SYSTEMATIC REVIEW

Outcomes associated with postoperative cognitive dysfunction: a systematic review and meta-analysis

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Abstract

Background: Postoperative cognitive dysfunction (POCD) manifests as a subtle decline in cognition, potentially leading to unfavourable postoperative outcomes. We explored the impact of POCD on physical function, length of hospital stay (LOS), dementia and mortality outcomes.
Methods: PubMed and Scopus were searched until May 2023. All studies of major surgical patients that assessed POCD and outcomes of interest were included. POCD effects were stratified by surgery type (cardiac and noncardiac) and time of POCD assessment (<30 and ≥ 30 days postsurgery).
Results: Of 2316 studies, 20 met the inclusion criteria. POCD was not associated with functional decline postsurgery. Patients who experienced POCD postcardiac surgery had an increased relative risk (RR) of death of 2.04 [(95% CI: 1.18, 3.50); $I^2 = 0.00\%$]. Sensitivity analyses showed associations with intermediate-term mortality among noncardiac surgical patients, with an RR of 1.84 [(95% CI: 1.26, 2.71); $I^2 = 0.00\%$]. Patients who developed POCD <30 days postcardiac and noncardiac surgeries experienced longer LOS than those who did not [mean difference (MD) = 1.37 days (95% CI: 0.35, 2.39); $I^2 = 92.38\%$ and MD = 1.94 days (95% CI: 0.48, 3.40); $I^2 = 83.29\%$, respectively]. Postoperative delirium (POD) may contribute to the heterogeneity observed, but limited data were reported within the studies included.
Conclusions: Patients undergoing cardiac and noncardiac surgeries who developed POCD <30 days postsurgery had poorer outcomes and an increased risk of premature death. Early recognition of perioperative neurocognitive disorders in at-risk patients may enable early intervention. However, POD may confound our findings, with further studies necessary to disentangle the effects of POD from POCD on clinical outcomes.

Key points

- Cardiac surgical patients who developed postoperative cognitive dysfunction (POCD) <30 days postsurgery were at increased risk of prolonged length of hospital stay (LOS) and mortality.
- Noncardiac surgical patients who developed POCD <30 days postsurgery had increased LOS and potentially increased intermediate-term mortality risk.
- Early recognition of perioperative neurocognitive disorders to improve the care process for at-risk populations may be beneficial.

Introduction

Postoperative cognitive dysfunction (POCD) is a disorder of multiple domains of cognition that develops after surgery and can persist for several months [1]. Despite a consensus statement in 1995 [2], variable diagnostic criteria remain [3]. Nevertheless, most studies define POCD as a decline of 1–2 standard deviations (SD) in postoperative cognitive score [3–8], which is in line with recent recommendations [9]. POCD has been commonly reported postsurgery in adult patients, ranging in incidence from 17% to 43% [4, 10]. Long-term impacts of POCD have been explored with inconsistent findings on postoperative performance, risk of developing dementia and premature mortality [4].

The central nervous system is dependent on adequate oxygen and blood supply to maintain sufficient internal environment homeostasis. Mechanisms that lead to hypoxia or alter the homeostatic cerebral metabolic state may lead to POCD [11]. Clinical consequences of POCD may vary according to surgery type and timing of POCD assessment. Cerebral hypoperfusion and cerebral microemboli are commonly considered contributing factors for POCD following cardiac surgery, and to a lesser extent noncardiac surgery, and may explain variations in length of hospital stay (LOS) and mortality risk following POCD [12–14].

Generally, transient factors affecting perioperative outcomes resolve by 30 days following surgery [9]. Previous studies have reported that neurocognitive disorders detected within 30 days lead to longer LOS, but not functional decline or premature mortality [4, 8]. By contrast, patients diagnosed with POCD ≥30 days postsurgery tend to have poorer function and higher mortality, but not extended hospitalisation [5–7].

Previous evidence has been inconsistent, possibly due to variation across studies in the power limitations of primary studies [5–8], surgery type, time of POCD assessment, diagnostic criteria and outcome measures. Systematic reviews and meta-analyses (SRMAs) have mostly focused on POCD incidence [10, 15, 16] and risk factors [17]; some SRMAs assessed postoperative outcomes associated with different types of anaesthesia [15, 18], but none have explored the consequences of POCD. Therefore, we conducted an SRMA with the following objectives: firstly, to pool and compare the mean difference (MD) in postoperative functional scores between patients with and without POCD, and secondly, to investigate associations between POCD and mortality, LOS and dementia.

Research design and methods

This SRMA followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [19] and was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42021272954) in September 2021.

Search strategy and selection criteria

Two authors (P.S. and S.S.) independently searched PubMed and Scopus databases through to 13 May 2023. The literature search strategy was developed without language restriction based on population (surgery types), exposure (POCD) and outcomes (function, mortality, LOS and dementia) (Appendix 1A and B). Reference lists of included studies were checked to identify additional studies. Searches were performed independently by P.S. and S.S., and discordance was resolved through discussion with V.S.

Cohort studies were eligible if they included patients aged ≥18 years who underwent major cardiac or noncardiac surgeries and were assessed for POCD and any defined outcomes. Studies with insufficient data for pooling were excluded after three failed attempts to contact the authors. For duplicate publications, studies with the longest follow-up time were selected.

Identification of postoperative cognitive dysfunction

POCD was defined according to the original study definition, i.e. a decline in cognitive performance postsurgery. Different cognitive tests were used to diagnose POCD across studies, including the Mini-Mental State Examination score (MMSE) [20], Montreal Cognitive Assessment Test (MoCA) [21] and neuropsychological test batteries (NTBs) [2, 22].

Outcome assessment

Postoperative function was assessed using several tools, including instrumental activities of daily living (IADL)

questionnaires [23], Lawton–Brody IADL [24], Adjusted Lawton Score (ALS) [25], Modified Lawton's Scale [26], Alzheimer's disease cooperative study-activities of daily living scale for use in mild cognitive impairment (ADCS-ADL-MCI) [27] and a 36-Item Short Form Survey (SF-36) [28] (Appendix 2).

Secondary outcomes included LOS, mortality and dementia. LOS was defined as the total number of days from admission to discharge or hospital death. Mortality included death reported at any time postsurgery. Dementia was defined according to the original study.

Data extraction

P.S. and T.K. independently extracted data, which included author, publication year, country, study design, sample size, mean age, surgery type and sites, postoperative delirium (POD), type of cognitive test, POCD diagnostic criteria, time to define POCD and outcomes of interest. For dichotomous outcomes, aggregated data (number of patients and number of events) or summary statistics [relative risk (RR) and 95% confidence intervals (CIs)] were extracted. For continuous outcomes, aggregated outcome data (mean and SD) or summary statistics (MD or linear regression beta-coefficient) were extracted. Median values with range were converted to mean and SD [29, 30]. In studies with mixed surgery types, outcome data were extracted by cardiac and noncardiac surgery strata.

Risk of bias assessment

The risk of bias (RoB) was independently appraised by P.S. and T.K. using the Newcastle–Ottawa Scale (NOS) for cohort studies [31]. Discrepancies were resolved through discussion with V.S.

Data synthesis and analysis

Data pooling was stratified by surgery type (cardiac and noncardiac) and the time of POCD assessment (<30 and ≥ 30 days postsurgery) [9]. For continuous outcomes, standardised mean differences (SMDs) of postoperative functional scores between POCD and non-POCD groups were calculated and pooled as different functional tools were used. For functional tools, higher scores represent better function [7, 8, 32–34], except IADL questionnaire [4] and ALS [25], where higher scores indicated lower function. Mean values for IADL questionnaire and ALS were multiplied by -1 to make directionality consistent across studies [35]. For LOS, unstandardised MDs were calculated and pooled. RR and associated variance were calculated and pooled for dichotomous outcomes.

Heterogeneity for each outcome was assessed using the Cochran's Q test and I^2 statistic. If no heterogeneity was present, a fixed-effects model was used; otherwise, a random-effects model was applied. Sources of heterogeneity were explored using sensitivity analyses or meta-regression, as appropriate. Potential factors for sensitivity and/or meta-regression models included age, duration of surgery, POD at baseline, POCD diagnostic tools and time to assess the outcomes [36–39]. Duration of surgery was dichotomised (<220 and ≥ 220 minutes) based on the median duration for the studies included. Each factor was included in a meta-regression model individually and subjected to subgroup analysis if a reduction in $I^2 > 50\%$ was detected.

Publication bias was assessed using a funnel plot and Egger's test. If positive, a contour-enhanced funnel plot was performed to determine if the cause of asymmetry was due to publication bias or heterogeneity. All analyses were performed using STATA 16, and a P-value $<.05$ was considered significant, except for the heterogeneity test, where the significance threshold was 0.10.

Results

Study selection

Of the 2316 articles identified, 20 studies met the eligibility criteria (Figure 1); 7 studies [4, 7, 8, 25, 32–34] for functional outcomes; 7 [4–6, 8, 40–42] for mortality; 13 [4, 7, 8, 40–49] for LOS; and 2 [6, 50] for dementia. Study selection agreement between both reviewers was 98%.

Study characteristics and risk of bias

Study characteristics are shown in Table 1. Study size varied from 31 to 1513 participants (median 226); average age was 66 ± 5.37 years. Eleven studies [6, 25, 32, 34, 41–43, 45, 46, 48, 49], 8 [4, 5, 7, 33, 40, 44, 47, 50] and 1 [8] focused on cardiac, noncardiac or both, respectively. Among 20 studies included, 12 [5, 6, 25, 32–34, 41, 43, 45, 46, 48, 50] did not report POD assessment, while 8 [4, 7, 8, 40, 42, 44, 47, 49] reported POD using varying diagnostic criteria, with incidence ranging from 3% to 33%. Of these, 3 [4, 8, 40] assessed POD during the same period as POCD assessment; 1 [44] evaluated POD at a different period to POCD, while the others did not report timing. The timing of POCD assessment varied between 7 days to 1 year postsurgery; we compared POCD assessment <30 days and ≥ 30 days. Seven studies assessed POCD <30 days [8, 42–46, 49], 7 assessed ≥ 30 days [6, 7, 32–34, 41, 48] and 6 assessed across both periods [4, 5, 25, 40, 47, 50]. Most studies used NTB to assess cognition [4–7, 25, 32, 34, 40, 41, 44–50], four used MoCA [8, 33] or MMSE [42, 43] (Appendix 2). Sixteen studies were considered to have low RoB [4–8, 25, 32, 33, 40, 41, 43, 45–48, 50], and 4 had high RoB [34, 42, 44, 49] (Appendix 3).

Postoperative function

Seven studies [4, 7, 8, 25, 32–34] reported functional outcomes; 6 [4, 7, 25, 32–34] assessed POCD ≥ 30 days, while 1 [8] assessed POCD at 7 days. Functional outcomes were measured between 3 and 12 months postoperatively using different tools (Table 1).

Identification of studies via databases and registers

Identification

Records identified from*:
PubMed (N = 877)
Scopus (N = 1,439)

→

Records removed *before screening*:
Duplicate records removed (N = 686)

Screening

Records screened
(N = 1,630)

→

Records excluded (N = 1,433):**
Not POCD (N = 740)
Not interested outcome (N = 371)
Not surgery or major surgery (N = 322)

Reports sought for retrieval
(N = 197)

→

Reports not retrieved
(N = 1)

Reports assessed for eligibility
(N = 196)

→

Reports excluded (N = 178):
Not POCD (N = 68)
Narrative review and review (N = 52)
Not interested outcome (N = 47)
Studies with the same cohort and duplicate samples (N = 5)
Not surgery or major surgery (N = 2)
Protocol (N = 2)
Studies with insufficient data (N = 2)

Included

Studies included in review
(N = 18)

Reports from reference review
(N = 2)

Postoperative function
(N = 7)

Mortality
(N = 7)

Length of hospital stay
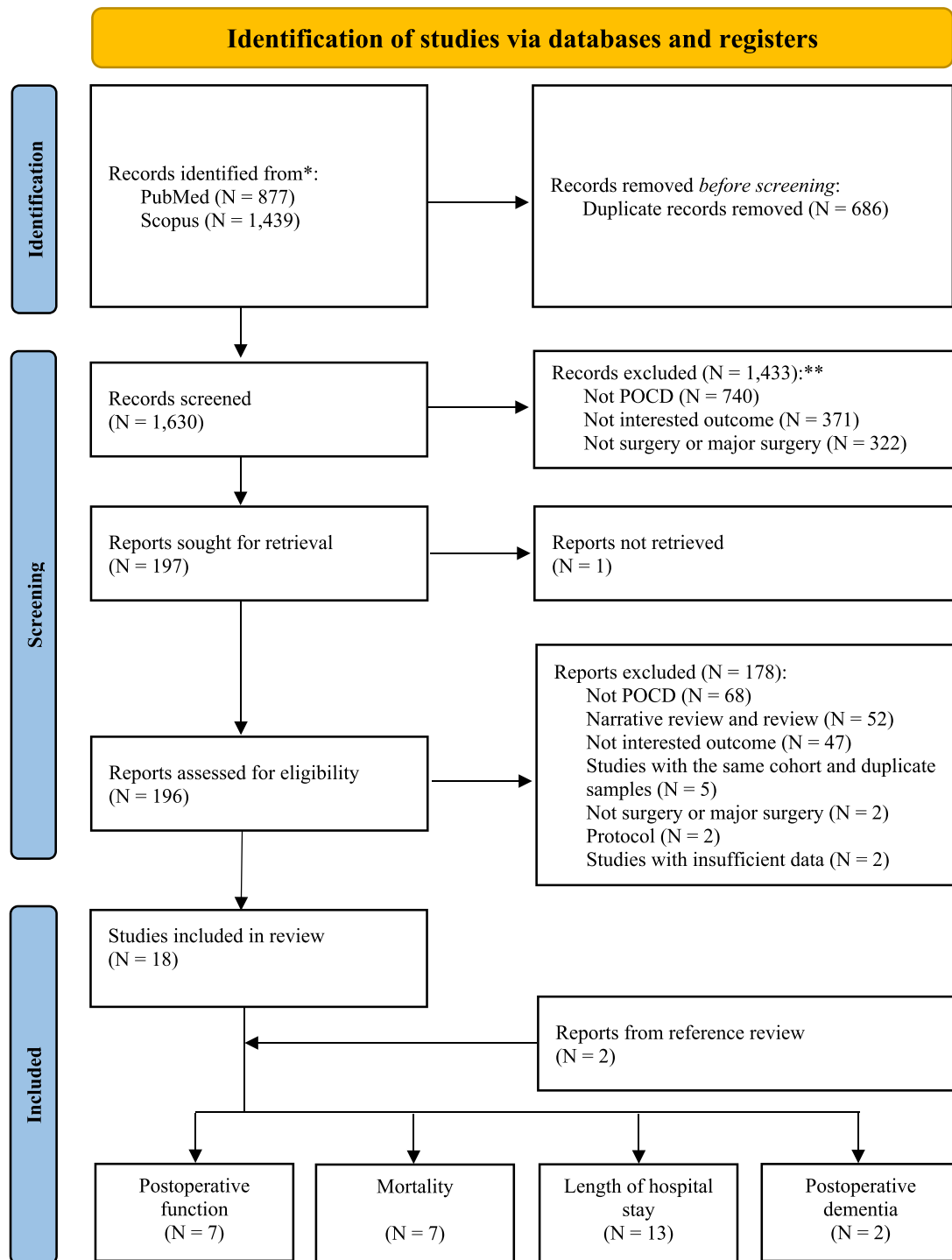(N = 13)

Postoperative dementia
(N = 2)

Figure 1. PRISMA flow. POCD, postoperative cognitive dysfunction; PRISMA, Preferred Reporting Items for Systematic Review and Meta-analysis.

Postoperative functional scores were pooled and stratified by surgical type, which included 4 cardiac (*n* = 374) [8, 25, 32, 34] and 4 noncardiac surgery studies (*n* = 1192) [4, 7, 8, 33], (Figure 2A and B). No differences in postoperative functional scores were detected between POCD and non-POCD groups for either cardiac [SMD = −0.18 (95% CI: −0.42,

0.05); I^2 = 0.00%] or noncardiac surgeries [SMD = −0.23 (95% CI, −0.84, 0.38); I^2 = 84.34%].

To explore heterogeneity among cardiac surgery studies, exclusion of a study [34] with a high RoB had no significant effect with SMD of −0.11 [(95% CI: −0.37, 0.14); I^2 = 0.00%] (Appendix 5.1A). Additionally, pooling 3

Table 1. Study characteristics

Author, year	Country	Surgery type	Cognitive test	POCD assessment (day after surgery)	POD assessment (%, day after surgery, tools)	Age (years)	Study size	Outcomes
Cardiac surgery								
Boodhwani, 2006 [46]	Canada	Cardiac (on-pump CABG)	NP test	7	NA	68.3	448	LOS
Hogue_1, 2008 [34]	USA	Cardiac (on-pump CABG and cardiac valve replacement)	NP test	30	NA	70	174	Function (180-day Modified Lawton's Scale)
Hogue, 2008 [48]	USA	Cardiac (on-pump CABG and cardiac valve replacement)	NP test	30	NA	70	174	LOS
Liu, 2009 [45]	China	Cardiac (on-/off-pump CABG)	NP test	7	NA	60	227	LOS
Norkiene, 2010 [49]	Lithuania	Cardiac (on-pump CABG)	NP test	7	6.3%, NM, DSM IV	60.9	127	LOS
Toeg, 2013 [41]	Canada	Cardiac (on-pump CABG)	NP test	90	NA	64.4	696	Mortality (90 days), LOS
Benvenuti, 2014 [25]	Italy	Cardiac (on-pump CABG and cardiac valve replacement)	NP test	7, 90	NA	63.8	79	Function (90-day Adjusted Lawton Score)
Evered, 2016 [6]	Australia	Cardiac (on-/off-pump CABG)	NP test	90, 365	NA	68.0	326	Mortality (7.5 years), dementia (7.5 years)
Hayashi, 2018 [43]	Japan	Cardiac (on-pump CABG, cardiac valve replacement and thoracic aortic surgery)	MMSE	14	NA	71.4	204	LOS
Momeni, 2019 [42]	Belgium	Cardiac (on-/off-pump CABG and TAVI)	MMSE	5	20%, NM, Validated chart review method	67.7	1513	Mortality (180 days), LOS
Tarasova, 2020 [32]	Russia	Cardiac (CABG)	NP test	365	NA	57.3	100	Function (1-year SF-36)
Noncardiac surgery								
Rodriguez, 2005 [47]	Canada	Noncardiac (TKA)	NP test	7, 90	6.5%, NM, CAM	69	31	LOS
Monk, 2008 [4]	USA	Noncardiac (47% abdominal or thoracic, 39% orthopaedic)	NP test	7, 90	3.3%, Day 1–7, CAM	50.6	1064	Function (90-day IADL questionnaire), Mortality (1 year), LOS
Steinmetz, 2009 [5]	Denmark	Noncardiac (56% abdominal, 20% orthopaedic)	NP test	7, 90	NA	67.3	701	Mortality (8.4 years)
Steinmetz, 2013 [50]	Denmark	Noncardiac (56% abdominal, 20% orthopaedic)	NP test	7, 90	NA	67.3	686	Dementia (10 years)
Krenk, 2014 [44]	Denmark	Noncardiac (THA and TKA)	NP test	12	-%, Day 1–3, DSM IV	68.3	225	LOS
Franck, 2016 [40]	Germany	Noncardiac (38% abdominal or thoracic, 29% orthopaedic)	NP test	7, 90	32.9%, Day 0–7, DSM IV-TR	69.6	850	Mortality (90 days), LOS
Borges, 2017 [33]	Portugal	Noncardiac (49% abdominal, 15% plastic)	MoCA	90	NA	63.7	41	Function (90-day SF-36)
Deiner, 2021 [7]	USA	Noncardiac (43% spine, 29% general)	NP test	90	25.3%, NM, CAM-ICU	70	167	Function (90-day ADCS-ADL-MCI), LOS
Mixed cardiac and noncardiac surgeries								
Suraarunsumrit, 2022 [8]	Thailand	Cardiac (on-pump CABG and cardiac valve replacement)	MoCA	7	20.4%, Day 1–7, DSM-5	69.9	119	Function (90-day Lawton–Brody-IADL), mortality (90 days), LOS
		Noncardiac (42% orthopaedic, 27.3% abdominal)	MoCA	7	6.6%, Day 1–7, DSM-5	75.7	88	Function (90-day Lawton–Brody-IADL), mortality (90 days), LOS

All are prospective cohort studies; ADCS-ADL-MCI, Alzheimer's disease cooperative study/activities of daily living scale, adapted for patients with mild cognitive impairment; CABG, coronary artery bypass graft; CAM, Confusion Assessment Method; CAM-ICU, Confusion Assessment Method for the intensive care unit; DSM IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; DSM IV-TR, Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, fifth edition; IADL, Instrumental activities of daily living; LOS, length of hospital stay; MMSE, Mini-Mental State Examination score; MoCA, Montreal Cognitive Assessment Test; NA, not available data; NM, not mentioned postoperative day; NP test, neuropsychological test battery; POCD, postoperative cognitive dysfunction; RCI, reliable change index methods; SD, standard deviation; SF-36, 36-Item Short Form Survey; TAVI, transcatheter aortic valve implantation; THA, total hip arthroplasty; TKA, total knee arthroplasty.
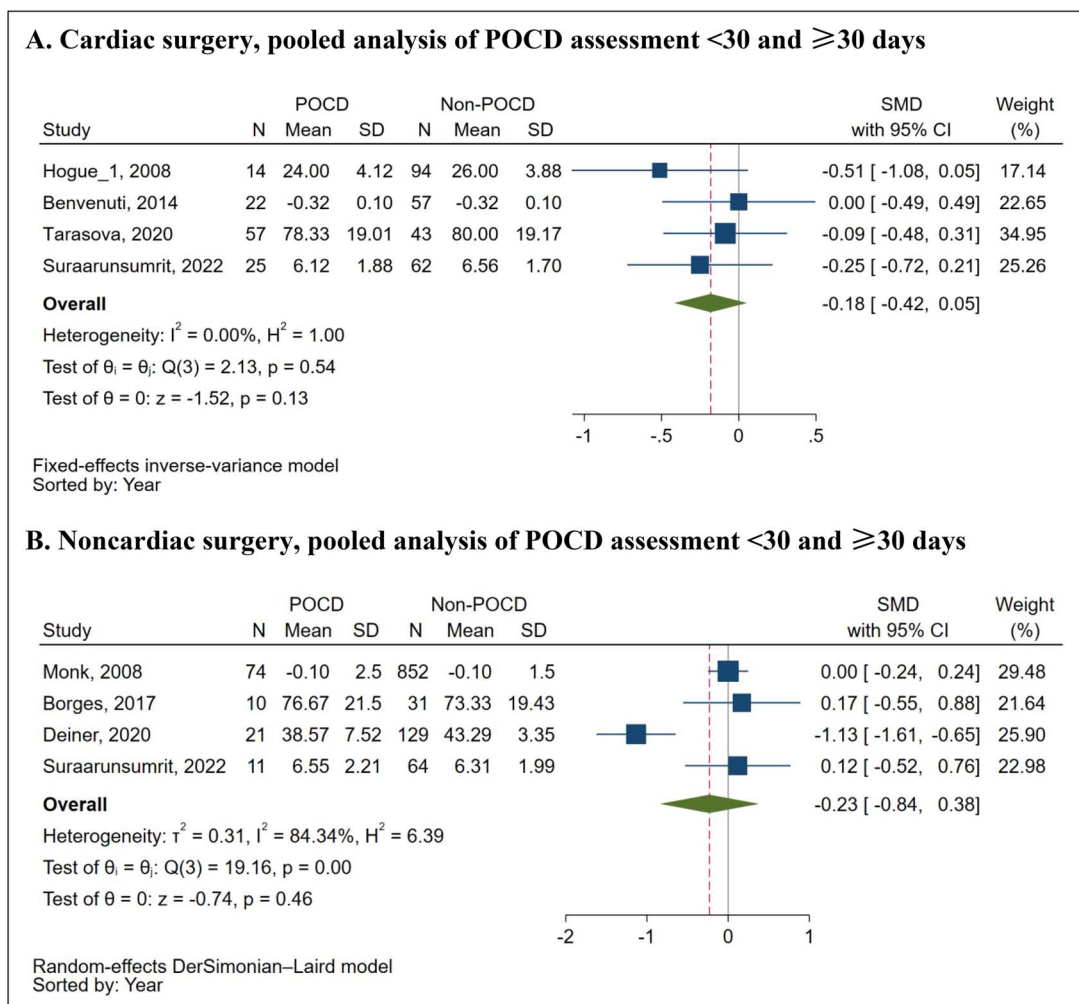
Figure 2. Forest plot of postoperative functions between POCD and non-POCD stratified by surgery type. POCD, postoperative cognitive dysfunction; SMD, standardised mean difference.

studies [25, 32, 34] without reported POD did not shift the effect size [SMD of −0.16 (95% CI: −0.43, 0.11); I^2 = 1.02%]. For noncardiac surgery, only duration of surgery was identified as a potential explanatory factor for heterogeneity (Appendix 4A); however, due to the limited number of studies, a subgroup analysis could not be undertaken. Exclusion of an outlier among noncardiac surgery studies, using the ADCS-ADL-MCI tool [7], reduced heterogeneity, but did not affect the difference in postoperative function [SMD = 0.03 (95% CI: −0.18, 0.24); I^2 = 0.00%] (Appendix 5.1B). POCD assessments among noncardiac surgery patients were performed at 90 days [4, 7, 33] and at 7 days [8] postsurgery; exclusion of the latter [8] did not reduce heterogeneity (I^2 = 89.09%) with SMD of −0.33 (95% CI: −1.12, 0.46) (Appendix 5.1C). Sensitivity analysis in noncardiac surgery, excluding a study [33] without POD assessment, did not materially change the result with SMD of −0.34 [(95% CI: −1.10, 0.42); I^2 = 89.05%] [4, 7, 8].

Mortality

Four and 4 studies reported mortality outcome following POCD in cardiac [6, 8, 41, 42] (n = 2410) and noncardiac [4, 5, 8, 40] (n = 2518) surgeries, respectively. For cardiac surgery, two studies assessed POCD <30 days [8, 42], and 2 assessed POCD ≥30 days [6, 41]. For noncardiac surgery, 4 assessed POCD <30 days [4, 5, 8, 40] (n = 2518), and 3 assessed POCD ≥30 days [4, 5, 40]. Three studies [4, 8, 40] defined POD separately from POCD assessment <30 days. Four studies reported intermediate-term mortality (up to 1 year) [4, 8, 40, 41], and 2 reported long-term mortality (up to 8 years) [5, 6] (Table 1).

For cardiac surgery, the number of studies was insufficient to undertake a stratified analysis by period of POCD. A pooled analysis of both POCD <30 days and POCD ≥30 days [6, 8, 41, 42] was associated with an increased risk of death with RR of 2.04 [(95% CI: 1.18, 3.50); I^2 = 0.00%] (Figure 3A). For noncardiac surgery, both POCD assessment <30 days [4, 5, 8, 40] (n = 2518) and POCD assessment
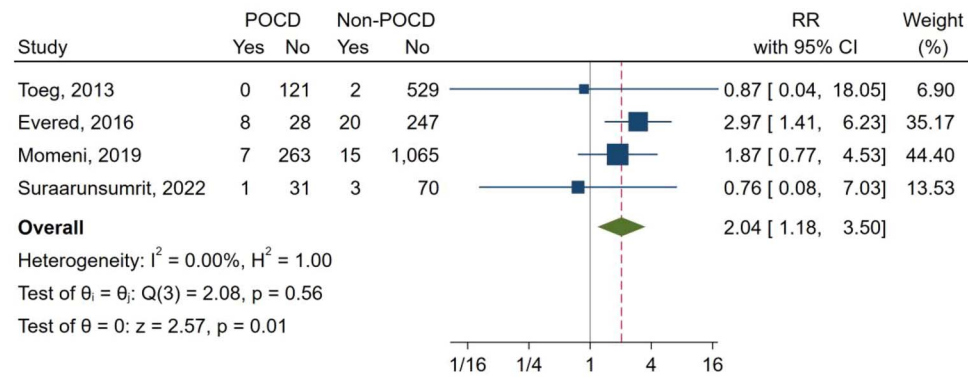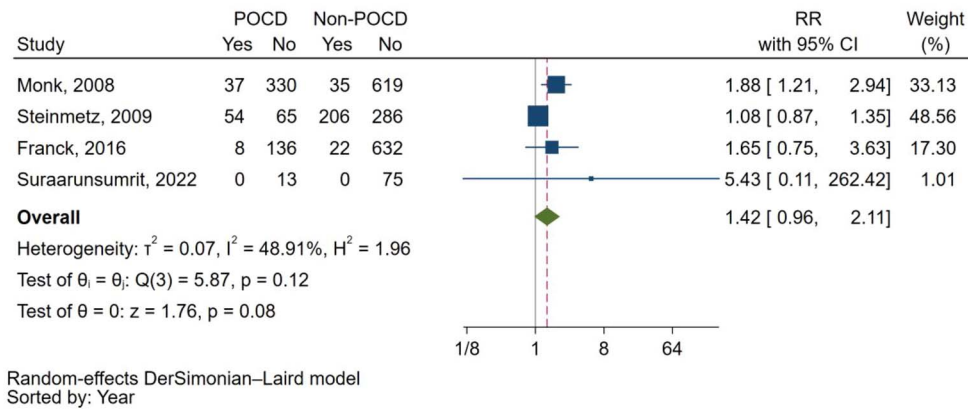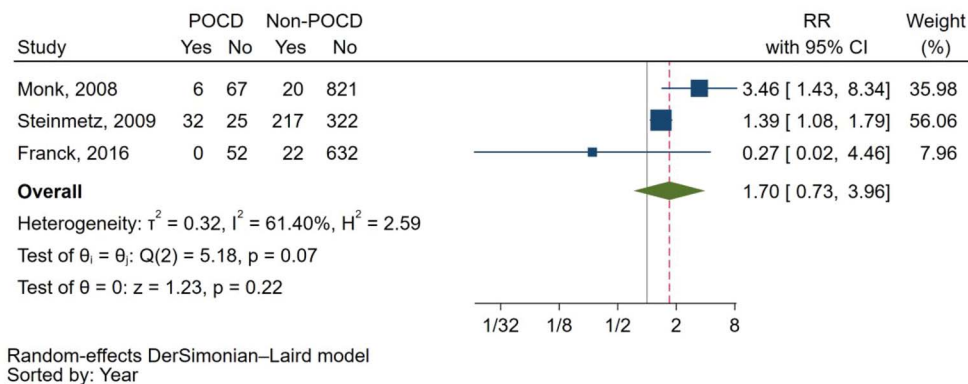
Figure 3. Forest plot of mortality risk between POCD and non-POCD stratified by surgery type and POCD assessment period. POCD, postoperative cognitive dysfunction; RR, relative risk.

≥30 days [4, 5, 40] (n = 2216) showed no significant mortality differences with RR of 1.42 [(95% CI: 0.96, 2.11); I^2 = 48.91%] and 1.70 [(95% CI: 0.73, 3.96); I^2 = 61.40%] respectively, (Figure 3B and C).

Sensitivity analysis among cardiac surgery studies excluded 1 study [42] with a high RoB with similar results [RR of 2.17 (95% CI: 1.10, 4.28); I^2 = 0.00%] (Appendix 5.2A). In addition, the exclusion of 2 studies [6, 41] that did not

assess POD did not substantially change results, with RR 1.61 [(95% CI: 0.71, 3.63); $I^2 = 0.00\%$] [8, 42].

Among noncardiac surgery studies, age, follow-up time and duration of surgery were potential explanatory factors for heterogeneity identified by meta-regression (Appendix 4B and C). However, subgroup analysis was not possible, given the small number of studies. In a sensitivity analysis to explore the effect of mortality–time follow-up, a study assessing long-term mortality [5] was excluded. Among studies reporting intermediate-term mortality, and which reported POCD separately from POD [4, 8, 40], noncardiac surgical patients who developed POCD <30 days had an increased mortality risk, with RR 1.84 [(95% CI: 1.26, 2.71); $I^2 = 0.00\%$] (Appendix 5.2B).

Length of hospital stay

Six [8, 42, 43, 45, 46, 49] ($n = 4589$) and 5 [4, 8, 40, 44, 47] ($n = 2156$) studies assessing POCD <30 days reported LOS following cardiac and noncardiac surgeries, respectively, and 3 studies [7, 40, 47] ($n = 884$) assessing POCD ≥30 days reported LOS postnoncardiac surgery (Table 1). Of these, 3 cardiac surgery [8, 42, 49] and all noncardiac surgery studies [4, 7, 8, 40, 44, 47] reported POD assessment. Patients with POCD <30 days tended to have a longer LOS of 1.37 days [(95% CI: 0.35, 2.39); $I^2 = 92.38\%$] following cardiac surgery [8, 42, 43, 45, 46, 49] and 1.94 days [(95% CI: 0.48, 3.40); $I^2 = 83.29\%$] following noncardiac surgery [4, 8, 40, 44, 47] compared to non-POCD patients (Figure 4A and B). The LOS for patients with POCD assessment ≥30 days postnoncardiac surgery [7, 40, 47] was not significant [MD = 0.97 (95% CI: −0.17, 2.11); $I^2 = 12.27\%$] (Figure 4C).

Meta-regression to explore heterogeneity in LOS following cardiac surgery showed heterogeneity could be reduced slightly by accounting for different subtypes of cardiac surgery [i.e. coronary artery bypass graft (CABG) and mixed CABG plus valve surgery] (Appendix 4D); for studies that included patients with mixed cardiac surgeries, LOS tended to be longer by 2.04 days [(95% CI: 1.65, 2.44); $I^2 = 0.00\%$] in the POCD group (Appendix 6.1). In addition, a subgroup analysis was also performed in studies that did and did not report POD in cardiac surgery. For studies reporting POD [8, 42, 49], POCD patients had an increased LOS of 2.66 days [(95% CI: 1.07, 4.24); $I^2 = 39.55\%$] compared to non-POCD patients (Appendix 6.2). A sensitivity analysis excluded 2 cardiac surgery studies [42, 49] with high RoB with no significant difference for LOS [MD = 0.81 (95% CI: −0.36, 1.98); $I^2 = 79.78\%$] (Appendix 5.3A). Among noncardiac surgery studies, no significant explanatory factors for heterogeneity were identified (Appendix 4E). A sensitivity analysis excluding one high RoB study [44] using fixed LOS (≤3 days) with noncardiac surgical patients with POCD assessed <30 days confirmed a longer LOS of 2.33 days [(95% CI: 1.24, 3.42); $I^2 = 28.94\%$] (Appendix 5.3B).

Publication bias

No publication bias for functional outcomes following cardiac surgeries (Appendix 7.1A) and mortality outcomes following cardiac and noncardiac surgeries was detected (Appendix 7.2A–C). Funnel plots were asymmetric for postoperative function following noncardiac surgery (Appendix 7.1B) and LOS following both cardiac and noncardiac surgeries (Appendix 7.3A and B). Contour-enhanced funnel plots indicated that funnel asymmetry was likely due to heterogeneity rather than publication bias.

Discussion

Our study demonstrated that patients who underwent cardiac surgery had an increased mortality risk following development of POCD regardless of time of POCD assessment. Although the overall risk of death did not differ significantly for patients who underwent noncardiac surgery and developed POCD, sensitivity analysis identified a significant association with intermediate-term mortality. Patients who developed POCD <30 days postsurgery were more likely to have extended LOS following both cardiac and noncardiac surgeries. The LOS was not significantly different for patients with POCD assessment ≥30 days postsurgery. Patients who developed POCD following either cardiac or noncardiac surgery did not experience significant functional decline postoperatively.

The pathogenesis of POCD remains unclear, and several contributing factors have been proposed [13, 14, 51, 52]. Various neuroinflammatory mechanisms play essential roles, supported by studies in animal models and humans following cardiac and noncardiac surgeries. Furthermore, several additional aetiologies, including preexisting cognitive impairment, anaesthetic agents and metabolic derangements, have also been proposed as potential contributory factors postsurgery. Cerebral hypoperfusion, cerebral microemboli and hemodynamic derangements have been proposed as potential mechanisms specifically following cardiac surgery [14, 51, 52]. These processes have the potential to lead to permanent anatomical and physiological changes that are less amenable to full recovery, possibly exacerbating associated postoperative complications [14, 53]. In contrast, some aetiological factors that contribute to POCD in noncardiac surgeries, such as metabolic derangements and medications, are nonanatomical and may be potentially reversible. Permanent irreversible lesions are likely to be associated with a more substantial impact or have synergistic effects with cardiovascular comorbidities and may explain negative outcomes, such as increased mortality, associated with POCD development following cardiac surgeries compared to noncardiac surgeries. A previous study reported most patients who developed POCD following noncardiac surgery showed cognitive recovery within 6 months [54], which may represent sufficient time to detect the effect of POCD on mortality in the intermediate term, as shown in our study. Nevertheless, given the heterogeneity across studies, stratification by surgery type

A. Cardiac surgery with POCD assessment <30 days

Study	POCD N	Mean	SD	Non-POCD N	Mean	SD		MD with 95% CI	Weight (%)
Boodhwani, 2006	265	6.9	.3	183	6.3	.2		0.60 [0.55, 0.65]	26.35
Liu, 2009	110	8.6	3.2	114	9.3	3.4		-0.70 [-1.57, 0.17]	22.16
Norkienė, 2010	59	20.3	15.9	68	14.8	5.4		5.50 [1.48, 9.52]	5.17
Hayashi, 2018	51	21.3	7.6	130	18.7	6		2.60 [0.50, 4.70]	12.44
Momeni, 2019	270	10	5.2	1,080	8	2.2		2.00 [1.59, 2.41]	25.31
Suraarunsumrit, 2022	46	13.6	10.5	73	10.6	5.4		3.00 [0.13, 5.87]	8.55
Overall								1.37 [0.35, 2.39]	

Heterogeneity: $\tau^2 = 1.03$, $I^2 = 92.38\%$, $H^2 = 13.13$

Test of $\theta_i = \theta_j$: Q(5) = 65.65, p = 0.00

Test of $\theta = 0$: z = 2.64, p = 0.01

Random-effects DerSimonian–Laird model
Sorted by: Year

B. Noncardiac surgery with POCD assessment <30 days

Study	POCD N	Mean	SD	Non-POCD N	Mean	SD		MD with 95% CI	Weight (%)
Rodriguez, 2005	12	8	2	17	6	1		2.00 [0.90, 3.10]	25.14
Monk, 2008	367	6.6	16.3	654	4.8	5.9		1.80 [0.41, 3.19]	23.20
Krenk, 2014	20	2.5	.8	200	2.3	.7		0.20 [-0.13, 0.53]	28.91
Franck, 2016	144	13	11.7	654	10	18.5		3.00 [-0.15, 6.15]	12.40
Suraarunsumrit, 2022	13	15	7.8	75	9.3	5.9		5.70 [2.05, 9.35]	10.36
Overall								1.94 [0.48, 3.40]	

Heterogeneity: $\tau^2 = 1.89$, $I^2 = 83.29\%$, $H^2 = 5.98$

Test of $\theta_i = \theta_j$: Q(4) = 23.93, p = 0.00

Test of $\theta = 0$: z = 2.60, p = 0.01

Random-effects DerSimonian–Laird model
Sorted by: Year

C. Noncardiac surgery with POCD assessment ⩾30 days

Study	POCD N	Mean	SD	Non-POCD N	Mean	SD		MD with 95% CI	Weight (%)
Rodriguez, 2005	5	8	2	23	7	2		1.00 [-0.93, 2.93]	29.84
Franck, 2016	52	15	28.3	654	10	18.5		5.00 [-0.47, 10.47]	4.27
Deiner, 2020	21	4	4	129	3.3	2.2		0.70 [-0.46, 1.86]	65.89
Overall								0.97 [-0.17, 2.11]	

Heterogeneity: $\tau^2 = 0.16$, $I^2 = 12.27\%$, $H^2 = 1.14$

Test of $\theta_i = \theta_j$: Q(2) = 2.28, p = 0.32

Test of $\theta = 0$: z = 1.67, p = 0.09

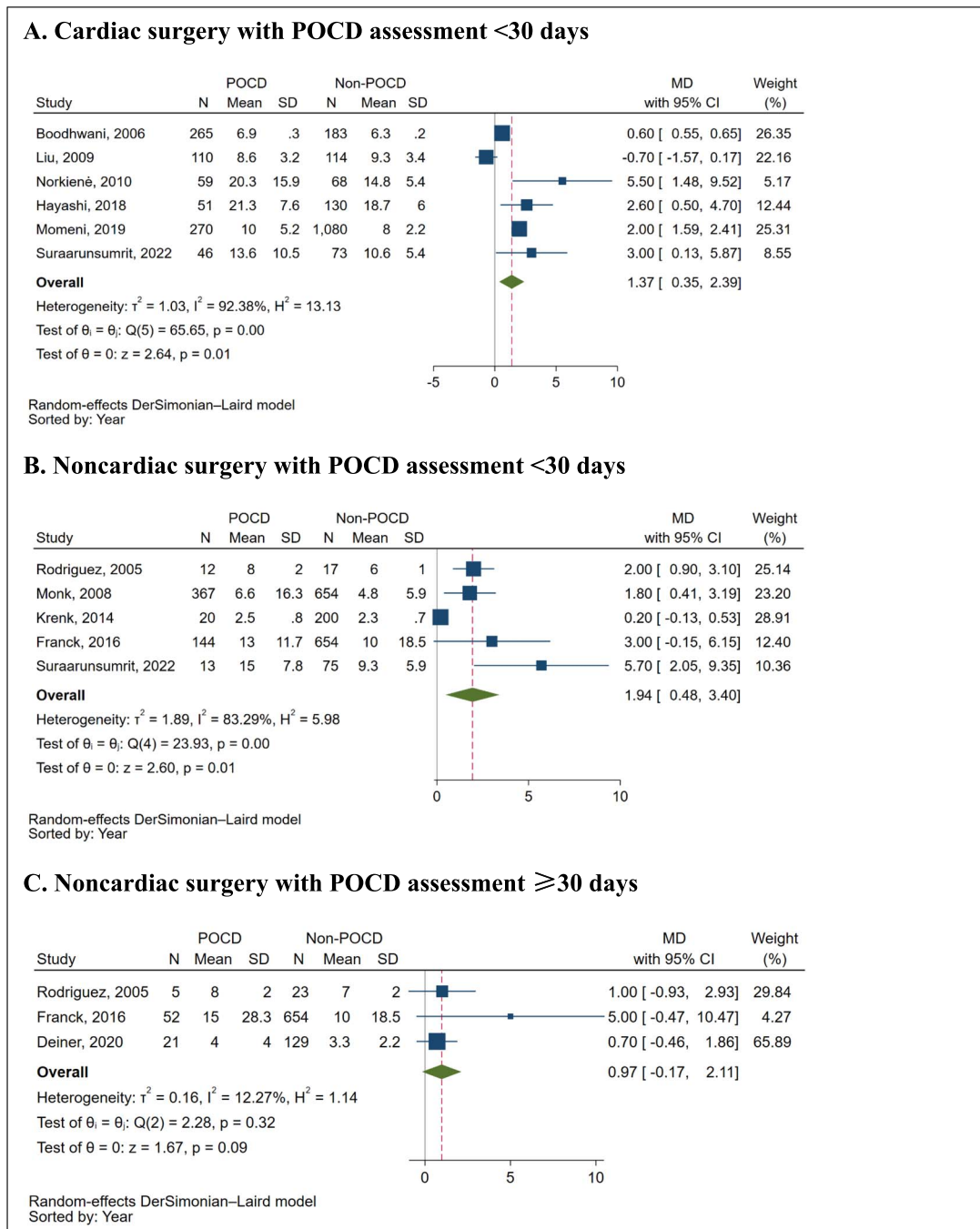Random-effects DerSimonian–Laird model
Sorted by: Year

Figure 4. Forest plot of length of hospital stay between POCD and non-POCD stratified by surgery type and POCD assessment period. POCD, postoperative cognitive dysfunction; MD, mean difference.

may not be sufficient to explore the occurrence and outcomes of POCD. Several complex vascular surgeries or neurosurgeries may exert effects on perioperative cognition similar to those observed following cardiac surgery. Nevertheless, we could not evaluate this given the limited number of studies available.

Patients who had POCD assessment <30 days were more likely to have an extended hospital stay following both cardiac and noncardiac surgeries. This finding is consistent with the explanation that patients with POCD may be vulnerable to in-hospital postoperative complications, contributing to

prolonged LOS [55]. The heterogeneity associated with LOS may be explained by several factors. Different types of cardiac surgery also affect the LOS, as evidenced in the subgroup analysis showing that only mixed CABG plus valve surgery was associated with longer LOS. Variations in the provision of postoperative care across different healthcare systems may also contribute to the heterogeneity observed [56].

No significant differences in postoperative physical function were observed in patients who developed POCD across all stratified analyses. However, one study used the ADCS-ADL-MCI assessment tool [7], which contains more items

to evaluate higher cognitive function, including the executive domain, which is crucial for higher-level functioning, such as financial management or critical decision-making [57]. Moreover, their study reported that patients who developed POCD were more likely to have lower function compared to patients who did not develop POCD. It is possible that most studies included in the present analysis had functional tools that may have lacked sufficient sensitivity to detect such subtle changes in executive function.

Both time of POCD assessment and time of functional evaluation play a role in the heterogeneity associated with the functional outcomes in our study. However, pooling POCD effects on functional outcomes following cardiac surgery identified no heterogeneity despite the assessment of functional outcomes at various time-points (i.e. 90–365 days). In contrast, the effect of POCD on functional outcomes following noncardiac surgery was highly heterogeneous, even though all four studies [4, 7, 8, 33] assessed functional outcomes at 90 days postsurgery. A sensitivity analysis that excluded one study [8] that assessed POCD at 7 days did not reduce heterogeneity. Further longitudinal cohort studies are needed to explore the temporal relationship between POCD and postoperative function and the optimal assessment time-point.

Our findings suggest that POCD is associated with increased mortality and LOS in both cardiac and noncardiac surgical patients, particularly those with POCD assessment <30 days. POD is a common occurrence that may also lead to negative outcomes similar to POCD [58]. POD and POCD could reflect a continuum of disease due to similar underlying pathology but could also confound the measurement of each other. However, POD assessment was reported in only 8 out of 20 studies included; sensitivity and subgroup analyses in these studies on mortality and LOS showed similar trends to the main findings, reducing the likelihood of confounding. Future studies should explicitly report the assessment of both conditions and analyse the effect of POCD separately from POD.

Our study has several strengths: this is the first SRMA to explore several clinical outcomes associated with POCD, with stratification by surgery type and time of POCD assessment. Although we had proposed *a priori* subgroup analyses, stratified analyses were undertaken given their influence on POCD occurrence and the associated heterogeneity observed. We undertook several sensitivity analyses to explore this, without major changes in effect size. Our findings highlight the potential negative POCD consequences that would benefit from a comprehensive geriatric assessment to improve in-hospital and longer-term perioperative outcomes.

There were several limitations to our study. Firstly, approximately one-fifth of the primary studies included were considered at high RoB. However, all studies scored at least 5 in the RoB assessment, which is considered acceptable for pooling [59]. Secondly, there was large variation in functional assessment tools within the meta-analysis; we therefore used SMD for comparisons across studies and explored sources of heterogeneity. Thirdly, various POCD diagnostic criteria across studies may further contribute to heterogeneity, but given the limited number of studies, studying this further was not possible. Fourthly, there is a conflicting classification that exists between previous and new studies for the definition of perioperative cognitive disorders [9]. POCD assessment <30 days, as defined in our study, may represent delayed neurocognitive recovery, while POCD assessed ≥30 days postsurgery may represent postoperative neurocognitive disorders, according to the 2018 nomenclature, although no included studies were considered fully compliant with the new nomenclature. We were, therefore, unable to reconcile our classification against the 2018 nomenclature. Fifthly, we could not pool association effects between POCD and dementia because of the limited number of studies that reported dementia outcomes. Lastly, we could not disentangle the effect of POD and POCD effect on clinical outcomes, given the limited number of studies reporting POD.

Conclusions

Patients undergoing cardiac surgery were at an increased mortality risk, and those diagnosed with POCD <30 days had an increased risk of prolonged LOS. Noncardiac surgical patients with POCD assessed <30 days also tended to have an increased LOS and higher intermediate-term mortality risk. Early recognition of POCD and the provision of comprehensive care for older patients may improve outcomes.

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