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Research article

Effects of glucocorticoids on postoperative delirium in patients undergoing elective non-cardiac surgery:A systematic review and meta-analysis

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ABSTRACT

Background: Postoperative delirium (POD) is common postoperative complications in non-cardiac surgery. While delirium prophylaxis has not yielded unequivocal support. The clinical effects of glucocorticoids on POD remains unclear.
Objective: To evaluate the effects of glucocorticoids on postoperative delirium (POD) in patients undergoing non-cardiac surgery.
Design: Systematic review with meta-analysis.
Methods: In strict accordance with the PRISMA statement, a systematic literature search was undertaken across PubMed, EMBASE, Web of Science and Cochrane Library databases in May 2023. We updated the search results on June 28, 2024. We used the Grading of the Recommendation Assessment, Development, and Evaluation (GRADE) system to evaluate the quality of evidence.
Results: This meta-analysis included twelve randomized controlled trials involving 1044 participants undergoing non-cardiac surgery. Compared with the control group, glucocorticoids significantly reduced the incidence of POD in patients undergoing non-cardiac surgery (RR:0.50, 95%CI:0.41 to 0.60, $P < 0.00001$, $I^2 = 26$ %, GRADE = high). Meanwhile, glucocorticoids was associated with reducing the severity of POD (RR: −0.67, 95%CI: −1.10 to −0.23, $P = 0.003$, $I^2 = 89$ %, GRADE = low). However, there were no significant differences with regards to patients receiving antipsychotic drug (RR: 0.91, 95%CI:0.43 to 1.92, $P = 0.80$, $I^2 = 0$ %, GRADE = moderate), length of hospital stay (RR: −0.52, 95%CI: −1.41 to 0.36, $P = 0.24$, $I^2 = 0$ %, GRADE = moderate), 30-day postoperative mortality (RR: 0.70, 95%CI:0.23 to 2.15, $P = 0.54$, $I^2 = 0$ %, GRADE = low) and postoperative infection (RR: 0.87 95%CI: 0.58 to 1.30, $P = 0.50$, $I^2 = 33$ %, GRADE = moderate).
Conclusions: This systematic review and meta-analysis suggests that glucocorticoids reduce the incidence of POD among adults and children undergoing non-cardiac surgery and mitigate the severity of POD in adults, which indicates that glucocorticoids exhibit preventive or therapeutic effects on POD.
Registration: CRD42023426836 (PROSPERO).

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1. Background

Postoperative delirium (POD) is an acute neurocognitive disorder that arises after surgery [1]. The cardinal features of POD include impaired attention, consciousness, and cognition. The onset of POD is usually within the first 24 h following surgery [2], and the duration ranges from several hours to a few days, with fluctuation in severity [3]. Emergency delirium (ED) is considered an acute neurological complication during recovery from anesthesia. ED may be characterized by disorientation, hallucinations, panic, depressive mood, and hyperactive physical behavior or hypoactive signs [4,5]. Postoperative delirium involves ED; ED represents the early onset of postoperative delirium [6–8]. ED in the PACU is a strong predictor of postoperative delirium [9]. POD has been linked to impaired postoperative recovery, prolonged length of hospital stay, escalated medical expenses, long-term cognitive decline, and heightened mortality risk [10,11]. POD is one of the most common postoperative complications in non-cardiac surgery, with an incidence of 12 %–51 % [12,13]. In this review, the terms POD and ED are used interchangeably, which differs from the approach taken in previous studies [9,14].

Currently, the efficacy of pharmacological prophylaxis for delirium remains ambiguous [15]. A systematic review indicates a lack of evidence substantiating the utilization of haloperidol or second-generation antipsychotics for delirium prophylaxis [16]. Dexmedetomidine also has some therapeutic effect on POD in clinical practice [17], but this comes at the expense of an increased risk of bradycardia and hypotension [18,19]. Thus, an alternative approach is necessitated.

The pathogenesis underlying delirium remains elusive. Neuroinflammation, which can be elicited by physiological stress, anesthetic agents, neurotransmitter imbalances, and other factors, represents a putative etiological pathway. This neuroinflammatory process is primarily incited by surgical trauma and infection, which then elicit a spectrum of immune responses. These responses induce neuronal damage, thereby precipitating delirium [20,21]. Glucocorticoids, renowned for their immunosuppressive properties, play a pivotal role in the therapy and prophylaxis of immune-mediated disorders [13]. Due to concerns over potential confounders that could alter the effects of glucocorticoids on POD [22], cardiac surgeries were excluded. Accordingly, we performed a systematic review and meta-analysis to address the hypothesis that glucocorticoids decrease the incidence and severity of POD in patients undergoing non-cardiac surgeries.

2. Methods

This meta-analysis was reported in strict accordance with the PRISMA [23] statement (Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement) and registered in PROSPERO(CRD42023426836). We used the Grading of the Recommendation Assessment, Development, and Evaluation (GRADE) system to evaluate the quality of evidence [24].

2.1. Search strategy

A systematic literature search was undertaken across PubMed, EMBASE, Web of Science and Cochrane Library databases in May 2023. The language was restricted to English. We updated the search results on June 28, 2024. Search terms included “delirium”, “glucocorticoids”, “Methylprednisolone”, “Dexamethasone”, “Prednisone”, “Hydrocortisone”, “Betamethasone”, and “Beclomethasone”. According to the search strategy, both Medical Subject Headings and Entry terms were used. In addition, the reference lists from retrieved articles were reviewed to identify potentially eligible trials.

2.2. Eligibility criteria

We included studies with the following criteria: (1) randomized controlled trials of elective non-cardiac surgery; (2) Perioperative administration of glucocorticoids encompassing preoperative, intraoperative, and postoperative infusion to safeguard against POD relative to placebo or untreated controls, irrespective of dosage regimen utilized; (3) One of the incidence or severity of POD as a primary or secondary outcome; (4) The language was restricted to English.

2.3. Exclusion criteria

Non-human studies, studies without available data can be extracted, studies devoid of accessible full text or lacking validated delirium assessment instrumentations to assess the incidence of POD.

2.4. Study selection

Two authors (JL and DW) independently screened titles and abstracts to find out relevant studies. If the title or abstract of the study was considered eligible, the full-text was retrieved. If there was a discrepancy between the two authors (JL and DW), it was resolved by discussion with another senior researcher(LPH).

2.5. Data extraction

With a pre-designed table, two authors (JL and DW) independently carried out the data extraction. The disputes were resolved by

the third author (LPH). The demographics and outcome data were extracted. The demographics of included studies embraced author and region, sample size, mean age, type of surgery, duration of surgery, type of anesthesia, intervention, type of glucocorticoid and dosage, control group, POD assessment tool, primary outcome, secondary outcome. Results reported in median (interquartile range) or median (interquartile range [range]) were calculated to mean (standard deviation) using the methods of Luo and Wan et al. [25–27].

The following outcomes were applied for comparison: the incidence and severity of POD, patients receiving antipsychotics drug, length of hospital stay, 30-day postoperative mortality, and postoperative infection. When the evaluation time-points are different, the results with the longest interval are included.

2.6. Risk of bias and quality assessment

Two authors (JL and DW) evaluated the risk of bias of included RCTs using the Cochrane Handbook for Systematic Reviewers (version 5.1.0) RCT risk of bias assessment instruments. Evaluation indicators include: (1) sequence generation (selection bias); (2) allocation concealment (selection bias); (3) blinding of patients and personnel (performance bias); (4) blinding of outcome assessors (detection bias); (5) incomplete outcome data (attrition bias); (6) elective reporting (reporting bias); (7) other bias. Each indicator encompasses three stratified levels: low risk, unclear and high risk. Disagreements were resolved by consulting a third reviewer (LPH).

2.7. Statistical analysis and data synthesis

Statistical analyses were performed with Review Manager 5.4.1 (Cochrane Collaboration, Oxford, UK) and Stata 16.0 (Stata Corp LP, College Station, Texas). Binary outcomes were calculated as relative risk (RR). Effect sizes were calculated as weighted mean difference (WMD) and 95 % confidence interval (95%CI) when the assessment tools for continuous outcomes were the same. In other cases, when different delirium assessment tools are employed, the standard mean difference (SMD) and 95 % confidence intervals (95 % CI) are utilized. Statistical heterogeneity among studies was evaluated using Cochran's Q test and Higgins I^2 statistics. If $I^2 > 50$ % or

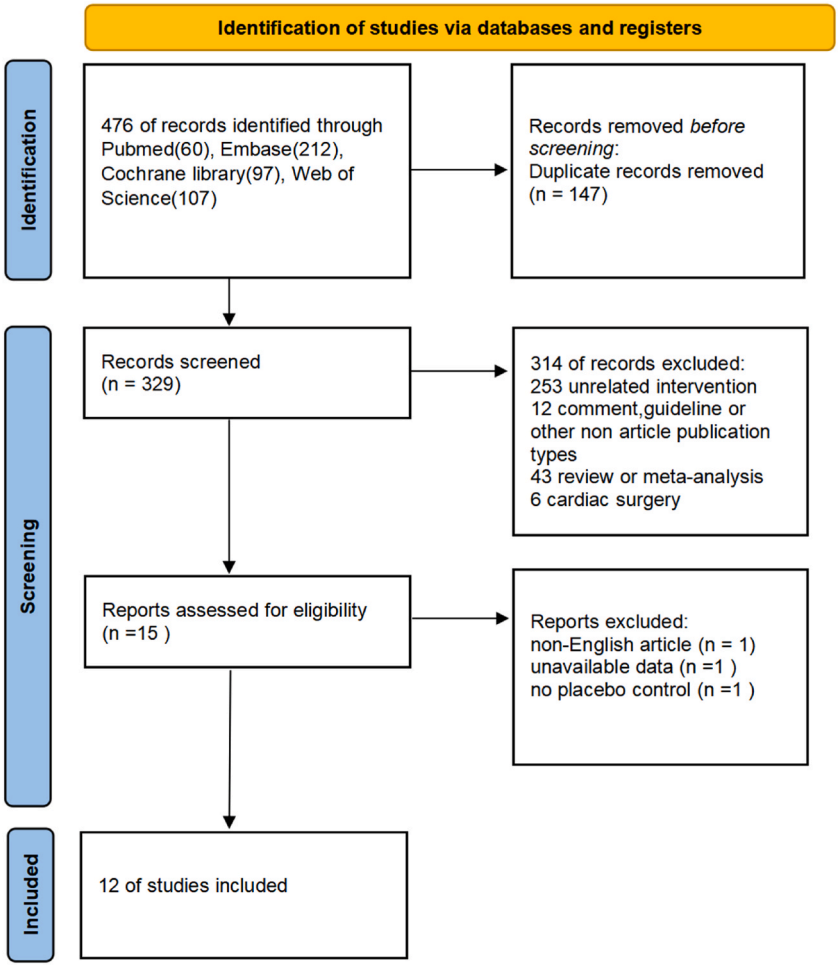


Fig. 1. Study flowchart showing results of selection.

$p < 0.05$ (indicating significant heterogeneity among studies), the data were combined using a random effects model. On the contrary, a fixed effects model was conducted. Sensitivity analysis was also conducted to evaluate the effect of the individual study data. Publication bias was evaluated via funnel plot analysis, with significant bias defined as obvious asymmetry. When $I^2 > 50$ % or $p < 0.05$ (indicating significant heterogeneity among studies), and subgroup analysis was performed to find the resource of heterogeneity. We planned to perform subgroup analysis by age and type of glucocorticoid.

3. Results

3.1. Study selection

According to the search strategy, a total of 476 potentially eligible studies were discerned. Among them, 147 studies were removed due to duplication. Subsequent to screening per titles and abstracts, 329 studies failing to fulfill eligibility criteria were excluded. Ultimately, 15 full-text articles were assessed for eligibility. In total, 12 RCTs could be included in our analysis. The flow of study selection was shown in Fig. 1.

3.2. Study characteristics

The detailed characteristics of these eligible studies are presented in Table 1. Seven of the included studies involved adults [28–34], the others involved children [35–39]. Five of the included studies were hip fracture surgery [28,31–34], two trials were adenotonsillectomy [38,39], the other five studies were gastrointestinal surgery [29], urologic surgery [30], upper gastrointestinal endoscopy (UGIE) [35], dental surgery and cleft palate repair surgery respectively [36,37]. Among the included studies, barring two employing intrathecal delivery [32,33], intravenous administration constituted the route of drug infusion. The outcome measures and assessment instruments were explicitly delineated across all studies.

3.3. Risk of bias in the included studies

Risk of bias and quality assessment was conducted according to Cochrane Handbook for Systematic Reviewers and the result was presented in Fig. 2. According to the primary outcome, three studies had a high risk of bias because of reporting bias [32,35,39].

3.4. Primary outcomes

3.4.1. Incidence of POD

Eleven studies with a total of 946 patients reported the incidence of POD, in which data were reported as the number of participants [28-34,36-39]. The delirium evaluation time-points ranged from 10 min to 5 days across the eleven studies. Hence, the final assessable dataset was utilized for meta-analysis. The results showed that glucocorticoids significantly reduced the incidence of POD among adults and children undergoing non-cardiac surgery contrast with control group (RR:0.50, 95%CI:0.41 to 0.60, $P < 0.00001$, $I^2 = 26$ %) (Fig. 3 A). Sensitivity analysis of the incidence of POD was performed by excluding each study individually and the results were found to be stable (Fig. Supplementary 1). Per the predefined stratification scheme, this finding was consistent in another subgroup analysis between adults (RR:0.47, 95%CI:0.34 to 0.64, $P < 0.00001$, $I^2 = 0$ %) and children (RR:0.53, 95%CI:0.42 to 0.67, $P < 0.00001$, $I^2 = 65$ %) (Fig. 3 Aa). Additionally, subgroup analysis stratified by the type of glucocorticoids demonstrated no significant differences ($P = 0.91$) between methylprednisolone (RR:0.48, 95%CI:0.29 to 0.79, $P = 0.004$, $I^2 = 0$ %) and dexamethasone (RR:0.50, 95%CI:0.40 to 0.62, $P < 0.00001$, $I^2 = 40$ %) (Fig. 3 Ab).

3.4.2. Severity of POD

Eight studies reported the severity of POD [28–31,34,35,37,39], in which the data were reported as cumulative scores on the respective delirium assessment tools. Similarly, the final assessable dataset was utilized for meta-analysis. In the studies conducted by Clemmesen, Xiang, Kluger et al. [28,29,31], data were reported as median (interquartile range) or median (interquartile range [range]). The approaches delineated by Luo and Wan et al. [25–27] were implemented to transform these data into mean (standard deviation) based on a predefined scheme. Meta-analysis results demonstrated that glucocorticoids conferring significant mitigation of delirium severity (RR: −0.67, 95%CI: −1.10 to −0.23, $P = 0.003$, $I^2 = 89$ %) (Fig. 3 B). However, the finding warrant judicious interpretation given the high heterogeneity observed. Despite we conducted two subgroup analyses, the source of heterogeneity remained unidentified (Fig. 3 Ba, Fig. 3 Bb). Additionally, the subgroup analysis based on age classification (RR: −0.65, 95%CI: −1.45 to 0.15, $P = 0.11$, $I^2 = 88$ %) did not demonstrate statistically significant effects of glucocorticoids in mitigating delirium severity of children.

3.5. Secondary outcomes

The patients received antipsychotic drug (RR: 0.91, 95%CI: 0.43 to 1.92, $P = 0.80$, $I^2 = 0$ %) (Fig. 3C) and 0-day postoperative mortality (RR: 0.70, 95%CI: 0.23 to 2.15, $P = 0.54$, $I^2 = 0$ %) (Fig. 3E) were reported in same three studies [28,29,31], results showed there was no significant difference between the glucocorticoids group and control group. In addition, length of hospital stay following surgery [28,29,31,33] (RR: −0.52, 95%CI: −1.41 to 0.36, $P = 0.24$, $I^2 = 0$ %) (Fig. 3D) and postoperative infection [28,29,31,34] (RR:

Table 1
Characteristics of the included studies.

Study ID	Region	No. of participants	Age(y)	Type of surgery	Surgery duration	Type of anesthesia	Intervention	Placebo	Delirium assessment	Primary outcome	Secondary outcomes
Clemmesen 2018	Denmark	MET:59 PLA:58	MET: 79 ± 8 PLA: 81 ± 9	Hip fracture surgery	MET: 69 (51–85) PLA: 74 (49–83)	GA/EA/ SA + EA	125 mg, i.v.	Not reported	CAM- S	Severity of delirium	Incidence of delirium, CAS, VRS, Antipsychotic drug administered, Infection, Length of stay, Completed/ partially completed physiotherapy, Pain on ambulation, 30-day postoperative mortality, 90-day postoperative mortality
Xiang 2022	China	MET:84 PLA:84	MET: 71 (68–74) PLA: 70 (68–73)	Gastrointestinal surgery	MET: 177 (137.5–213.8) PLA: 161 (128.3–210.0)	GA	2 mg/kg, i.v.	NS	CAM-S	Incidence of delirium	Cumulative CAM-S score, Patients received haloperidol, Exhausttime, Infection, Anastomotic leakage, NRS, Length of stay, 30-day mortality
Cho 2022	Korea	DEX: 45 PLA: 45	DEX: 59.6 ± 9.0 PLA: 54.4 ± 15.4	Urologic surgery	DEX: 55.0 (27.5–90.0) PLA: 40.0 (27.5–60.0)	GA	10 mg. i.v.	NS	RSAS	Incidence and severity of CRBD	Incidence and severity of delirium, NRS pain score
Kluger 2021	New Zealand	DEX: 40 PLA: 39	DEX: 81.4 ± 7.2 PLA: 81.4 ± 8.9	Hip fracture surgery	DEX: 165 ± 39 PLA: 150 ± 36	GA/SA/ SA + GA	20 mg, i.v.	NS	4AT + MDAS	Incidence and severity of delirium	Pain at rest, Pain on movement, Length of stay, Mortality 30 days, Mortality 6 months,
Moheimani 2019	Iran	DEX: 49 PLA: 49	DEX: 7.8 ± 2.8 PLA: 7.2 ± 3	UGIE	Not reported	GA	0.1 mg/kg, i.v.	NS	PAED	Incidence of PONV	The incidence of bronchospasm or laryngospasm, Emergence delirium score, Modified Aldrete score, Patient recovery time
Shama 2023	Egypt	DEX: 25 PLA: 25	DEX: 8.52 ± 1.50 PLA: 8.80 ± 1.35	Dental surgery	DEX: 101.60 ± 32.68 PLA: 106.12 ± 29.98	GA	0.15 mg/kg, i.v.	NS	PAED	Incidence of PONV	Incidence of delirium, PAED score, Number and percentage of patients requiring rescue antiemetic, Postoperative pain, Postsurgical complications
Elsonbaty 2016	Egypt	DEX: 30 PLA: 30	DEX:3.7 ± 1.36 PLA:3.6 ± 1.16	Cleft palate repair surgery	Not reported	GA	0.15 mg/kg, i.v.	Blank control	Watcha score	Incidence of delirium	Blood glucose level, Incidence of PONV
Sakic 2015	Croatia	DEX: 17 PLA: 11	DEX: 83 (73–95) PLA: 78 (54–91)	Hip fracture surgery	DEX: 114.54 (65.15–170) PLA: 108.30 (63–175)	SA	8 mg, i.t.	Blank control	CAM	Incidence of delirium, Plasma cortisol level	Severity of pain, Blood glucose level, Recovery
Sajedi 2014	Iran	DEX: 32 PLA: 32	DEX: 4.56 ± 1.2 PLA: 4.71 ± 1.3	Adenotonsillectomy	DEX: 41 ± 7.8 PLA: 42.18 ± 6.4	GA	0.2 mg/kg, i.v.	NS	Richmond agitation sedation score	Incidence of delirium	Incidence of pain and complications, Recovery time, Duration of agitation, Time to agitation appearance, Meperidine consumption, Meperidine consumption, Midazolam consumption,

(*continued on next page*)

Table 1 (*continued*)

Study ID	Region	No. of participants	Age(y)	Type of surgery	Surgery duration	Type of anesthesia	Intervention	Placebo	Delirium assessment	Primary outcome	Secondary outcomes
											Nurse satisfaction score, Time to extubation, Anesthesia time, Surgery time
Khalili 2012	Iran	DEX: 35 PLA: 35	DEX: 4.71 ± 1.33 PLA: 4.66 ± 1.16	Adenotonsillectomy	DEX: 39.86 ± 11.5 PLA: 39.12 ± 11.3	GA	0.2 mg/kg, i.v.	NS	5 point rating scale	Incidence of delirium	Incidence of pain, Mean agitation and pain scores
Sakic2023	Croatia	DEX: 30 PLA: 30	DEX: 81.63 ± 6.94 PLA: 79.69 ± 10.17	Hip fracture surgery	Not reported	SA	8 mg, i.t.	Blank control	CAM	Plasma cortisol level, Incidence of cognitive disturbances	Duration of analgesia, Length of hospital stay, Postoperative pain intensity at first hour postop, as well as the third, fifth and tenth days after surgery
Huang 2023	China	DEX: 80 PLA: 80	DEX: 84.5 (79.0–89.0) PLA: 85.0 (79.8–90.2)	Hip fracture surgery	DEX: 76.0 (62.8–90.5) PLA: 74.0 (60.0–93.5)	GA + SA	10 mg, i.v.	NS	Nu-DESC + MDAS	Incidence and severity of delirium	Infection, Hyperglycemia, Maximum glucose in the frst 3 days postoperatively

Date presented as mean ± SD or median (interquartile range); CAM = Confusion Assessment Method; CAM-S = Confusion Assessment Method—Severity; CAS = Cumulated Ambulation Score; DEX = dexamethasone; EA = epidural anesthesia; GA = general anesthesia; i.v. = intravenous injection; i.t. = intrathecal injection; MET = methylprednisolone; MDAS = Memorial Delirium Assessment Scale; Nu-DESC = Nursing Delirium Screening Scale; NS = normal saline; NRS = numerical rating scale; PLA = placebo; PONV = postoperative nausea and vomiting; PAED = Pediatric Anesthesia Emergence Delirium; RSAS = Riker Sedation-Agitation Scale; RASS = Richmond Agitation Sedation Scale; SA = spinal anesthesia; UGIE = upper gastrointestinal endoscopy; VRS = verbal rating scale; 4AT = arousal, attention, abbreviated Mental Test.

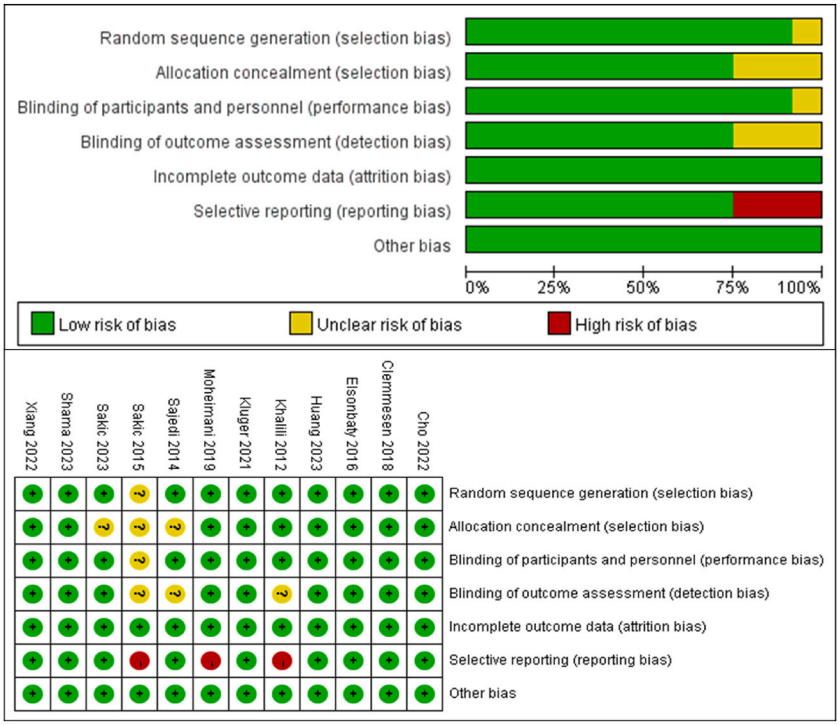


Fig. 2. Risk of bias assessment for each included study per the Cochrane risk of bias framework.

0.87, 95%CI: 0.58 to 1.30, P = 0.50, I^2 = 33 %) (Fig. 3F) were documented in four studies, again not showing statistically significant differences with meta-analyses results. We should interpret the conclusion of postoperative infection carefully because of the heterogeneity. However, additional meta-analyses were precluded by the paucity of data.

3.6. Publication bias

There was no significant publication bias examined by ocular-estimation of funnel plot (Fig. Supplementary 2) for the effects of glucocorticoids administration on POD.

3.7. Level of certainty for outcomes (GRADE)

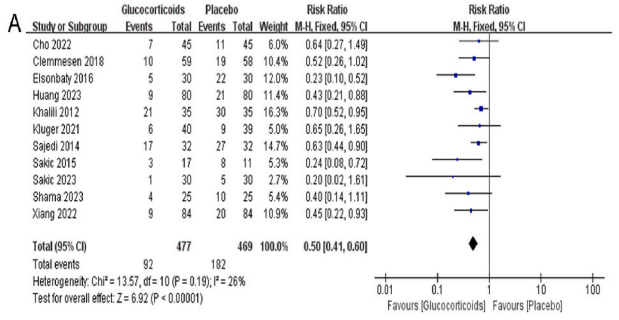
Employing the GRADE system, the certainty of evidence for main outcomes was appraised, exhibiting level of certainty as delineated in Table 2.

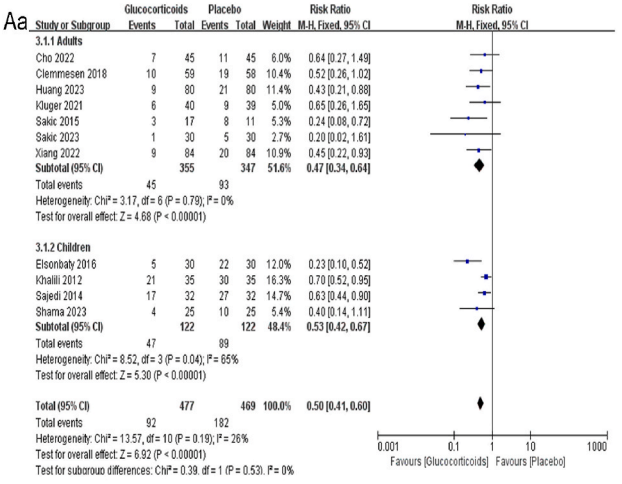
4. Discussion

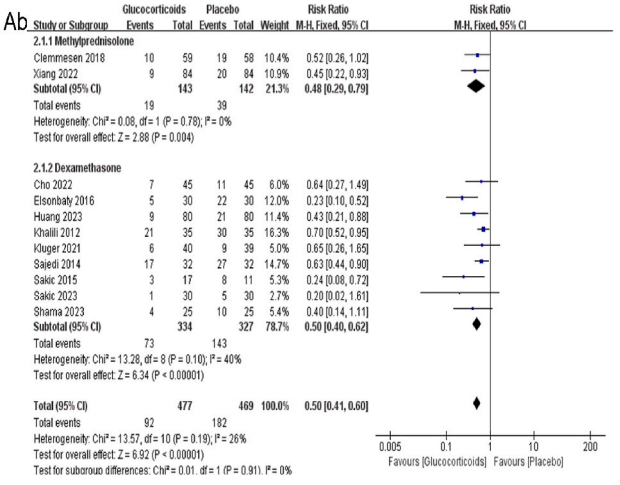
This systematic review and meta-analysis suggested that glucocorticoids reduce the incidence of POD among both adults and children after non-cardiac surgery, a finding consistent across two subgroup analyses. Moreover, glucocorticoid infusion was associated with a reduction in the severity after the onset of delirium. However, no significant difference was observed between groups in patients receiving antipsychotic drugs, in the length of hospital stay, in 30-day postoperative mortality, or in postoperative infection rates. According to the GRADE framework, the certainty of the evidence varied from low to high.

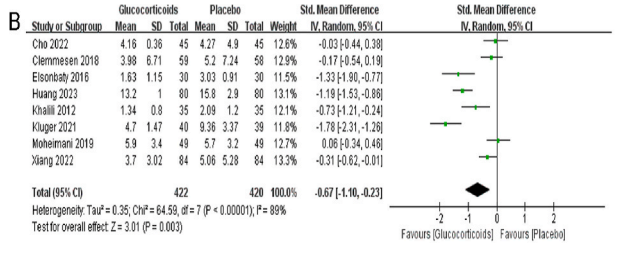
Although the pathogenesis of delirium is unknown, studies have shown that patients' chronological age, preoperative cognitive function, anesthetic dosage, neuro-inflammation, cardiopulmonary bypass, temperature management, postoperative pain, duration of surgery, and other factors are associated with the incidence of POD [22,40–44]. Neuroinflammation is pivotal in the initiation of delirium, and systemic injury can lead to elevated levels of the pro-inflammatory cytokine IL-1β within regions previously affected in the central nervous system [20,21]. Preoperative glucocorticoids have been used across various surgical contexts to mitigate the harmful effects of inflammation caused by surgical trauma and anesthetic exposure [45]. Multiple studies have demonstrated that preoperative glucocorticoid treatment reduces peripheral inflammatory markers in hepatic resection [46,47]. Based on these findings, it seems plausible that glucocorticoids may offer preventative or therapeutic benefits against delirium.

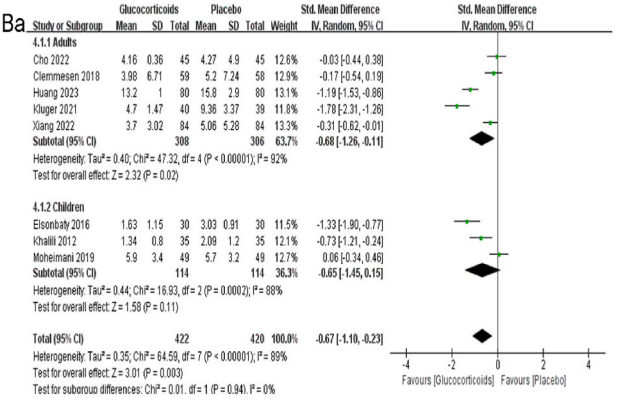
There were three similar meta-analyses [48–50] which drew the opposite conclusion versus this review. Our meta-analysis differs from the aforementioned three studies in that they all included patients undergoing cardiac surgery while omitting pediatric patients. On the one hand, potential reasons underlying the discrepant results may relate to heightened delirium incidence following cardiac

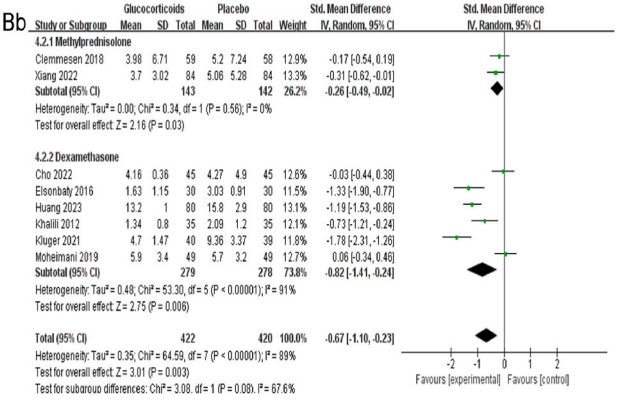


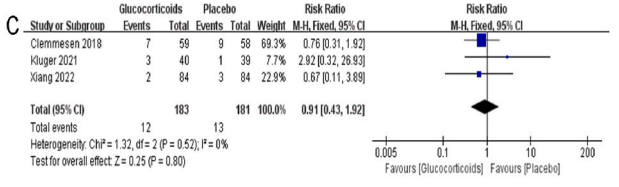


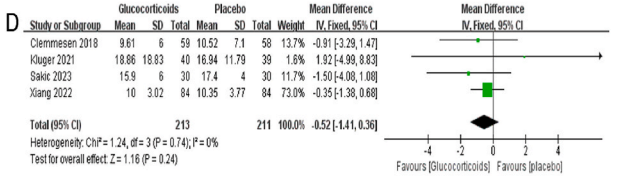


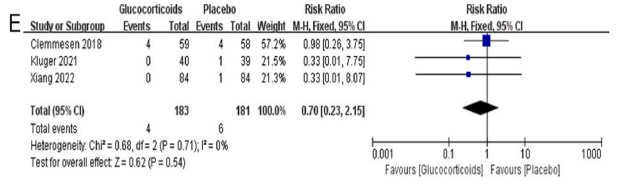












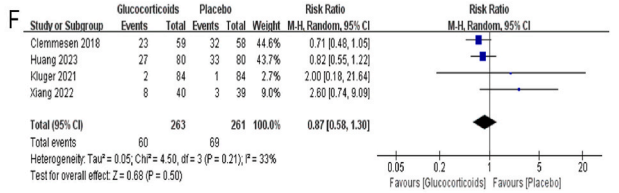


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Fig. 3. A: Forest plot of the incidence of POD; Aa, Ab: Subgroup analysis of the incidence of POD stratified by age classification and the type of glucocorticoids; B: Forest plot of the severity of POD; Ba, Bb: Subgroup analysis of the severity of POD stratified by age classification and the type of glucocorticoids; C: Forest plot of patients received antipsychotic drug; D: Forest plot of length of hospital stay; E: Forest plot of 30-day postoperative mortality; F: Forest plot of postoperative infection.

Table 2
GRADE evidence for outcomes.

Outcomes	No of studies	No of patients	Quality assessment					Quality
			Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	
Incidence of delirium	11	946	Not serious	Not serious	Not serious	Not serious	Not serious	High
Cumulative score	8	842	Not serious	Serious[a]	Not serious	Serious[c]	Not serious	Low
Patients received antipsychotic drug	3	364	Not serious	Not serious	Not serious	Serious[d]	Not serious	Moderate
Length of hospital stay	4	424	Not serious	Not serious	Not serious	Serious[c]	Not serious	Moderate
30-day postoperative mortality	3	364	Not serious	Not serious	Serious[b]	Serious[d,e]	Not serious	Low
Infection	4	524	Not serious	Serious[a]	Not serious	Serious	Not serious	Moderate

[a] Inconsistency due to significant statistical heterogeneity.
[b] Potential confounding by the underlying pathology and surgical modality cannot be excluded.
[c] We used the median (interquartile range) or median (interquartile range [range]) to approach the means (SD), which might decrease confidence in the estimate and the 95 % CI.
[d] The quality was rated for imprecision due to total sample size is less than 400.
[e] The quality was rated for imprecision due to the wide range of 95 % confidence intervals.

versus non-cardiac surgery, attributable to cardiopulmonary bypass, specialized anesthetic regimens, augmented drug administration, prolonged operative duration, extensive surgical insult in the former and so on, thus underestimating the effects of glucocorticoids on postoperative delirium. In a study by Hovens et al. [51], both cardiac and abdominal surgery induced changes in hippocampal BDNF signaling in rats, while increased plasma and NGAL (neutrophil gelatinase associated lipocalin) activity in the hypothalamic paraventricular nucleus and microglia activity in the hippocampus and prefrontal cortex after cardiac surgery, but not after abdominal surgery. These results suggest that cardiac surgery has more extensive and complex effects on the brain than non-cardiac surgery.

On the other hand, although advanced age constituting a salient POD risk factor [52,53], the susceptibility of delirium is not confined to elderly individuals, but contingent on the precipitating risk factors across all age groups [52]. Moreover, pediatric and adult patients exhibited a similar spectrum of delirium symptoms. The onset of delirium was rapid in both groups, and they presented with fluctuating symptoms, including attention and consciousness disorders, cognitive impairments, sleep-wake cycle disruptions, neuromotor abnormalities, and emotional disturbances. The gold standard for the diagnosis of delirium in children and adults is based on the criteria set forth in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) issued by the American Psychiatric Association, which is applicable to both adult and pediatric patients [21,54]. Additionally, ED in pediatric patients represents an early stage of POD within the spectrum of delirium progression [6,7]. As such, it is not unexpected that both conditions are incorporated in the analysis when considering the development of delirium. The insufficient number of included studies may have affected the outcome of glucocorticoids on POD in patients undergoing non-cardiac surgery. Our subgroup analysis showed that perioperative glucocorticoid infusion was equally effective in controlling POD in non-adult patients (children). Nevertheless, the results require judicious interpretation given the possibility of small study bias introduced by the cumulative sample size of 244 patients across the 4 studies. Besides, statistical analysis exhibited significant heterogeneity within the children subgroup. Sequential exclusion of individual studies revealed markedly reduced heterogeneity ($I^2 = 0$ %) upon ruling out the study of Elsonbaty et al. [37]. Potential reason includes variances in delirium assessment instruments, where the Watcha scale is a simpler tool and may confer higher sensitivity compared to the PAED scale [55], with possible preclusion of additional in-depth analyses due to insufficient incorporated data.

Based on our approach, we included studies with "incidence or severity of POD" as the endpoint. However, the studies we included were not able to make recommendations on the optimal dose of glucocorticoids to prevent delirium. Notably, while perioperative glucocorticoid administration could enhance patient outcomes by attenuating inflammation, potential adverse sequela including osteoporosis, osteonecrosis, cardiovascular disease and so on must also be considered [56]. Thus, a reliable optimal dosage remains unresolved, pending further research.

To the best of our knowledge, this is the first meta-analysis of the effects of glucocorticoids on the severity of POD. The results of meta-analysis showed that there was a statistically significant difference ($P = 0.003$) on reducing the severity of POD in adults undergoing non-cardiac surgery. Regrettably, the results revealed a significant degree of heterogeneity. The conducted subgroup analyses confirmed that neither age nor hormone type contributed to the observed heterogeneity. Considering the diverse patient populations,

surgical procedures, and glucocorticoid dosages, clinical heterogeneity is likely the underlying reason for the observed variation. However, the scarcity of available data hinders more extensive investigations into potential sources of heterogeneity. A low quality of evidence was rated by GRADE precluding definitive recommendations. The cause of the low quality of evidence as shown in Table 2. Our subgroup analysis based on age classification suggested that perioperative administration of glucocorticoids did not reduce the severity of POD in children. Although, the children subgroup analysis is comprised merely of three studies with limited sample sizes, and the results exhibited substantial heterogeneity in the results. Furthermore, it is unreasonable to conclude that glucocorticoids are associated with an increased risk of infection [56] based on the results of the meta-analysis, as confirmed by another meta-analysis encompassing 37 studies substantiates this notion [57]. In addition, we investigated patients who received antipsychotic drug, length of hospital stay, 30-day postoperative mortality. Less data was included as secondary outcomes, which decreased the quality of evidence and required dedicated research to uncover more valuable information.

4.1. Limitations

Initially, while neuroinflammation represents a potential etiological factor in delirium episodes, insufficient data currently precludes a comprehensive analysis of the correlation between delirium incidence and inflammatory mediators like cortisol. Future research endeavors should prioritize addressing this gap in understanding. Besides, there are several potential limitations in this study that parallel those encountered in other meta-analyses of a similar nature. First, the sample sizes of all included studies were small, which generally implies a risk of small study effect bias; the quality of evidence for secondary outcomes is therefore downgraded. Second, not all endpoints correlated with perioperative glucocorticoid administration were included, with preferential inclusion of commonly documented occurrences as outcomes, potentially predisposing to omission of significant adverse sequelae and clinical endpoints. Third, time-points of delirium evaluation ranged from 10 min to 5 days postoperatively across the included studies, with variability in assessment instrumentation. Since data from the final evaluable time-point was synthesized, timing disparities could impact the observed incidence of postoperative delirium (POD). Furthermore, variability in sensitivity among assessment tools may additionally influence the measurement of the incidence of POD. Fourth, it is very difficult to perform a subgroup analysis based on the dose of glucocorticoids administration due to a few included studies had identical dosing regimens. To prevent POD after non-cardiac surgery, future trials should adopt a standardized protocol. Additionally, the included studies involved emergence agitation (EA), which was also referred to as emergence delirium (ED). The terms EA and ED have been used interchangeably in several studies [58, 59]. Moreover, the same assessment tools (e.g., the Riker Sedation-Agitation Scale or the Richmond Agitation-Sedation Scale) have been used for both EA and ED.

5. Conclusion

In this meta-analysis of 12 RCTs, glucocorticoids demonstrated significant benefits in reducing the incidence of POD among adults and children after non-cardiac surgery. In addition, glucocorticoids may be associated with attenuating the severity of POD in adults after non-cardiac surgery, which needs to be validated in clinical studies with larger samples using recognized evaluation criteria.

CRediT authorship contribution statement

Zicen Li: Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation. **Jing Lu:** Supervision, Formal analysis. **Di Wang:** Methodology, Formal analysis. **Liping Han:** Writing – review & editing, Project administration, Methodology, Conceptualization.

Ethical statement

The research was conducted according to ethical standards.

Data availability statement

As this research is a meta-analysis of previous data, no new data were generated.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e40914.

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