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REVIEW

Predictors of cognitive dysfunction after cardiac surgery: a systematic review

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Aims Postoperative cognitive dysfunction (POCD) is often experienced by cardiac surgery patients; however, it is not known if some groups of patients experience this more frequently or severely than others.
The aim of this systematic review was to identify preoperative and postoperative predictors of cognitive dysfunction in adults following cardiac surgery.

Methods and results Eight bibliographic databases were searched (January 2005 to March 2021) in relation to cardiac surgery and cognition. Studies including adult patients who had undergone open cardiac surgery and using a validated measurement of cognitive function were included. Full-text review for inclusion, quality assessment, and data extraction were undertaken independently by two authors.
A total of 2870 papers were identified, of which 36 papers met the inclusion criteria and were included in the review. The majority were prospective observational studies [$n = 28$ (75.7%)]. In total, 61 independent predictors (45 preoperative and 16 postoperative) were identified as significant in at least one study; advancing age and education level appear important. Age has emerged as the most common predictor of cognitive outcome.

Conclusion Although a number of predictors of POCD have been identified, they have inconsistently been reported as significantly affecting cognitive outcome. Consistent with previous research, our findings indicate that older patients and those with lower educational levels should be prioritized when developing and trialling interventions to improve cognitive function. These findings are less than surprising if we consider the methodological shortcomings of included studies. It is evident that further high-quality research exploring predictors of POCD is required.

Keywords Cardiac surgical procedures • Cognitive dysfunction • Predictor

Implications for practice

- Advancing age and fewer years of education are important predictors of postoperative cognitive dysfunction (POCD).
- Older patients and those with lower education levels should be prioritized when developing and trialling interventions to improve cognitive function.
- Rigorous research exploring predictors of POCD is required to enable practitioners to identify patients most likely to benefit from cognition-based interventions.

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Introduction

Postoperative cognitive dysfunction (POCD), defined as a decline in cognitive function from baseline performance measured with neuropsychological tests before and after surgery,[1] affects between 25% and 70% of patients after cardiac surgery.[2,3] Cognitive dysfunction is usually transient; however, it is associated with prolonged hospital length of stay, increased morbidity and mortality, and reduced quality of life, resulting in a significant healthcare and resource burden on the healthcare system.[2,3]

A key challenge in understanding and managing POCD can be attributed to methodological heterogeneity in the definitions of POCD used across studies, the variety of tests used to diagnose POCD, and timing of testing.[4–7] Furthermore, POCD lacks a formal definition in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[8] or the International Classification of Diseases (ICD-10).[9] The need for a standardized approach to the assessment of, and the diagnostic criteria associated with POCD, has been widely recognized.[4,7,10] Recently, consensus recommendations have been published, proposing revised nomenclature for cognitive impairment identified in the perioperative period.[11] These include postoperative cognitive decline diagnosed up to 30 days postoperatively (delayed neurocognitive recovery) or 12 months postoperatively [postoperative neurocognitive disorder (POCD)].[11] In this article, the term POCD will be used to describe an objective postoperative decline in cognitive function from baseline level of performance to reflect the existing body of knowledge and to allow the impact of the revised nomenclature[11] to become evident within the literature.

POCD has received a lot of research attention, particularly in relation to understanding the pathogenesis,[12,13] markers of neuronal injury,[14,15] and preventative strategies.[16] Despite this, its causes, mechanisms, and significance are still poorly understood. Risk factors associated with POCD and predictors of POCD have also been explored; however, the terms 'risk factor' and 'predictor' are often used interchangeably. Furthermore, the term 'risk factor' encompasses two conflated concepts: prediction and explanation.[17] Generally, 'risk factor' is used to describe a potential causal factor, that is a factor or variable whose manipulation changes the outcome (explanation). In contrast, 'predictor' is used to describe a factor or variable that is associated with a subsequent clinical outcome (prediction). Importantly, predictors are not necessarily causally related to an outcome.[17–19] The overwhelming focus of the literature related to POCD risk factors is explanatory in nature. POCD risk factors are often divided into three main categories: patient-related risk factors, anaesthesia-related risk factors, and surgery-related risk factors. Numerous risk factors have been implicated in the development of POCD,[1,5] however those most commonly identified include increasing age, lower education level, preoperative cognitive impairment, prior stroke, diabetes, poor functional status, duration of surgery, and depth of anaesthesia.[1,20] A systematic review exploring perioperative risk factors associated with POCD after cardiac surgery determined that the pathogenesis of POCD remains unclear, and that further research is required to determine whether certain anaesthetic approaches or interventions lower the potential risk of developing POCD in susceptible individuals.[5] To our knowledge, no systematic reviews of studies specifically exploring predictors of POCD to identify people or groups at risk of developing this complication has been conducted. Thus, the aim of this systematic review was to identify preoperative and postoperative predictors of cognitive dysfunction in adults following cardiac surgery.

Methods

Search strategy and screening of citations

This systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[21] and was registered on Prospero (CRD42020167037). Eight bibliographic databases [MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, PsycINFO, Cochrane Library, ProQuest Dissertations and Theses Global, Open Grey, and Web of Science Conference Proceedings Citation Index] were searched between January 2005 (to reflect the introduction of the Consensus statement[10]) and March 2021. In collaboration with an information specialist, searches were devised without methodological search filters that would limit results to specific study designs. Subject headings and keywords were used in the search in relation to two concepts: cardiac surgery and cognition, with the concepts combined using 'AND' for the final search (search syntax in Supplementary material online, *Table S1*). The reference lists of all identified systematic reviews were screened for potential eligible papers. Non-English papers were translated using online translation software; this applied to one of the included papers.

Titles and abstracts of identified articles were subject to blind independent review by two authors (T.B. and either L.M.A., C.S.H., or J.S.) for suitability against the inclusion and exclusion criteria (*Table 1*); conflicts were resolved through discussion with reference to a third reviewer if needed. Full-text of eligible articles were reviewed using a similar process.

Data extraction and quality assessment

Data extraction (using a standardized proforma) and quality assessment [using the Critical Appraisal Skills Programme (CASP)] template for cohort studies[22] was performed by two authors (T.B. and either L.M.A., C.S.H., or J.S.) with disagreements resolved through discussion until consensus was achieved. The agreed quality assessment information was used to generate a risk of bias graph and a risk of bias summary using RevMan,[23] addressing the domains of selection bias, detection bias, confounding bias, attrition bias, and other biases.[24]

Data synthesis

The key features and findings of included studies were evaluated and summarized by T.B., then discussed with the review team until agreement was reached. Due to heterogeneity of the included studies, meta-analysis was not performed. Instead, results were summarized using descriptive statistics, tables, and narrative synthesis. As a result of the variation in the timing of postoperative neuropsychological assessment, and therefore the time point at which predictive modelling occurred, the independent predictors identified were grouped by follow-up time point: 7 days to 6 weeks, 3 months, 6 months, 12–18 months, and 3–5 years.

Results

Study selection

A total of 2870 papers were identified for possible inclusion (*Figure 1*) with 196 papers undergoing independent full-text assessment. Reasons for exclusion are presented in Supplementary material

Table I Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Adult patients (≥18 years of age) • Patients undergoing cardiac surgical procedures • Published between January 2005 and March 2021 • Measurement of cognitive function measured using an objective validated tool, measured at least 7 days postoperatively	• Operations other than cardiac surgery • Cardiac transplantation • Sternal wound repair • Thoracic surgery • Transcatheter aortic valve implantation (TAVI) or transcatheter aortic valve replacement (TAVR) • Studies that focus solely on significant comorbidities, the effects of intraoperative factors, or delirium as an outcome • Studies that did not include multivariable analysis of predictors of POCD

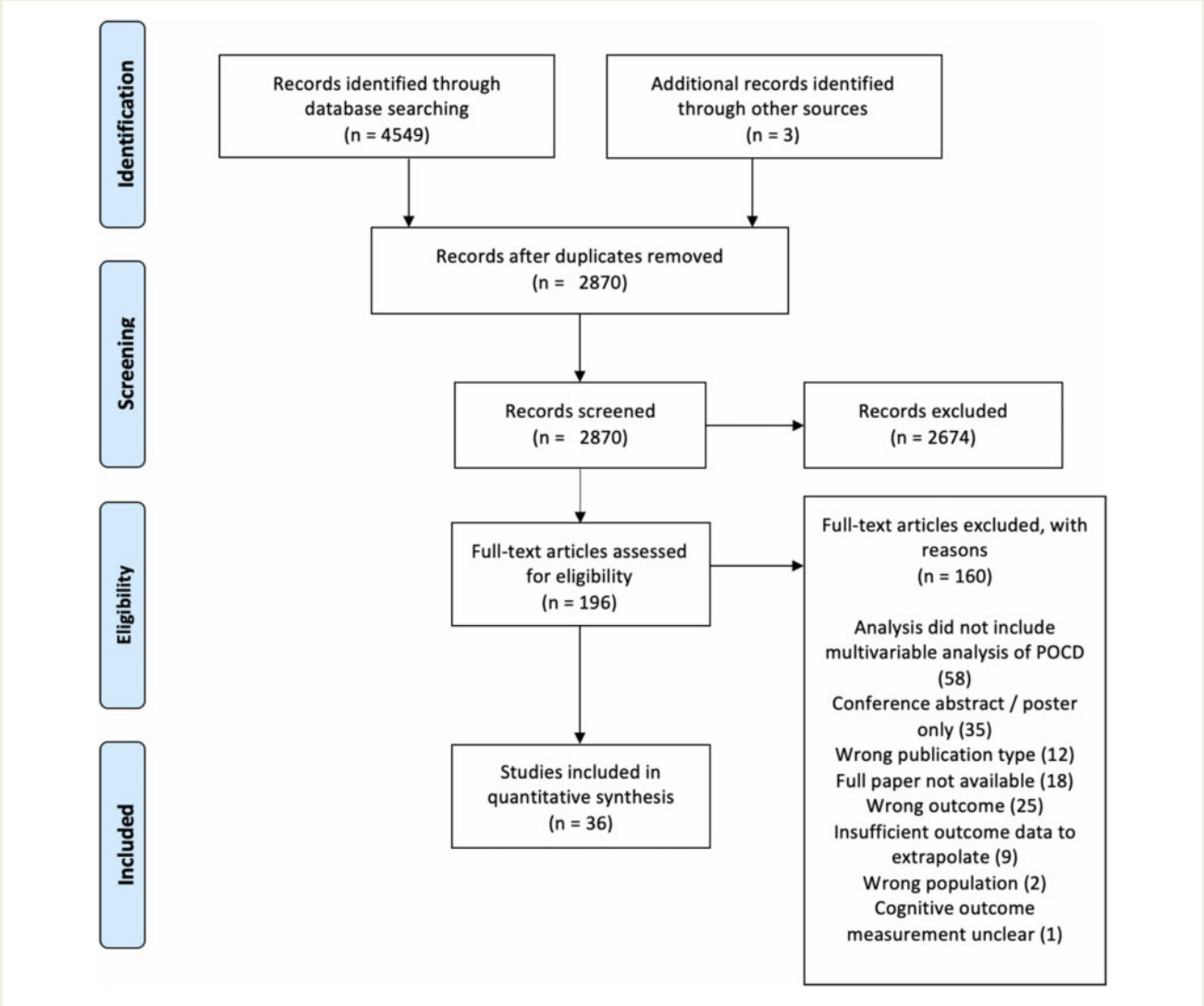

Figure 1 PRISMA flow chart.

Table 2 Study characteristics of included studies

Primary Author (year), country	Design (including single or multicentre)	Type of surgery	Cognitive outcome measure(s)	Post-operative cognitive function follow-up time-points
Bartels (2015), USA[25]	Retrospective cohort, single centre	CABG ± valve, on and off pump	RMT, WMS-R, WAIS-R digit span, WAIS-R digit symbol, TMT-B	5 years
Boodhwani (2006), Canada[26]	Prospective cohort, single centre	Non-emergent isolated CABG	SRT*, (WAIS-R) digit span, TMT-A, TMT-B, GP, SDMT, RAVLT+, WMS-III+ (* study 1 only, +study 2 only)	7 days
Brown (2018), USA[27]	Prospective cohort, single centre	Primary or re-operative CABG ± valve surgery ± aortic root surgery, with CPB	RAVLT, CFT, COWAT, SDMT, TMT-A, TMT-B, GP	1 and 12 months
Dieleman (2009), Netherlands[28]	Unclear, multicentre (3)	First time isolated CABG	RAVLT, GP, TMT-A, TMT-B, Sternberg memory comparison, line orientation test, SCWT, CPTA, self-ordering tasks, visuospatial working memory, SDMT	3 months, 12 months, and 5 years
Evered (2010),[a] Australia[29]	Unclear, multicentre (3)	Elective, first time CABG	CERAD auditory verbal learning test, DSST, TMT-A, TMT-B, COWAT, semantic fluency, GP (dominant and non-dominant)	3 and 12 months
Evered (2009),[a] Australia[30]	Unclear, multicentre (3)	Elective, first time CABG	CERAD auditory verbal learning test, DSST, TMT-A, TMT-B, COWAT, semantic fluency, GP (dominant and non-dominant)	3 and 12 months
Fontes (2013), USA[31]	Retrospective cohort, single centre	Elective CABG ± valve with CPB	RMT (short story module), WMS (modified visual reproduction test), WAIS-R digit span, WAIS-R digit symbol, TMT-A, TMT-B	6 weeks, 12 months
Forrest (2011), UK[32]	Prospective cohort, single centre	CABG	AVLT, SCWT, Stroop C, TMT-A, TMT-B, PP	3 months
Ge (2014), China[33]	Prospective cohort, single centre	Elective CABG	MMSE, WVLT, Digit symbol, Digit span, TMT (not specified if A, B, or both)	7 days, 3 months
Gerriets (2010), Germany[34]	Prospective cohort, single centre	Elective, first time CABG	SKT, TMT-A, D-CAT, SCWT, TMT-B, NVLT, VLMT short term learning, VLMT delayed recognition, line tracing, WAIS-IV block design	3 months
Ghaffary (2015), Iran[35]	Cohort, unclear if prospective or retrospective, single centre	Elective cardiac surgery (CABG, CABG + valve, other)	WMT-R	3 months
Hayashi (2018), Japan[36]	Prospective cohort, single centre	Elective cardiac operation (CABG, valve replacement, a thoracic aortic operation, or a combination of these)	MMSE	2 weeks
Hudetz (2010), USA[37]	Prospective cohort, single centre	≥55 elective CABG ± valve repair/replacement with CPB	RBANS (story memory), RBANS (word list memory), BVMT-R, WIS (digits backward), Semantic fluency, Phonemic fluency	7 days

Continued

Table 2 *Continued*

Primary Author (year), country	Design (including single or multicentre)	Type of surgery	Cognitive outcome measure(s)	Post-operative cognitive function follow-up time-points
Hudetz (2010), USA[38]	Prospective cohort, single centre	≥55 elective CABG ± valve repair/replacement with CPB	RBANS (story memory), RBANS (word list memory), BVMT-R, WIS—digits backward, Semantic fluency, Phonemic fluency	7 days
Hudetz (2009), USA[39]	Prospective cohort, single centre	≥55 elective CABG ± valve repair/replacement with CPB	RBANS (story memory), RBANS (word list memory), BVMT-R, WIS (digits backward), Semantic fluency, Phonemic fluency	7 days
Kadoi (2011), Japan[40]	Prospective cohort, single centre	Elective CABG	MMSE, RAVLT, TMT-A, TMT-B, digit span forwards, GP,	7 days, 6 months
Kadoi (2006), Japan[41]	Prospective cohort, single centre	Elective CABG	MMSE, RAVLT, TMT-A, TMT-B, digit span forwards, GP,	6 months
Kadoi (2005), Japan[42]	Prospective cohort, single centre	Elective CABG	MMSE, RAVLT, TMT-A, TMT-B, digit span forwards, GP,	7 days, 6 months
Kidher (2014), UK[43]	Prospective cohort, single centre	Elective AVR ± CABG	CANTAB	12 months
Klinger (2018), USA[44]	Prospective cohort (with retrospective control data), single centre	CABG ± valve with CPB	HVLT, RMT, WMS (modified visual reproduction test), WAIS-R digit span, WAIS-R digit symbol, WAIS-R vocabulary, TMT-A, TMT-B	6 weeks, 12 months, 3 years
Kok (2017), Netherlands[45]	Secondary data analysis from an RCT, single centre	CABG ± CPB	Cogstate Brief Battery	3 months, 15 months
Lyketsos (2006), USA[46]	Prospective cohort, community based	CABG (self-report)	3MS	3 years, 4 years
Maekawa (2014), Japan[47]	Prospective cohort, single centre	≥60 elective cardiac surgery (CABG with CPB, mitral valve repair or replacement, or AVR)	MMSE, WMS-R digit span, WAIS DDST, Kana pick out test, TMT-A, TMT-B	2 weeks
Mathew (2007), USA[48]	Prospective cohort, single centre	Isolated CABG using CPB	RMT (short story module), WMS (modified visual reproduction test), WAIS-R digit span, WAIS-R digit symbol, TMT-B	6 weeks
Mu (2013), China[49]	Prospective cohort, multicentre (2)	≥18 first time elective CABG without concomitant procedure	WMS Mental Control, WMS digit span, WMS visual retention, WMS paired associate verbal learning, WAIS-R digit symbol, TMT-A, GP	7 days
Norkienė (2010), Lithuania[50]	Prospective cohort, single centre	CABG (on CPB)	MMSE, RAVLT, TMT-A, TMT-B, Digit Span, DSST, cube drawing	7–9 days
Patron (2013), Italy[51]	Prospective cohort, single centre	first time elective cardiac surgery (CABG ± valve) with CPB	TMT-A, TMT-B, memory with 10/30-s interference, phonemic verbal fluency,	discharge (approximately 7 days) 18 months

Continued

Table 2 *Continued*

Primary Author (year), country	Design (including single or multicentre)	Type of surgery	Cognitive outcome measure(s)	Post-operative cognitive function follow-up time-points
Pérez-Belmonte (2015), Spain[52]	Prospective cohort, single centre	elective off pump CABG	TMT (not specified if A, B or both), SCWIT, FCSR, SVFT, PVFT, JLO	1 month, 6 months, 12 months
Plaschke (2013), Germany[53]	Prospective cohort, single centre	≥55 elective CABG ± AVR	WAIS-R digit span, GVLT, TMT-A, TMT-B, digit symbol test, SCWIT	3 months
Sakurai (2005), Japan[54]	Prospective cohort, single centre	Elective cardiovascular surgery ± CPB (CABG, valve, combined, or thoracic aortic aneurysm), aged 50–80	HDS	Day of discharge (mean interval for postoperative follow-up 20.2 ± 6.4 days)
Shiraboina (2014), India[55]	Prospective cohort, single centre	Elective cardiac surgery (CABG, AVR, other) with Katz grading of 6	MMSE	7 days
Silbert (2008),[b] Australia[56]	Prospective cohort, multi-centre (2)	≥55 elective first time on-pump CABG	CERAD auditory verbal learning test, DSST, TMT-A, TMT-B, COWAT, Semantic fluency test, GP	3 months, 12 months
Tang (2017), China[57]	Prospective cohort, single centre	First time elective valve replacement under CPB, 45–80 years	TMT-A, DSST, SCWT, AVLT	7 days
Toeg (2013), Canada[58]	Unclear, single centre	≥60 non-urgent CABG	SRT, RAVLT, WAIS-R digit span, FTT, letter and category fluency, TMT-A, TMT-B, GP, SDMT	Hospital discharge (no further details) 3 months
Tully (2009), Australia[59]	Prospective cohort, single centre	≥18 isolated CABG with CPB	CVLT, PP, TMT-A, TMT-B, WAIS-R digit symbol, BNT, COWAT	6 months, 5 years
Zhang (2020), China[60]	Prospective cohort, single centre (pilot study)	Elective valve surgery (repair or replacement)	MMSE (Chinese version), MoCA (Chinese version)	7 days

3MS, modified mini mental state exam; AVLT, auditory-verbal learning test; BNT, Boston naming test; BVMT-R, brief visuospatial memory test—revised; CANTAB, Cambridge neuropsychological test automated battery; CERAD, consortium to establish a registry for Alzheimer's disease; CFT, complex figure test; COWAT, controlled oral word association test; CPB, cardiopulmonary bypass; CPTA, continuous performance test of attention; CVLT, California verbal learning test; D-CAT, digit cancellation test; DSST, digit symbol substitution test; FCSR, free and cued selective reminding test; FTT, finger tapping test; GP, Grooved Pegboard; GVLT, German verbal learning test; HDS, Hasegawa dementia scale; HVLT, Hopkins verbal learning test; JLO, judgement of line orientation; MMSE, mini mental state exam; NVLT, non-verbal learning test; PP, Purdue Pegboard; PTSD, post-traumatic stress disorder; PVFT, phonologic verbal fluency test; RAVLT, Rey auditory and verbal learning test; RBANS, repeatable battery for the assessment of neuropsychological status; RMT, Randt memory test; SCWIT, Stroop colour and word interference test; SCWT, Stroop colour and word test; SDMT, symbol digit modalities test; SKT, syndrome Kurztest; SRT, Buschke selective reminding test; Stroop C, Stroop control; SVFT, semantic verbal fluency test; TMT, trail making test; VLMT, verbal learning and memory test; VVLT, visual verbal learning test; WAIS(-R) , Wechsler adult intelligence scale (-revised); WIS, Wechsler intelligence scale; WMS, Wechsler memory scale; WMT(-R), Wechsler memory test (-revised).

[a]Both studies use data from the 349 patients who participated in the Australian Trial Investigating Postoperative Cognitive Deficit, Early extubation and Survival (ANTIPODES) trial.

[b]This study used data from 291 patients from two of the three hospitals that participated in the ANTIPODES trial.

online, *Table S2*. Overall, 36 papers were included for data synthesis. Inter-rater reliability for inclusion was good [Kappa (κ) statistic 0.773–0.808].

Study characteristics and quality appraisal

Studies were conducted across four continents: Asia ($n = 12$), Australia ($n = 4$), Europe ($n = 9$), and North America ($n = 11$), and the majority were prospective observational studies [$n = 28$ (75.7%), *Table 2*, Supplementary material online, *Table S3*]. Most studies were single centre [$n = 30$ (81.1%)], with significant variation in the type of surgery patients had undergone, including coronary artery bypass graft (CABG) surgery only ($n = 19$), CABG and/or valve surgery ($n = 10$), valve only surgery ($n = 2$), or CABG and/or valve and other ($n = 5$). Of the studies including CABG surgery only, most were performed on pump [$n = 14$ (73.7%)]. Of the remaining CABG surgery only studies, operative techniques included off-pump only ($n = 1$), on-pump vs. off-pump ($n = 4$), and unknown ($n = 1$).

The majority of studies reported baseline cognitive function [$n = 35$ (97.2%)], measured the day before surgery ($n = 14$), within 1 week of surgery ($n = 7$), or within 2 weeks of surgery ($n = 2$). Eleven studies measuring baseline (preoperative) cognitive function did not specify the timing of assessment. There was significant variation in the timing of postoperative cognitive function measurement with the most frequent occurring at 7 days ($n = 13$). The remaining studies opted for postoperative cognitive function assessments at 2 weeks ($n = 2$), 20 days ($n = 1$), 1 month ($n = 2$), 6 weeks ($n = 3$), 3 months ($n = 11$), 6 months ($n = 5$), or 1 year ($n = 9$). Six studies measured cognitive function beyond 1 year, ranging from 15 months to 5 years.

Thirty-four of the included studies reported predictors of POCD, one reported predictors of cognitive recovery, and one reported predictors of both POCD and cognitive recovery. The criteria used to define POCD varied across the studies (Supplementary material online, *Table S3*). The standard decline criterion [$n = 14$ (37.8%)] and the use of the *z* score [$n = 7$ (23.5%)] were most commonly used, while seven studies did not provide a POCD definition. Cognitive function measurement was achieved through a variety of domain-specific measures in 31 studies, with the remaining five opting for measures of global cognition. The cognitive domains assessed were similarly variable: complex attention ($n = 30$), learning and memory ($n = 28$), executive function ($n = 16$), perceptual-motor function ($n = 16$), and language ($n = 4$), as was the variability in reported cognitive domains being measured by the tests employed (Supplementary material online, *Table S4*).

Risk of bias was generally moderate, with minimal detection and attrition bias (*Figure 2*, Supplementary material online, *Figure S1*). Thirty-one studies were deemed to be at high risk of confounding bias (Supplementary material online, *Table S5*) for failing to evaluate key factors.

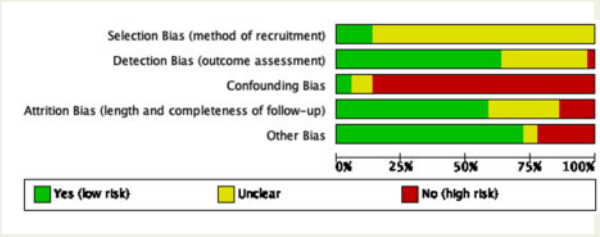

Figure 2 Risk of bias across studies ($n = 36$).

Independent predictors of POCD

Predictors (and non-predictors) of POCD after cardiac surgery were identified on multivariable analysis across 35 studies (*Table 3*, Supplementary material online, *Table S6*). Preoperative variables focused on patient-related factors, comorbidities, and biochemical variables, while postoperative variables included intensive care unit (ICU)-related variables, postoperative complications, and biochemical variables. Sixty-one independent predictors (45 preoperative and 16 postoperative) were identified across five time points (*Table 3*).

In terms of preoperative variables, age was predictive of outcome at all five time points and commonly identified across studies [$n = 16$ (45.7%)]. Education level, baseline cognitive function, and diabetes were independently predictive of outcome at three time points, while abnormal left ventricular function, the presence of collateral circulation, hypertension, serum creatinine, baseline perceptual-motor function, diabetic retinopathy, and depression were predictive at two time points. Of the 16 identified postoperative variables, only ICU length of stay was predictive of outcome at two time points while the remaining 15 were predictive at only one time point.

Independent predictors of cognitive recovery

Of the two studies exploring predictors of cognitive recovery, both at 12 months, no common variables were identified as predictive of outcome (Supplementary material online, *Table S6*).

Discussion

We sought to identify preoperative and postoperative predictors of POCD in adults following cardiac surgery to inform development of appropriate interventions. While a number of predictors have been identified, as found previously, these have been reported inconsistently across studies. Advancing age and education level appear to be the most important predictors identified, as older patients and those with lower educational levels can be prioritized when developing and trialling interventions to improve cognitive function. While advancing age has emerged as the most common predictor of cognitive outcome,[25,28,30,33,36,40–43,46,48,50,54,56,57] this was reported inconsistently. Those that found age to be non-predictive of cognitive outcome tended to have smaller sample sizes.[47,55] Furthermore, some of the larger studies reporting age as non-predictive of POCD did not use control groups to compare the rate of cognitive decline in age-matched populations who were not exposed to anaesthesia or surgery,[26,27] a recognized limitation of POCD research.[4,10,61,62] Older patients are more likely to have neurovascular disease risk factors, structural brain changes, and dementia development, placing them at higher risk of POCD.[1,3]

Our findings are consistent with previous research,[63] suggesting that education level influences cognitive outcome, with lower

Table 3 Comparison of significant and non-significant predictors of postoperative cognitive dysfunction by follow-up time point

		Follow-up time point									
		Between 7 days and 6 weeks		3 months		6 months		Between 12 and 18 months		Between 3 years and 5 years	
		Significant	Non-significant	Significant	Non-significant	Significant	Non-significant	Significant	Non-significant	Significant	Non-significant
Preoperative variables	Demographic variables										
	6-min walking distance	$n=1$[36]									
	Age	$n=7$[36,40,42,48,50,54,57]	$n=6$[26,27,39,47,49,55]	$n=4$[30,32,33,56a]	$n=5$[28,29,32,35,53b,c]	$n=1$[41]	$n=2$[40,42]	$n=1$[43d]	$n=2$[28,29]	$n=2$[25,28]	
	Alcoholism	$n=1$[39]			$n=2$[33,35]						
	BMI		$n=4$[26,36,49,50]		$n=2$[33,35]			$n=1$[52]	$n=1$[43]		
	Education	$n=3$[26,48,57]	$n=2$[27,49]	$n=1$[45]	$n=2$[33,34]					$n=1$[25]	
	Gender		$n=8$[26,27,36,40,42,47,49,50]	$n=1$[32a]	$n=7$[28–30,32,33,53,56b,c,e,f]		$n=3$[40–42]		$n=3$[28,29,56]		$n=1$[28]
	Smoking		$n=3$[49,50,54]		$n=4$[29,30,33,56]		$n=2$[41,42]	$n=1$[52]	$n=3$[29,43,56]		
	Cerebrovascular variables										
	Carotid artery disease	$n=2$[47,50]	$n=8$[26,36,40,42,47–49,54]		$n=1$[33]		$n=3$[40–42]				
	Grey matter loss in the median temporal lobe	$n=1$[47]									
	Cardiovascular variables										
	Abnormal left ventricular function	$n=1$[26]	$n=7$[36,40,42,47–50]		$n=3$[29,30,35]		$n=3$[40–42]	$n=1$[43g]	$n=1$[29]		
	Aortic atherosclerosis	$n=2$[40,42]	$n=1$[47]		$n=1$[29]		$n=3$[40–42]		$n=1$[29]		
	Aortic pulse wave velocity							$n=1$[43d,h,i,j]			
	Aortic valve area							$n=1$[43i]			
	Arrhythmia	$n=1$[60]	$n=2$[49,50]								
	Collaterals present			$n=1$[28]				$n=1$[28]			$n=1$[28]
	Diastolic blood pressure ≤50mmHg							$n=1$[52]			
	Hypertension	$n=2$[40,42]	$n=5$[36,47–50]	$n=2$[29,30]	$n=5$[28,33–35,56]		$n=3$[40–42]		$n=3$[28,29,56]		$n=1$[28]
	NYHA classification	$n=1$[49]	$n=1$[50]		$n=1$[33]						
	Peripheral arterial disease		$n=1$[47]					$n=1$[52]			
	Biochemical variables										
	Amyloid beta (Aβ) peptides $Aβ_{40}$ and $Aβ_{42}$			$n=1$[30]							
	Kynurenic acid			$n=1$[32b,e]							
	Neopterin			$n=1$[32a]							
	APOε4 allele									$n=1$[25]	
	CRP 1059G/C SNP	$n=1$[48]									
	Haematocrit ≤30%							$n=1$[52]			
	HbA1c		$n=1$[42]			$n=2$[40,42]					

Continued

Table 3 *Continued*

		Follow-up time point									
		Between 7 days and 6 weeks		3 months		6 months		Between 12 and 18 months		Between 3 years and 5 years	
		Significant	Non-significant	Significant	Non-significant	Significant	Non-significant	Significant	Non-significant	Significant	Non-significant
	Hs-TnT							$n = 1$[45]			
	SELP 1087G/A SNP	$n = 1$[48]									
	Serum creatinine	$n = 1$[26]		$n = 1$[35k]							
	Cognitive variables[l]										
	Baseline cognitive function	$n = 2$[36,48]	$n = 5$[47,49,51,54,55]	$n = 1$[45]					$n = 1$[51]	$n = 1$[25]	
	Baseline complex attention			$n = 1$[32c,f]	$n = 1$[32b,e]						
	Baseline perceptual-motor function	$n = 1$[49]		$n = 1$[32a]							
	Baseline learning and memory			$n = 1$[32k,m]							
	Comorbidities										
	Chronic kidney disease		$n = 1$[36]			$n = 1$[41]					
	Diabetes	$n = 2$[40,42]	$n = 8$[26,36,47–50,54,55]		$n = 7$[28–30,33–35,56]	$n = 3$[40–42]		$n = 1$[52]	$n = 4$[28,29,43,56]		$n = 2$[25,28]
	Diabetic retinopathy	$n = 2$[40,42]				$n = 2$[40,42]					
	Anaemia		$n = 3$[36,42,50]				$n = 2$[41,42]	$n = 1$[52]			
	COPD		$n = 2$[36,49]	$n = 1$[35m]							
	Psychosocial variables										
	Depression	$n = 1$[40]	$n = 1$[38]		$n = 4$[29,30,53,56]	$n = 1$[40]			$n = 2$[29,56]		
	Centre for Epidemiological Studies of Depression scale		$n = 1$[51]					$n = 1$[51]			
	PTSD	$n = 1$[37]									
	Dispositional optimism	$n = 1$[38]									
	Preoperative medications										
	Nitrates			$n = 1$[35k]							
	Penehyclidine (premedication)	$n = 1$[49]									
Postoperative variables	Intensive care unit (ICU)-related variables										
	ICU length of stay	$n = 3$[26,36,50]	$n = 2$[39,55]	$n = 1$[58]	$n = 1$[34]						
	Inotropic support		$n = 1$[50]					$n = 1$[43d]			
	Systemic inflammatory response syndrome score			$n = 1$[33]							
	Ventilation time ≥6 h	$n = 1$[50]	$n = 2$[26,36]		$n = 1$[33]						
	Complications										
	Delirium	$n = 2$[27,39]	$n = 2$[47,50]		$n = 1$[53]				$n = 1$[27]		
		$n = 1$[49]									

Continued

Table 3 *Continued*

	Follow-up time point									
	Between 7 days and 6 weeks		3 months		6 months		Between 12 and 18 months		Between 3 years and 5 years	
	Significant	Non-significant	Significant	Non-significant	Significant	Non-significant	Significant	Non-significant	Significant	Non-significant
Occurrence of postoperative complications within 7 days of surgery										
Postoperative atrial fibrillation		$n = 3$[26,36,50]					$n = 1$[43m]			
Biochemical variables										
Insulin resistance index measured at 6 h[n]	$n = 1$[57]									
Insulin resistance index measured at 7 days[n]	$n = 1$[57]									
Interleukin-6 (IL-6) measured 6 h after surgery	$n = 1$[57]									
Serum cortisol level	$n = 1$[49]									
Serum albumin	$n = 1$[60]									
Tumour necrosis factor-alpha (TNF-a)	$n = 1$[57]									
Cognitive variables										
Early POCD (2–7 days)			$n = 1$[34]					$n = 1$[51]		
POCD *z* score at 3 months							$n = 1$[45]			
Psychosocial										
Self-rating depression scale (SDS)	$n = 1$[57]									

APOE-ε4, apolipoprotein epsilon 4; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; HbA1c, glycosylated haemoglobin; HS-TnT, high-sensitivity cardiac troponin T; NYHA, New York Heart Association; PTSD, post-traumatic stress disorder; SELP, P-selectin gene; SNP, single-nucleotide polymorphism.

[a]PP (non-dominant).
[b]TMT-A.
[c]TMT-B.
[d]Rapid visual information processing (RVP) total missed.
[e]Stroop C.
[f]SCWT.[32]
[g]Pattern recognition memory (PRM) delayed, % correct.
[h]One touch stockings of Cambridge (OTS) problems solved on first choice.
[i]OTS choices correct to level-5.
[j]OTS latency to correct level-5.
[k]Change in WMT score (model B).
[l]Categorized according to the DSM-V neuropsychological domains.
[m]RVP A (measure of sensitivity to the target stimulus).[43]
[m]Postoperative WMT score (model A).[35]
[n]Measured using homeostasis model assessment-2 HOMA2 software.

educational levels being predictive of POCD[25,26,45,46,48,57] and higher educational levels being predictive of cognitive recovery.[31] It has been postulated that those with higher educational levels have greater cognitive reserve; in educated individuals the brain is exposed to challenging mental activities that potentially decrease the susceptibility to clinical manifestations of structural brain changes.[64] However, the results are inconclusive with some studies reporting educational level as non-predictive,[27,33,34,49] therefore further investigation is warranted.

Lower preoperative baseline cognitive scores, indicating cognitive decline, has previously been linked with a potential increase in POCD risk.[65] However, overall, baseline cognitive function was found to be an inconsistent predictor of POCD. Interestingly, when baseline perceptual-motor function was assessed using the Purdue Pegboard Test,[32] and the Grooved Pegboard Test[49] baseline performance was more consistently identified as an important predictor. Despite this, assessment of motor function occurs less frequently than the domains of memory and attention,[6,61] even though the Grooved Pegboard Test is one of the core recommended tests in the Statement of Consensus on assessment of neurobehavioral outcomes after cardiac surgery.[10]

Recent studies have explored the role of biochemical markers of cognitive function, as adjuncts to neuropsychological testing, risk factors, and predictors for the development for POCD. Studies included in this review have investigated the role of amyloid beta (Aβ,) isoforms Aβ40 and Aβ42,[30] kynurenic acid,[32] neopterin,[32] apolipoprotein ε4 allele,[25] and high-sensitivity troponin T[45]; however, there was minimal overlap between studies exploring the predictive role of these variables making it difficult to draw conclusions.

The inconsistencies in our findings are most likely explained by the heterogeneity in relation to cognitive outcomes measured across the studies, including the neurocognitive tests, the diagnostic criteria, and the timing of assessments used to diagnose POCD. Methodological issues of POCD research have been widely reported, however despite recommendations for a standardized approach,[4,10,11] such variability remains.[7] Reducing heterogeneity in future studies will allow more meaningful comparisons between studies and strengthen the conclusions of systematic reviews in this area. Larger multi-site studies with methodological consistency is one way to achieve this. Furthermore, identification of the predictors of POCD could help practitioners identify patients most likely to benefit from targeted cognition-based interventions aimed at improving cognitive function.

As previously indicated, POCD has been researched extensively. Despite this, the causes, mechanisms, and significance of POCD are still poorly understood. In this review, we have focused on preoperative predictors of POCD (as well as postoperative predictors) to determine if designing an intervention (that could be delivered either preoperatively or postoperatively) was appropriate and feasible. Though we have not included intraoperative factors in this review, it is important to acknowledge the importance of such factors in the development of POCD, for example the type and invasiveness of surgery, duration of surgery, repeat procedures, operative technique (e.g. on- or off-pump), depth of anaesthesia, pain, and pain management.[5] Within this emerging area of investigation, a number of studies have explored intraoperative preventative strategies, including anaesthetic approaches, cerebral perfusion pressure management, and the individual anaesthetic drugs used. Without any definitive preventative or treatment strategies, further research is required in this area to prevent patients from developing POCD and to treat POCD once it develops.[1,66]

Strengths and limitations

This systematic review has several limitations. First, no study was excluded on the basis of quality assessment and this may be considered a limitation but helped ensure potentially valuable results were included in the final synthesis; it also resulted in the risk of bias of included studies being generally moderate. It was remarkable that none of the studies had an overall low risk of bias. In addition, methodological heterogeneity meant that meta-analysis was not possible. Second, we were unable to obtain full-text versions of some potentially eligible papers. Authors from the primary studies were not contacted. Finally, as previously highlighted, intraoperative factors undoubtedly play an important role in the development of POCD. Subsequently, there is a lot of interest in developing intraoperative strategies to improve cognitive outcomes. We have focused on preoperative and postoperative predictors of POCD in this review; however, it is clear that a contemporary appraisal and synthesis of intraoperative predictors and risk factors of POCD is required.

To the best of our knowledge, this is the first review exploring predictors of POCD in cardiac surgical patients. Other strengths include the robustness of our review process including dual screening, quality assessment, and data extraction. Finally, a comprehensive search strategy was employed, which included non-English papers, again ensuring potentially valuable results were included in the final synthesis.

Conclusion

In conclusion, although a number of preoperative and postoperative predictors of POCD have been identified in this systematic review, they have been reported inconsistently across studies. These findings are less surprising if we consider the methodological shortcomings of included studies. Advancing age and fewer years of education were consistently identified as important predictors of POCD, therefore older patients and those with lower education levels should be prioritized when developing and trialling interventions to improve cognitive function. Though a considerable body of research exists in relation to risk factors associated with POCD, less attention has been paid to predictors of POCD. It is evident that further high-quality research exploring predictors of POCD is required to enable practitioners to identify patients most likely to benefit from cognition-based interventions.

Supplementary material

Supplementary material is available at *European Journal of Cardiovascular Nursing* online.

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