Original article

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Comparative efficacy of progesterone and vitamin D in improving functional outcomes after traumatic brain injury

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Background: Traumatic brain injury (TBI) remains a major clinical challenge in neurosurgery due to its heterogeneous pathophysiology and the limited availability of effective pharmacological interventions. Progesterone and vitamin D have demonstrated neuroprotective and anti-inflammatory properties in preclinical models; however, their translational efficacy in clinical trials remains inconclusive. Clarifying their therapeutic roles may help inform adjunctive strategies in the acute management of neurotrauma.

Objectives: To assess the neuroprotective effects of progesterone and vitamin D in enhancing functional recovery following moderate to severe TBI, and to compare the clinical efficacy of these agents based on standardized neurological outcome measures derived from randomized controlled trials (RCTs).

Methods: A systematic review and meta-analysis were conducted in accordance with the PRISMA guidelines. Randomized controlled trials (RCTs) were identified through searches of PubMed, EMBASE, Web of Science, and the Cochrane Library, comparing progesterone and/or vitamin D with placebo in patients with traumatic brain injury (TBI). Studies reporting Glasgow Outcome Scale–Extended (GOS-E) outcomes were included. Standardized mean differences (SMDs) with 95% confidence intervals (CIs) were calculated using Review Manager version 5.4. Study quality and heterogeneity were assessed.

Results: Six RCTs were included: three progesterone trials (n = 1,426) and three vitamin D trials (n = 192). Progesterone showed no significant improvement in functional outcomes compared with placebo (SMD = −0.07; 95% CI: −0.32 to 0.19; p = 0.60; I^2 = 58%). Vitamin D demonstrated a non-significant trend toward improved outcomes (SMD = 0.37; 95% CI: −0.27 to 1.02; p = 0.26; I^2 = 78%). Variability in trial design, timing of intervention, and baseline vitamin D deficiency status may have influenced the observed effects.

Conclusions: Although neither agent showed standalone efficacy, their safety and complementary mechanisms suggest promise for combinatorial or biomarker-guided approaches. This meta-analysis highlights the need for early, precision-targeted, and stratified neuroprotective trials in TBI care.

Keywords: *traumatic brain injury (TBI); progesterone; vitamin D; functional outcome*

Introduction

Traumatic brain injury (TBI) remains a significant global health concern, contributing to substantial morbidity, long-term disability, and mortality, particularly among young adults [1]. The pathophysiology of TBI is complex, involving both immediate primary injury and subsequent secondary cascades including neuroinflammation, oxidative stress, excitotoxicity, mitochondrial dysfunction, and apoptosis [2]. Current therapeutic strategies are predominantly supportive, and despite decades of research, effective pharmacologic interventions that significantly improve neurological outcomes remain elusive.

Progesterone, a neurosteroid with pleiotropic neuroprotective properties, has garnered attention for its potential to modulate secondary brain injury. Experimental studies have demonstrated its anti-inflammatory, anti-apoptotic, and neurodegenerative effects [3]. Several randomized controlled trials (RCTs) have evaluated progesterone administration following TBI; however, results regarding its efficacy in improving functional recovery have been inconsistent. [4]. Vitamin D, traditionally known for its role in calcium homeostasis, has emerged as a neuroimmunomodulator with potential therapeutic implications in central nervous system injuries. It exerts neuroprotective effects through regulation of neurotrophic factors, attenuation of oxidative damage, and modulation of immune responses [5]. Preclinical studies and early-phase clinical trials have suggested a beneficial role of vitamin D in TBI, though robust evidence from randomized trials remains limited [6]. The Glasgow Outcome Scale–Extended

(GOS-E) is a validated and widely used measure of functional recovery following TBI. As a standardized outcome scale, it facilitates comparison across studies and enables evaluation of treatment efficacy based on meaningful improvements in neurological function and disability status [7].

Given the increasing interest in hormone-based and vitamin-based neuroprotective therapies, this meta-analysis aims to systematically compare the efficacy of progesterone and vitamin D in improving functional outcomes in patients with TBI, as assessed by GOS-E scores, using data from randomized controlled trials. By synthesizing available evidence, this study seeks to provide clarity on their comparative therapeutic value and guide future clinical decision-making.

Materials and methods

Search strategy

A comprehensive literature search was conducted in PubMed, EMBASE, Web of Science, and the Cochrane Library to identify studies published from 2005 to March 2025. The search strategy combined Medical Subject Headings (MeSH) and free-text terms, including "Traumatic Brain Injury" OR "TBI," "Progesterone," "Vitamin D," and "Randomized Controlled Trial," using Boolean operators and synonyms to maximize sensitivity. Reference lists of relevant studies and prior systematic reviews were manually screened to identify additional eligible trials.

Study selection

Eligible studies were randomized controlled trials published in English with a placebo-controlled design, enrolling patients with clinically confirmed moderate to severe traumatic brain injury. TBI diagnosis was established based on clinical assessment and/or neuroimaging, such as CT or MRI. Trials were required to report at least one functional outcome, with the GOS-E prioritized as the primary endpoint, and to include sufficient follow-up to evaluate functional recovery. Studies were included only if key intervention details—including dosage, route of administration, and timing relative to injury—were clearly reported. Studies with significant methodological limitations, non-randomized designs, non-clinical populations, or incomplete outcome reporting were excluded.

Data extraction

Data extraction was independently performed by two reviewers using a standardized form, with discrepancies resolved through discussion or consultation with a third reviewer. Extracted data included study characteristics, intervention details, patient demographics, and baseline functional status where available. Timing of therapy initiation relative to the injury phase was recorded, categorized as acute (≤24 hours), subacute (1–7 days), or chronic (>7 days), as this factor can influence treatment response. The primary outcome of interest was functional recovery assessed by GOS-E, while secondary outcomes included neurological improvement and safety endpoints, such as treatment-related adverse events, discontinuations, and total dropouts. When standard deviations were not directly reported, they were derived from standard errors, confidence intervals, t-values, or p-values using established conversion methods.

Statistical analysis

Meta-analysis was performed using Review Manager (RevMan) version 5.4. Continuous outcomes, particularly GOS-E scores, were synthesized using mean differences or standardized mean differences with 95% confidence intervals. Statistical heterogeneity was assessed using Cochran's Q test and quantified with the I^2 statistic, with I^2 values greater than 50% or $p<0.10$ considered indicative of substantial heterogeneity. Planned subgroup analyses explored the influence of intervention timing, TBI severity, and type of neuroprotective agent on functional outcomes.

Results

Literature search findings

The search strategy yielded 36 citations in PubMed, EMBASE, Web of Science, and the Cochrane Library of Systematic Reviews. ***Fig. 1*** shows the results of the literature search and study selection. A total of 32 potentially relevant articles were identified in the initial search; however, only six studies met the inclusion criteria and were included in the meta-analysis. Of these, three progesterone trials (Wright *et al*., 2007; Wright *et al*., 2014; Skolnick *et al*., 2014), and three vitamin D trials (Sharma *et al*., 2020; Shafiei *et al*., 2022; Intiso *et al*., 2024) were included in the review. The design and population characteristics of the progesterone and vitamin D tests are shown in ***Table 1 and 2***.

Effects and adverse events of progesterone intervention

A total of three RCTs comprising 1,426 patients (742 in the progesterone group and 684 in the placebo group) were included in the meta-analysis. All studies assessed the efficacy of intravenous progesterone in patients with moderate to severe TBI, with follow-up periods ranging from 30 days to 6 months.

The pooled analysis of SMD revealed no statistically significant improvement in neurological outcomes with progesterone therapy compared to placebo (SMD=–0.07; 95% CI: –0.32 to 0.19; p=0.60). Subgroup analysis showed mixed results across studies. Wright *et al*. (2014) reported a slight benefit in the placebo group (SMD=–0.35; 95% CI: –0.68 to –0.02), whereas Skolnick *et al*. (2014) found no significant difference (SMD=0.00; 95% CI: –0.11 to 0.12), and Wright *et al*. (2007) favored progesterone, albeit not significantly (SMD=0.17; 95% CI: –0.29 to 0.64). The heterogeneity was moderate (I^2=58%, p=0.09), suggesting variability in study designs or populations.

Baseline characteristics were generally similar across studies, with the mean age of participants around 35 years and a predominance of male patients (71% to 78.5%). Progesterone dosing protocols were consistent, utilizing a loading dose of 0.71 mg/kg followed by maintenance infusions ranging from 11 to 119 hours. Notably, only Wright *et al*. (2007) reported a statistically significant reduction in 30-day mortality (13% vs. 30.4% in placebo), while the other two trials did not demonstrate significant clinical benefit in long-term functional outcomes (***Fig. 2***).

Adverse events were reported across all trials, with the largest number observed in Skolnick *et al*. (2014) study (n=4,025). Dropout rates ranged from 3.9% to

15.5%, and very few adverse events directly led to participant withdrawal (0–3 cases per study).

Effects and adverse events of vitamin D intervention

Three RCTs comprising 192 patients (98 in the vitamin D group and 94 in the placebo group) were included in this meta-analysis to evaluate the effects of vitamin D supplementation on neurological recovery in moderate to severe TBI patients.

The pooled SMD favored vitamin D over placebo, but the effect was not statistically significant (SMD=0.37; 95% CI: –0.27 to 1.02; p=0.26). Individual studies showed variable outcomes. Sharma *et al*. (2020) reported a significant improvement in the GOS-E scores at 14 days in the vitamin D group (mean 4.80 vs. 2.21, p<0.0001), while Shafiei *et al*. (2022) also demonstrated a statistically significant higher proportion of favorable outcomes at 3 months (p=0.03). In contrast, Intiso *et al*. (2024) found no significant difference in GOS-E scores between groups.

There was a high degree of heterogeneity among the included studies (I^2=78%, p=0.01), which may be attributed to differences in dosing regimens, patient ages, and follow-up durations. Intiso *et al*. (2024) used a bolus plus maintenance approach, while the other two studies administered single high-dose oral regimens (***Fig. 3***).

Baseline characteristics showed comparable TBI severity across studies. However, patient age varied, with the Intiso *et al*. cohort having a markedly higher mean age (57.5 years) compared to others (~36 years). The male proportion was similar (58.3%–71.4%).

No adverse events or dropouts due to treatment were reported in any of the included trials.

Participant demographics

Across the included studies, male participants constituted the majority, with proportions ranging from 58.3% to 78.5%. Female representation was consistently low, highlighting a clear gender imbalance in both progesterone and vitamin D trials for traumatic brain injury. This limited inclusion of women may affect the generalizability of study findings, as sex-based differences in injury response, hormonal influences, and recovery trajectories are well-documented in TBI research. Future clinical trials should aim for more balanced recruitment or sex-stratified analyses to ensure outcomes are applicable to a broader patient population.

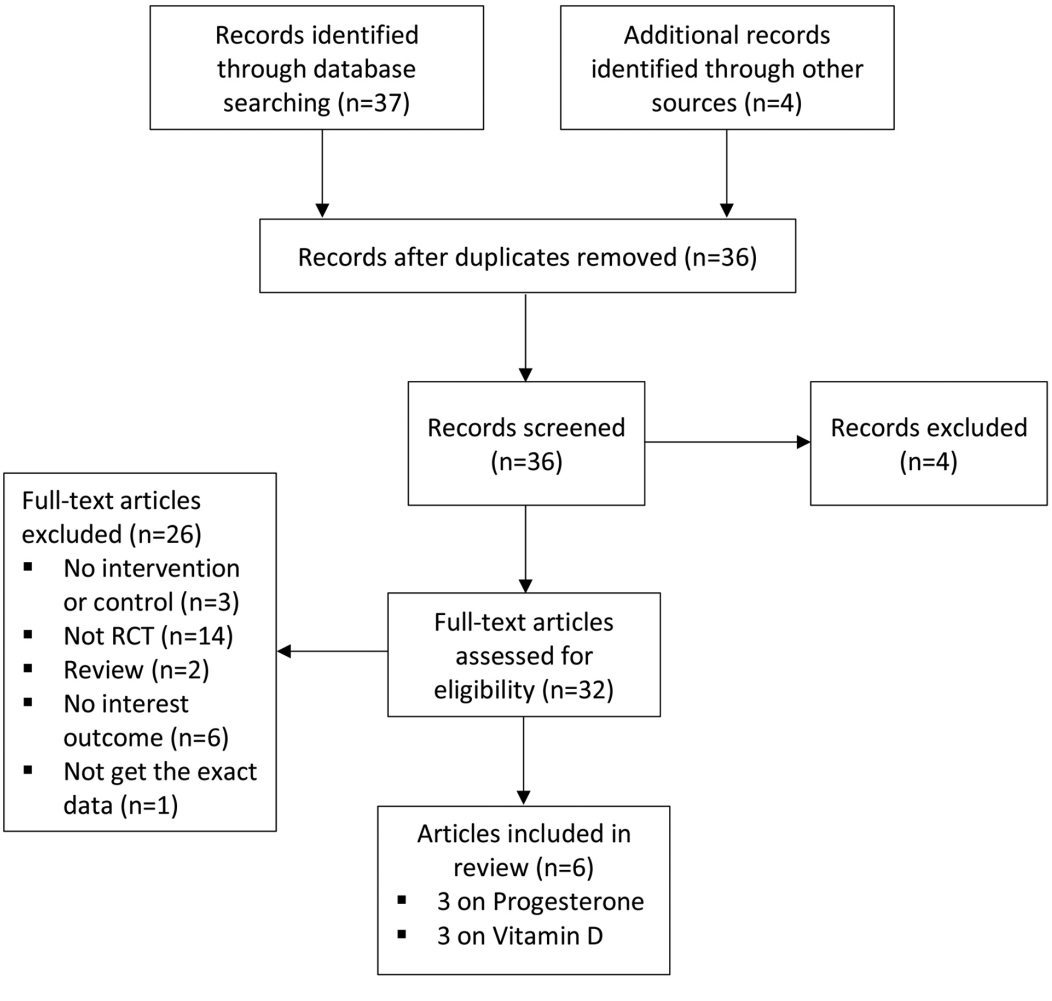

Fig. 1. Flowchart describing the approach used to identify all eligible studies of meta-analysis

Table 1. Baseline characteristics of studies included in the meta-analysis, by Progesterone intervention.

Study	Country	Dose (number of patients)	Male (%)	Mean age (SD)	TBI severity	Drug dosing regimen	Duration (weeks)	Results	Dropout rate (%)	Adverse events leading to dropout (n)	Total adverse events (n)
Wright *et al.*, 2007	USA	0.71 mg/kg loading, then 0.5 mg/kg/h (77)	71	35.3 (14.3)	Moderate to severe	IV infusion: 0.71 mg/kg over 1 h, 0.5 mg/kg/h for 11 h, followed by five 12-h infusions	1	Lower 30-day mortality in progesterone group (13% vs 30.4%)	3.9	0	21 types reported (exact number not provided)
Wright *et al.*, 2014	USA	0.71 mg/kg loading, then 0.5 mg/kg/h (442)	74.5	35.2 (15.7)	Moderate to severe	IV infusion: 0.71 mg/kg over 1 h, 0.5 mg/kg/h for 71 h, tapered over 24 h	2	No significant improvement vs placebo	15.5	3	278
Skolnick *et al.*, 2014	21 countries	0.71 mg/kg loading, then 0.5 mg/kg/h for 119 h (591)	78.5	35 (20.7)	Severe	IV infusion: 0.71 mg/kg/h × 1 h, then 0.5 mg/ kg/h × 119 h (total 120 h)	1	No significant benefit vs placebo in GOS at 6 months (OR 0.96, $p>0.05$)	4.9	1	4025

Notes. TBI (Traumatic Brain Injury), GOS-E (Glasgow Outcome Scale Extended) (range 1–8, higher scores indicate better outcome), IU (International Units), SD (Standard Deviation).

Table 2. Baseline characteristics of studies included in the meta-analysis, by Vitamin D intervention.

Study	Country	Dose (number of patients)	Male (%)	Age (SD)	TBI severity	Drug dosing regimen	Duration (weeks)	Results	Dropout rate (%)	Adverse events leading to dropout (n)	Total adverse events (n
Sharma *et al.*, 2020	India	Oral 120,000 IU (n=20)	71.4	36.4 (16.4)	Moderate to severe	Single oral dose	2	Higher GOS-E at 14 days (4.80 vs 2.21 in control, $p<0.0001$)	0	0	0
Shafiei *et al.*, 2022	Iran	Oral 150,000 IU (n=42)	71.4	36.76 (16.12)	Moderate to severe	Single oral dose	12	Higher GOS-E at 3 months: 62.8% favorable vs 49.7% (placebo), $p=0.03$	0	0	0
Intiso *et al.*, 2024	Italy	Oral 50,000 IU once + 1,000 IU/day (36)	58.3	57.5 (14.9)	Severe	Oral (bolus + maintenance)	8	GOS-E: no significant difference	0	0	0

Notes. TBI (Traumatic Brain Injury), GOS-E (Glasgow Outcome Scale Extended) (range 1–8, higher scores indicate better outcome), IU (International Units), SD (Standard Deviation)

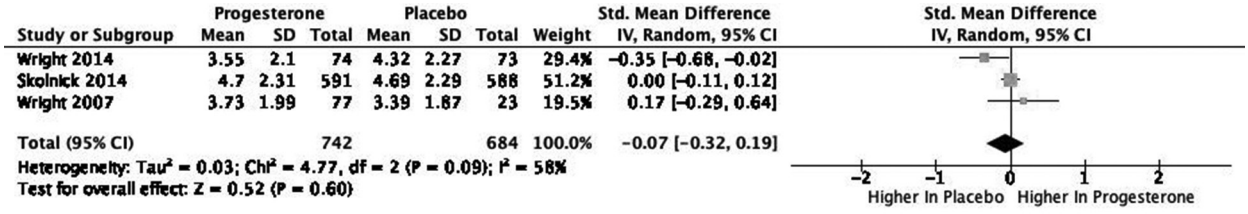

Fig. 2. Functional outcomes based on Glasgow Outcome Scale–Extended (GOS-E) scores in traumatic brain injury patients receiving progesterone treatment

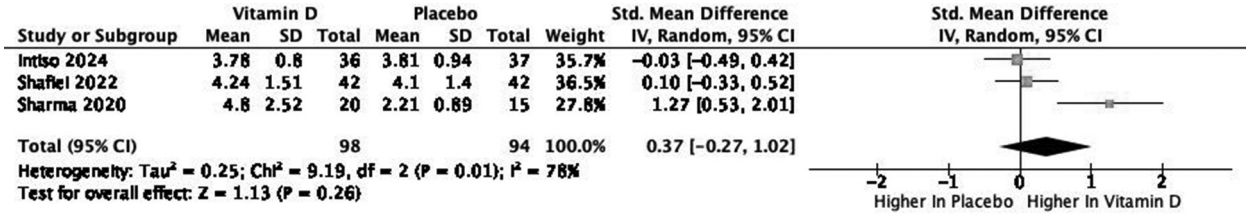

Fig. 3. Functional outcomes based on Glasgow Outcome Scale–Extended (GOS-E) scores in traumatic brain injury patients receiving vitamin D treatment

Discussion

The meta-analysis highlights the challenges of translating the preclinical neuroprotective mechanisms of progesterone and vitamin D into clinically meaningful functional improvements after moderate to severe TBI. While both agents demonstrate biological plausibility, their efficacy remains inconsistent in human trials, underscoring the complexity of TBI pathophysiology and the limitations of monotherapy approaches.

Despite robust preclinical evidence of progesterone's anti-inflammatory and anti-apoptotic effects, pooled data from three RCTs (n=1,426) revealed no significant improvement in GOS-E scores (SMD=−0.07; p=0.60). This finding aligns with the failures of Phase III trials, where delays in treatment initiation (often >6 hours post-injury) and heterogeneous injury patterns may have blunted therapeutic effects [8]. Notably, one trial reported a mortality reduction (13.6% vs. 30.4% in controls), but this did not correlate with long-term functional recovery. The moderate heterogeneity (I^2=58%) across studies suggests variability in dosing regimens or patient stratification, emphasizing the need for precision in trial design [9].

Vitamin D supplementation showed a non-significant trend toward improved outcomes (SMD=0.37; p=0.26), with high heterogeneity (I^2=78%) likely reflecting divergent protocols (e.g., single high-dose vs. maintenance regimens). Preclinical models suggest a role in modulating oxidative stress and neurotrophic factors, but clinical translation is hampered by small sample sizes (n=192 total) and inconsistent reporting of baseline deficiency status—a critical confounder given vitamin D's pleiotropic mechanisms. Age-related metabolic differences may further explain null findings in older cohorts [10].

Notably, a network meta-analysis identified the combination of progesterone and vitamin D as superior to either agent alone, with higher rates of favorable outcomes and reduced mortality [11]. Preclinical data support this synergy; in rodent models, progesterone combined with low-dose vitamin D enhanced spatial memory preservation and astrocyte activation compared to monotherapy (p<0.05) [12]. Vitamin D deficiency has been shown to blunt progesterone's efficacy, suggesting metabolic interdependence. These findings align with the hypothesis that TBI's multifactorial pathology demands multitarget therapies. For instance, progesterone mitigates edema, while vitamin D addresses chronic inflammation and oxidative stress—a dual approach that may counteract secondary injury cascades more effectively [13].

The neutral efficacy findings for progesterone and vitamin D as standalone therapies do not negate their potential utility in optimized regimens. First, progesterone's neuroprotective effects appear critically time-dependent, with preclinical models demonstrating maximal benefit when administered within ≤2 hours post-injury. This contrasts with clinical trials where treatment initiation often exceeded 6 hours—a delay that may explain the diminished therapeutic effects [14]. Incorporating real-time biomarkers such as S100B or glial fibrillary acidic protein (GFAP) could help identify patients within this narrow therapeutic window. [15]. Second, patient stratification based on injury phenotype (e.g., diffuse axonal injury) or baseline vitamin D status might enhance responsiveness, though current trials lack such precision in enrollment [16]. Finally, both agents exhibit excellent safety profiles, positioning them as viable adjuncts to rehabilitation or emerging neuroprotectants in multimodal strategies.

This analysis has several constraints: the small number of vitamin D trials (n=3) limits statistical power; heterogeneity in GOS-E assessment timelines, ranging from 30 days to 6 months complicates outcome comparisons; and incomplete reporting of baseline vitamin D status obscures deficiency-driven treatment effects. Future research should prioritize Phase III trials evaluating progesterone and vitamin D in combination,

leveraging their complementary mechanisms (e.g., progesterone's acute anti-inflammatory effects paired with vitamin D's chronic anti-inflammatory properties). Integrating biomarkers to guide treatment timing and patient selection could enhance precision, while expanding cohorts to include pediatric and geriatric populations—groups with high vitamin D deficiency rates and distinct neuroplasticity profiles—may clarify context-specific efficacy.

A critical limitation of the included trials is the disproportionate male representation, with male participants comprising 58–79% of enrolled cohorts. This underrepresentation of women limits the generalizability of findings, as sex-based differences in neuroinflammation, hormonal responses, and recovery trajectories are increasingly recognized in TBI research. Future trials should adopt sex-stratified enrollment and analyses to determine whether therapeutic responses differ by gender, particularly given progesterone's hormonal interactions and the variable prevalence of vitamin D deficiency across sexes.

Another consideration is potential publication bias. The small number of vitamin D studies and the predominance of neutral-to-negative progesterone trials increase the risk that positive preclinical findings are preferentially published, while underreporting of null or adverse results in early-phase studies could skew the perceived therapeutic promise. Formal assessment using funnel plots or Egger's regression was not feasible given the limited number of included trials, but this bias may inflate the apparent consistency between animal models and selected human studies. Addressing publication bias will require prospective trial registration, rigorous reporting of all outcomes, and the inclusion of unpublished data in future meta-analyses.

Conclusion

Based on the meta-analysis of randomized controlled trials, current evidence does not demonstrate a statistically significant improvement in functional outcomes, as measured by the GOS-E, with either progesterone or vitamin D supplementation in patients with moderate to severe TBI. While progesterone showed no overall benefit, vitamin D exhibited a trend toward improved neurological recovery, though this finding was not statistically significant. The limitations of the existing studies, including small sample sizes and high heterogeneity, highlight the need for larger, well-designed clinical trials to further investigate the therapeutic potential of vitamin D, particularly in combination with other neuroprotective strategies.

Author contributions

Conceptualization, K.O.W. and N.P.U.; Methodology, K.O.W.; Formal Analysis, M.A.W.; Writing—Original Draft Preparation, K.O.W.; Writing—Review & Editing, E.B.S. and N.P.U.; Visualization, M.A.W.; Supervision, E.B.S. All authors have read and agreed to the published version of the manuscript.

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Institutional review board statement

Not applicable.

Informed consent statement

Not applicable.

Data availability statement

All the data supporting the findings of this study are available in the included publications referenced in this meta-analysis.

Conflict of interest

The authors declare no conflict of interest and accept the terms and conditions.

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