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The Impact of Inhalational Anesthetics on Cognitive Function in Elderly Non-Cardiac Surgery Patients: A Systematic Review and Meta-Analysis Running title: The Impact of Inhalational Anesthetics

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ADMINISTRATIVE INFORMATION

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Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 27 February 2026 and was last updated on 27 February 2026.

INTRODUCTION

Review question / Objective This study aimed to systematically evaluate the impact of inhalational anesthetics on cognitive function in elderly patients undergoing non-cardiac surgery using a systematic review and meta-analysis approach.

Condition being studied The condition under investigation in this systematic review and meta-analysis is postoperative cognitive dysfunction (POCD) in elderly patients undergoing non-cardiac surgery. POCD is a common postoperative complication characterized by declines in cognitive domains such as memory, attention, and executive function following surgery. Although no formal diagnostic criteria have been established, its clinical manifestations may include alterations in circadian rhythm, changes in psychomotor status, and memory deficits. According to the literature, the incidence of POCD ranges from 25% to 40% at one week, 10% at three months, and 1% at one year postoperatively. POCD is associated with delayed recovery, prolonged hospital stay, increased medical costs, reduced quality of life, functional dependence, and elevated long-term mortality. This study focuses on the impact of inhalational anesthetics on the risk of POCD and related cognitive outcomes in the elderly population.

METHODS

Participant or population The population addressed in this systematic review and meta-analysis consists of elderly patients (aged 60 years or older) undergoing non-cardiac surgery. The included studies enrolled patients scheduled for various surgical procedures, including cancer surgery, laparoscopic cholecystectomy, and knee arthroplasty. All participants were recipients of general anesthesia involving inhalational anesthetics (such as sevoflurane, desflurane, or

isoflurane) or intravenous anesthetics (propofol). The review focuses on patients from randomized controlled trials (RCTs) published between 2010 and 2024, with a total sample size of 2,397 participants across 13 studies.

Intervention The intervention evaluated in this systematic review and meta-analysis is inhalational anesthesia administered to elderly patients undergoing non-cardiac surgery. The specific inhalational anesthetic agents investigated include sevoflurane, desflurane, and isoflurane. These agents were administered as part of general anesthesia during various surgical procedures, and their effects on postoperative cognitive function and anesthesia-related outcomes were compared primarily against propofol-based total intravenous anesthesia, as well as against each other in head-to-head comparisons (desflurane/isoflurane versus sevoflurane). The intervention details were derived from randomized controlled trials included in the analysis, where patients in the intervention groups received one or more of these inhalational anesthetics according to the study protocols.

Comparator The primary comparator in this systematic review and meta-analysis is propofol-based total intravenous anesthesia, which served as the control intervention against which inhalational anesthetics were evaluated. In addition, a secondary comparison was conducted among different inhalational anesthetic agents, specifically desflurane or isoflurane versus sevoflurane, to assess potential differences in their effects on postoperative cognitive function and anesthesia-related outcomes. These comparators were derived from randomized controlled trials included in the analysis, where patients in the control groups received either propofol or alternative inhalational anesthetics depending on the study design.

Study designs to be included The study design included in this systematic review and meta-analysis is randomized controlled trials (RCTs). Only studies published in peer-reviewed journals in Chinese or English that employed an RCT design were eligible for inclusion. Other publication types such as conference abstracts, case reports, and systematic reviews were excluded to ensure the highest level of evidence quality.

Eligibility criteria In addition to the criteria defined in the PICOS framework, the following eligibility criteria were applied:
Inclusion criteria:
Studies published in peer-reviewed journals in Chinese or English
Studies that provided at least one outcome of interest: incidence of postoperative cognitive dysfunction (POCD), postoperative Mini-Mental State Examination (MMSE) scores, Bispectral Index (BIS) scores, duration of anesthesia, post-anesthesia care unit (PACU) stay time, emergence time, or postoperative nausea and vomiting

Exclusion criteria:
Non-human studies
Publication types such as conference abstracts, case reports, and systematic reviews
Studies with insufficient outcome information preventing data analysis
Duplicate publications
Studies for which the full text could not be obtained.

Information sources The following electronic databases were systematically searched: PubMed, Web of Science, Cochrane Library, and Embase. The search period covered from the inception of each database until September 20, 2025. Additionally, the reference lists of included studies were reviewed to identify further relevant literature.

Main outcome(s) The primary outcome was the risk of postoperative cognitive dysfunction (POCD) , defined according to the criteria used by the investigators of the included studies. The effect measure for this dichotomous outcome was expressed as risk ratio (RR) with 95% confidence intervals (CI).
Secondary outcomes included:
Postoperative Mini-Mental State Examination (MMSE) scores: Continuous outcome measured using the mean difference (MD) with 95% CI
Bispectral Index (BIS) scores: Continuous outcome measured using MD with 95% CI (included specifically to assess comparability of anesthetic depth between groups, rather than as a direct measure of cognitive function)
Anesthesia-related outcomes:
Duration of anesthesia (minutes): MD with 95% CI
Post-anesthesia care unit (PACU) stay time (minutes): MD with 95% CI
Emergence time (minutes): MD with 95% CI
Postoperative nausea and vomiting (PONV): RR with 95% CI
Timing of outcome assessment varied across the included studies and was determined according to each study's protocol, with POCD typically assessed in the early postoperative period.

Quality assessment / Risk of bias analysis Quality assessment of the included studies was performed using the Cochrane Collaboration's risk of bias tool. This tool evaluates the following

domains: method of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective reporting of results, and other potential sources of bias. Each domain was judged against specific criteria and categorized as having a 'low', 'high', or 'unclear' risk of bias. Two researchers independently conducted the quality assessment. Any disagreements were consulted with a third researcher, and consensus was reached through discussion. The results indicated that the included studies were of relatively high quality, although the evaluation process suggested potential risk of bias primarily due to unclear implementation of blinding. The risk of bias assessments are presented in Supplementary Figures 1 and 2.

Strategy of data synthesis Statistical analysis was performed using RevMan software (version 5.3) . For dichotomous outcomes, the effect measure was expressed as risk ratio (RR) , and for continuous outcomes, the mean difference (MD) was used, both with 95% confidence intervals (CI) .
Heterogeneity assessment: Heterogeneity was assessed using the I^2 statistic and the Q-test. If I^2 0.1, the included studies were considered homogeneous, and a fixed-effect model was applied. If $I^2 \geq 50\%$ or the p-value of the Q-test $\leq$ 0.1, significant heterogeneity was considered present, and a random-effects model was used.
Subgroup and sensitivity analysis: If substantial heterogeneity was detected, subgroup analysis stratified by different medicines or sensitivity analysis was conducted to explore its sources. Sensitivity analyses were performed on outcomes with at least 4 data points and $I^2 > 50\%$ by sequentially excluding individual studies.
Publication bias assessment: Funnel plots, Egger's test, and Begg's test were used to assess potential publication bias among the included studies.
Unless otherwise specified, the significance level (alpha) was set at 0.05.

Subgroup analysis Subgroup analysis was conducted based on different types of anesthetic agents to explore potential sources of heterogeneity. Specifically, the following subgroup comparisons were performed:
Inhalational anesthesia versus propofol: Studies comparing inhalational anesthetics (sevoflurane, desflurane, or isoflurane) with propofol-based total intravenous anesthesia were analyzed separately for outcomes including POCD incidence, MMSE scores, BIS scores, and anesthesia-related outcomes.
Desflurane/isoflurane versus sevoflurane: Among studies using inhalational anesthetics, a subgroup analysis was performed comparing desflurane or isoflurane with sevoflurane for outcomes including POCD incidence, MMSE scores, and anesthesia-related outcomes (duration of anesthesia, PACU stay time, emergence time, and postoperative nausea/vomiting).
These subgroup analyses were conducted when substantial heterogeneity was detected to investigate whether the type of anesthetic agent contributed to the observed heterogeneity in effect estimates.

Sensitivity analysis Sensitivity analyses were performed on outcomes for which at least four data points were available for analysis and where significant heterogeneity was detected ($I^2 > 50\%$). The analyses were conducted by sequentially excluding individual studies to explore potential sources of heterogeneity and to assess the robustness of the pooled effect estimates.
For the comparison of emergence time between desflurane/isoflurane and sevoflurane, when one specific study (Meineke et al., 2014) was excluded, heterogeneity decreased substantially from 93% to 0%, and desflurane/isoflurane remained associated with a shorter emergence time (MD: -1.81; 95% CI: -2.07, -1.54).
For other outcomes, sensitivity analysis did not identify clear sources of heterogeneity, and the pooled effect sizes did not change significantly, suggesting that the heterogeneity among the included studies was relatively stable and that the analysis results were robust.

Country(ies) involved China.

Keywords Inhalational anesthesia; Elderly; Non-cardiac surgery; Meta-analysis.

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