

Cognitive dysfunction after cardiac surgery: A systematic review and meta-analysis on the mini-mental state examination findings

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Abstract. Postoperative cognitive dysfunction (POCD) is a frequent complication of cardiac surgery. The present study aimed to quantify changes in Mini-Mental State Examination (MMSE) scores following on-pump cardiac surgery and explore potential study-level moderators associated with variability in cognitive outcomes. A systematic review and random-effects meta-analysis was performed following PRISMA guidelines. MEDLINE, Embase, Cumulative Index to Nursing & Allied Health Literature, Cochrane, PsycINFO, Web of Science, and Scopus were searched up to May 2025; eight prospective single-center cohorts (867 patients) met predefined criteria, providing 14 independent pre/postoperative comparisons of cognitive function. The mean MMSE score was extracted at baseline and final reported follow-up (7 days to 6 months). Hedges' *g* was pooled using a random-effects model; heterogeneity was summarized with τ^2 and I^2 , and a 95% prediction interval (PI) was calculated. Overall, cardiac surgery was associated with a moderate decline in MMSE scores ($g=-0.60$, 95% confidence interval, -0.85 to -0.35 ; $P<0.001$). Heterogeneity was high ($\tau^2=0.178$; $I^2=88.8\%$), yet leave-one-out and Hartung-Knapp adjustments produced similar estimates. The 95% PI (-1.56 to 0.36) spans both negative and slightly positive values, indicating that while most cohorts show cognitive decline, the inclusion of values above zero suggests that small improvements remain possible in some populations. Subgroup analysis showed a large decline

among patients meeting POCD criteria ($g=-0.893$) compared with a small, non-significant change in non-POCD patients ($g=-0.274$; $Q_{\text{between}}=9.08$, $P=0.003$). Meta-regression identified cardiopulmonary-bypass time as the only statistically significant moderator ($\beta=-0.014$ MMSE SD units/min; $P=0.023$), explaining $\sim 50\%$ of between-study variance. Funnel-plot tests suggested possible small-study effects, but trim-and-fill imputed no missing studies and Rosenthal's fail-safe *N* was 431, supporting the robustness of the pooled estimate. These findings suggest that on-pump cardiac surgery is frequently associated with a moderate decline in global cognitive performance as measured by the MMSE, particularly among patients who develop clinical POCD. Awareness of this association may support perioperative cognitive monitoring and efforts to minimize modifiable intraoperative factors such as prolonged cardiopulmonary bypass duration.

Introduction

Perioperative neurocognitive disorders (PNDs) represent a spectrum of cognitive impairments that occur in association with anesthesia and surgery. A multidisciplinary consensus working group in 2018 recommended the term PND as an overarching classification that includes pre-existing cognitive impairment, postoperative delirium, delayed neurocognitive recovery, and postoperative neurocognitive disorder (1). This updated nomenclature aligns perioperative cognitive research with Diagnostic and Statistical Manual of Mental Disorders-5 neurocognitive disorder terminology and aims to standardize the description of cognitive changes occurring before or following surgery (2).

Postoperative cognitive dysfunction (POCD), a term historically used in perioperative research, refers to a measurable decline in cognitive domains such as memory, attention, and executive function following surgery and anesthesia (1). It is prevalent in older patients and has been increasingly observed after major surgeries, including cardiac surgery (1,3). The incidence of POCD following cardiac surgery is 10-40% of patients at 6 weeks post-surgery, and recovery is not always complete; $\sim 45\%$ of these patients achieve full recovery within 1 year (1). POCD is associated with delayed surgical recovery, prolonged hospital stays, impaired activities of daily living,

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and a lower likelihood of independent living (4). For example, patients developing POCD following cardiac surgery have over twice the relative risk of death (~2.04) compared with non-POCD patients and experience an additional average hospital stay of 1-2 days (4). These findings underscore the health costs and morbidity associated with POCD in patients undergoing cardiac surgery. As populations age and more cardiac surgery is performed, the morbidity burden from POCD is expected to rise.

Accurate POCD identification relies on standardized neurocognitive testing (1,4). A comprehensive battery covering multiple cognitive domains is ideal, but in practice, simpler screening tools are typically used. The most widely used brief cognitive test in perioperative literature is the Mini-Mental State Examination (MMSE) (5). The 30-point MMSE is applied to measure global cognitive function (orientation, memory, language, visuospatial), but was not designed to detect the more subtle changes of POCD (6). The MMSE has limitations as a POCD screen: it is not sensitive to mild impairment and under-identifies cognitive decline in surgical patients (7). For example, 15% of elderly patients were classified as cognitively impaired using the MMSE (cutoff <24), whereas 33% were identified as impaired when applying the more stringent Montreal Cognitive Assessment criteria (6-7). Similarly, poor sensitivity and lack of validated cutoffs have been found in other analyses for perioperative cognitive screening using MMSE (6-7). Studies relying on the MMSE may underestimate the true incidence of POCD, and comparisons between trials are difficult because different studies use different cognitive assessment tools.

Variations in reported POCD incidence have arisen from differences in testing procedures (instruments used, follow-up timing, and scoring criteria) (7-9). To the best of our knowledge, few studies have employed a consistent tool such as the MMSE to compare cognitive outcomes, particularly in cardiac surgery, directly (10-16). Therefore, the present systematic review and meta-analysis focusing on MMSE-based cognitive outcomes following cardiac surgery aimed to quantify changes in MMSE scores from preoperative baseline to postoperative follow-up among patients undergoing cardiac surgery, explore study-level factors associated with variability in cognitive outcomes, and evaluate the methodological characteristics of MMSE use across studies.

Materials and methods

Data sources and search strategy. The present systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines (9). The study methods, inclusion criteria, and analysis plan were defined *a priori* before the literature search and data extraction.

MEDLINE/PubMed (pubmed.ncbi.nlm.nih.gov/), Embase (<https://www.embase.com/>), Cumulative Index to Nursing & Allied Health Literature (about.ebsco.com/products/research-databases/cinahl-database), the Cochrane Library (<https://www.cochranelibrary.com/>), PsycINFO (<https://www.apa.org/pubs/databases/psycinfo>), Web of Science (<https://mjl.clarivate.com/home>), and Scopus (<https://www.scopus.com/sources>) were searched for relevant

literature from inception until May 2025 without regard to date or language. Search terms (Data S1) for 'cardiac surgery' [such as coronary artery bypass grafting (CABG), valve, or aortic surgery], 'postoperative cognitive dysfunction', and 'Mini-Mental State Examination' combined keywords and MeSH/Emtree terms. The reference lists of relevant reviews, dissertations, and conference proceedings were also searched.

Titles, abstracts, and full texts were independently screened by two reviewers against the predefined inclusion criteria. Inter-rater agreement during the screening process was assessed using Cohen's κ statistic after the initial title-abstract screening stage to quantify reviewer consistency. Any discrepancies were resolved through discussion or consultation with a third reviewer.

Inclusion and exclusion criteria. The inclusion criteria for the studies were as follows: i) Adult patients (age ≥ 18 years) undergoing cardiac surgery (CABG, valve, or aortic surgery); ii) cognitive function assessed using the MMSE both before and after surgery; iii) sufficient data reported (mean and SD or change scores) to calculate the standardized mean difference (SMD) and iv) original clinical studies (randomized trials or observational cohort studies).

Studies that did not use the MMSE for cognitive assessment, case reports, reviews, pediatric populations, or non-cardiac procedures (thoracic surgery, cardiac transplantation, or transcatheter valve replacement) were excluded. No restriction on publication year was applied.

Because included studies reported postoperative MMSE assessments at different follow-up intervals, data were extracted from the longest postoperative follow-up reported in each study when multiple time points were available. When studies reported several clinically distinct follow-up windows (early and late postoperative assessments), these were considered separate comparisons in the meta-analysis provided that independent summary statistics were available.

Data extraction. For subgroup analyses, patients were categorized as having POCD or not (non-POCD) according to the definitions reported in the original studies. In the perioperative literature, POCD is generally defined as a decline in cognitive performance relative to the patient's preoperative baseline measured using neuropsychological tests (2). However, there is currently no universally standardized diagnostic threshold, and studies typically employ different statistical approaches to determine cognitive decline (decreases of $\geq 1-2$ SD from baseline performance, percentage decline in test scores, or composite indices derived from multiple cognitive tests) (1). POCD classification was therefore based on the criteria used in the original publications, which typically relied on postoperative deterioration in cognitive test performance, assessed using the MMSE or broader neuropsychological test batteries, relative to baseline values. Because diagnostic thresholds, testing batteries, and timing of postoperative assessments vary across studies, study-specific definitions were used rather than attempting to retrospectively standardize the classification using a single cutoff, which would not have been feasible with the available summary data (9).

Data were independently extracted by two investigators using a pre-piloted standardized form. Extracted

variables included study design (prospective or retrospective; single-center or multicenter), country and setting, sample size, patient demographic characteristics (age and sex distribution), type of cardiac surgery, and timing of MMSE assessment. For each eligible comparison, the number of participants and the mean MMSE scores at baseline and postoperative time points or the reported change in MMSE when available were extracted.

When information was missing or unclear, attempts were made to contact the study authors for clarification. Any discrepancies in data extraction were resolved through discussion until consensus was reached. In addition, key study characteristics, including differences in surgical procedures, follow-up intervals, and study design, were recorded to facilitate interpretation of heterogeneity across studies.

Evaluation of quality. A total of two reviewers independently evaluated methodological quality using the Critical Appraisal Skills Programme (CASP) checklist for cohort studies (8). The CASP tool includes 12 items evaluating study validity, methodological rigor, and relevance across domains such as selection bias, measurement of outcomes, confounding control, and applicability. Each item was scored as 'yes', 'no', or 'unclear'. Studies were categorized according to the number of criteria fulfilled as follows: ≥ 10 , good quality; 7-9, fair quality, and ≤ 6 , low quality. Disagreements were resolved through discussion until a consensus was reached.

Statistical analysis. All meta-analytic computations were conducted using Comprehensive Meta-Analysis software, version 4 (Biostat, Inc.). The effect size for postoperative change in cognitive performance was estimated using SMD (Hedges' g) with corresponding 95% confidence intervals (CIs). Effect sizes were calculated from the reported preoperative and postoperative mean MMSE for each cohort. This approach standardizes the mean difference using the pooled SD of the two measurements and therefore does not require explicit imputation of the within-subject association between pre- and postoperative scores. Because the primary studies did not consistently report change-score variances or pre-post association, no fixed correlation coefficient was assumed in the analysis. Where only medians with ranges or interquartile ranges were reported, means and SD were estimated using established conversion formulas, and SD was back-calculated from reported standard errors or CI when necessary (17).

When primary studies reported >1 eligible comparison (distinct postoperative follow-up time points or separate patient strata), each comparison was treated as an independent effect size when it represented a clinically distinct contrast with separate summary statistics (means and SD). This approach allows the meta-analysis to incorporate all available evidence while preserving the specific clinical context of each comparison.

To account for anticipated between-study heterogeneity, a random-effects model was prespecified. Subgroup analyses were conducted using a mixed-effects approach, in which random-effects models were applied within each subgroup, while differences between subgroups were assessed using a fixed-effect Q_{between} statistic. Between-study variance (τ^2) was estimated using the DerSimonian-Laird method.

Sensitivity analyses were performed using the Paule-Mandel, Sidik-Jonkman, and restricted maximum-likelihood estimators, and the Hartung-Knapp-Sidik-Jonkman adjustment was applied to the pooled variance. Statistical heterogeneity was quantified using Cochran's Q statistic ($P < 0.10$), I^2 , τ^2 , and τ . In addition to 95% CI, 95% prediction interval (PI) was calculated for each pooled SMD to estimate the range within which the true effect of a comparable future study was likely to lie.

Robustness of the findings was assessed through several sensitivity analyses, including leave-one-out influence analysis, Baujat plots to identify influential comparisons, comparison with a fixed-effect model, exclusion of studies at higher risk of bias, and reanalysis using alternative effect-size metrics (raw MMSE point change). Potential publication bias and small-study effects were evaluated by visual inspection of funnel plots of SMDs against their standard errors, Egger's weighted regression test, and Begg's rank-correlation test (two-tailed $P < 0.1$) and Duval and Tweedie's trim-and-fill method when asymmetry was detected to estimate the number of potentially missing studies and generate an adjusted pooled effect size. In addition, Rosenthal's and Orwin's fail-safe N statistics were calculated to estimate how many null studies would be required to overturn the overall result.

$P < 0.05$ was considered to indicate a statistically significant difference, and all tests were two-tailed unless otherwise specified ($P < 0.10$ for Cochran's Q and funnel-plot asymmetry tests). CI, PI, and test statistics were based on the t -distribution with $k-1$ degrees of freedom (df).

Results

Search strategy outcome. The systematic database search identified 1,564 records. Following removal of 312 duplicates, 1,252 titles and abstracts were screened, of which 1,160 were excluded for not meeting the criteria (non-cardiac surgery, pediatric populations or absence of a cognitive outcome; Fig. 1). In total, 72 full-text articles were assessed for eligibility and 64 were excluded for the following reasons: No MMSE data ($n=21$), review, editorial or conference abstract ($n=13$), ineligible study design (no original data; $n=12$), mixed surgical cohorts without extractable cardiac subgroup data ($n=10$) and duplicate or overlapping populations ($n=8$). In total, eight studies met the eligibility criteria and were included in the qualitative synthesis (10-16,18), yielding 14 independent comparisons (distinct patient groups, time points, or surgical strata).

General characteristics of the included studies. All eight studies (10-16,18) were prospective single-center cohorts published between 2005 and 2024; four were conducted in Japan (10-13), with one each in India (16), Sweden (14), China (18), and Malaysia (15). A total of 867 patients (sample size range, 28-280) undergoing on-pump CABG or valve surgery were analyzed. Mean or median age was between 60 and 65 in the Japanese (10-13) and Swedish (14) cohorts and ~ 50 years in the Chinese valve cohort (18); the overall proportion of male patients was $\sim 70\%$, but was lower (39%) in the study by Zhang *et al* (18). All studies assessed MMSE scores pre-operatively and at ≥ 1 early postoperative time point [within the first postoperative week or at hospital discharge in six studies, 2 weeks in Maekawa *et al* (13), and 6 weeks in

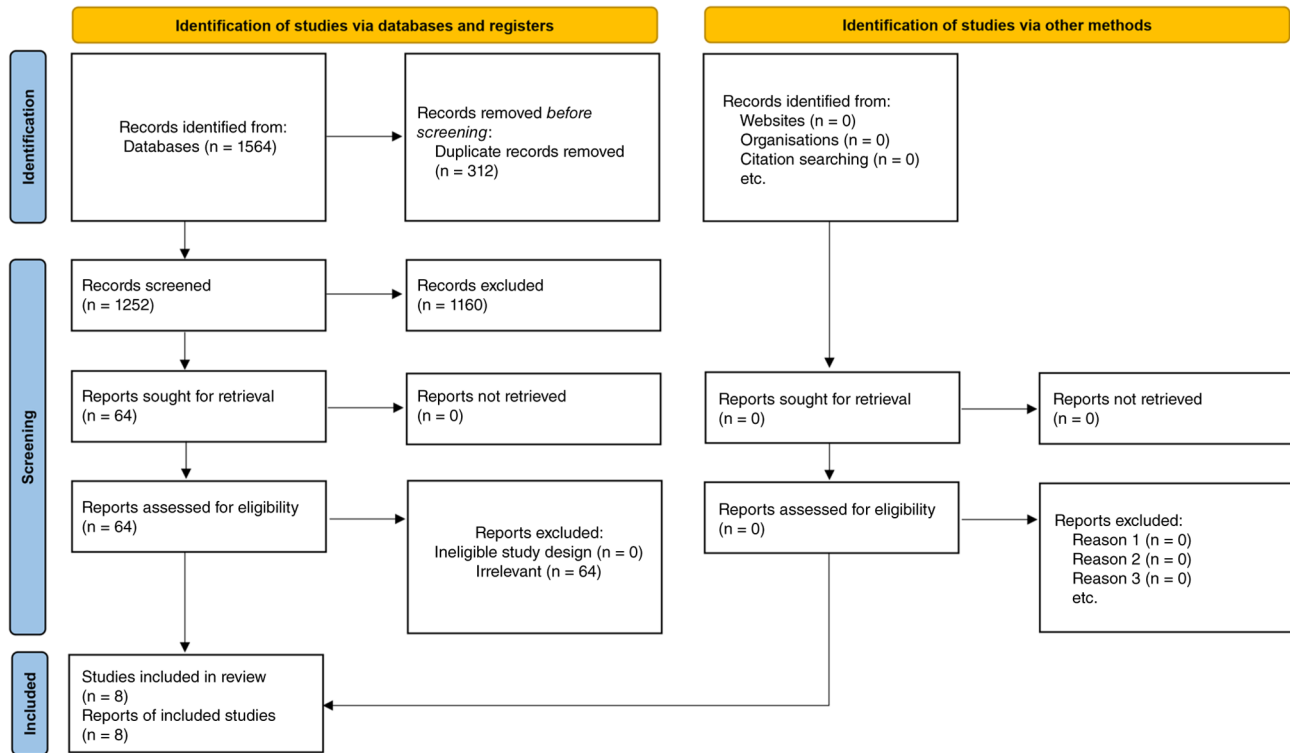


Figure 1. PRISMA flow diagram of study selection. Of 1,564 records identified and 24 additional references from manual search, 312 duplicates were removed, leaving 1,252 titles/abstracts for screening. Following exclusion of 1,160 ineligible citations, 72 full-text articles were assessed; 64 were excluded for predefined reasons (no Mini-Mental State Examination data, $n=21$; review/editorial/abstract, $n=13$; ineligible study design, $n=12$; mixed cohorts without extractable cardiac subgroup, $n=10$; overlapping populations, $n=8$). In total, eight studies met all criteria and yielded 14 independent pre/post comparisons included in qualitative and quantitative synthesis.

Yazit *et al* (15)]. Several cohorts also included longer follow-up assessments up to 6 months (Table I) (10). Postoperative cognitive assessment spanned the very early phase (≤ 1 week), an intermediate window (2 weeks), and a later window (6 weeks–6 months), yielding 14 independent comparisons included in the meta-analysis. Baseline MMSE scores ranged from 26 to 29 points, indicating generally preserved preoperative cognitive function across the populations.

Quantitative synthesis of pre- vs. postoperative cognitive function via MMSE. Cardiac surgery was associated with a significant decline in MMSE (Hedges $g=-0.60$, 95% CI -0.85 to -0.35 , $P<0.001$; Fig. 2). For clinical interpretability, the pooled standardized effect size was translated into an approximate change in raw MMSE points. Using the typical baseline SD reported across the included cohorts (~ 3 MMSE points), the pooled effect size ($g=-0.60$) corresponded to an estimated decline of 1–2 points on the 30-point MMSE scale. Between-study heterogeneity was notable ($\tau^2=0.178$, $\tau=0.422$; $Q=116.4$, $df=13$, $P<0.001$; $I^2=88.8\%$). The 95% PI (-1.56 to 0.36) spanned both negative and slightly positive values, indicating that while most cohorts are expected to show cognitive decline, the inclusion of values above zero suggests that small improvements remain possible in some populations. A fixed-effect model yielded a smaller but significant estimate ($g=-0.35$, 95% CI -0.43 to -0.27 , $P<0.001$).

Subgroup analysis. Using the prespecified mixed-effects model, patients who developed POCD (eight comparisons)

showed a significant decline in MMSE scores (Hedges' $g=-0.893$, 95% CI -1.258 to -0.527 ; $P<0.001$; 95% PI -2.114 to 0.328), whereas patients without POCD (six comparisons) showed a non-significant change ($g=-0.274$, 95% CI -0.631 to 0.084 ; $P=0.134$; 95% PI, -1.517 to 0.970 ; Fig. 3). Heterogeneity was high in both subgroups ($I^2=88-89\%$), but the between-group test showed a significant difference in effect sizes ($Q_{\text{between}}=9.08$, $df=1$, $P=0.003$). Across all 14 comparisons, the pooled mixed-effects estimate was $g=-0.576$ (95% CI -0.832 to -0.321 ; $P<0.001$; 95% PI -1.539 to 0.386), indicating that the overall postoperative decline was driven primarily by the subgroup with clinical POCD.

Sensitivity analysis. Sequential leave-one-out sensitivity analysis showed that omission of any single comparison changed the pooled standardized mean difference by <0.08 . In every iteration, the pooled estimate remained negative and significant (all $P\leq 0.002$), indicating that the overall result was not driven by any individual comparison (Fig. 4). Taken together, these findings support the robustness of the conclusion that cardiac surgery was associated with a significant postoperative decline in MMSE score.

Heterogeneity assessment using PI analysis. For the primary random-effects model (14 comparisons), the 95% PI ranged from -1.56 to 0.36 SMD units (with the null value falling within the interval), indicating that most future studies of similar design are likely to observe a postoperative decline in MMSE, although a small improvement remains possible in

Table I. Characteristics of the studies included in the systematic review and meta-analysis.

First author, year	Design/setting	Country	Sample size	Mean age, years	Male, %	Cardiac procedure	Baseline MMSE	Post-operative MMSE	(Refs.)
Kadoi and Goto, 2006	Prospective cohort, single center	Japan	88	NR	NR	On-pump CABG	NR	6 mo: 41.5±4.1	(10)
Kadoi <i>et al</i> , 2011	Prospective cohort, single center	Japan	90	65±9	76	On-pump CABG	28.6±1.9	POD7: 26.5±2.4; 6 mo: 27.9±2.1	(11)
Kadoi <i>et al</i> , 2005	Prospective cohort, single center	Japan	280	64±11	78	On-pump CABG	28.5±1.7	POD7: 26.7±2.3; 6 mo: 27.9±2.0	(12)
Maekawa <i>et al</i> , 2014	Prospective cohort, single center	Japan	28	≥60	NR	CABG/valve	26.8±1.9	2 wk: 24.4±2.1	(13)
Veliz-Reissmüller <i>et al</i> , 2007	Prospective cohort	Sweden	103	≥60	NR	CABG ± valve	Median, 29.0 (IQR NR)	Discharge median, 26.5 (delirium group)	(14)
Yazit <i>et al</i> , 2024	Prospective cohort	Malaysia	188	NR	NR	Mixed cardiac surgery	27.5±2.5	Discharge: 26.3±4.0; 6 wk: 27.4±3.6	(15)
Shiraboina <i>et al</i> , 2014	Prospective cohort	India	62	NR	62	CABG/AVR	NR	POD7 proportion ≤24	(16)
Zhang <i>et al</i> , 2021	Prospective cohort	China	71	51 (45-55)	39	Valve surgery with CPB	28.2±1.6	POD7: 27.4±2.2	(18)

Cognitive scores are presented as mean ± standard deviation unless otherwise specified. MMSE, Mini-Mental State Examination; CABG, coronary artery bypass grafting; POD, postoperative day; mo, month; NR, not reported; wk, week; AVR, aortic valve replacement; CPB, cardiopulmonary bypass.

certain cohorts (Fig. 5). The subgroup analyses supported this pattern. Specifically, cohorts consisting primarily of patients with POCD are expected to report a marked cognitive decline, whereas studies including only patients without POCD may plausibly observe outcomes ranging from a modest decline to a modest improvement.

The range of the PI reflects substantial between-study heterogeneity; its predominantly negative distribution supports the overall conclusion that cognitive performance, as measured by the MMSE, generally declined following on-pump cardiac surgery.

Publication bias assessment. Visual inspection of the funnel plot (Fig. 6) suggested an absence of large studies reporting null effects, which was supported by statistical tests. Egger's regression

test yielded an intercept of -3.69 (95% CI -6.81 to -0.58; P=0.024), and Begg and Mazumdar's rank-correlation test indicated significant asymmetry (Kendall's τ =-0.43, z =2.14; two-tailed P=0.033). Despite this asymmetry, Duval and Tweedie's trim-and-fill procedure did not identify any potentially missing studies ($k_{\text{trimmed}}=0$), and the bias-adjusted random-effects estimate was unchanged compared with the original pooled estimate (Hedges' g =-0.598, 95% CI -0.847 to -0.349).

Rosenthal's classic fail-safe N indicated that 431 additional null studies would be required to increase the pooled P-value to >0.05, exceeding the conventional tolerance threshold ($5 \times k + 10=80$). Together, these analyses suggest that although small-study effects may be present, they were unlikely to materially alter the conclusion that cardiac surgery is associated with a significant postoperative decline in MMSE score.

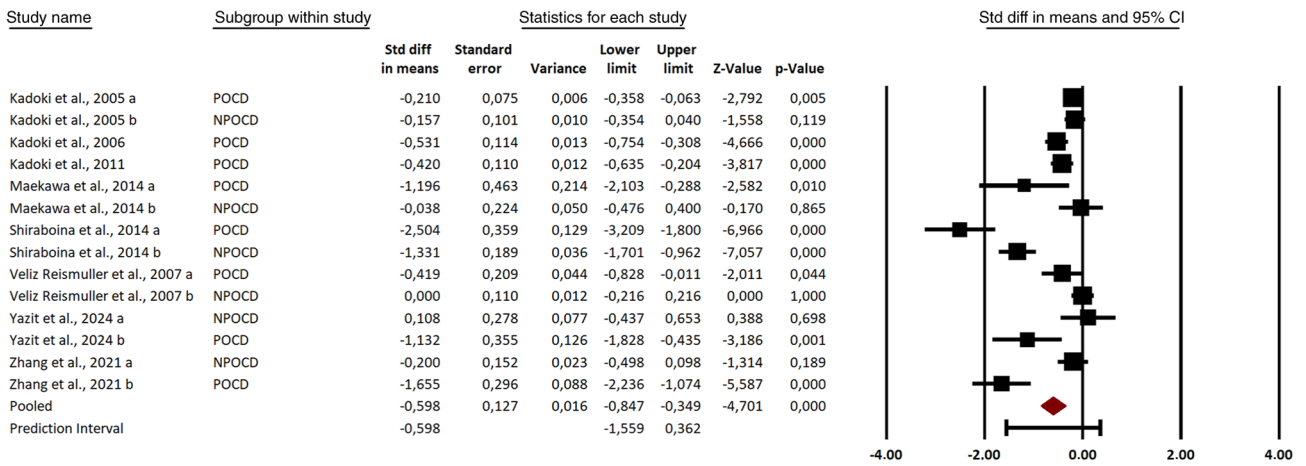


Figure 2. Forest plot of pre- vs. postoperative Mini-Mental State Examination change in cardiac surgery patients. Each horizontal line shows the study-specific Hedges *g* and 95% CI; squares are centered on point estimates and scaled to study weight. The diamond represents the pooled random-effects estimate ($g = -0.60$, 95% CI -0.85 to -0.35). Substantial between-study heterogeneity is reflected by $\tau^2 = 0.178$ ($I^2 = 88.8\%$). A 95% prediction interval (-1.56 to 0.36) beneath the pooled diamond indicated the range in which the true effect of a future comparable study is likely to lie. Std diff, standard difference; NPOCD, no postoperative cognitive dysfunction.

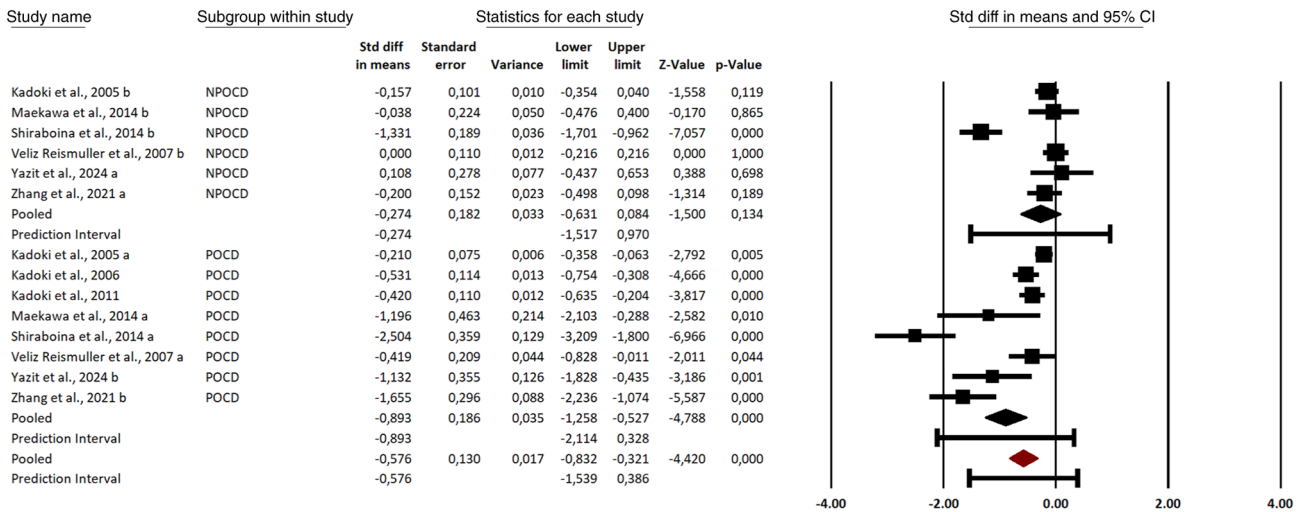


Figure 3. Subgroup forest plot comparing patients with and without POCD. Separate pooled estimates are shown for POCD (eight comparisons) and NPOCD (six comparisons). Patients with POCD exhibited a large decline ($g = -0.893$, 95% CI -1.258 to -0.527), whereas patients with NPOCD show a small, non-significant change ($g = -0.274$, 95% CI -0.631 to 0.084). The test for subgroup difference yielded $Q_{\text{between}} = 9.08$ ($P = 0.003$). Std diff, standard difference; NPOCD, no postoperative cognitive dysfunction.

Meta-regression (moderator analysis). To explore sources of the large between-study heterogeneity ($\tau^2 = 0.178$; $I^2 = \sim 89\%$), mixed-effects meta-regression analysis was performed, including five *a priori* clinical moderators: Mean age, cardiopulmonary bypass (CPB) time, study-level prevalence of hypertension and diabetes mellitus, and male sex. The simultaneous (multivariable) model was significant ($Q_{\text{model}} = 11.22$, $df = 5$, $P = 0.047$) and accounted for part of the between-study heterogeneity, although only CPB time was an independent predictor (Table II). Specifically, each 1 min increase in CPB duration was associated with an additional decline of 0.014 SD units in MMSE scores ($\beta = -0.014 \pm 0.006$, $Z = -2.27$, $P = 0.023$), corresponding to ~ 0.9 SD greater decline for 1 h additional bypass time.

When each moderator was entered separately (univariate models; Table III), CPB time showed the strongest association and explained $\sim 50\%$ of the between-study variance

($R^2_{\text{analog}} = 0.50$; τ^2 decreased from 0.198 to 0.100; $Q = 18.68$, $P = 0.0001$), whereas age explained $\sim 29\%$ of the heterogeneity ($Q = 7.23$, $P = 0.007$). The remaining covariates contributed little to explaining the variability across studies.

Diagnostic plots and jackknife influence analyses indicated that no single comparison exerted a disproportionate influence on the regression estimates (largest studentized residual = 2.10; Cook's distance < 1 for all points). Furthermore, no problematic multicollinearity was detected among predictors; the highest correlation was $|r| = 0.80$ between age and hypertension, and all variance inflation factors were ≤ 1.34 (Fig. 7).

Study quality assessment. In total, 5/8 studies achieved good methodological quality. All of these were prospective single-center cohorts with clearly stated aims, well-described recruitment, and rigorous multivariable adjustment;

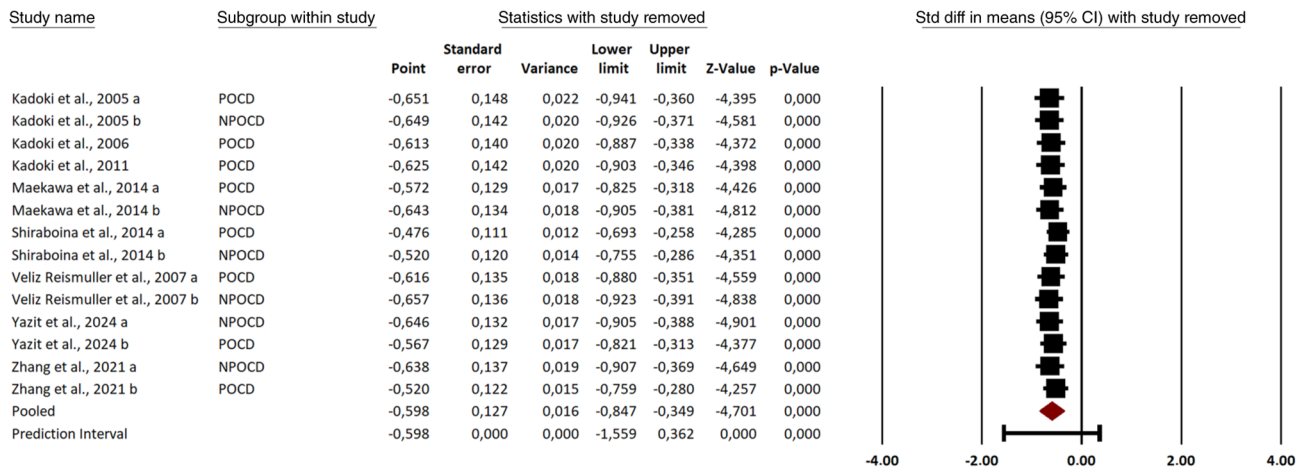


Figure 4. Leave-one-out sensitivity plot for the pooled Mini-Mental State Examination effect. Each point represents the overall Hedges'g recalculated after omitting one comparison at a time; the vertical dashed line marks the complete-data estimate ($g=-0.60$). Horizontal error bars show 95% CIs for each re-pooled estimate. All values remain negative and significant (range, -0.68 to -0.52; $P\leq 0.002$), indicating no single study unduly contributed to the overall result. Std diff, standard difference; NPOCD, no postoperative cognitive dysfunction.

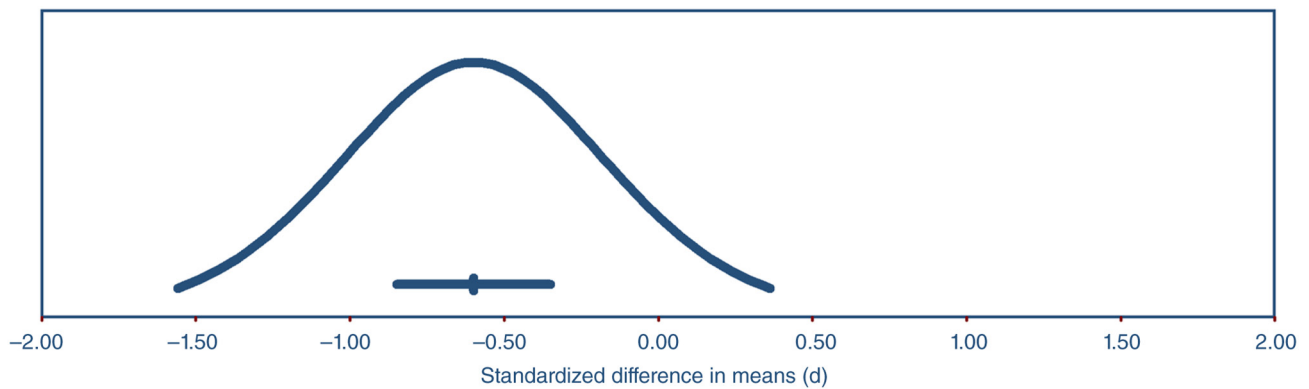


Figure 5. Prediction-interval plot of Mini-Mental State Examination effect sizes. Standard errors are plotted against Hedges' g on a reversed standard-error scale.

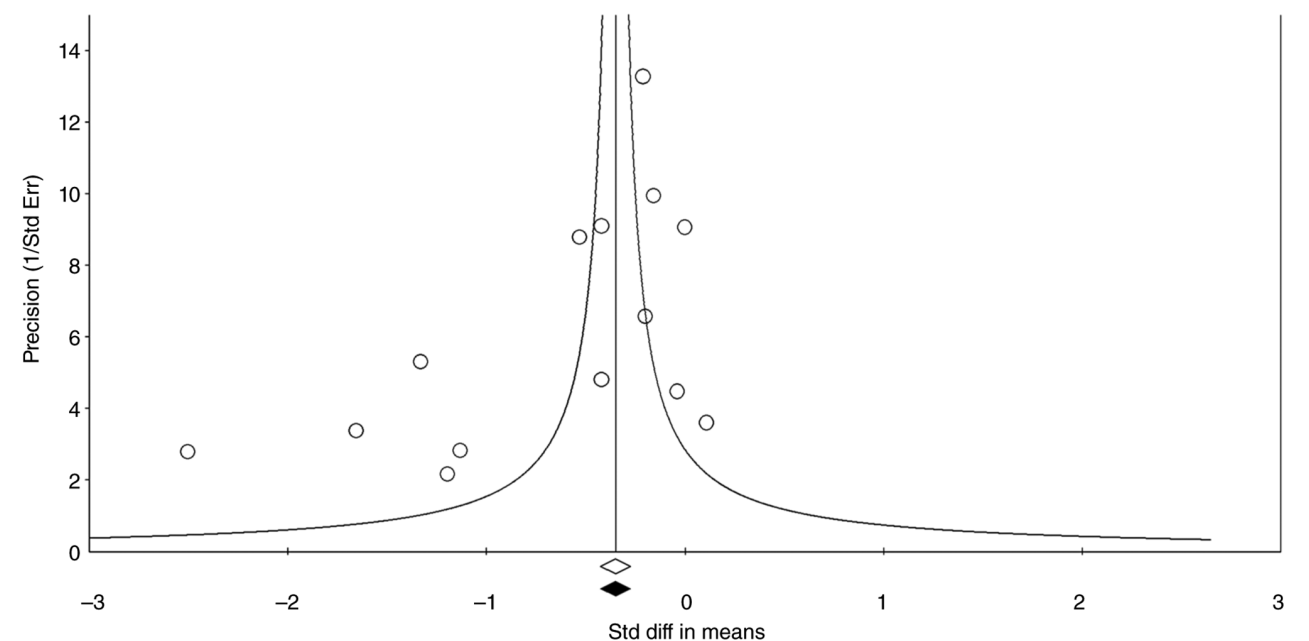


Figure 6. Funnel plot with Egger's regression line assessing publication bias. Scatter of study effect sizes vs. standard errors reveals a slight asymmetry, with a relative lack of large, null-effect studies on the right. The solid regression line depicts Egger's test (intercept=-3.69, $P=0.024$). Std diff, standard difference.

Table II. Multivariable meta-regression of mini-mental state examination change after cardiac surgery.

Moderator (k=14)	β (SMD-units)	95% CI	Z-value	P-value
Intercept	-2.3838	-6.673 to 1.905	-1.09	0.276
Age	+0.0642	-0.016 to 0.145	1.56	0.118
CPB time	-0.0143	-0.0265 to -0.0020	-2.27	0.023
Hypertension	+0.0079	-0.030 to 0.046	0.40	0.686
Diabetes	-0.0013	-0.013 to 0.011	-0.21	0.836
Male	-0.0119	-0.054 to 0.030	-0.56	0.578

SMD, standardized mean difference; CPB, cardiopulmonary bypass.

Table III. Explained heterogeneity in separate (one-predictor) models.

Model	τ^2	R ²	Q _{model} (df=1)	P-value
Intercept only	0.198	-	-	-
Intercept + age	0.140	29	7.23	0.007
Intercept + CPB time	0.100	50	18.68	0.001
Intercept + hypertension	0.141	29	15.17	0.002
Intercept + diabetes	0.204	0	12.17	0.016
Intercept + male	0.237	0	11.22	0.047

CPB, cardiopulmonary bypass; df, degrees of freedom; -, not applicable.

for example, Kadoi *et al* (12) and Kadoi *et al* (11) used consensus neuropsychology batteries and logistic regression. Maekawa *et al* (13) and Shiraboina *et al* (16) were graded as fair, chiefly because short follow-up windows (≤ 2 weeks) or limited reporting made it unclear whether all relevant confounders were handled; nevertheless, both used validated cognitive outcomes (MMSE + extended batteries) and prospective designs. No study was downgraded for imprecision (every cohort reported effect sizes with either CI or full regression output), and the absence of serious loss to follow-up across studies supported internal validity. External generalizability was highest for the larger cohorts [Yazit *et al* (15), 188 patients; Kadoi and Goto (10), 280 patients], whereas single-surgeon pilots require cautious extrapolation. Overall, the evidence base was methodologically sound, with minor limitations concentrated in the smaller exploratory studies (Table IV).

Discussion

The present meta-analysis, which included 14 independent pre/postoperative comparisons and 867 patients, demonstrated a moderate overall decline in MMSE score following on-pump cardiac surgery. Although small improvements cannot be excluded, the 95% PI suggested that most future cohorts may observe some degree of POCD. Despite notable heterogeneity, the pooled estimate remained robust across sensitivity analyses and trim-and-fill procedures, together with a large fail-safe N (431 studies), suggesting that publication bias was unlikely to meaningfully influence the results.

Cognitive outcomes differed markedly according to POCD status. Patients meeting formal POCD criteria experienced a significant decline in MMSE, whereas those without POCD showed only a non-significant change. These findings indicate that the overall POCD observed across studies was largely driven by patients who develop clinically notable neurocognitive impairment.

The pooled standardized effect size corresponded to a decrease of 1-2 points on the 30-point MMSE scale, which is consistent with the magnitude of early postoperative cognitive changes reported in previous studies (19,20). Greaves *et al* (19) reported cognitive impairment in ~43% of patients immediately following coronary artery bypass surgery, declining to 19% at 6 months but increasing again to 39% after 5 years. The present results, therefore, align with the early POCD reported in large observational cohorts. However, the PI indicated that outcomes may vary across populations, and small improvements may occur in certain cohorts, such as patients with impaired cerebral perfusion who benefit from improved postoperative hemodynamics following revascularization (21).

Several biological mechanisms have been proposed to explain postoperative neurocognitive decline following cardiac surgery (22-24). Current evidence suggests that perioperative neurocognitive disorder is multifactorial and involves interactions between cerebral microembolism, systemic inflammatory activation, and transient cerebral hypoperfusion during CPB (24). Microembolic particles, including air bubbles, fat droplets, platelet aggregates, and fragments of atherosclerotic plaque, may enter the cerebral

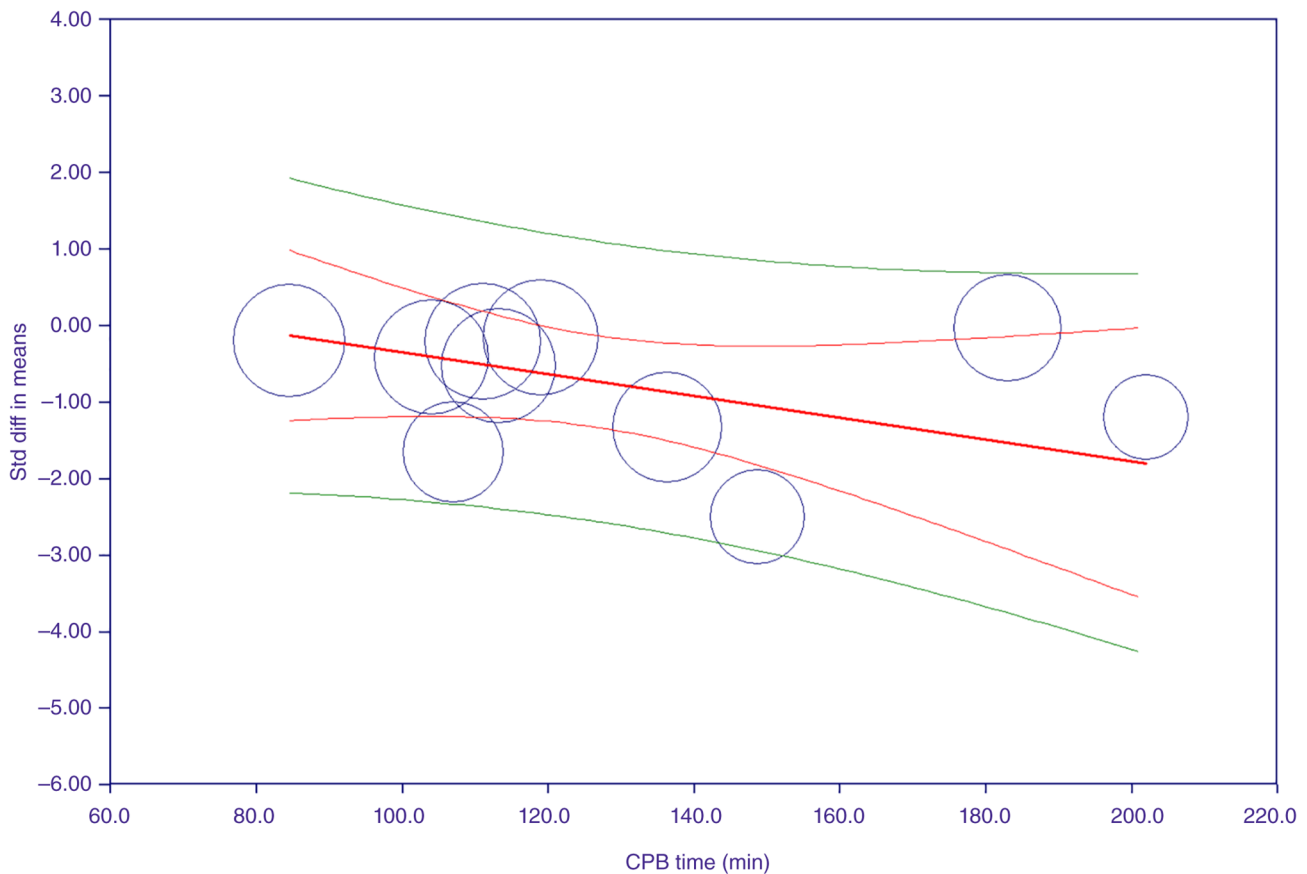


Figure 7. Meta-regression of CPB time vs. change in MMSE. Bubble area is proportional to the inverse of its within-study variance (larger bubbles indicate greater weight). The thick line is the fitted regression ($\beta=-0.014$ SMD/min CPB; $Z=-2.27$; $P=0.023$), with the green band marking its 95% confidence limits. The model explains 50% of the between-study heterogeneity ($R^2_{\text{analog}}=0.50$), decreasing τ^2 from 0.198 to 0.100. The plot shows a clear negative slope: Comparisons with longer bypass runs cluster toward larger cognitive declines, while those with shorter CPB times tend toward smaller or negligible MMSE changes, supporting CPB duration as an independent moderator of postoperative cognitive outcome. CPB, cardiopulmonary bypass; MMSE, Mini-Mental State Examination; std diff, standard difference.

circulation during aortic manipulation or extracorporeal circulation, leading to occlusion of small cerebral vessels and focal neuronal injury (24). In addition, CPB activates inflammatory pathways through contact between circulating blood and artificial circuit surfaces, resulting in complement activation and the release of pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor- α . These inflammatory responses may disrupt the blood-brain barrier and promote neuroinflammation, which is a key contributor to POCD (24). Transient cerebral hypoperfusion and ischemia-reperfusion injury may exacerbate neuronal vulnerability and impair synaptic function, contributing to POCD (22-24).

In addition to these established mechanisms, mitochondrial dysfunction may represent a key downstream pathway in postoperative neurocognitive decline (25-30). Surgery, anesthesia, ischemia-reperfusion, and systemic inflammation can impair mitochondrial respiration, decrease ATP production, increase oxidative stress, disrupt calcium homeostasis, and interfere with mitophagy and other mitochondrial quality-control processes (25,30,31). These changes may impair synaptic plasticity and neuronal integrity, thereby contributing to POCD (25). Preclinical and narrative review data further suggest that modulation of mitochondrial dynamics and homeostasis may represent a promising therapeutic direction, although such approaches remain investigational

and have not been established in routine perioperative practice (25-28).

Subgroup analysis confirmed that patients meeting POCD criteria experienced notably greater cognitive decline than those without POCD. Notably, the non-POCD subgroup demonstrated a non-significant reduction in MMSE scores, suggesting that subtle cognitive changes may occur in patients who do not meet formal diagnostic thresholds. This is consistent with prior evidence showing that patients undergoing cardiac surgery without overt neurocognitive complications may experience modest postoperative declines in cognitive performance (32). For example, Saczynski *et al* (32) reported that patients who did not develop postoperative delirium demonstrated an average MMSE reduction of ~ 2 points in the early postoperative period.

Because the number of available comparisons was relatively small, the present meta-regression analyses were considered exploratory and interpreted with caution to minimize the risk of overfitting. The analysis was conducted using study-level covariates rather than individual patient data; therefore, the observed associations represent ecological associations at the study level and should not be interpreted as causal effects at the individual level. The present meta-regression analysis identified CPB duration as the only significant moderator associated with variability in postoperative MMSE decline.

Table IV. Critical Appraisal Skills Program cohort-study checklist applied to the included studies.

First author, year	Focused issue	Acceptable recruitment	Exposure well-measured	Outcome well-measured	Confounders considered	Adequate follow-up	Clearly stated results	Precision	Internal validity	External applicability	Consistent with evidence	Practice implication	Overall rating (Refs.)
Kadoi and Goto, 2006	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Good (10)
Kadoi <i>et al.</i> , 2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Good (11)
Kadoi <i>et al.</i> , 2005	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Good (12)
Maekawa <i>et al.</i> , 2014	Y	Y	Y	Y	U	U ^a	Y	U	Y	U	Y	U	Fair (13)
Veliz-Reissmüller <i>et al.</i> , 2007	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Good (14)
Yazit <i>et al.</i> , 2024	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Good (15)
Shiraboina <i>et al.</i> , 2014	Y	Y	U	Y	Y	Y	Y	Y	Y	U	Y	U	Fair (16)
Zhang <i>et al.</i> , 2021	Y	Y	Y	Y	Y	Y ^b	Y	Y	Y	U	Y	U	Good (18)

^aFollowed patients only for 2 weeks and did not adjust for potential confounders beyond imaging variables; ^bfollowed patients for 7 days only but had no loss to follow-up. Y, yes; N, no; U, unclear.

Each additional minute of CPB was associated with a small increase in cognitive impairment (33). Prolonged CPB may increase neurological vulnerability through mechanisms such as increased embolic load, systemic inflammatory activation, and alterations in cerebral perfusion (34). However, CPB duration may also reflect surgical complexity, as longer bypass times typically occur in patients undergoing more complicated procedures or combined operations.

Beyond bypass duration, several patient-level and procedural factors are associated with POCD. In particular, advanced age has consistently been identified as an important risk factor (35,36). Older patients may have decreased cognitive reserve and greater cerebrovascular disease burden, which may increase vulnerability to perioperative cerebral insult (37).

From a clinical perspective, several perioperative strategies have been proposed to mitigate postoperative neurocognitive complications (38-41). Multicomponent perioperative care pathways, typically referred to as delirium prevention bundles, decrease postoperative delirium and may improve broader neurocognitive outcomes (41). These interventions typically include early mobilization, measures to promote normal sleep-wake patterns and maintain patient orientation to their surroundings, adequate pain control, minimization of sedative medications, and prompt removal of unnecessary invasive devices (33). In addition, increasing attention has been directed toward cognitive prehabilitation (42,43), which aims to enhance cognitive reserve before surgery through interventions such as cognitive training, optimization of vascular risk factors, and patient education (38-43). Intraoperative strategies, including monitoring of anesthetic depth and cerebral oxygenation, may also contribute to decreasing neurological injury during cardiac surgery (38-41).

The robustness of the present findings is supported by methodological strengths, including independent dual data extraction, high methodological quality among included studies, the use of both CI and PI, and comprehensive sensitivity analyses. Furthermore, the use of a uniform cognitive outcome measure (MMSE) across all studies allowed direct comparison of cognitive changes across cohorts and avoided the heterogeneity that arises when different neuropsychological batteries are combined.

However, the present study had several limitations. First, substantial residual heterogeneity remained despite moderator analysis, suggesting that additional factors, such as genetic susceptibility, anesthetic depth, and cerebral autoregulation, may influence postoperative cognitive outcomes. Second, follow-up durations were relatively limited, with the longest postoperative assessment occurring at 6 months, preventing evaluation of the long-term cognitive trajectory. Third, effect sizes were derived from reported pre- and postoperative means and SD; because most primary studies did not report the correlation between paired measurements, assumptions regarding within-subject dependence could not be directly verified, which may influence the precision of standardized effect estimates. Fourth, reliance on the MMSE may underestimate subtle cognitive impairments, as patients with mild deficits achieve near-normal total scores, and the test includes only limited assessment of executive function

and processing speed, which are commonly affected in POCD. In addition, MMSE performance may be influenced by cultural and educational factors, which may introduce measurement bias when comparing heterogeneous populations across countries and healthcare settings. Fifth, the included studies lacked non-surgical control groups, making it difficult to distinguish cognitive changes attributable specifically to cardiac surgery from those associated with aging, comorbidities, or perioperative hospitalization. Finally, meta-regression analyses were based on study-level data and a relatively small number of comparisons, which limited statistical power and introduced potential ecological bias and residual confounding. The review protocol was not prospectively registered, which may decrease transparency. Variability in diagnostic criteria for POCD across studies may also have introduced misclassification bias. Although publication bias analyses were performed, the small number of included studies requires cautious interpretation because statistical tests for funnel plot asymmetry have limited power when <10 studies are available.

Overall, cardiac surgery is typically associated with moderate postoperative cognitive decline, particularly among patients who develop POCD. Awareness of this risk may support perioperative cognitive monitoring and targeted prevention strategies. Patients at higher risk, especially older adults or those with pre-existing cognitive vulnerability, may benefit from preoperative cognitive screening and structured postoperative follow-up. Early cognitive rehabilitation may also be considered for patients experiencing postoperative cognitive impairment.

The present analysis indicates that on-pump cardiac surgery is associated with a moderate postoperative decline in MMSE score, although cognitive outcomes vary across patients and study populations. Patients who met formal criteria for POCD demonstrated particularly pronounced declines, whereas individuals without POCD showed non-significant changes. The present exploratory analyses also identified longer CPB duration as a study-level factor associated with greater postoperative cognitive decline, although this should be interpreted cautiously given the observational nature of the included studies and the potential for residual confounding.

The present findings contribute to the growing body of evidence that PNDs represent a key clinical concern following cardiac surgery (44-46). From a clinical perspective, awareness of potential postoperative cognitive changes may support improved perioperative counseling, cognitive monitoring, and early identification of patients at higher risk for neurocognitive complications. More broadly, the present study supported the integration of perioperative neurocognitive assessment into cardiac surgical care pathways and highlighted potentially modifiable intraoperative factors that may inform future brain-protective strategies. Future research should focus on strategies aimed at mitigating neurological injury during cardiac surgery, including optimization of CPB management, improved cerebral perfusion monitoring, and the evaluation of perioperative neuroprotective approaches. In addition, longer-term prospective studies, ideally including appropriate non-surgical control groups, are needed to

clarify whether postoperative cognitive changes reflect surgery-associated effects, underlying patient vulnerability, or the natural trajectory of cognitive aging. To the best of our knowledge, evidence is still lacking regarding the standardization of cognitive outcome assessment, the role of mechanistic biomarkers and neuroimaging, and the real-world feasibility and effectiveness of preventive interventions in routine perioperative practice. Improved understanding of these mechanisms and risk factors may facilitate better risk stratification, targeted preventive interventions, and improved neurological outcomes for patients undergoing cardiac surgery.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

XL and JWu designed the study, interpreted data, and drafting of the manuscript. ZH interpreted the data. JWa conceived and designed the study, interpretation, and critically revised and finalized the manuscript. XC and JWa confirm the authenticity of all the raw data. HC conceived and designed the study and interpreted data. YY performed the literature review. XC and WY analyzed data. XL and JWu wrote the manuscript. ZH revised the manuscript. JWu supervised the study. JWa provided overall guidance and finalized the manuscript. All authors have reviewed and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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