Meta-analysis

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Effects of dexmedetomidine on neurocognitive disturbance after elective non-cardiac surgery in senile patients: a systematic review and meta-analysis

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Abstract

Objective: Senile patients often experience neurocognitive disturbance after non-cardiac surgery. Several clinical trials have investigated if the perioperative intravenous use of dexmedetomidine has a positive effect on the prevention of neurocognitive dysfunction, but the results have been inconsistent. We performed a meta-analysis to investigate the effects of dexmedetomidine on neurocognitive disturbance after elective non-cardiac surgery in senile patients.

Methods: The PubMed, Cochrane Library, EMBASE and China National Knowledge Infrastructure databases were comprehensively searched for all randomized controlled trials published before 1 February 2020 that investigated the efficacy of dexmedetomidine in the prevention of postoperative delirium (POD) or postoperative cognitive dysfunction (POCD).

Results: Sixteen studies involving 4376 patients were included in this meta-analysis. Compared with the control (i.e., saline), the perioperative intravenous use of dexmedetomidine significantly reduced the incidence of POD and POCD. However, patients in the dexmedetomidine group were more likely to develop bradycardia and hypotension during the administration of dexmedetomidine than patients in the control group. There were no differences between the two groups in the incidence of nausea and vomiting or mortality rate.

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Conclusion: Dexmedetomidine has a positive effect on the prevention of neurocognitive disturbance in senile patients after elective non-cardiac surgery.

Keywords
Anesthesiology, postoperative cognitive disturbance, non-cardiac surgery, dexmedetomidine, postoperative delirium, senile

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Introduction

Postoperative neurocognitive disturbance includes postoperative delirium (POD) and postoperative cognitive dysfunction (POCD). In general, POD occurs within 3 days after surgery,[1] whereas POCD is characterized by long-term cognitive impairment, such as the loss of memory and impaired comprehension.[2–5] It was reported that 13% to 50% of senile patients develop neurocognitive disturbance after surgery,[6–8] which is an important risk factor for many undesirable outcomes, such as a longer length of hospital stay, disability, even higher postoperative mortality rates and others.[9–12] Therefore, many clinicians have attempted to identify better approaches to prevent POD/POCD in senile patients after surgery.[6,13]

Dexmedetomidine, a selective α2-adrenaline receptor agonist, has a dose-dependent sedative effect on respiration with minimal depressive effects. It also shows a modest analgesic effect through the inhibition of pain signals.[14–16] The efficacy of the perioperative use of dexmedetomidine in the prevention of POD/POCD after cardiac surgery has been clearly demonstrated.[17,18]

Scientists have found that dexmedetomidine improves the cognitive function of older rats after splenectomy.[19] Several clinical trials have investigated the efficacy and safety of dexmedetomidine in the prevention of POD and POCD; however, there are inconsistencies among the results of these studies. For instance, both Deiner *et al*[20] and Ma *et al*[21] concluded that the perioperative intravenous use of dexmedetomidine did not significantly reduce POD among elderly patients after non-cardiac surgery. In contrast, other clinicians have reported opposite findings.[22,23] Furthermore, two meta-analyses showed the efficacy of the perioperative intravenous use of dexmedetomidine in the prevention of POD in elderly patients after non-cardiac surgery.[24,25] However, they both included a relatively small number of samples, and neither mentioned POCD. Therefore, we performed a meta-analysis with a larger sample size to investigate the effects of dexmedetomidine on neurocognitive disturbance after elective non-cardiac surgery in senile patients and draw a more convincing conclusion, which may provide guidelines for future clinical work.

Methods and materials

Study design

We conducted this systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[26] PRISMA is an evidence-based minimum set of items for reporting

in systematic reviews and meta-analyses that can be used as a basis for reporting systematic reviews of different types of research. Because our study did not involve any interventions in patients or animals, ethical approval was not applicable.

Search strategies

The PubMed, Cochrane Library, EMBASE and China National Knowledge Infrastructure databases were comprehensively searched for randomized controlled clinical trials (RCTs) published before February 2020 that investigated the effects of dexmedetomidine on neurocognitive disturbance after elective non-cardiac surgery in senile patients. In addition, the reference lists of all included studies were checked for any potential additional publications. We used the keywords of *dexmedetomidine, postoperative delirium, postoperative cognitive dysfunction*, *POD* and *POCD*. The detailed search strategies for each database were presented in the Supplemental materials (Supplementary Table 1).

Inclusion and exclusion criteria

For a published article to be included in our study, it had to meet the following criteria: (1) RCT design, (2) investigated the effects of dexmedetomidine on POD/POCD after elective non-cardiac surgery in senile patients, (3) compared dexmedetomidine with normal saline and (4) full text available.

Studies were excluded if they were duplicate publications, reviews, editorials, abstracts, commentaries, case reports, meetings, involved animals or included patients younger than 60 years old.

Data extraction

Two reviewers (Bi and Wei) independently screened the titles and abstracts of papers and selected the relevant studies. The same two reviewers (Bi and Wei) independently extracted the data from the studies according to a prespecified protocol with any disagreement settled by a third reviewer (Zhang). If data were missing, we e-mailed the corresponding author of the original article and asked if they could provide the required information.

The following items were extracted: name of the first author; publication year; type of surgery; sample size (classified by the participants' sex); participants' age; anesthesia technique; measurement method for POD/POCD; method of dexmedetomidine administration; and incidence of POD/POCD, bradycardia and hypotension during the intervention, postoperative nausea and/or vomiting (PONV) and postoperative mortality.

The primary outcome of the meta-analysis was the incidence of POD/POCD. The descriptions of instruments used in the enrolled trials were summarized in Supplementary Table 3. The secondary outcome was the incidence of bradycardia and hypotension during the intervention, PONV and postoperative mortality. Postoperative mortality was defined as all-cause mortality within 30 days after surgery. The raw data were presented in the supplementary materials.

Data synthesis and statistical analysis

This meta-analysis was performed using Review Manager (RevMan) Version 5.3 (Copenhagen, The Nordic Cochrane Centre, the Cochrane Collaboration, 2014). Cochran's Q test and the I^2 statistical test were used to assess the statistical heterogeneity of the pooled results. If $0\% \leq I^2 < 25\%$, the results showed no heterogeneity; if $25\% \leq I^2 < 50\%$, the results showed a low level of heterogeneity; if $50\% \leq I^2 < 75\%$, the results showed a medium level of heterogeneity; and if $75\% \leq I^2 \leq 100\%$, the results showed a high level

of heterogeneity. Data from all eligible RCTs were pooled, and the Mantel–Haenszel method was used to calculate the risk ratio (RR) with 95% confidence intervals (CI) for these dichotomous outcomes. A pooled estimate of RR was computed using the DerSimonian and Laird random-effects model. This model provides an appropriate estimate of the average treatment effect when studies are statistically heterogeneous, and it typically yields relatively wide CIs resulting in a more conservative statistical claim.

The risk of bias assessment was performed using the Cochrane Collaboration tool (Cochrane, London, UK). Subgroup analyses were conducted by classifying these included studies according to their medication timing and dose and their primary outcome (POD or POCD). In addition, a sensitivity analysis was used to assess the robustness of the results by excluding specific studies, and a funnel plot was used to assess potential publication bias. Two reviewers (Bi and Wei) independently synthesized the data with any disagreement settled by a third reviewer (Zhang). A p value of <0.05 was considered statistically significant.

Results

Literature search

The literature search identified 1144 articles, of which 16 articles[20–23,27–38] met the inclusion criteria (Supplementary Figure 1). The characteristics of the 16 studies involving 4376 participants were summarized in Supplementary Table 2. All raw data extracted from the original articles were available online.

Primary outcome

After synthesizing the data, the results showed that the perioperative intravenous use of dexmedetomidine significantly reduced the incidence of POD and POCD in senile patients after non-cardiac surgery compared with the control group (RR: 0.53; 95% CI: 0.46–0.61; $p < 0.001$; $I^2 = 37\%$) (Figure 1).

Subgroup analyses

Of the 16 studies, 3 studies[28,32,33] investigated the relationship between the perioperative use of dexmedetomidine and POCD, and the other 13 studies[20–23,27–31,34–38] assessed whether the perioperative use of dexmedetomidine could prevent POD. As shown in Figure 2, the perioperative intravenous use of dexmedetomidine significantly reduced the incidence of POD (RR: 0.53; 95% CI: 0.43–0.67; $p < 0.001$; $I^2 = 48\%$) and POCD (RR: 0.44; 95% CI: 0.29–0.69; $p < 0.001$; $I^2 = 0\%$).

Regarding the timing of dexmedetomidine use, 9 studies[21,23,28,29,31–34,37] reported the intraoperative use of dexmedetomidine, the patients in 6 studies[22,27,30,35,36,38] were given dexmedetomidine postoperatively, and Deiner *et al*[21] administered a continuous infusion of dexmedetomidine from the start of surgery to 24 hours after surgery. As shown in Figure 3, both intraoperative (RR: 0.46; 95% CI: 0.36–0.57; $p < 0.001$; $I^2 = 0\%$) and postoperative (RR: 0.52; 95% CI: 0.39–0.70; $p < 0.001$; $I^2 = 46\%$) use of dexmedetomidine significantly reduced the incidence of postoperative neurocognitive cognitive disturbance compared with the control group. However, the only study that investigated the continuous use of dexmedetomidine showed that there was no significant difference between the experimental group and the control group (RR: 1.03; 95% CI: 0.67–1.59; $I^2 =$ not applicable).

After classifying all studies by whether there was a loading dose or not, we found that patients in the dexmedetomidine group experienced a lower rate of postoperative

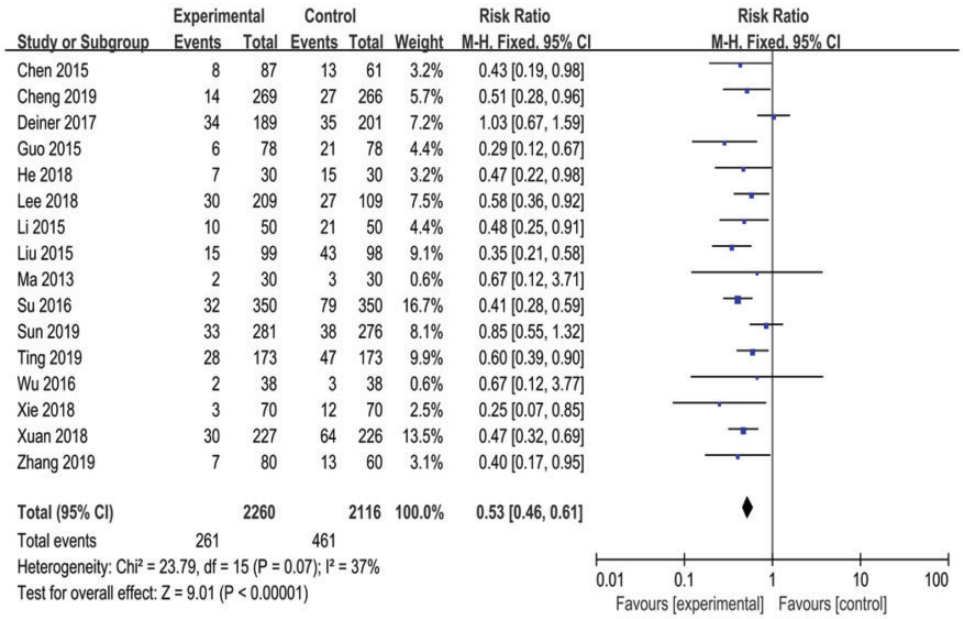

Figure 1. Meta-analysis of the perioperative intravenous use of dexmedetomidine in the prevention of POD and POCD in senile patients after non-cardiac surgery. Each diamond represents the summary of all presented data.
POD, postoperative delirium; POCD, postoperative cognitive dysfunction; CI, confidence interval.

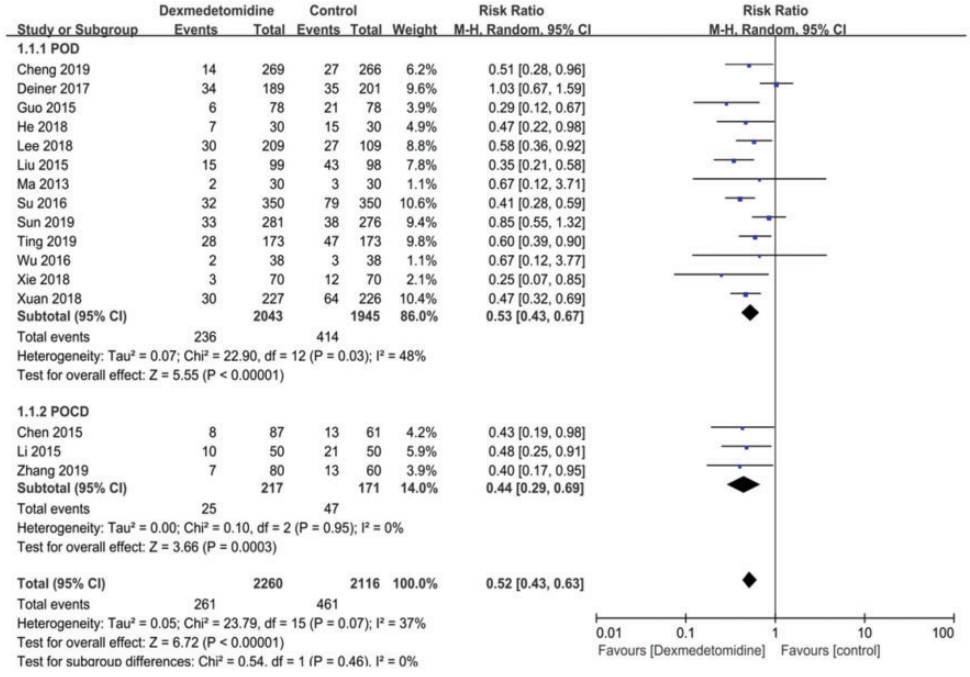

Figure 2. Subgroup analysis based on the type of postoperative neurocognitive disturbance.
CI, confidence interval.

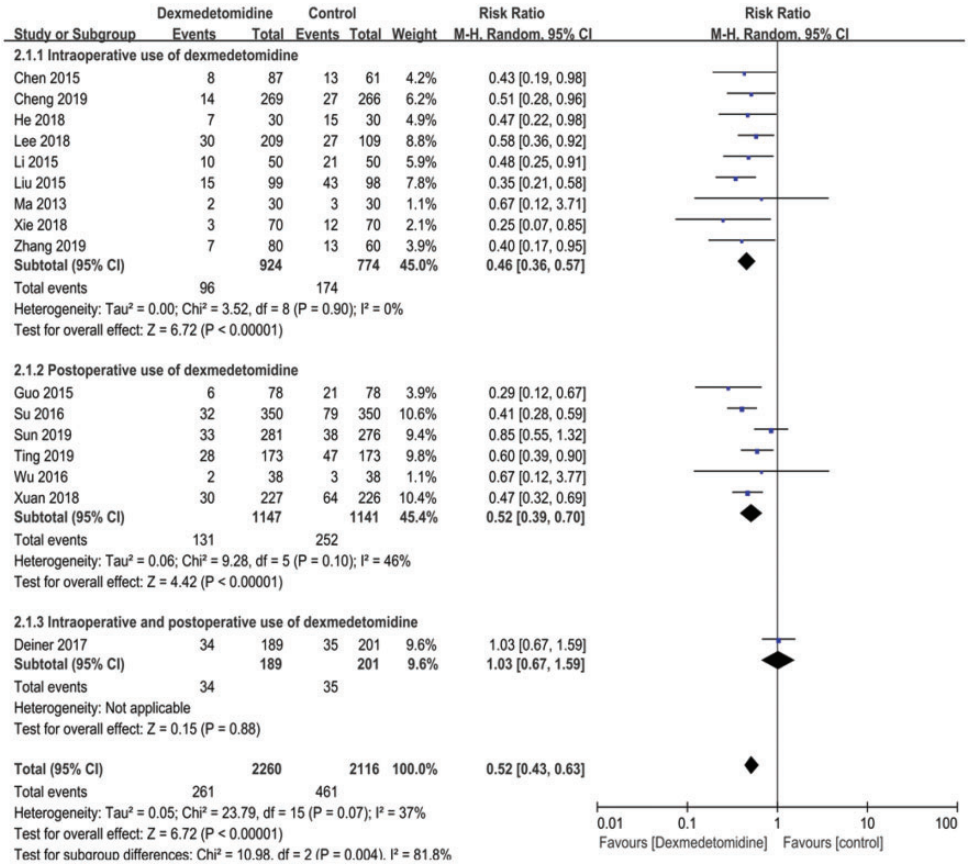

Figure 3. Subgroup analysis based on the timing of dexmedetomidine use.
CI, confidence interval.

neurocognitive cognitive disturbance (RR: 0.52; 95% CI: 0.43–0.63; $p < 0.001$; I^2=37%) regardless of whether a loading dose was applied (Figure 4).

Secondary outcomes

Adverse events related to the use of dexmedetomidine were analyzed as our secondary outcomes. Of note, we e-mailed the corresponding author of Ting *et al*[30] to ask for the data regarding adverse events because they only summarized the adverse events and did not present them separately.

Patients in the dexmedetomidine group were more likely to experience hypotension during dexmedetomidine use (RR: 1.29; 95% CI: 1.12–1.49; p=0.0006; I^2=3%) (Supplementary Figure 2). As shown in Supplementary Figure 3, patients in the dexmedetomidine group had a higher incidence of bradycardia than those in the control group (RR: 1.39; 95% CI: 1.15–1.67; p=0.0008; I^2=0%). The synthesized data showed that there was no significant difference between the dexmedetomidine group and the control group in the incidence of PONV (RR: 0.83; 95% CI: 0.58–1.17; I^2=11%) (Supplementary Figure 4). Last,

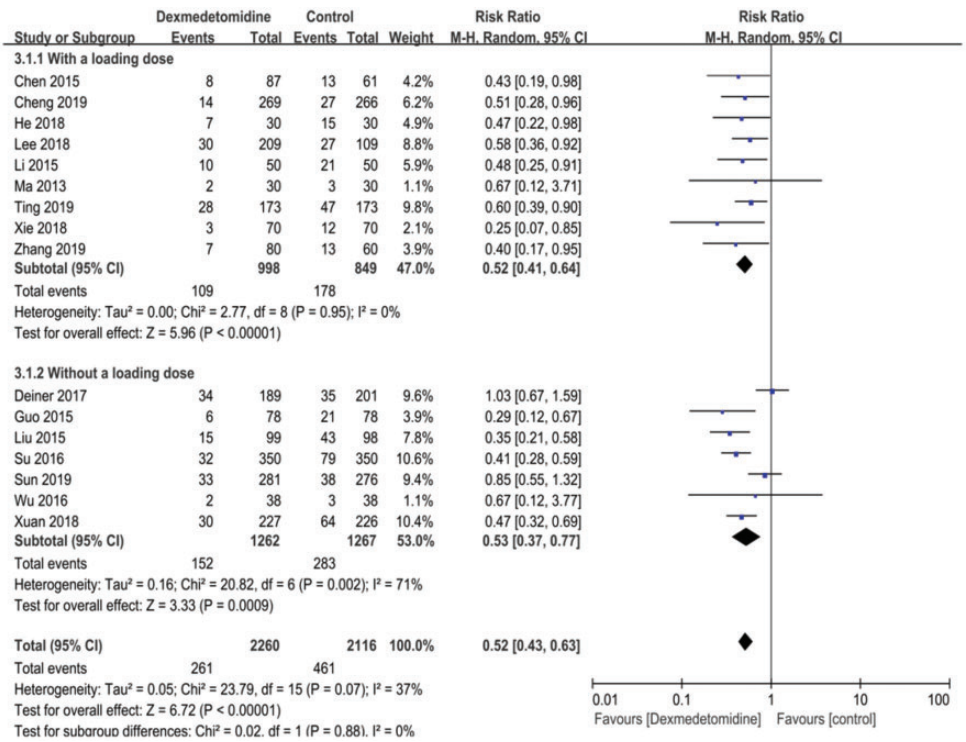

Figure 4. Subgroup analysis based on the use of a loading dose.
CI, confidence interval.

patients in both groups exhibited the same mortality rate after surgery (RR: 0.72; 95% CI: 0.28–1.84; I^2=0%) (Supplementary Figure 5).

Sensitivity analysis

Three studies[20,23,32] included patients with preoperative mild cognitive impairment, which we thought might be the source of the heterogeneity. Therefore, we performed a sensitivity analysis by excluding these 3 studies, and the heterogeneity decreased to zero (RR: 0.50; 95% CI: 0.42–0.59; I^2=0%) (Supplementary Figure 6).

Bias assessment

As shown in the risk of bias summary (Supplementary Figure 7) and risk of bias graph (Supplementary Figure 8), two studies[31,33] had a high risk for performance bias, one study[38] had a high risk for reporting bias, and one study[28] was rated as high risk for selection bias. Regarding publication bias, there was no significant asymmetry in the funnel plot (Supplementary Figure 9), indicating that no significant publication bias existed.

Discussion

We concluded that the perioperative intravenous use of dexmedetomidine has a positive effect on the prevention of postoperative cognitive disturbance based on the results of our meta-analysis. Only one study[20] reported both the intraoperative and postoperative use of dexmedetomidine (i.e., continuous infusion of dexmedetomidine from the start of surgery

to 24 hours after surgery) and showed that there was no significant difference between the experimental group and the control group.

Postoperative neurocognitive disturbance is closely related to the age of patients.[6,35] Additionally, studies have shown that postoperative cognitive disturbance has a certain relationship with anesthesia, especially the use of general anesthetic drugs.[39]

Dexmedetomidine is a derivative of medetomidine, which inhibits the sympathetic nervous system and reduces the release of norepinephrine.[40] Promisingly, its brain-protective effect in senile patients is currently being widely investigated by clinicians.[41]

Nine studies reported the use of a loading dose. The most frequently used loading dose was 0.5 μg/kg for 10 to 15 minutes before or after induction, whereas the other studies reported a loading dose of 1 μg/kg for 10 to 15 minutes before or after induction. The maintenance rate of dexmedetomidine ranged from 0.2 to 0.7 μg/kg/minute throughout the entire surgery or for 30 minutes before the end of surgery. Six studies reported the postoperative use of dexmedetomidine at a rate of 0.1 to 0.2 μg/kg/minute for several hours or even as long as 3 days. The dose was relatively smaller when patients were awake after anesthesia. Generally, the perioperative intravenous use of dexmedetomidine prevented postoperative cognitive disturbance regardless of whether a loading dose was applied.

Hypotension and bradycardia are the most common side effects of dexmedetomidine and are caused by its inhibition of the sympathetic nervous system.[42] It is not surprising that patients in the experimental group experienced a higher incidence of hypotension and bradycardia. Importantly, these are transient side effects and have no significant impact on the prognosis of patients. Previous studies have demonstrated that the perioperative use of dexmedetomidine improved patient prognosis and shortened their length of hospital stay.[43] Nevertheless, the use of dexmedetomidine had no effect on reducing PONV.

The effects of dexmedetomidine on delirium have been evaluated in different patient populations, including non-cardiac surgical elderly patients and cardiac surgical patients. An article published in 2020 in The Lancet showed no benefit from perioperative dexmedetomidine use in cardiac surgery regarding the postoperative complications of delirium and atrial fibrillation.[44] The results varied among different participants.

A medium level of heterogeneity was observed among all studies included in this meta-analysis (I^2=37%). Three studies[20,23,31] included patients with preoperative mild cognitive impairment, which we thought might be the source of the heterogeneity. After the exclusion of these three studies, the I^2 was decreased to zero, demonstrating that the heterogeneity was derived from these three studies.

This study has several limitations. First, we only found one study[21] that reported the intraoperative and postoperative use of dexmedetomidine, and it showed that dexmedetomidine did not prevent postoperative cognitive disturbance. Therefore, further studies should focus on the timing of the combined intraoperative and postoperative use of dexmedetomidine. Second, only four studies reported the occurrence of PONV, and the results showed that the perioperative intravenous use of dexmedetomidine did not reduce the incidence of PONV. This result contradicted our hypothesis that dexmedetomidine reduces the incidence of PONV due to its inhibition of the sympathetic nervous system and sedative effect. Thus, further studies should be performed to investigate the efficacy of the

perioperative use of dexmedetomidine in the prevention of PONV.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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Author contributions

Xiaobo Bi participated in designing the study, screening the articles, data extraction and data synthesis, and preparing the first draft of the manuscript. Xia Zhang participated in designing the study, solving the discrepancies between different reviewers, critically revising the manuscript, and providing funding support. Jingxia Wei participated in screening the articles, data extraction, and data synthesis.

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Supplemental Material

Supplemental material for this article is available online.

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