperative delirium: perioperative assessment, risk reduction, and management. *Br J Anaesth* 2020;125:492–504.
- [8] Mei X, Zheng HL, Li C, *et al.* The effects of propofol and sevoflurane on postoperative delirium in older patients: a randomized clinical trial study. *J Alzheimers Dis* 2020;76:1627–36.
- [9] Brown CH 4th, Probert J, Healy R, *et al.* Cognitive decline after delirium in patients undergoing cardiac surgery. *Anesthesiology* 2018;129:406–16.
- [10] Li T, Li J, Yuan L, *et al.* Effect of regional vs general anesthesia on incidence of postoperative delirium in older patients undergoing hip fracture surgery: the RAGA randomized trial. *JAMA* 2022;327:50–58.
- [11] Hsieh TT, Fong TG, Marcantonio ER, Inouye SK. Cholinergic deficiency hypothesis in delirium: a synthesis of current evidence. *J Gerontol A Biol Sci Med Sci* 2008;63:764–72.
- [12] Hirsch J, Vacas S, Terrando N, *et al.* Perioperative cerebrospinal fluid and plasma inflammatory markers after orthopedic surgery. *J Neuroinflammation* 2016;13:211.
- [13] Berger M, Murdoch DM, Staats JS, *et al.* Flow cytometry characterization of cerebrospinal fluid monocytes in patients with postoperative cognitive dysfunction: a pilot study. *Anesth Analg* 2019;129:e150–e154.
- [14] Casey CP, Lindroth H, Mohanty R, *et al.* Postoperative delirium is associated with increased plasma neurofilament light. *Brain* 2020;143:47–54.
- [15] Mahanna-Gabrielli E, Schenning KJ, Eriksson LI, *et al.* State of the clinical science of perioperative brain health: report from the American society of anesthesiologists brain health initiative summit 2018. *Br J Anaesth* 2019;123:464–78.
- [16] Lewis LD, Ching S, Weiner VS, *et al.* Local cortical dynamics of burst suppression in the anaesthetized brain. *Brain* 2013;136:2727–37.
- [17] Brown EN, Lydic R, Schiff ND. General anesthesia, sleep, and coma. *N Engl J Med* 2010;363:2638–50.
- [18] Whittington RA, Bretteville A, Dickler MF, Planel E. Anesthesia and tau pathology. *Prog Neuropsychopharmacol Biol Psychiatry* 2013;47:147–55.
- [19] Pedemonte JC, Plummer GS, Chamadia S, *et al.* Electroencephalogram burst-suppression during cardiopulmonary bypass in elderly patients mediates postoperative delirium. *Anesthesiology* 2020;133:280–92.
- [20] Park SK, Han DW, Chang CH, Jung H, Kang H, Song Y. Association between intraoperative electroencephalogram burst suppression and postoperative delirium: a systematic review and meta-analysis. *Anesthesiology* 2025;142:107–20.
- [21] Hesse S, Kreuzer M, Hight D, *et al.* Association of electroencephalogram trajectories during emergence from anaesthesia with delirium in the postanesthesia care unit: an early sign of postoperative complications. *Br J Anaesth* 2019;122:622–34.
- [22] Purdon PL, Sampson A, Pavone KJ, *et al.* Clinical electroencephalography for anesthesiologists: part I: background and basic signatures. *Anesthesiology* 2015;123:937–60.
- [23] Aldecoa C, Bettelli G, Bilotta F, *et al.* Update of the European society of anaesthesiology and intensive care medicine evidence-based and consensus-based guideline on postoperative delirium in adult patients. *Eur J Anaesthesiol* 2024;41:81–108.
- [24] Wildes TS, Mickle AM, Ben Abdallah A, *et al.* Effect of electroencephalography-guided anesthetic administration on postoperative delirium among older adults undergoing major surgery: the ENGAGES randomized clinical trial. *JAMA* 2019;321:473–83.
- [25] Evered LA, Chan MTV, Han R, *et al.* Anaesthetic depth and delirium after major surgery: a randomised clinical trial. *Br J Anaesth* 2021;127:704–12.

- [26] Sumner M, Deng C, Evered L, *et al.* Processed electroencephalography-guided general anaesthesia to reduce postoperative delirium: a systematic review and meta-analysis. *Br J Anaesth* 2023;130:e243–e253.
- [27] Deschamps A, Ben Abdallah A, Jacobsohn E, *et al.* Electroencephalography-guided anesthesia and delirium in older adults after cardiac surgery: the ENGAGES-Canada randomized clinical trial. *JAMA* 2024;332:112–23.
- [28] Page MJ, McKenzie JE, Bossuyt PM, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
- [29] Shea BJ, Reeves BC, Wells G, *et al.* AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* 2017;358:j4008.
- [30] Agha RA, Mathew G, Rashid R, *et al.* Transparency in the reporting of artificial intelligence – the TITAN guideline. *Prem J Sci* 2025;10:100082.
- [31] Inouye SK, van Dyck Ch, Alessi CA, Balkin S, Siegel AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med* 1990;113:941–48.
- [32] Ely EW, Inouye SK, Bernard GR, *et al.* Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 2001;286:2703–10.
- [33] Sterne JAC, Savović J, Page MJ, *et al.* RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.
- [34] Guyatt GH, Oxman AD, Vist GE, *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–26.
- [35] Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health* 2019;22:153–60.
- [36] Veroniki AA, Jackson D, Viechtbauer W, *et al.* Methods to estimate the between-study variance and its uncertainty in meta-analysis. *Res Synth Methods* 2016;7:55–79.
- [37] Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res* 2018;27:1785–805.
- [38] Deeks JJ, Higgins JPT, Altman DG, eds. Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, eds. *Cochrane Handbook for Systematic Reviews of Interventions* version 6.4 (updated August 2023). Cochrane; 2023.
- [39] CODA Trial Group, Chan MT, Cheng BC, Lee TM, Gin T. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. *J Neurosurg Anesthesiol* 2013;25:33–42.
- [40] Chen X, Li L, Yang L, *et al.* A randomized trial: bispectral-guided anesthesia decreases incidence of delayed neurocognitive recovery and postoperative neurocognitive disorder but not postoperative delirium. *Am J Transl Res* 2022;14:2081–91.
- [41] Jildensstål P, Hallén JL, Rawal N, Berggren L. Does depth of anesthesia influence postoperative cognitive dysfunction or inflammatory response following major ENT surgery? *J Anesth Clin Res* 2014;3:220.
- [42] Radtke FM, Franck M, Lendner J, *et al.* Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction. *Br J Anaesth* 2013;110:i98–i105.
- [43] Sponholz C, Schuwirth C, Koenig L, *et al.* Intraoperative reduction of vasopressors using processed electroencephalographic monitoring in patients undergoing elective cardiac surgery: a randomized clinical trial. *J Clin Monit Comput* 2020;34:71–80.
- [44] Tang CJ, Jin Z, Sands LP, *et al.* ADAPT-2: a randomized clinical trial to reduce intraoperative EEG suppression in older surgical patients undergoing major noncardiac surgery. *Anesth Analg* 2020;131:1228–36.
- [45] Wang E, Wang L, Ye C, *et al.* Effect of electroencephalography Spectral Edge Frequency (SEF) and Patient State Index (PSI)-guided propofol-remifentanyl anesthesia on delirium after laparoscopic surgery: the eMODIPOD randomized controlled trial. *J Neurosurg Anesthesiol* 2022;34:183–92.
- [46] Whitlock EL, Torres BA, Lin N, *et al.* Postoperative delirium in a substudy of cardiothoracic surgical patients in the BAG-RECALL clinical trial. *Anesth Analg* 2014;118:809–17.
- [47] Zhou Y, Li Y, Wang K. Bispectral index monitoring during anesthesia promotes early postoperative recovery of cognitive function and reduces acute delirium in elderly patients with colon carcinoma: a prospective controlled study using the attention network test. *Med Sci Monit* 2018;24:7785–93.
- [48] Sun Y, Ye F, Wang J, *et al.* Electroencephalography-guided anesthetic delivery for preventing postoperative delirium in adults: an updated meta-analysis. *Anesth Analg* 2020;131:712–19.
- [49] Jung C, Hinken L, Fischer-Kumbruch M, *et al.* Intraoperative monitoring parameters and postoperative delirium: results of a prospective cross-sectional trial. *Medicine (Baltimore)* 2021;100:e24160.
- [50] Persson NDÅ, Uusalo P, Nedergaard M, *et al.* Could dexmedetomidine be repurposed as a glymphatic enhancer? *Trends Pharmacol Sci* 2022;43:1030–40.
- [51] Fritz BA, Kalarickal PL, Maybrier HR, *et al.* Intraoperative electroencephalogram suppression predicts postoperative delirium. *Anesth Analg* 2016;122:234–42.
- [52] Hao D, Fritz BA, Saddawi-Konefka D, Palanca BJA. Pro-con debate: electroencephalography-guided anesthesia for reducing postoperative delirium. *Anesth Analg* 2023;137:976–82.
- [53] Pawar N, Barreto Chang OL. Burst suppression during general anesthesia and postoperative outcomes: mini review. *Front Syst Neurosci* 2022;15:767489.
- [54] Spence J, Devereaux PJ, Lee SF, *et al.* Benzodiazepine-free cardiac anesthesia for reduction of postoperative delirium: a cluster randomized crossover trial. *JAMA Surg* 2025;160:286–94.
- [55] Li H, Liu C, Yang Y, *et al.* Effect of intraoperative midazolam on postoperative delirium in older surgical patients: a prospective multicenter cohort study. *Anesthesiology* 2025;142:268–77.
- [56] Egberts A, Moreno-Gonzalez R, Alan H, Ziere G, Mattace-Raso FUS. Anticholinergic drug burden and delirium: a systematic review. *J Am Med Dir Assoc* 2021;22:65–73.e4.
- [57] Lipp M, Schneider G, Kreuzer M, Pilge S. Substance-dependent EEG during recovery from anesthesia and optimization of monitoring. *J Clin Monit Comput* 2024;38:603–12.
- [58] Swarbrick CJ, Partridge JSL. Evidence-based strategies to reduce the incidence of postoperative delirium: a narrative review. *Anaesthesia* 2022;77:92–101.
- [59] Ma H, Ahrens E, Wachtendorf LJ, *et al.* Intraoperative use of phenylephrine versus ephedrine and postoperative delirium: a multicenter retrospective cohort study. *Anesthesiology* 2024;140:657–67.
- [60] Hight D, Kreuzer M, Ugen G, *et al.* Five commercial ‘depth of anaesthesia’ monitors provide discordant clinical recommendations in response to identical emergence-like EEG signals. *Br J Anaesth* 2023;130:536–45.
- [61] Muhlhofer WG, Zak R, Kamal T, *et al.* Burst-suppression ratio underestimates absolute duration of electroencephalogram suppression compared with visual analysis of intraoperative electroencephalogram. *Br J Anaesth* 2017;118:755–61.
- [62] Mathur S, Patel J, Goldstein S, Hendrix JM, Jain A. Bispectral Index. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023.
- [63] Purdon PL, Pavone KJ, Akeju O, *et al.* The ageing brain: age-dependent changes in the electroencephalogram during propofol and sevoflurane general anaesthesia. *Br J Anaesth* 2015;115:i46–i57.
- [64] Tanabe S, Mohanty R, Lindroth H, *et al.* Cohort study into the neural correlates of postoperative delirium: the role of connectivity and slow-wave activity. *Br J Anaesth* 2020;125:55–66.
- [65] Gutierrez R, Egaña JL, Saez I, *et al.* Intraoperative low alpha power in the electroencephalogram is associated with postoperative subsyndromal delirium. *Front Syst Neurosci* 2019;13:56.