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META-ANALYSIS

Zhou et al: Remimazolam vs propofol for POD

Remimazolam vs propofol for postoperative delirium in adults undergoing general anesthesia: A meta-analysis

Huijin Zhou[1*], Jing Zhang[2], and Chunyan Du[1]

[1]Department of Anesthesiology, Beijing University of Chinese Medicine Third Affiliated Hospital, Beijing, China;

[2]Department of Pharmacy, Beijing Huilongguan Hospital, Beijing, China.

*Correspondence to Huijin Zhou: huijinzhou_thbcm@hotmail.com

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ABSTRACT

Postoperative delirium (POD) is a prevalent and serious complication in adults undergoing surgery with general anesthesia. Remimazolam, an innovative ultra-short-acting benzodiazepine, has been identified as a potential alternative to propofol due to its advantageous pharmacological properties. However, its impact on POD remains uncertain. This study conducted a systematic review and meta-analysis following PRISMA guidelines. A comprehensive search of the PubMed, Embase, Cochrane Library, Web of Science, CNKI, and Wanfang databases was performed up to March 29, 2025. Randomized controlled trials (RCTs) comparing remimazolam and propofol in adult surgical patients under general anesthesia, specifically reporting on POD incidence, were included. A random-effects model was utilized to calculate pooled odds ratios (ORs) with 95% confidence intervals (CIs), accounting for heterogeneity. The analysis included seventeen RCTs encompassing 3,133 patients. Overall, remimazolam significantly decreased the risk of POD compared to propofol (OR: 0.71, 95% CI: 0.52–0.97, $p = 0.03$; $I^2 = 36\%$). Sensitivity analyses, which involved excluding one study at a time, yielded consistent results, reinforcing the robustness of the findings. Subgroup analyses revealed uniform effects across different study designs (single-blind vs. double-blind; OR: 0.73 vs. 0.64; $p = 0.71$) and age groups (adults vs. elderly; OR: 0.64 vs. 0.72; $p = 0.79$). A trend toward greater benefit was observed in studies with longer follow-up periods (7 days: OR: 0.42) and in those employing the CAM or CAM-ICU for POD diagnosis, although subgroup differences were not statistically significant. In conclusion, remimazolam is associated with a significantly reduced risk of POD compared to propofol in adults undergoing general anesthesia.

Keywords: Remimazolam, propofol, postoperative delirium, incidence, general anesthesia.

INTRODUCTION

Postoperative delirium (POD) is an acute and fluctuating disturbance in attention, awareness, and cognition that commonly occurs within days after surgery, particularly in elderly or high-risk patients [1, 2]. POD affects approximately 10–50% of adults undergoing major surgery under general anesthesia, with even higher rates reported in older populations and those with comorbidities or preexisting cognitive impairment [3]. The development of POD has been independently associated with numerous adverse outcomes, including prolonged hospitalization, increased risk of postoperative complications, long-term cognitive decline, and elevated mortality [4, 5]. Identifying modifiable perioperative risk factors and preventive strategies is therefore of critical importance for improving patient outcomes [6].

Among the many contributors to POD, anesthetic agents have attracted growing attention due to their direct influence on central nervous system function [7, 8]. In line with the growing interest in pharmacologic approaches to improve postoperative neurocognitive outcomes, a recent study reported that parecoxib administration was associated with improved postoperative cognitive function in elderly patients [9]. Of note, remimazolam is a novel ultra-short-acting benzodiazepine that acts on gamma-aminobutyric acid type A (GABA_A) receptors, offering rapid onset and recovery with minimal accumulation [10]. It is characterized by organ-independent metabolism through tissue esterases, stable hemodynamic effects, and a low risk of respiratory depression [11]. These pharmacological properties make remimazolam a promising alternative to propofol for general anesthesia, especially in vulnerable populations [12, 13]. Moreover, remimazolam may potentially reduce the risk of POD by avoiding deep sedation, preserving circadian rhythms, and exerting less suppression on cortical arousal and melatonin regulation—though the precise mechanisms remain to be fully elucidated [14].

Several randomized controlled trials (RCTs) have recently compared remimazolam and propofol for general anesthesia, with a subset reporting on the incidence of POD [15-31]. While some trials suggest a lower risk of POD with remimazolam [18, 24, 26], most studies report comparable effects [15-17, 19-23, 25, 27-31], and their findings vary depending on patient age, surgical type, anesthetic protocol, and duration of follow-up. Although a few meta-analyses have explored this topic [14, 32, 33], they have been limited by the small number of included RCTs. In light of the

growing body of evidence, the present study aimed to perform an updated and comprehensive meta-analysis of RCTs to evaluate the effect of remimazolam versus propofol on the incidence of POD in adult patients undergoing surgery under general anesthesia.

MATERIAL AND METHODS

During the design and implementation of this study, we followed the guidelines set forth by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [34, 35] and the Cochrane Handbook [36]. The protocol of the meta-analysis has been registered at PROSPERO with the identifier CRD420251055246.

Study inclusion and exclusion criteria

This meta-analysis included studies that met the inclusion criteria specified in the PICOS principle.

P (patients): Adult patients (aged 18 years or older) receiving surgeries under general anesthesia;

I (intervention): Administration of remimazolam as the primary induction and/or maintenance agent for general anesthesia;

C (control): Administration of propofol as the primary induction and/or maintenance agent for general anesthesia;

O (outcome): Incidence of POD, with adequate description of diagnostic criteria and tools.

S (study design): RCTs with parallel groups.

Excluded from the analysis were reviews, editorials, preclinical studies, studies not designed as RCTs, studies involving pediatric patients, patients that did not receive surgeries, or patients not under general anesthesia, studies that did not compare remimazolam to propofol, studies that did not report the outcome of POD, or did not describe the diagnostic criteria or tools for POD. If studies with overlapped patients were retrieved, the one with the largest sample size was analyzed in the meta-analysis.

Database search

The Medline (PubMed), Embase (Ovid), CENTER (Cochrane Library), Web of Science, Wanfang, and CNKI (China National Knowledge Infrastructure) databases were searched using the combination of the following terms: (1) "remimazolam" OR "CNS 7056" OR "ONO 2745"; (2) "propofol" OR "ICI 35868" OR "disoprofol"; (3) "delirium" OR "confusion" OR "disorientation" OR "cognitive" OR "cognition"; and (4) "random" OR "randomized" OR "randomised" OR "RCT" OR "RCTs" OR "randomly". Only studies that included human subjects and were published as full-length articles in peer-reviewed journals were considered. Grey literature and conference abstracts were not included because these literatures are generally not peer-reviewed and may lack sufficient methodological detail, which could affect the reliability and reproducibility of the results. Additionally, references to related reviews and original articles were screened as part of the final database search. The final database search was conducted on March 29, 2025. The detailed search strategy for each database is shown in **Supplemental File 1**.

Data collection and quality evaluation

Two authors conducted independent database searches, data collection, and quality assessment. In the event of disagreements, discussions were held with the corresponding author. A standardized electronic data extraction form was used to collect information on study characteristics, patient demographics, interventions, comparators, diagnostic criteria for POD, and outcomes. Inter-reviewer agreement was high, with κ values of 0.88 for data extraction and 0.84 for risk of bias assessment. For studies with overlapping cohorts or duplicate publications, only the dataset with the largest sample size was included. The data collected encompassed various aspects, including overall study information (such as first author, publication year, and study country), study design (double-blind or single blind), patient and surgery characteristics (number of patients, mean age, sex, American Society of Anesthesiologists [ASA] class, and type of surgery), details of intervention with remimazolam and controls with propofol, follow-up durations, and tools for the diagnosis of POD. The quality of the included RCTs was assessed using the Cochrane Risk of Bias Tool [36]. This tool evaluated various aspects such as random-sequence generation, allocation concealment, blinding of participants and outcome assessment, addressing incomplete outcome data, selective reporting, and other sources of bias. In

addition, two reviewers independently assessed the certainty of evidence using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) system, which includes risk of bias, inconsistency, indirectness, imprecision and publication bias [37]. The certainty of evidence was classified as very low, low, moderate or high. Disagreements were resolved by discussion with the corresponding author.

Statistical analysis

The influence of remimazolam on the incidence of POD was summarized as odds ratio (OR) and corresponding 95% confidence interval (CI) [36]. Heterogeneity was assessed using the Cochrane Q test [36]. The I^2 statistic was also calculated, with $I^2 <$ 25%, 25~75%, and > 75% indicating mild, moderate, and substantial heterogeneity, respectively [38]. A random-effects model was used to pool the results, applying the generic inverse variance method in RevMan with the DerSimonian–Laird estimator for between-study variance, as this approach incorporates the potential influence of heterogeneity [36]. For studies with zero-event arm, in accordance with Cochrane guidance [36], we applied a standard continuity correction of 0.5 to both arms of that study to enable calculation of OR. Sensitivity analyses by excluding one study at a time was used to evaluate the robustness of the finding [36]. In addition, subgroup analysis was also conducted to evaluate the study characteristics on the outcomes, such as study design (single-blind versus double-blind), patient age group (adults versus aged only [60 years or older]), follow-up durations, and tools for the diagnosis of POD. An evaluation of the publication bias was conducted via a visual inspection using funnel plots and by performing Egger's regression asymmetry test [39]. A $p <$ 0.05 was considered statistically significant. Statistical analyses were conducted using RevMan (Version 5.1; Cochrane, Oxford, UK) and Stata software (version 17.0; Stata Corporation, College Station, TX, USA).

RESULTS

Literature search

Figure 1 depicts the flowchart that outlines the process of database searching and study identification, ultimately leading to the selection of studies for inclusion. Initially, a total of 344 articles were obtained through the database search, which was subsequently reduced to 236 after eliminating duplicate records. Subsequently, 200

articles were excluded based on an evaluation of their titles and abstracts, primarily due to their lack of relevance to the objective of the present meta-analysis. Then, 19 out of the remaining 36 articles were excluded after full-text reviews for reasons outlined in **Figure 1**.Ultimately, 17 RCTs [15-31] were deemed suitable for quantitative analysis.

Study characteristics and data quality

An overview of the included studies can be found in **Table 1**. A total of 17 RCTs [15-31] published between 2022 and 2025 were included in this meta-analysis. The studies were conducted in China, Japan, and multiple European countries, enrolling a total of 3,133 adult patients undergoing various surgeries under general anesthesia. The surgeries performed included orthopedic procedures, urologic surgeries, rigid bronchoscopy, cerebral endovascular procedures, cardiac valve surgery, and neurovascular interventions etc.. The mean ages of the included patients ranged from 47.7 to 83.7 years, and the proportion of male patients varied between 35.0% and 90.0%. All included trials compared remimazolam and propofol as anesthetic agents during surgery and reported on the incidence of POD. The duration of POD observation ranged from 1 to 7 days, with various diagnostic tools used, including Confusion Assessment Method (CAM), Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), 3-Minute Diagnostic Interview for CAM-defined Delirium (3D-CAM), and Nursing Delirium Screening Scale (Nu-DESC). In terms of quality evaluation using the Cochrane Risk of Bias Tool, all the 17 studies were judged to be at low risk of bias for random sequence generation and outcome data completeness, while nine studies [15-17, 20, 21, 25, 27, 30, 31] were at low risk of allocation concealment. However, blinding of participants and personnel was considered high risk in 10 studies [16-18, 20-23, 26, 28, 31], reflecting the practical challenges of maintaining blinding in anesthesia trials. Blinding of outcome assessment was adequate in most studies, though three were marked as unclear in this domain [19, 20, 29]. Overall, there was no indication of selective outcome reporting or other major threats to validity in any study.

Comparing the influence of remimazolam versus propofol on POD

Overall, 1,651 patients were allocated to the intervention group of remimazolam, and 1,482 to the control group. A total of 423 (13.5%) patients were diagnosed as POD,

with 186 (11.3%) patients in the intervention group, and 237 (16.0%) in the control group. The pooled results of the 17 RCTs [15-31] showed that compared to propofol, remimazolam significantly reduced the risk of POD in adult patients receiving surgeries under general anesthesia (OR: 0.71, 95% CI: 0.52 to 0.97, p = 0.03; **Figure 2**) with moderate heterogeneity (I^2 = 36%). This represents an absolute risk reduction of 4.7%, corresponding to a number needed to treat of approximately 21, indicating that for every 21 patients receiving remimazolam instead of propofol, one case of POD could potentially be prevented. Summarized certainty of evidence using the GRADE system is shown in **Table 3**. We downgraded evidence by one level for the possible risk of bias due to blinding limitations in some included studies. We judged the evidence to be of moderate certainty. Sensitivity analyses by excluding one study at a time showed consistent results (OR: 0.66 to 0.76, p all < 0.05). Subsequent subgroup analyses showed similar results in single-blind and double-blind studies (OR: 0.73 versus 0.64, p for subgroup difference = 0.71; **Figure 3A**). When restricted to the five double-blind studies with adequate blinding of both participants/personnel and outcome assessment, the association between remimazolam and reduced POD risk remained in the same direction but was no longer statistically significant (OR: 0.64, 95% CI: 0.38 to 1.09, p = 0.10; **Figure 3A**), likely due to reduced statistical power from the smaller sample size. The results were no significant different between studies involving overall adult patients and older patients only (OR: 0.64 versus 0.72, p for subgroup difference = 0.79; **Figure 3B**). Interestingly, remimazolam seemed to be associated with a lower risk of POD in studies with follow-up duration of 7 days, as compared to those of 3 or 1 day (OR: 0.42 versus 0.85 and 0.90), although the difference between the subgroup is not significant (p = 0.10; **Figure 4A**). In addition, remimazolam was associated with a lower risk of POD in studies with CAM, 3D-CAM/CAM-ICU, but not in studies with Nu-DESC (OR: 0.51 and 0.79 versus 1.97). However, the difference between the subgroup is not significant either (p = 0.19; **Figure 4B**).

Publication bias

The funnel plots for the meta-analysis comparing the influence of remimazolam versus propofol on POD is shown in **Figure 5**. These plots are symmetrical on visual inspection, suggesting a low risk of publication bias. Egger's regression test also indicated a low risk of publication bias (p = 0.74).

DISCUSSION

This comprehensive meta-analysis of 17 RCTs involving 3,133 adult patients demonstrated that remimazolam was associated with a significantly lower risk of POD compared to propofol in surgeries under general anesthesia. Sensitivity analyses confirmed the robustness of this result, while subgroup analyses showed consistent effects across study design (single- vs. double-blind), age groups (adults vs. elderly), and POD diagnostic tools. Although not statistically significant, a trend toward greater benefit was observed in studies with longer follow-up and those using validated tools like CAM or CAM-ICU.

The beneficial effects of remimazolam on reducing postoperative delirium may be attributed to its distinct pharmacological and molecular characteristics. Remimazolam is a novel, ultra-short-acting benzodiazepine that acts as a γ-aminobutyric acid type A (GABA_A) receptor agonist, similar to midazolam [40]. However, unlike traditional benzodiazepines, remimazolam is rapidly metabolized by tissue esterases into an inactive metabolite, enabling quick onset, short duration of action, and minimal drug accumulation, even with prolonged use [11, 41]. This property contributes to its smooth induction and rapid recovery profile, with reduced risk of oversedation or delayed emergence from anesthesia [42]. In contrast, propofol, although widely used for its rapid induction and recovery, can cause significant cardiovascular depression, including hypotension and bradycardia, especially in elderly or hemodynamically unstable patients [43]. Propofol is also known to induce deep sedation and suppress the natural sleep-wake cycle, potentially interfering with circadian regulation [44]. At the molecular level, propofol has been shown to interact with not only GABA_A receptors but also muscarinic acetylcholine receptors, whose dysfunction is implicated in the development of delirium [45]. Furthermore, propofol has been associated with reduced melatonin secretion and disruption of the sleep-wake rhythm, both of which are critical to cognitive stability postoperatively [46, 47]. By contrast, remimazolam is thought to preserve sleep architecture and maintain more physiologic arousal patterns [48]. Its gentle modulation of cortical activity and avoidance of deep sedation may help maintain neural network integrity and cognitive function [49, 50]. These features, along with its favorable hemodynamic profile, may contribute to its protective effect against POD, particularly in vulnerable populations such as the elderly and those with preexisting cognitive risk factors [51].

Our subgroup analyses support the robustness of the overall findings. The effect of remimazolam on reducing POD remained consistent in both single- and double-blind studies, as well as across adult and elderly populations. Notably, studies with longer follow-up durations (≥ 7 days) showed a stronger protective association, suggesting that the benefits of remimazolam may be more apparent when POD is assessed beyond the early postoperative period. Additionally, studies using CAM or CAM-ICU—tools with high specificity for POD—showed a protective association, whereas the small Nu-DESC subgroup yielded a point estimate above unity (OR 1.97) with a wide confidence interval, suggesting possible harm but with considerable imprecision. This divergence may reflect measurement characteristics, as Nu-DESC is a brief nursing screening tool that can be less specific than CAM-based instruments, and may also relate to differences in case mix or surgical context in the Nu-DESC trials [52].

Compared to prior meta-analyses, the current study offers several strengths. First, it includes a larger number of RCTs and a broader patient population. Second, strict inclusion criteria were applied—focusing solely on adult patients undergoing general anesthesia and using validated tools for POD diagnosis. Third, multiple sensitivity and subgroup analyses were conducted to assess the consistency of results across different study characteristics. In contrast, previous meta-analyses included fewer studies (6~11) [14, 32, 33], some with mixed anesthesia types or procedural sedation [14, 32], and reported non-significant associations between remimazolam and POD [14, 32, 33]. The present meta-analysis, by focusing exclusively on intraoperative use during general anesthesia, addresses these limitations and provides a more refined estimate of effect.

Nonetheless, several limitations should be acknowledged. Moderate heterogeneity was observed ($I^2 = 36\%$), possibly due to variations in surgical types, patient characteristics, and dosing regimens of remimazolam and propofol. Although most studies involved elderly or high-risk patients, demographic and clinical variability might affect POD risk. Additionally, the diagnostic criteria and follow-up durations for POD varied across studies, ranging from 1 to 7 days postoperatively, potentially leading to underestimation or misclassification. Most studies were conducted in China, which may limit generalizability to broader international populations. In addition, the predominance of Asian participants, particularly Chinese patients, means that potential ethnic variations in pharmacogenetics, as well as differences in perioperative

care protocols and anesthetic practice patterns, may influence both baseline POD risk and the comparative effects of remimazolam and propofol. Caution is therefore warranted when extrapolating these findings to non-Asian populations. Another consideration is the variation in induction and maintenance doses of remimazolam and propofol across the included trials. Such differences may influence arousal depth and thereby affect POD risk. However, inconsistent reporting and the absence of complete dose data in several studies precluded calculation of pooled mean doses. This heterogeneity in dosing should be taken into account when interpreting the results and applying them in clinical practice. Lastly, as this meta-analysis is based on study-level rather than individual patient-level data, residual confounding factors could not be fully accounted for.

Clinically, these findings support the consideration of remimazolam as a safer anesthetic alternative to propofol in patients at risk of POD, particularly the elderly or those undergoing high-risk surgeries. Its favorable hemodynamic profile and reduced neurocognitive side effects may enhance recovery and reduce postoperative complications [53]. Future studies should investigate dose-response relationships, the impact of remimazolam in specific surgical populations (e.g., cardiac, neurosurgical), and its comparative effects against other anesthetics like dexmedetomidine [53]. Moreover, large-scale, multicenter RCTs from diverse healthcare settings are warranted to validate these findings.

CONCLUSION

In conclusion, this meta-analysis suggests that remimazolam is associated with a significantly lower incidence of POD compared to propofol in adult patients undergoing general anesthesia. With its pharmacological advantages and consistent performance across studies, remimazolam may represent a promising strategy for delirium prevention in perioperative care.

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TABLES AND FIGURES WITH LEGENDS

Table 1. Characteristics of the included randomized controlled trials (RCTs)

Study	Country	Design	Patients and surgery	No. of patients	Mean age (years)	Men (%)	ASA class	Intervention (remimazolam)	Control (propofol)	Follow-up duration (days)	Diagnosis of POD
Mao 2022	China	R, DB	Adult patients undergoing elective urologic surgery under general anesthesia	128	51.3	67.2	I-III	Induction: 0.2–0.3 mg/kg remimazolam + 0.3–0.5 μg/kg sufentanil; Maintenance: 1–2 mg/kg/h remimazolam + 0.2–0.3 μg/kg/min remifentanil	Induction: 2–3 mg/kg propofol + 0.3–0.5 μg/kg sufentanil; Maintenance: 4–10 mg/kg/h propofol + 0.2–0.3 μg/kg/min remifentanil	1	Nu-DESC
Pan 2023	China	R, SB	Adult patients undergoing rigid	30	60.6	90	II-IV	Induction: Remimazolam 0.4 mg/kg IV bolus;	Induction: Propofol 1.5 mg/kg IV bolus; Maintenance:	1	Nu-DESC

			bronchoscopy procedures (tumor resection or stent placement)					Maintenance: Remimazolam 1 mg/kg/h + remifentanil 6–8 μg/kg/h	Propofol 4–8 mg/kg/h + remifentanil 6–8 μg/kg/h		
Yang 2023	China	R, SB	Adults ≥60 years receiving orthopedic surgery under general anesthesia	300	68.5	39	I-III	Induction: Remimazolam 0.2–0.3 mg/kg + alfentanil 0.04–0.06 mg/kg; Maintenance: Inhaled desflurane (0.3 MAC) + remimazolam (dose titrated to BIS 40–60)	Induction: Propofol 1.0–1.5 mg/kg + alfentanil 0.04–0.06 mg/kg; Maintenance: Inhaled desflurane (0.3 MAC) + propofol (dose titrated to BIS 40–60)	3	CAM
Fechne	Multipl	R, SB	Adult	365	68	73	III-	Remimazolam	Propofol infusion	1	Nu-DESC

r 2024	e countries in Europe		patients undergoing elective non-cardiac surgery of ≥90 minutes				IV	infusion (mean 1.03 mg/min during surgery), administered from induction to end of surgery; paired with remifentanil	(mean 4.98 mg/kg/h during surgery), administered similarly with remifentanil		
Li 2024a	China	R, DB	Adults ≥80 years undergoing elective surgery	146	81	60.8	I-III	Remimazolam: 0.16 mg/kg (ED90) IV bolus over 30s; Rescue dose: 0.05 mg/kg if BIS > 65	Propofol: 0.916 mg/kg (ED90) IV bolus over 30s; Rescue dose: 0.5 mg/kg if BIS > 65	1	CAM
Duan 2024	China	R, SB	Elderly patients (age 65–90),	106	76.3	46	II-III	Remimazolam: loading dose: 0.05 mg/kg IV over 1 min;	Propofol: loading dose: 0.3–0.5 mg/kg IV over 1 min; Maintenance:	7	CAM

			undergoing hip fracture surgery					Maintenance: 0.1–0.3 mg/kg/h infusion	0.5–3 mg/kg/h infusion		
Kotani 2024	Japan	R, SB	Adults ≥20 years undergoing TAVR under general anesthesia	34	83.7	35	NR	Induction: Remimazolam 12 mg/kg/h via IV continuous infusion + Remifentanil (0.2 μg/kg/min); Maintenance: Remimazolam adjusted per SedLine PSI (25–50)	Induction: Propofol 2.5 μg/mL TCI + remifentanil (0.2 μg/kg/min); Maintenance: TCI with adjustments based on SedLine PSI	1	CAM-ICU
Zhang 2024	China	R, DB	Adults undergoing cerebral endovascul	142	56.3	47.9	I-III	Remimazolam: 0.1 mg/kg IV for induction, 0.3–	Propofol: 1–1.5 mg/kg IV for induction, 4–10 mg/kg/h	3	CAM-ICU

			ar procedures					0.7 mg/kg/h maintenance	maintenance		
Liu 2024a	China	R, SB	Elderly patients (60–80 years), undergoing elective cerebral endovascular surgery under general anesthesia	103	70	46.6	I-III	Remimazolam: Induction: 12 mg/kg/h until loss of consciousness; Maintenance: 1–2 mg/kg/h	Propofol :Induction: 1.5–2 mg/kg; Maintenance: 4–8 mg/kg/h	7	CAM-ICU
Ma 2024	China	R, SB	Elderly patients (65–80 years) undergoing hip fracture surgery	80	66.4	40	I-III	Remimazolam: Induction: 0.2–0.4 mg/kg; Maintenance: 0.3–0.5 mg/kg/h	Propofol: Induction: 1.5–2 mg/kg; Maintenance: 4–8 mg/kg/h	3	CAM

			under general anesthesia								
Zhou 2024	China	R, SB	Frail elderly patients (≥60 years) with hip fractures, undergoing hip surgery under general anesthesia	210	67.9	44	NR	Remimazolam: Induction: 0.15–0.35 mg/kg IV bolus; Maintenance: 0.3–1.0 mg/kg/h infusion; Adjunct: sufentanil 0.4–0.5 μg/kg, cisatracurium 0.2 mg/kg	Propofol: Induction: 1.0–2.5 mg/kg IV bolus; Maintenance: 4–12 mg/kg/h infusion; Same adjunct drugs as intervention	3	3D-CAM
Wang 2024	China	R, DB	Elderly patients (≥65 years) undergoing	160	72.1	47.5	II-III	Remimazolam: 0.3 mg/kg induction + 0.3–0.8	Propofol: 2.0 mg/kg induction + 4–6 mg/kg/h maintenance	7	CAM

			lumbar spine surgery					mg/kg/h maintenance			
Tian 2024	China	R, SB	Adults undergoing neurovascular intervention surgery under general anesthesia	98	52	52	I-III	Remimazolam: 0.15 mg/(kg·h) continuous IV infusion; Adjunct: remifentanil 0.1–0.3 μg/(kg·min)	Propofol :2 mg/kg IV bolus; Adjunct: remifentanil 0.1–0.3 μg/(kg·min)	7	CAM
Liu 2024b	China	R, DB	Elderly patients (≥65 years) undergoing elective laparoscopic radical resection of colon	100	71.5	43	I-III	Remimazolam: Induction: 0.1–0.2 mg/kg; Maintenance: 0.4–1.2 mg/kg/h; Adjunct: sufentanil (0.1–2 μg/kg),	Propofol: Induction: 1–2 mg/kg; Maintenance: 4–10 mg/kg/h; Same adjuncts as intervention group	7	CAM-ICU

			cancer under general anesthesia					cisatracurium (0.2 mg/kg), remifentanil (0.1–0.2 μg/kg/min)			
Li 2024b	China	R, SB	Adults (aged 35–59 years) undergoing various laparoscopic surgeries under general anesthesia	84	47.7	52.4	I-II	Remimazolam: Induction: 1–1.5 mg/kg + rocuronium 0.6 mg/kg + sufentanil 0.2 μg/kg; Maintenance: 0.4–0.8 mg/kg/h + rocuronium + remifentanil (0.05–0.2 μg/kg/min)	Propofol: Induction: 1–1.5 mg/kg + rocuronium 0.6 mg/kg + sufentanil 0.2 μg/kg; Maintenance: 4–8 mg/kg/h + rocuronium + remifentanil (0.05–0.2 μg/kg/min)	1	CAM
Fan 2024	China	R, SB	Elderly patients	319	71.1	42.9	II-III	Remimazolam: Induction: 0.2–	Propofol: Induction: 1.0–2.0	3	CAM-ICU

			undergoing cardiac valvular surgery under general anesthesia					0.3 mg/kg; Maintenance: 0.5–1.0 mg/kg/h	mg/kg; Maintenance: 4–10 mg/kg/h		
Fang 2025	China	R, SB	Older patients (60–90 years) undergoing hip surgery under general anesthesia	728	73	36.1	I-III	Remimazolam: Induction: 0.2–0.25 mg/kg IV; Maintenance: continuous IV infusion (rate not specified); Combined with sufentanil (0.2–0.3 μg/kg), cisatracurium	Induction: 1.5–2.0 mg/kg IV; Maintenance: continuous infusion, titrated to BIS 45–60; Same adjuncts as intervention group	3	3D-CAM or CAM-ICU

Abbreviations: R, randomized; DB, double-blind; SB, single-blind; OL, open-label; ASA, American Society of Anesthesiologists; NR, not reported; POD, postoperative delirium; CAM, confusion assessment method; CAM-ICU, confusion assessment method for the

intensive care unit; 3D-CAM, 3-minute diagnostic interview for CAM-defined delirium; Nu-DESC, nursing delirium screening scale; BIS, bispectral index; IV, intravenous; TAVR, transcatheter aortic valve replacement; MAC, minimum alveolar concentration; PSI, patient state index; TCI, target-controlled infusion.

Table 2. Evaluation of study quality using the Cochrane risk-of-bias tool

Studies	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other potential threats
Mao 2022	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Pan 2023	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Yang 2023	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Fechner 2024	Low risk	Low risk	High risk	Unclear	Low risk	Low risk	Low risk
Li 2024a	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Duan 2024	Low risk	Unclear	High risk	Low risk	Low risk	Low risk	Low risk
Kotani 2024	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Zhang 2024	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Liu 2024a	Low risk	Unclear	High risk	Low risk	Low risk	Low risk	Low risk
Ma 2024	Low risk	Unclear	High risk	Low risk	Low risk	Low risk	Low risk
Zhou 2024	Low risk	Unclear	High risk	Low risk	Low risk	Low risk	Low risk
Wang 2024	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Tian 2024	Low risk	Unclear	High risk	Low risk	Low risk	Low risk	Low risk
Liu 2024b	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Li 2024b	Low risk	Unclear	Low risk	Unclear	Low risk	Low risk	Low risk
Fan 2024	Low risk	Unclear	Low risk	Unclear	Low risk	Low risk	Low risk

Fang 2025	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk

Table 3. Summarized certainty of evidence using the GRADE system

Outcome	No. of participants (studies)	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative effect (95% CI)	Absolute effect	Certainty of Evidence (GRADE)	Comments
POD incidence (remimazolam vs. propofol)	3,133 (17 RCTs)	Randomized controlled trials	Serious Some studies had high or unclear risk in blinding	Not serious Moderate heterogeneity (I^2 = 36%) but consistent direction of effect	Not serious Population, interventions, and outcomes directly relevant	Not serious 95% CI excludes no effect and is clinically meaningful	None	OR: 0.71 (95% CI: 0.52–0.97)	Risk with propofol: 160 per 1,000 Risk with remimazolam: 116 per 1,000 (95% CI: 88 to 153)	⊕⊕⊕◯ Moderate	Remimazolam reduces POD risk compared with propofol. Findings are based on direct comparisons in surgery patients under general anesthesia. Downgrade

											d for risk of bias due to blinding limitations in some included studies.

Note: Specific reasons for each GRADE domain, including - Risk of bias: Downgraded if a significant proportion of studies had unclear or high risk of bias in key domains (e.g., random sequence generation, allocation concealment, or selective reporting); Inconsistency: Downgraded if substantial heterogeneity was observed ($I^2 > 50\%$) and could not be explained by subgroup analyses or meta-regression; Indirectness: Evaluated but not downgraded, as all included studies directly assessed the population and outcomes of interest; Imprecision: Downgraded if confidence intervals were wide, overlapping no effect, or if the overall sample size was small; Publication bias: Assessed using funnel plots and Egger's test; downgraded if significant asymmetry suggested potential bias. Abbreviations: GRADE, Grading of Recommendations, Assessment, Development and Evaluation; RCTs, randomized controlled trials; OR, odds ratio; CI, confidence interval.

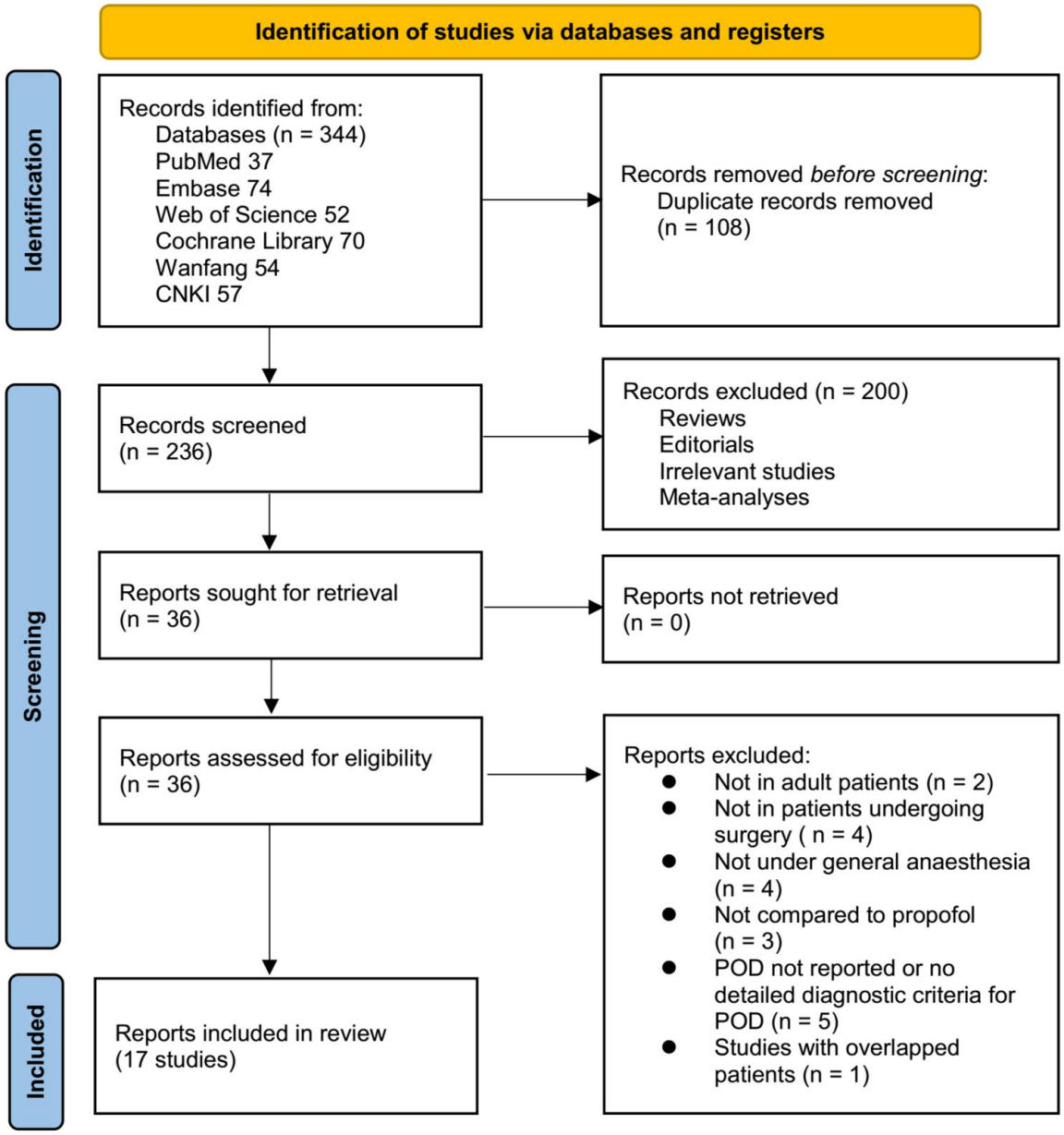

Figure 1. Flowchart for the literature search and study inclusion.

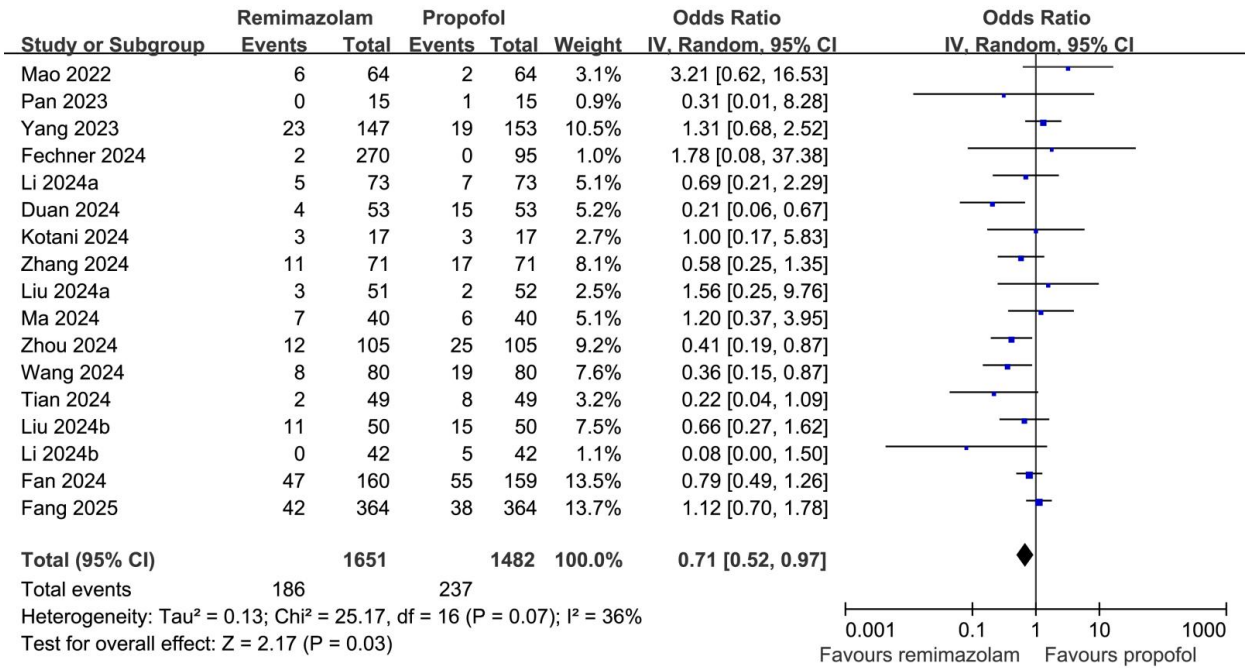

Figure 2. Forest plot comparing the effect of remimazolam versus propofol on the incidence of postoperative delirium (POD) in adult surgical patients under general anesthesia. The figure presents individual and pooled odds ratios with 95% confidence intervals from randomized controlled trials. Abbreviations: POD, postoperative delirium; OR, odds ratio; CI, confidence interval; IV, inverse variance; RCT, randomized controlled trial.

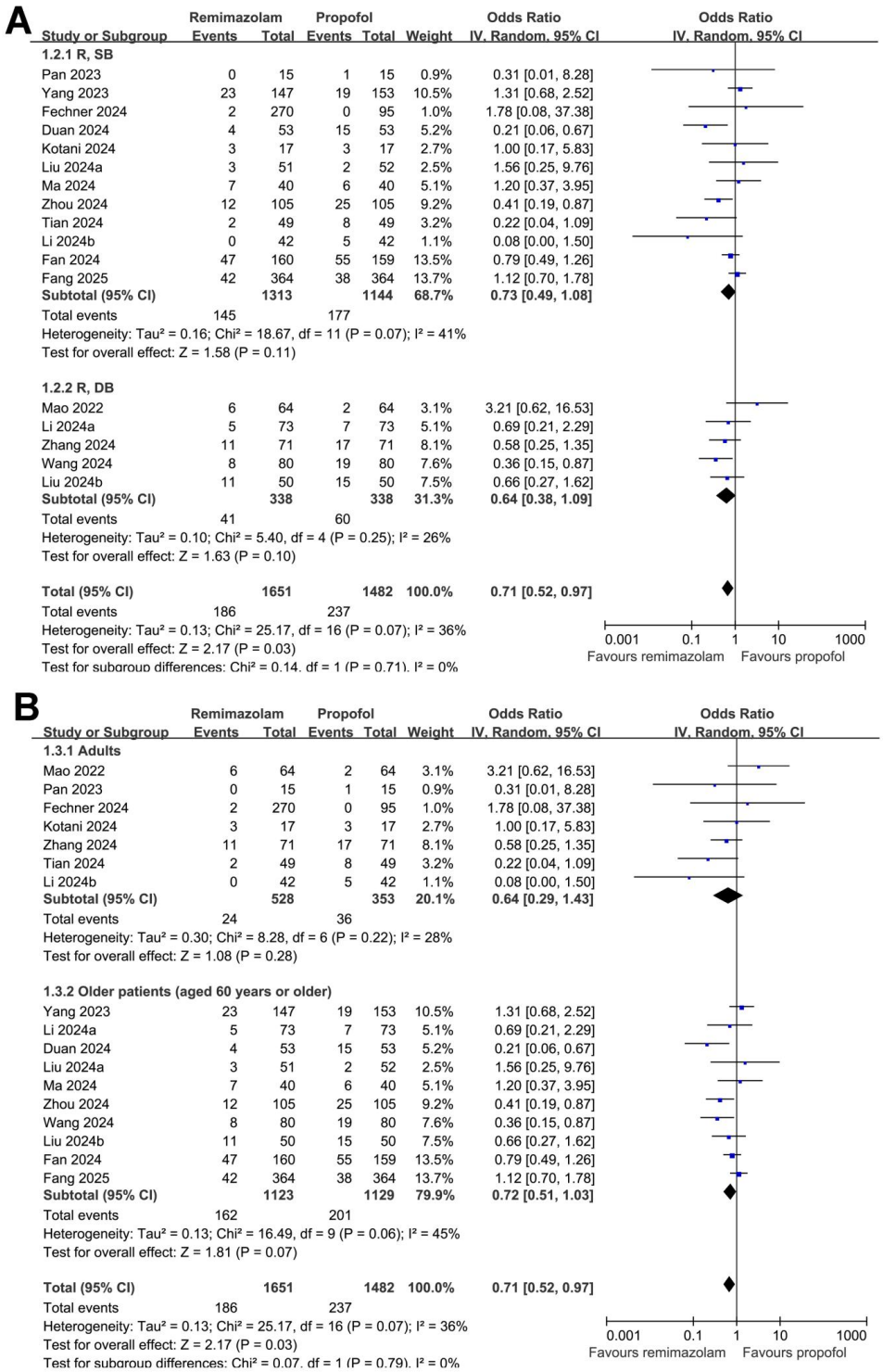

Figure 3. Forest plot of subgroup analyses comparing the effects of remimazolam versus propofol on the incidence of postoperative delirium (POD). (A) Subgroup analysis by blinding method (single-blind vs. double-blind). (B) Subgroup analysis by patient age (overall adults vs. older patients). Abbreviations: POD, postoperative delirium; OR, odds ratio; CI, confidence interval; R, SB, randomized single-blind; R, DB, randomized double-blind.

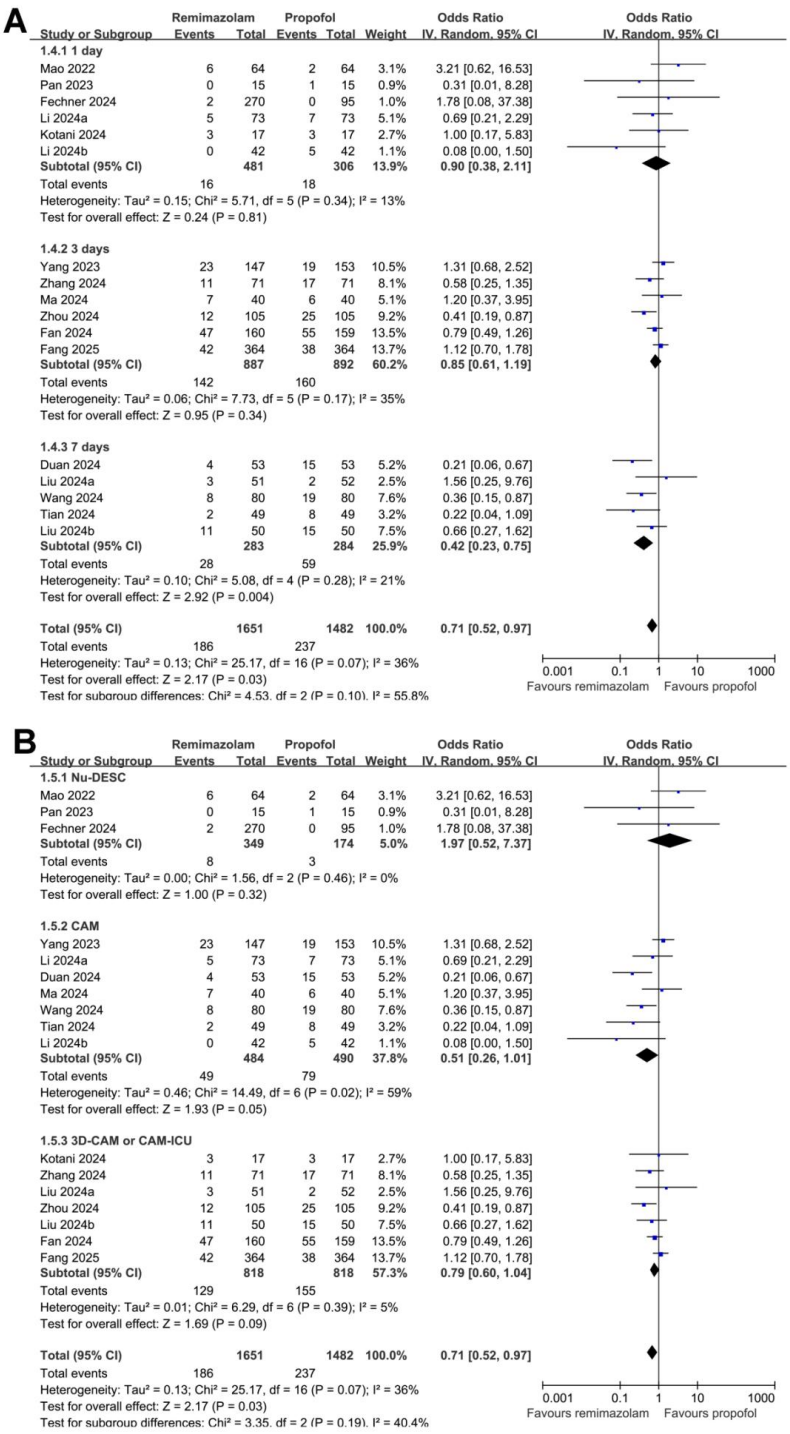

Figure 4. Forest plot of subgroup analyses comparing the effects of remimazolam versus propofol on the incidence of postoperative delirium (POD). (A) Subgroup analysis by follow-up duration (1 day, 3 days, or 7 days). (B) Subgroup analysis by delirium assessment tool (Nu-DESC, CAM, or 3D-CAM/CAM-ICU). Abbreviations: POD, postoperative delirium; OR, odds ratio; CI, confidence interval; Nu-DESC, nursing delirium screening scale; CAM, confusion assessment method; CAM-ICU, confusion assessment method for the intensive care unit.

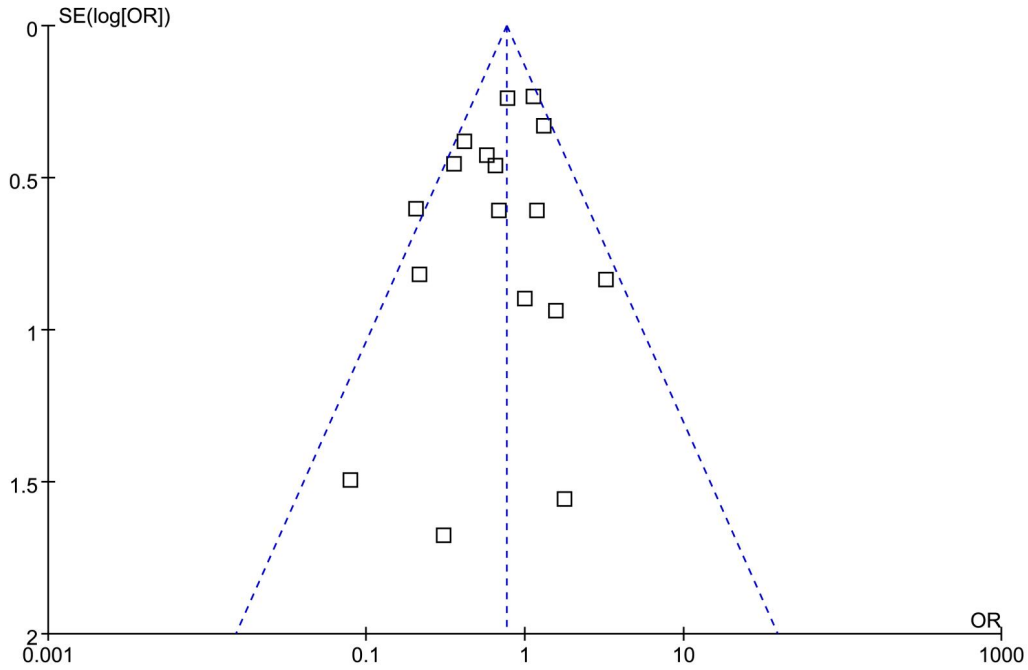

Figure 5. Funnel plots evaluating the publication bias underlying the meta-analysis comparing remimazolam with propofol on POD.

SUPPLEMENTAL DATA

Supplemental File 1

Detailed search strategy for each database

PubMed

("Remimazolam"[Supplementary Concept] OR remimazolam[tiab] OR "CNS 7056"[tiab] OR "ONO 2745"[tiab]) AND ("Propofol"[MeSH Terms] OR propofol[tiab] OR "ICI 35868"[tiab] OR disoprofol[tiab]) AND ("Delirium"[MeSH Terms] OR delirium[tiab] OR confusion[tiab] OR disorientation[tiab] OR cognitive[tiab] OR cognition[tiab]) AND ("Randomized Controlled Trial"[Publication Type] OR randomized[tiab] OR randomly[tiab] OR RCT[tiab] OR RCTs[tiab])

Embase

('remimazolam'/exp OR remimazolam:ti,ab OR 'CNS 7056':ti,ab OR 'ONO 2745':ti,ab) AND ('propofol'/exp OR propofol:ti,ab OR 'ICI 35868':ti,ab OR disoprofol:ti,ab) AND ('delirium'/exp OR delirium:ti,ab OR confusion:ti,ab OR disorientation:ti,ab OR cognitive:ti,ab OR cognition:ti,ab) AND ('randomized controlled trial'/exp OR random*:ti,ab OR RCT:ti,ab OR RCTs:ti,ab) AND [humans]/lim

Cochrane Library (CENTRAL)

(remimazolam OR "CNS 7056" OR "ONO 2745") AND (propofol OR "ICI 35868" OR disoprofol) AND (delirium OR confusion OR disorientation OR cognitive OR cognition) AND (randomized controlled trial OR randomized OR randomly OR RCT OR RCTs)

Web of Science

TS=(remimazolam OR "CNS 7056" OR "ONO 2745") AND TS=(propofol OR "ICI 35868" OR disoprofol) AND TS=(delirium OR confusion OR disorientation OR cognitive OR cognition) AND TS=(randomized OR randomly OR RCT OR RCTs)

CNKI

(主题: "瑞美唑仑" OR "CNS 7056" OR "ONO 2745") AND (主题: "丙泊酚" OR "ICI 35868" OR "disoprofol") AND (主题: "术后谵妄" OR "谵妄" OR "意识障碍"

OR "意识模糊" OR "认知功能障碍" OR "认知") AND (主题: "随机对照试验" OR "RCT" OR "随机" OR "随机分组")

English translation

(Subject: "Remimazolam" OR "CNS 7056" OR "ONO 2745") AND (Subject: "Propofol" OR "ICI 35868" OR "disoprofol") AND (Subject: "Postoperative delirium" OR "Delirium" OR "Disorders of consciousness" OR "Disorientation" OR "Cognitive impairment" OR "Cognition") AND (Subject: "Randomized controlled trial" OR "RCT" OR "Randomized" OR "Random allocation")

Wanfang Data

主题: ("瑞美唑仑" OR "CNS 7056" OR "ONO 2745") AND 主题: ("丙泊酚" OR "ICI 35868" OR "disoprofol") AND 主题: ("术后谵妄" OR "谵妄" OR "意识障碍" OR "认知障碍" OR "认知") AND 主题: ("随机对照试验" OR "随机" OR "RCT")

English translation

Subject: ("Remimazolam" OR "CNS 7056" OR "ONO 2745") AND Subject: ("Propofol" OR "ICI 35868" OR "disoprofol") AND Subject: ("Postoperative delirium" OR "Delirium" OR "Disorders of consciousness" OR "Cognitive impairment" OR "Cognition") AND Subject: ("Randomized controlled trial" OR "Randomized" OR "RCT")