



## Review Article

Korean J Anesthesiol 2021;74(1):15-22  
<https://doi.org/10.4097/kja.20294>  
pISSN 2005-6419 • eISSN 2005-7563

Received: June 5, 2020

Accepted: July 1, 2020

### Corresponding author:

Setayesh Reza Tasbihgou, M.D.  
Department of Anesthesiology, University  
Medical Center Groningen, University of  
Groningen, Groningen 9713 GZ, The  
Netherlands  
Tel: +31-503612892  
Email: [s.r.tasbihgou@umcg.nl](mailto:s.r.tasbihgou@umcg.nl)  
ORCID: <https://orcid.org/0000-0002-6147-6163>

# Postoperative neurocognitive disorders

Setayesh Reza Tasbihgou, Anthony Ray Absalom

*Department of Anesthesiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands*

A decline in cognitive function is a frequent complication of major surgery. Postoperative cognitive impairments have generally been divided into short-(postoperative delirium) and long-term disturbances (postoperative cognitive dysfunction [POCD]). Long-term impairments are often subtle and overlooked. They need to be objectively assessed using neuropsychological tests to be diagnosed. Although POCD has been the subject of considerable research over the past decades, it remains uncertain why some patients do not return to preoperative levels of cognitive function. Surgery and anesthesia have both been implicated to play a role in POCD development, and certain patient-related factors, such as advanced age and low preoperative baseline cognitive function, have consistently been found to predict postoperative cognitive decline. This article will present an overview of POCD and its etiology and provide advice on possible strategies on its prevention.

**Keywords:** Aged; Delirium; Frail elderly; Inflammation; Neurocognitive disorders; Perioperative care; Postoperative cognitive complications.

## Introduction

It has been over five decades since Bedford observed that surgery in elderly patients was followed by a significant cognitive decline that lasted for an extensive period [1]. Through interviews (with patients and relatives) and subjective assessment, he found that 7% of his (elderly) patients who underwent surgery and received general anesthesia showed signs of cognitive impairment. He published these findings in *The Lancet*, concluding that “the allegation ‘He’s never been the same since his operation’ is sometimes true, and that an irreversible gross dementia is occasionally the aftermath of surgical operations under general anesthesia [1].”

By the late 1980s, psychometric tests were used to objectively assess cognitive decline after surgery, particularly in patients undergoing cardiac surgery [2]. The studies also consistently documented long-term cognitive disorder in elderly patients, although there were varying incidences and severities [3–5]. As a result, the concept of postoperative cognitive dysfunction (POCD) was developed as a diagnosis based on these objective measurements. Although surgery and anesthesia have improved dramatically since then, the exact understanding of when, how, and why some patients do not return to baseline cognitive function remains elusive. As cognitive dysfunction, in the form of delirium, has been shown to be important for perioperative outcome and mortality [6–8], it is also important to consider the effects of long-term cognitive impairment and its possible risk factors. In this review, we present a brief overview of POCD and its etiology and provide advice on possible strategies on its prevention.

© The Korean Society of Anesthesiologists, 2021

© This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

## Postoperative cognitive impairment: delirium and POCD

Postoperative cognitive impairments have generally been divided into short-(delirium) and long-term disturbances (POCD) [9]. The former is familiar among many clinicians and well defined according to the Diagnostic and Statistical Manual of Medical Disorders (DSM)-5 [10]. It states that delirium consists of impairments in attention, awareness, and cognition. Cognition is considered to be a dynamic state, involving multiple domains, such as memory, orientation, language, visuospatial ability, and perception [11]. It fluctuates throughout the day and is affected by both endogenous and exogenous factors [12]. The incidence of postoperative delirium is between 20% and 45% in older adult patients undergoing surgery [13,14].

In contrast, the term POCD has been used to refer to any signs of new cognitive impairment that exceeds the expected length of time needed to recover from the acute effects of surgery and anesthesia [9,15,16]. Unlike delirium, which is a relatively simple and recognizable syndrome, POCD is clinically far less apparent as it often only manifests as mild cognitive decline in one or more cognitive domains [9,17,18]. Furthermore, the DSM-5 does not list POCD as a diagnosis. In 2018, this prompted an expert panel of scientists and clinicians, The International Perioperative Cognition Nomenclature Working Group, to address, clarify, and give structure to POCD and other perioperative cognitive impairments, while proposing new nomenclature to be used in relation to these terms [5].

This working group stated that all cognitive changes associated with surgery and anesthesia should be summarized under the term “perioperative neurocognitive disorders,” thus aligning these impairments with the clinical diagnostic criteria for “neurocognitive disorders (NCDs)” already applied in the DSM-5 [5,10]. The working group recommended POCD assessment at least 30 days postoperatively, at which point most patients are expected to have recovered, physically, physiologically, and emotionally from surgery and hospitalization [5]. If assessment is performed too early, the effects of POCD may be overshadowed by acute postoperative

delirium or other cognitive complications that may arise from immobility, sleep deprivation, and ongoing pharmacological interventions [2]. When cognitive impairment manifests itself beyond 12 months postoperatively, mild or major (e.g., dementia) NCDs should be considered over POCD [5].

The term “delayed neurocognitive recovery” may be used to describe a cognitive disorder that is detected within 30 days after surgery when delirium has been excluded. Table 1 summarizes the recommendations offered by the working group [5,12].

### POCD assessment

Unlike delirium, the diagnosis of POCD has primarily been confined to research. Its diagnosis relies on objectively measurable cognitive decline assessed with neuropsychological tests [15,16,19]. Subjective reports of cognitive changes by patients or proxies are also relevant; however, most studies comparing cognitive complaints and neuropsychological test results were unable to find a significant correlation [16,20]. Certain cognitive functions may be less relevant to a patient’s daily life, and as such, any dysfunction may be overlooked by the patient. There is no agreed upon definition for POCD, but it generally refers to impairment of memory, learning, concentration, attention, or psychomotor performance [5,15]. Neuropsychological tests are often specific to one of these cognitive domains.

Neuropsychological tests that were used in a key international multicenter study on POCD (International Study of Post-Operative Cognitive Dysfunction [ISPOCD] 1) are described in Table 2. There are a wide variety of neuropsychological tests, which all have different levels of sensitivity and reliability. The ISPOCD mostly used written tests. However, our research group favors computerized tests, such as the Cogstate Computerized Cognitive Test Battery®, because of its ease of use, versatility, and availability of age-matched control group test data.

Certain tests are more vulnerable to the effects of practice and have a poor test-retest reliability [12,16,19]. Others notoriously have floor and ceiling effects resulting from tests being either too difficult or too easy to detect subtle changes [16]. The method

**Table 1.** A Summary of the Recommendations for the New Nomenclature of Perioperative Disorders, from the International Perioperative Cognition Nomenclature Working Group [5]

Terms	Period
Neurocognitive disorder (mild or major [e.g., dementia])	Preexisting/preoperative cognitive impairment or cognitive impairment developing after 12 months of surgery.
Emergence delirium	Delirium diagnosed within minutes or hours after surgery.
Postoperative delirium	Delirium diagnosed within days after surgery, up to 1 week or until discharge.
Delayed neurocognitive recovery	Cognitive decline up to 30 days postoperatively.
Postoperative (neuro)cognitive dysfunction	Cognitive impairment detected between 30 days and 12 months postoperatively.

**Table 2.** Neuropsychological Tests Used in the International Study of Post-Operative Cognitive Dysfunction 1 (ISPOCD 1)

Tests	
Mini-mental state examination (MMSE) [70]	A commonly used assessment, initially developed to evaluate dementia. It assesses multiple cognitive domains, including attention, memory, and orientation.
Visual verbal learning test [71]	Based on Rey's auditive recall test. It assesses verbal memory by asking patients to recall a list of words that they were presented with earlier.
Concept shifting test (trail-making test) [72]	Also known as trail-making tests A and B. It is used to assess executive function and attention by asking subjects to connect a series of consecutive numbers, letters, or both as quickly as possible.
Stroop color word interference test [73]	This test evaluates the ability to inhibit cognitive interference from multiple congruent and incongruent stimuli.
Letter-digit coding test (symbol-digit substitution task) [74]	Used to assess executive function. Patients are presented with a series of digits and letters that are paired and another list of only digits. Then, they are asked to write the corresponding letter as fast as possible.
Four boxes test [75]	This test is computer based. It is used to measure reaction time by asking patients to select a black circle in one of four boxes on a screen as quickly as possible.

with which these test results are interpreted also varies throughout the literature [2]. Test batteries, consisting of multiple tests, are able to assess various cognitive domains and are recommended as they are able to describe brain functions in more detail and with increased sensitivity [2,16]. To measure cognitive decline, investigators should determine the change between baseline preoperative and postoperative cognitive functions. To correct for age-related test-retest variability, determining the change in cognitive function with the use of a reliable change index is recommended, as it calculates this change with reference to the expected change found within an age-matched control group [16].

## Incidence of POCD

The incidence of POCD ranges from 20% to 50% in older patients 3 months after cardiac surgery and 5% to 55% in those undergoing major noncardiac surgeries [15,21–25]. This large variation is the result of the methodological differences between studies, making data comparison often difficult. In addition to the various types of test that may be administered for measuring cognitive change, the degree of change and cutoffs necessary for determining POCD have also varied throughout literature. Generally, POCD is divided into mild or major neurocognitive decline, if testing exhibits a decline of > 1 or > 2 standard deviations of cognitive function compared to preoperative cognitive performance, respectively. As described above, the timing of tests is also a known source of variability; the later the cognitive assessment is conducted and the more stringent the statistical criteria for identifying POCD, the lower the reported incidence [16].

This point is illustrated by the large multicenter ISPOCD study conducted in 1998, which observed 1000 patients (age > 60 years) undergoing various noncardiac surgeries [15]. A comprehensive neuropsychological test battery was administered with a strict cri-

terion for POCD. This study found that 25.8% (95% CI: 23.1, 28.5) of patients showed signs of cognitive dysfunction 1 week postoperatively. Cognitive dysfunction at 3 months postoperatively was 9.9% (95% CI: 8.1, 12.0). A later study by Monk et al. found similar incidences of POCD in 365 patients undergoing noncardiac surgery: 41.4% (95% CI: 36.2, 46.7) at discharge and 12.7% (95% CI: 8.9, 16.4) at 3 months [25]. A recent systematic review of 24 studies found that the incidence of POCD at 3 months was 11.7% (95% CI: 10.9, 12.5), although they concluded that major differences in methodology and definitions accounted for variations in the results [26].

## Pathogenesis of POCD

Despite a growing volume of research concerning POCD, the exact etiology for cognitive decline after surgery and anesthesia is still not well understood. Surgery-, anesthesia-, and patient-related factors have all been implicated in playing a role in POCD development, and support for various hypotheses has changed markedly over the years. Historically, a poor cognitive outcome after surgery was often regarded as a consequence of cerebral hypoperfusion and hypoxemia [2,17]. Indeed, inadequate cerebral oxygenation will result in brain damage and cognitive decline. Although intuitively compelling, no strong evidence has been found in favor of POCD being the direct consequence of impaired cerebral hemodynamics and oxygenation [2,24,27]. This was also confirmed by the ISPOCD, which monitored perioperative blood pressure and oxygenation and showed that POCD developed in the absence of perioperative hypoxemia or hypotension [15].

Factors such as the type and duration of surgery and anesthesia have also often been presumed to be associated with the incidence of POCD. However, this has not yet been conclusive. A comprehensive study by Evered et al. [21] compared the incidence of

POCD after coronary angiography under sedation, total hip replacement, and coronary artery bypass graft under general anesthesia. Interestingly, the incidence of POCD was similar and thus independent of the nature of surgery or type of anesthesia administered. Furthermore, evidence on whether the use of volatile or intravenous anesthetics may be related to POCD has also been controversial and conflicting [28]. Moreover, other studies have not found any correlation between regional or general anesthesia and incidence of POCD, which further supports the argument that the type of anesthesia appears to be unrelated to POCD development [29,30]. Therefore, it is unlikely that POCD is solely caused by anesthesia or surgery.

A recurring theme and current rationale for the pathogenesis of cognitive dysfunction encompass the role of an inflammatory response to surgery and anesthesia [2,17,27]. It is commonly known that inflammatory processes, such as those associated with pneumonia or urinary tract infection, are regularly accompanied by cognitive decline, particularly in the elderly population [31,32]. Extending this model to POCD, it is thought that the release of proinflammatory mediators, triggered by peripheral surgical stress or trauma, may result in an exaggerated systemic inflammatory response, leading to neuroinflammation in vulnerable individuals [17,27,33]. The release of inflammatory cytokines is known to lead to endothelial dysfunction and also disruption of tight junctions, which results in an increased blood-brain-barrier (BBB) permeability [27,34]. Consequently, systemic inflammatory cytokines will penetrate the BBB, triggering neuroinflammation and activation of the neuronal immune system, including microglia and astrocytes [27,33,35]. Inflammatory mediators are also produced within the brain, as a result of peripheral-to-central signaling via humoral and neuronal pathways [36]. The consequences of this immune response are healing, but if excessive, it may also result in further (cerebral) tissue damage in the form of increased synaptic dysfunction, inhibition of neurogenesis, and neuronal death [27].

In mouse models, surgery caused hippocampal-dependent memory impairment that was associated with increased expression of plasma cytokines and reactive microgliosis and interleukin (IL)-1 $\beta$  transcription and expression in the hippocampus [37,38]. By inhibiting IL-1 $\beta$ , these neuroinflammatory changes were mitigated. Another study showed that tumor necrosis factor (TNF)- $\alpha$  inhibition was also able to limit the release of IL-1 and prevent neuroinflammation and cognitive decline in mice [39]. Thus, peripheral surgical injury can result in inflammation and neuroinflammation. However, interpreting and determining the significance of an inflammatory marker is challenging, as inflammation is a normal physiological response to injury [27].

Generally, inflammation is only harmful when proinflammatory responses outweigh the anti-inflammatory response. Certain patient-related factors are known to exacerbate proinflammatory responses or increase the vulnerability of some patients to the effects of inflammation. Advanced age has been consistently associated with POCD throughout the literature [2,12]. Structural cerebral changes, such as a reduction in gray matter volume and myelinated axon length, are normal changes that occur with aging [27,40]. The normal decline in cognitive function in the elderly population might possibly be further exacerbated by the loss of neuronal dendrite spines and alterations in synaptic transmission and receptors [41]. Furthermore, BBB dysfunction has also been found in older patients even in the absence of surgery [42]. Thus, this decline in “cognitive reserve” may explain how elderly patients are more susceptible to effects of inflammation and therefore neuronal injury. A low preoperative cognitive function and lower education level have also been frequently associated with POCD, also suggesting the vulnerability of a reduced “cognitive reserve” [2,15,25,43].

Predisposing patient factors may also exaggerate an inflammatory response, as a result of “immune priming” [27]. For instance, normal aging without any comorbidities has been associated with a low-grade inflammatory activity and increased plasma TNF- $\alpha$  and IL-6 levels compared to younger patients [44]. Elderly patients are also more susceptible to sepsis [45]. It is unsurprising that patients of advanced age may be more likely to develop an exaggerated inflammatory response as a consequence of surgery. The immune system activation caused by atherosclerosis or neurodegenerative disorders, such as Alzheimer’s and Parkinson’s diseases, may also prime individuals to develop an excessive inflammatory response [46,47]. The presence of Alzheimer’s dementia biomarkers in the cerebrospinal fluid has been shown to be associated with POCD at 3 months, which has also led to the notion that they may involve similar mechanisms [48].

Considering the role of inflammation, several studies have attempted to prevent POCD using anti-inflammatory drugs [17,49]. One study on the effects of high-dose intraoperative dexamethasone administration in cardiac surgery showed that it did not reduce the risk of POCD [50]. Furthermore, other studies have found that lidocaine, magnesium, and complement cascade inhibitors also failed to prevent POCD [51–53]. These negative findings and the understanding that not all elderly patients undergoing major surgery develop POCD or not all patients with atherosclerosis develop POCD after cardiac surgery reflect the pathophysiological complexity of POCD.

## Prevention of POCD

Although there is no firm understanding of the causes of POCD, improving cognitive outcome after surgery remains an important objective for anesthesiologists and surgeons alike. To date, no pharmacological intervention has convincingly been shown to mitigate the incidence or magnitude of POCD [17]. Dexmedetomidine, an anesthetic agent with neural anti-inflammatory effects, has been found to be potentially effective at reducing the incidence of postoperative delirium; however, any evidence that it may be effective at reducing POCD is incomplete [54,55]. Deep sedation has also been identified as a risk factor for delirium, and several studies have found that measuring the depth of anesthesia (with electroencephalogram monitors) was effective at reducing postoperative delirium. However, there is conflicting evidence that POCD can also be prevented with the same measures [56–60]. If possible, deliriogenic [pre]medications, such as benzodiazepines, should also be avoided [61,62]. Pain and increased postoperative opioid consumption are known to increase the risk of delirium and have also been associated with POCD [62]. Although sufficient pain-management is mandatory, opioid-sparing analgesia may be an effective measure at alleviating this risk. Early postoperative mobilization and a fast-track postoperative approach may help in this respect [63].

Generally, for [non-pharmacological] preventive measures to be significantly effective, multiple (interdisciplinary) interventions, covering various domains, should be considered [2,12,17]. Patients with a possible high risk for POCD should be preoperatively identified and cognitively assessed. When possible, predisposing factors should be modified and adjusted so that patients are sufficiently prepared for surgery. Preparing patients and their relatives adequately by informing them about possible postoperative cognitive changes is also beneficial [64]. Extended periods of preoperative fasting and dehydration should be avoided, as should unnecessary postponement of surgery [65]. Peri- and postoperative patient (re)orientation is essential. Encouraging patients to wear their glasses and hearing aids and early removal of catheters and lines are known to be effective at reducing the risk of postoperative delirium and will help orientate patients and mobilize them earlier, which may likely be effective at preventing POCD [62].

Numerous novel approaches that have been shown to improve cognitive function in older adults have also been proposed as possible interventions that may prevent or protect patients against POCD. These proposed interventions involve diet interventions, physical exercise programs, and brain stimulation and cognitive training [17,66]. Although these strategies are known to improve

overall cognition, a few of them have been investigated as potential and feasible interventions for POCD [2]. One study by Kawano et al. [67] found that preoperative environmental enrichment, consisting of both cognitive and physical activities, was able to attenuate neuroinflammation and improve cognitive function in old rats after abdominal surgery. In humans, there is some evidence that preoperative physical status may improve postoperative morbidity; however, cognitive advantages, if any, are still unknown [68,69]. Nonetheless, for treatments of cognitive decline, there appears to be some potential in improving lifestyle-based factors, although further investigation is necessary.

## Conclusion

Many studies have drawn attention to neurocognitive dysfunction after surgery using neuropsychological assessments before and after surgery. The results on the incidence and severity of postoperative cognitive decline vary, mostly due to different definitions for diagnosing POCD.

Although the etiology of POCD is still not fully understood, inflammatory processes are currently considered to be central to its genesis. Presently, no clear anesthetic and surgical components have been found to influence POCD. Nevertheless, several patient-related factors, such as advanced age, have been associated with an increased risk for cognitive decline. As the age of the general population undergoing surgery is growing older, investigations on preventive measures and interventions are warranted, and they should be aptly applied.

## Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

## Author Contributions

Setayesh Reza Tasbihgou (Conceptualization; Investigation; Writing – original draft; Writing – review & editing)

Anthony Ray Absalom (Conceptualization; Project administration; Supervision; Writing – review & editing)

## ORCID

Setayesh Reza Tasbihgou, <https://orcid.org/0000-0002-6147-6163>

Anthony Ray Absalom, <https://orcid.org/0000-0001-7563-9157>

## References

1. Bedford PD. Adverse cerebral effects of anaesthesia on old people. *Lancet* 1955; 269: 259-63.
2. Evered LA, Silbert BS. Postoperative cognitive dysfunction and noncardiac surgery. *Anesth Analg* 2018; 127: 496-505.
3. O'Keeffe ST, Ní Chonchubhair A. Postoperative delirium in the elderly. *Br J Anaesth* 1994; 73: 673-87.
4. Gustafson Y, Berggren D, Brännström B, Bucht G, Norberg A, Hansson LI, et al. Acute confusional states in elderly patients treated for femoral neck fracture. *J Am Geriatr Soc* 1988; 36: 525-30.
5. Evered L, Silbert B, Knopman DS, Scott DA, DeKosky ST, Rasmussen LS, et al. Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery-2018. *Br J Anaesth* 2018; 121: 1005-12.
6. Kiely DK, Jones RN, Bergmann MA, Murphy KM, Orav EJ, Marcantonio ER. Association between delirium resolution and functional recovery among newly admitted postacute facility patients. *J Gerontol A Biol Sci Med Sci* 2006; 61: 204-8.
7. Kiely DK, Marcantonio ER, Inouye SK, Shaffer ML, Bergmann MA, Yang FM, et al. Persistent delirium predicts greater mortality. *J Am Geriatr Soc* 2009; 57: 55-61.
8. Deiner S, Silverstein JH. Postoperative delirium and cognitive dysfunction. *Br J Anaesth* 2009; 103 (Suppl 1): i41-6.
9. Monk TG, Price CC. Postoperative cognitive disorders. *Curr Opin Crit Care* 2011; 17: 376-81.
10. American Psychiatric Association. American Psychiatric Association. DSM-5 Task Force. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Washington DC, American Psychiatric Association. 2013, p 947.
11. Sachdev PS, Blacker D, Blazer DG, Ganguli M, Jeste DV, Paulsen JS, et al. Classifying neurocognitive disorders: the DSM-5 approach. *Nat Rev Neurol* 2014; 10: 634-42.
12. Olotu C. Postoperative neurocognitive disorders. *Curr Opin Anaesthesiol* 2020; 33: 101-8.
13. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet* 2014; 383: 911-22.
14. Rudolph JL, Marcantonio ER. Review articles: postoperative delirium: acute change with long-term implications. *Anesth Analg* 2011; 112: 1202-11.
15. Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, et al. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. *Lancet* 1998; 351: 857-61.
16. Rasmussen LS, Larsen K, Houx P, Skovgaard LT, Hanning CD, Moller JT. The International Study of Postoperative Cognitive Dysfunction. The assessment of postoperative cognitive function. *Acta Anaesthesiol Scand* 2001; 45: 275-89.
17. Berger M, Terrando N, Smith SK, Browndyke JN, Newman MF, Mathew JP. Neurocognitive Function after Cardiac Surgery: From Phenotypes to Mechanisms. *Anesthesiology* 2018; 129: 829-51.
18. Daiello LA, Racine AM, Yun Gou R, Marcantonio ER, Xie Z, Kunze LJ, et al. Postoperative Delirium and Postoperative Cognitive Dysfunction: Overlap and Divergence. *Anesthesiology* 2019; 131: 477-91.
19. Rudolph JL, Schreiber KA, Culley DJ, McGlinchey RE, Crosby G, Levitsky S, et al. Measurement of post-operative cognitive dysfunction after cardiac surgery: a systematic review. *Acta Anaesthesiol Scand* 2010; 54: 663-77.
20. Newman S, Klinger L, Venn G, Smith P, Harrison M, Treasure T. Subjective reports of cognition in relation to assessed cognitive performance following coronary artery bypass surgery. *J Psychosom Res* 1989; 33: 227-33.
21. Evered L, Scott DA, Silbert B, Maruff P. Postoperative cognitive dysfunction is independent of type of surgery and anesthetic. *Anesth Analg* 2011; 112: 1179-85.
22. McDonagh DL, Mathew JP, White WD, Phillips-Bute B, Laskowitz DT, Podgoreanu MV, et al. Cognitive function after major noncardiac surgery, apolipoprotein E4 genotype, and biomarkers of brain injury. *Anesthesiology* 2010; 112: 852-9.
23. Newman MF, Kirchner JL, Phillips-Bute B, Gaver V, Grocott H, Jones RH, et al. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. *N Engl J Med* 2001; 344: 395-402.
24. Kok WF, van Harten AE, Koene BM, Mariani MA, Koerts J, Tucha O, et al. A pilot study of cerebral tissue oxygenation and postoperative cognitive dysfunction among patients undergoing coronary artery bypass grafting randomised to surgery with or without cardiopulmonary bypass\*. *Anaesthesia* 2014; 69: 613-22.
25. Monk TG, Weldon BC, Garvan CW, Dede DE, van der Aa MT, Heilman KM, et al. Predictors of cognitive dysfunction after major noncardiac surgery. *Anesthesiology* 2008; 108: 18-30.
26. Paredes S, Cortinez L, Contreras V, Silbert B. Post-operative cognitive dysfunction at 3 months in adults after non-cardiac surgery: a qualitative systematic review. *Acta Anaesthesiol Scand* 2016; 60: 1043-58.
27. van Harten AE, Scheeren TW, Absalom AR. A review of postoperative cognitive dysfunction and neuroinflammation associated with cardiac surgery and anaesthesia. *Anaesthesia* 2012; 67: 280-93.

28. Miller D, Lewis SR, Pritchard MW, Schofield-Robinson OJ, Shelton CL, Alderson P, et al. Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery. *Cochrane Database Syst Rev* 2018; 8: CD012317.
29. Rasmussen LS, Johnson T, Kuipers HM, Kristensen D, Siersma VD, Vila P, et al. Does anaesthesia cause postoperative cognitive dysfunction? A randomised study of regional versus general anaesthesia in 438 elderly patients. *Acta Anaesthesiol Scand* 2003; 47: 260-6.
30. Wu CL, Hsu W, Richman JM, Raja SN. Postoperative cognitive function as an outcome of regional anesthesia and analgesia. *Reg Anesth Pain Med* 2004; 29: 257-68.
31. Dunn N, Mullee M, Perry VH, Holmes C. Association between dementia and infectious disease: evidence from a case-control study. *Alzheimer Dis Assoc Disord* 2005; 19: 91-4.
32. Perry VH, Cunningham C, Holmes C. Systemic infections and inflammation affect chronic neurodegeneration. *Nat Rev Immunol* 2007; 7: 161-7.
33. Eckenhoff RG, Laudansky KF. Anesthesia, surgery, illness and Alzheimer's disease. *Prog Neuropsychopharmacol Biol Psychiatry* 2013; 47: 162-6.
34. Hovens IB, Schoemaker RG, van der Zee EA, Absalom AR, Heineman E, van Leeuwen BL. Postoperative cognitive dysfunction: Involvement of neuroinflammation and neuronal functioning. *Brain Behav Immun* 2014; 38: 202-10.
35. Alam A, Hana Z, Jin Z, Suen KC, Ma D. Surgery, neuroinflammation and cognitive impairment. *EBioMedicine* 2018; 37: 547-56.
36. Steinberg BE, Sundman E, Terrando N, Eriksson LI, Olofsson PS. Neural control of inflammation: implications for perioperative and critical care. *Anesthesiology* 2016; 124: 1174-89.
37. Cibelli M, Fidalgo AR, Terrando N, Ma D, Monaco C, Feldmann M, et al. Role of interleukin-1beta in postoperative cognitive dysfunction. *Ann Neurol* 2010; 68: 360-8.
38. Terrando N, Rei Fidalgo A, Vizcaychipi M, Cibelli M, Ma D, Monaco C, et al. The impact of IL-1 modulation on the development of lipopolysaccharide-induced cognitive dysfunction. *Crit Care* 2010; 14: R88.
39. Terrando N, Monaco C, Ma D, Foxwell BM, Feldmann M, Maze M. Tumor necrosis factor-alpha triggers a cytokine cascade yielding postoperative cognitive decline. *Proc Natl Acad Sci U S A* 2010; 107: 20518-22.
40. Fjell AM, Walhovd KB. Structural brain changes in aging: courses, causes and cognitive consequences. *Rev Neurosci* 2010; 21: 187-221.
41. Dickstein DL, Kabaso D, Rocher AB, Luebke JI, Wearne SL, Hof PR. Changes in the structural complexity of the aged brain. *Aging Cell* 2007; 6: 275-84.
42. Hainsworth AH, Minett T, Andoh J, Forster G, Bhide I, Barrick TR, et al. Neuropathology of white matter lesions, blood-brain barrier dysfunction, and dementia. *Stroke* 2017; 48: 2799-804.
43. Gao L, Taha R, Gauvin D, Othmen LB, Wang Y, Blaise G. Postoperative cognitive dysfunction after cardiac surgery. *Chest* 2005; 128: 3664-70.
44. Brüünsgaard H, Pedersen BK. Age-related inflammatory cytokines and disease. *Immunol Allergy Clin North Am* 2003; 23: 15-39.
45. Martin GS, Mannino DM, Moss M. The effect of age on the development and outcome of adult sepsis. *Crit Care Med* 2006; 34: 15-21.
46. Bartels AL, Willemsen AT, Doorduyn J, de Vries EF, Dierckx RA, Leenders KL. [11C]-PK11195 PET: quantification of neuroinflammation and a monitor of anti-inflammatory treatment in Parkinson's disease? *Parkinsonism Relat Disord* 2010; 16: 57-9.
47. Doorduyn J, de Vries EF, Willemsen AT, de Groot JC, Dierckx RA, Klein HC. Neuroinflammation in schizophrenia-related psychosis: a PET study. *J Nucl Med* 2009; 50: 1801-7.
48. Evered L, Silbert B, Scott DA, Ames D, Maruff P, Blennow K. Cerebrospinal fluid biomarker for alzheimer disease predicts postoperative cognitive dysfunction. *Anesthesiology* 2016; 124: 353-61.
49. Rasmussen LS. Postoperative cognitive dysfunction: incidence and prevention. *Best Pract Res Clin Anaesthesiol* 2006; 20: 315-30.
50. Ottens TH, Dieleman JM, Sauër AM, Peelen LM, Nierich AP, de Groot WJ, et al. Effects of dexamethasone on cognitive decline after cardiac surgery: a randomized clinical trial. *Anesthesiology* 2014; 121: 492-500.
51. Mathew JP, Mackensen GB, Phillips-Bute B, Grocott HP, Glower DD, Laskowitz DT, et al. Randomized, double-blinded, placebo controlled study of neuroprotection with lidocaine in cardiac surgery. *Stroke* 2009; 40: 880-7.
52. Mathew JP, Shernan SK, White WD, Fitch JC, Chen JC, Bell L, et al. Preliminary report of the effects of complement suppression with pexelizumab on neurocognitive decline after coronary artery bypass graft surgery. *Stroke* 2004; 35: 2335-9.
53. Mathew JP, White WD, Schinderle DB, Podgoreanu MV, Berger M, Milano CA, et al. Intraoperative magnesium administration does not improve neurocognitive function after cardiac surgery. *Stroke* 2013; 44: 3407-13.
54. Carr ZJ, Cios TJ, Potter KE, Swick JT. Does dexmedetomidine ameliorate postoperative cognitive dysfunction? a brief review of the recent literature. *Curr Neurol Neurosci Rep* 2018; 18: 64.

55. Hu J, Vacas S, Feng X, Lutrin D, Uchida Y, Lai IK, et al. Dexmedetomidine prevents cognitive decline by enhancing resolution of high mobility group box 1 protein-induced inflammation through a vagomimetic action in mice. *Anesthesiology* 2018; 128: 921-31.
56. Lu X, Jin X, Yang S, Xia Y. The correlation of the depth of anesthesia and postoperative cognitive impairment: A meta-analysis based on randomized controlled trials. *J Clin Anesth* 2018; 45: 55-9.
57. Chan MT, Cheng BC, Lee TM, Gin T. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. *J Neurosurg Anesthesiol* 2013; 25: 33-42.
58. Radtke FM, Franck M, Lendner J, Krüger S, Wernecke KD, Spies CD. Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction. *Br J Anaesth* 2013; 110 Suppl 1: i98-105.
59. Punjasawadwong Y, Chau-In W, Laopaiboon M, Punjasawadwong S, Pin-On P. Processed electroencephalogram and evoked potential techniques for amelioration of postoperative delirium and cognitive dysfunction following non-cardiac and non-neurosurgical procedures in adults. *Cochrane Database Syst Rev* 2018; 5: CD011283.
60. Bocskai T, Kovács M, Szakács Z, Gede N, Hegyi P, Varga G, et al. Is the bispectral index monitoring protective against postoperative cognitive decline? A systematic review with meta-analysis. *PLoS One* 2020; 15: e0229018.
61. Aldecoa C, Bettelli G, Bilotta F, Sanders RD, Audisio R, Borozdina A, et al. European Society of Anaesthesiology evidence-based and consensus-based guideline on postoperative delirium. *Eur J Anaesthesiol* 2017; 34: 192-214.
62. Inouye SK. A practical program for preventing delirium in hospitalized elderly patients. *Cleve Clin J Med* 2004; 71: 890-6.
63. Awada HN, Luna IE, Kehlet H, Wede HR, Hoevsgaard SJ, Aasvang EK. Postoperative cognitive dysfunction is rare after fast-track hip- and knee arthroplasty - But potentially related to opioid use. *J Clin Anesth* 2019; 57: 80-6.
64. Hshieh TT, Yang T, Gartaganis SL, Yue J, Inouye SK. Hospital elder life program: systematic review and meta-analysis of effectiveness. *Am J Geriatr Psychiatry* 2018; 26: 1015-33.
65. Radtke FM, Franck M, MacGuill M, Seeling M, Lütz A, Westhoff S, et al. Duration of fluid fasting and choice of analgesic are modifiable factors for early postoperative delirium. *Eur J Anaesthesiol* 2010; 27: 411-6.
66. Ngandu T, Lehtisalo J, Solomon A, Levälähti E, Ahtiluoto S, Antikainen R, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet* 2015; 385: 2255-63.
67. Kawano T, Eguchi S, Iwata H, Tamura T, Kumagai N, Yokoyama M. Impact of preoperative environmental enrichment on prevention of development of cognitive impairment following abdominal surgery in a rat model. *Anesthesiology* 2015; 123: 160-70.
68. Robinson TN, Wu DS, Pointer L, Dunn CL, Cleveland JC Jr, Moss M. Simple frailty score predicts postoperative complications across surgical specialties. *Am J Surg* 2013; 206: 544-50.
69. Robinson TN, Wu DS, Sauer A, Dunn CL, Stevens-Lapsley JE, Moss M, et al. Slower walking speed forecasts increased postoperative morbidity and 1-year mortality across surgical specialties. *Ann Surg* 2013; 258: 582-8.
70. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12: 189-98.
71. Brand N, Jolles J. Learning and retrieval rate of words presented auditorily and visually. *J Gen Psychol* 1985; 112: 201-10.
72. Reitan RM. Validity of the trail making test as an indicator of organic brain damage. *Percept Mot Skills* 1958; 8: 271-6.
73. Bohnen N, Twijnstra A, Jolles J. Performance in the Stroop color word test in relationship to the persistence of symptoms following mild head injury. *Acta Neurol Scand* 1992; 85: 116-21.
74. Axelrod BN. Validity of the Wechsler abbreviated scale of intelligence and other very short forms of estimating intellectual functioning. *Assessment* 2002; 9: 17-23.
75. Houx PJ, Jolles J. Age-related decline of psychomotor speed: effects of age, brain health, sex, and education. *Percept Mot Skills* 1993; 76: 195-211.