Perioperative cognitive trajectory in adults

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Editor’s key points
- Postoperative cognitive decline is recognized as a major impact of surgery.
- Cognitive impairment appears to be affected adversely by other postoperative complications, including ongoing pain.
- In the absence of such complications, the elderly can be expected to resume their preoperative cognitive trajectory, and may even experience cognitive improvement if surgery results in alleviation of significant symptoms.

Summary. Approximately a quarter of a billion people undergo surgery every year hoping that the operation will alleviate symptoms, cure diseases, and improve quality-of-life. A concern has arisen that, despite the benefits of surgery, elderly patients might suffer neurological injury from surgery and general anaesthesia leading to persistent cognitive decline. However, many studies of postoperative cognition have had methodological weaknesses, including lack of suitable control groups, dissociation of cognitive outcomes from surgical outcomes, sub-optimal statistical techniques, and absence of longitudinal preoperative cognitive assessments. Emerging evidence suggests that after early cognitive decline, most patients return to their preoperative cognitive trajectories within 3 months of surgery; some even experience subsequent cognitive improvement. In this review, we summarize the scientific literature on perioperative cognition. We propose that the most important determinants of the postoperative cognitive trajectory are the preoperative cognitive trajectory, the success of the surgery, and events in the perioperative period. Postoperative complications, ongoing inflammation, and chronic pain are probably modifiable risk factors for persistent postoperative cognitive decline. When surgery is successful with minimal perioperative physiological perturbations, elderly patients can expect cognition to follow its preoperative course. Furthermore, when surgery alleviates symptoms and enhances quality-of-life, postoperative cognitive improvement is a possible and desirable outcome.

Keywords: anesthesia recovery period; postoperative period, cognition; preoperative period;

For the last 60 yr, there has been a strong perception that many elderly patients experience persistent cognitive decline that is directly attributable to surgery and general anaesthesia. Particular surgeries, most notably, cardiac surgery and major orthopaedic surgery, have been associated with persistent postoperative cognitive decline (POCD) in up to 50% of patients. Based on limited clinical data and laboratory experimentation, it has been hypothesized that surgery and anaesthesia could either accelerate the onset of or even cause dementia. If these concerns regarding persistent POCD were proved to be true, we would face a growing public health problem as an increasing number of elderly patients underwent elective surgeries. Older patients and their families would need to factor in the risk of persistent POCD when deciding whether or not to proceed with elective surgical procedures.

There is strong evidence to suggest that pain and inflammation carry a cognitive burden, people who have chronic inflammatory states or unremitting pain may suffer from accelerated cognitive decline. Acute postoperative pain and inflammation probably also affect cognition and might exacerbate or cause delirium, which is a well-defined, common, and clinically important postoperative complication. Furthermore, with ongoing pain or inflammation, cognition may be impaired for several weeks after surgery, analogous to the cognitive impairment that occurs after acute medical illnesses. However, recent research suggests that this initial POCD usually resolves within months of surgery.

The scientific study of POCD has been compromised by the lack of a consensus definition of POCD and by conflicting data regarding its time course and clinical impact. The medical literature in this area is permeated with data from studies with key methodological limitations, highlighted in a recent review, including retrospective designs, unsuitable or lack of non-surgical control groups, failure to detect pre-existing cognitive impairment, missing information on preoperative cognitive trajectories, insufficient long-term follow-up, and suboptimal statistical analyses. Interestingly, emerging studies that have addressed some of these limitations have found that when surgery is successful, quality-of-life, functional status, and cognition might all improve in the intermediate term. Resolution of pain and inflammation might be important prerequisites for
postoperative cognitive improvement (POCI), which might occur even with older patients as the brain retains neuroplastic potential throughout life.\(^{11}14\ 48–50\) Mounting evidence suggests that for many patients, after transient POCD, intermediate-term cognitive trajectories are likely to be unchanged or even improved compared with preoperative trajectories.\(^{51–53}\) As such, the authors of this review believe that a paradigm shift regarding postoperative cognition is warranted. We propose that when surgery alleviates symptoms and enhances quality-of-life, POCI is a possible and desirable outcome.

In this review, we shall address whether there is a vulnerable subgroup of patients who might be afflicted with long-lasting cognitive decline and, conversely, whether some patients may exhibit cognitive improvement after recovery from surgery. From the outset it is necessary to qualify that the published literature can be interpreted in various ways, and currently there is a range of views surrounding the clinical relevance of persistent POCD. In the last few years, several clinical review articles and expert commentaries on POCD and postoperative dementia have been published.\(^{27} 28\ 54–63\) While consensus on many issues is emerging, some of the emphases and nuances expressed in scientific reviews differ from our opinions. Reading some of these pertinent review articles might help to enrich perspectives on this controversial topic.

**Limitations of POCD research**

(1) Aging, even during the fifth decade of life, is associated with measurable cognitive decline\(^6\) and an increasing incidence of dementia. The prevalence of Alzheimer’s dementia alone in people over 60 is >5%,\(^{65}66\) and an estimated one-third of people over 85 have Alzheimer’s.\(^67,68\) Thus, any study that follows older people longitudinally will observe cognitive decline and incident dementia. If patients are followed after a surgical event without an age-appropriate control group, cognitive decline, incident dementia, or both might be incorrectly attributed to the surgery (Table 1).\(^{51}\)

(2) Critical illness after surgery is often associated with multi-organ dysfunction, including neurological impairment.\(^69\) Certain critical care diagnoses have been independently linked to a consequent diagnosis of dementia.\(^70\) When patients suffer a serious postoperative complication, such as pneumonia or acute renal failure, subsequent persistent cognitive decline, or incident dementia might be ascribed to the surgery, whereas the root cause of brain injury might be the pathological processes associated with critical illness.

(3) Underlying comorbidities, such as vascular disease, are associated with cognitive decline and dementia.\(^27\ 41\ 71\) Cognitive decline, incident dementia, or both may be wrongly attributed to a surgical event, rather than to other risk factors.\(^27\ 41\)

(4) A lack of a consensus definition for POCD leads to marked discrepancies in the quoted incidence (e.g. from 5 to 50%) depending on the arbitrary diagnostic criteria that have been used.\(^3\ 28\) For example, a very liberal criterion that has been used is a standard deviation (SD) decline in any of several administered cognitive tests, regardless of whether or not patients improve in any of the other cognitive tests. With such a permissive definition, it is likely that POCD would be diagnosed purely by chance in about a third of all patients.\(^72\)

(5) Studies often correct for the learning effect of repeat cognitive testing based on measured learning in a ‘control’ group. However, this assumes that learning in surgical patients is relatively uniform and patients undergoing surgical procedures will learn as effectively as controls in a non-surgical group. It is unlikely that this assumption is appropriate as patients who are preparing for or recovering from surgery are less likely to learn as efficiently as a control group. Correcting for learning based on a non-surgical control group could lead to an over-estimate of the extent or incidence of POCD. This limitation was made salient in a study by Evered and colleagues,\(^73\) which enrolled four cohorts: patients undergoing cardiac surgery, patients undergoing orthopaedic surgery, a control group undergoing coronary angiography, and a second control group not undergoing any procedure. Using the results in the non-procedural control group to correct for learning, this study found that at 3 months the cohort that underwent coronary angiography (i.e. no surgery and no general anaesthesia) had the highest incidence of cognitive decline. These results demonstrate that correcting for learning in a surgical (or procedural) group according to learning in a non-surgical control group could lead to an artificial diagnosis of POCD. Figure 1 illustrates the limitation of previous approaches used to correct for learning. Alternative statistical approaches, like mixed effects models, have been used in studies of POCD and are probably more robust than methods that rely on correction for learning based on a non-procedural control group.\(^27\ 29\ 36\)

(6) Preoperative cognitive trajectories are likely to determine postoperative cognitive trajectories. For example, a patient assessed at a single point in time could be on many different cognitive trajectories making a single preoperative test suboptimal for assessing the cognitive trajectory (Fig. 2). There is compelling evidence that patients who have declining trajectories before surgery, such as those who have mild cognitive impairment (MCI) or early dementia, are more likely to decline cognitively after surgery, at least acutely.\(^20\ 29\ 74\)

These barriers to POCD research leave us in a quandary regarding the exact nature of POCD. While most researchers would agree that cognitive dysfunction often occurs in the short term following surgery, manifesting either as delirium or a subtler problem, the limitations of many existing studies generate scepticism regarding the hypothesis that persistent POCD is a common occurrence.
Timeline of postoperative cognitive alterations

Delirium

In the early postoperative phase, typically 24–96 h after surgery, patients often experience delirium, an acute and fluctuating cognitive dysfunction that is associated with morbidity and mortality, with reduced function and independence. Delirium occurs in 10–70% of patients older than 65 undergoing major surgical procedures. Various non-modifiable patient factors are hypothesized to predispose patients to delirium including age, preoperative cognitive impairment, and dementia. It is currently unknown whether or not the occurrence of postoperative delirium independently alters the

Table 1 Limitations of prior research and suggested improvements for future research. CSF, cerebrospinal fluid; MCI, mild cognitive impairment; POCD, postoperative cognitive decline; POCI, postoperative cognitive improvement

<table>
<thead>
<tr>
<th>Challenges</th>
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<td>Evaluate cognitive trajectory over time without a threshold for POCD</td>
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<td>Learning effect</td>
<td>With repeat cognitive testing there is learning</td>
<td>Do not correct for learning; compare overall trajectories with appropriate controls</td>
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<td>Statistical approach</td>
<td>Simple statistical approaches are unsuitable for repeated measurements over time</td>
<td>Use linear mixed effects model; account for variable duration of assessments, confounders, and multiple measures</td>
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<tr>
<td>Cognitive decline occurs with normal aging</td>
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<td>Include appropriate, age-matched non-surgical controls</td>
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<td>Pain and inflammation</td>
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<tr>
<td>Pain and inflammation carry a cognitive burden</td>
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<td>Assess pain and measure inflammatory markers</td>
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<tr>
<td>Comorbidities</td>
<td>Comorbidities (e.g. vascular disease, hypertension) are associated with cognitive decline</td>
<td>Include controls with similar comorbidities and characteristics</td>
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<td>Vulnerability</td>
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<td>Some surgical cohorts might be more vulnerable than others</td>
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<td>Focus on a homogenous surgical population considered to be at high risk of POCD</td>
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<td>Preoperative cognitive trajectory</td>
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<td>Postoperative cognitive course is likely to be linked to preoperative trajectory</td>
<td>Used single baseline preoperative measurements, which do not allow for determination of preoperative trajectory</td>
<td>Enrol patients before surgery to assess preoperative cognitive trajectory (obtain &gt;1 preoperative measurement)</td>
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<td>MCI and dementia strongly predict cognitive decline</td>
<td>Excluded patients with MCI or dementia</td>
<td>Include patients with MCI and early dementia</td>
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<td>Pathology precedes dementia</td>
<td>Did not consider brain pathology</td>
<td>Measure biomarkers (CSF or neuroimaging)</td>
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<tr>
<td>Postoperative events</td>
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<td>Quality-of-life</td>
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<tr>
<td>Postoperative cognitive trajectory</td>
<td>POCD is often transient</td>
<td>Follow patients for at least 1 yr after operation</td>
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<tr>
<td>There may be potential for POCI</td>
<td>Dismissed cognitive improvement as artifact</td>
<td>Consider both decline and improvement</td>
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cognitive trajectory or merely unmasks patients with pre-existing neurological vulnerability.

**Early POCD**

Within a few weeks to months of surgery, many patients are debilitated, in pain and unable to function in daily life as they were before surgery. Similarly, POCD and general decrements in quality-of-life measures are common. POCD lasting up to 3 months occurs in up to 10% of elderly patients. Indeed, studies have suggested that early POCD affects all age groups, but resolves faster in younger patients. POCD in the early postoperative period might have an adverse impact on recovery from surgery. Additionally, two studies from the International Study of POCD (ISPOCD) investigators found an association between early POCD and premature departure from the workforce and intermediate-term (1–2 yr) postoperative mortality. It is important to qualify that these observational studies do not establish causality; patients with undetected vulnerabilities could be independently susceptible to both early POCD and subsequent negative outcomes.

**Persistent POCD**

The case for persistent POCD, arbitrarily defined as POCD longer than 6 months, has been questioned based on review of the available literature. Nonetheless, among clinicians and in the public, there remains a strong perception that persistent POCD is common, based largely on investigations of cardiac surgical patients showing decline at 5 yr after operation and non-cardiac surgical patients showing decline at 1 yr after operation. However, both of these landmark studies used a permissive definition for POCD of >1 SD decline in any cognitive domain and neither study reported cognitive improvement according to the reciprocal diagnostic criterion. Furthermore, these studies did not include a matched non-surgical control group; thus, it is unclear whether the observed cognitive decline was attributable to the surgical event. Despite the limitations, these studies have reinforced the pervasive view that surgery and anaesthesia induce a lasting cognitive decline, affecting quality-of-life and function.

In general, the determination of persistent POCD is complicated by limitations of statistical analysis and length of follow-up. Longitudinal analyses are preferential as they provide information on the entire cognitive trajectory of a patient. Additionally, many POCD studies are greatly limited by the absence of appropriately matched non-surgical controls.
A review of non-cardiac surgical studies published in 2007 showed that no studies that included control groups found any difference between groups in cognitive decline beyond 6 months. Similarly, a subsequent review of both cardiac and non-cardiac surgical studies confirmed that when studies included appropriate non-surgical control groups, persistent POCD was generally not found. A recent study that enrolled 192 surgical patients and an age-matched control group (n = 138) has challenged this conclusion. After correcting for learning in the control group, the investigators found that 11.2% of surgical patients compared with 3.8% of controls had cognitive decline at 1 yr (P = 0.02). These data suggest that there might be a subset of vulnerable patients who are at risk of persistent POCD.

**Postoperative cognitive improvement**

Intriguing new evidence suggests that there is potential for cognitive improvement after surgery, although this hypothesis is controversial. POCI could conceivably occur when surgery improves health, enhances quality-of-life, decreases inflammation, or alleviates pain. It is important to elaborate that POCI could be considered either as net cognitive improvement or as slowing or arresting of preoperative decline. While prior studies have noted evidence of POCI, many of these studies have dismissed improvement as statistical artifact or learning effect. A provocative recent meta-analysis included 28 previous trials and observational studies evaluating cognitive function before and after coronary artery bypass grafting (CABG) surgery and, similar to previous studies, found evidence of early POCD. However, at 3 months after operation, all cognitive measures (psychomotor speed, memory, and executive function) showed significant improvement relative to baseline. At 6–12-month follow-up, continued improvement was seen in all measures of cognitive function. An important strength of this meta-analysis, hypothetically limiting the practice effect, was the inclusion of only studies that used neuropsychological tests with parallel forms and established test–retest reliability as suggested by previous consensus.

Further support for the reliability of the results is that the initial decline might not have been expected if these results were strongly biased by practice effect. Important considerations regarding this meta-analysis, however, are that pooled data may not be applicable to individual patient cognitive trajectories, preoperative cognitive function may not be fully considered, and the analyses cannot account for patient dropout which could bias results. Nonetheless, another recent meta-analysis of randomized controlled trials evaluating cognitive outcomes after CABG surgery in both on- and off-pump procedures also found significant POCD at 3 months in verbal memory, motor capacity, attention, and information processing; these improvements were maintained at 6–12 months after operation with the addition of improvement in working memory and executive function. These results are weakened by the lack of non-surgical controls in the included studies, and the apparent POCD may simply reflect the learning effect. A recent, small-cohort study attempted to address some limitations by including a broader surgical population (both cardiac and non-cardiac surgery patients) and matched controls. This study showed evidence of POCD at 1 week after operation with resolution of POCD or even POCI in the majority of all surgical patients at 8 weeks after operation.

**Factors that may affect cognitive trajectory**

Factors associated with early POCD have been explored, but the uncertainties surrounding persistent POCD constrain our ability to evaluate risk factors. As POCI has only recently been proposed, there has been limited examination of factors that might predispose patients to improve cognitively, although certain hypotheses can reasonably be posited.

**Non-modifiable factors: age, genes and dementia**

Increasing age has been associated with risk of POCD at 1 week and at 3 months, promoting a hypothesis that this is attributable to diminished ‘cognitive reserve’ in older patients. However, it is unclear to what extent inadequate adjustment for comorbidities and preoperative cognitive trajectory has led to age being identified as an independent risk factor. Translational research suggests that general anaesthetic agents might accelerate pathological processes (e.g. generation of beta-amyloid or phosphorylated tau protein in the brain) that have been associated with the pathogenesis of Alzheimer’s disease. Nonetheless, before 2013, most studies did not find a link between surgery, or anaesthesia, or even early POCD, and subsequent incident dementia. The exception was an observational study in cardiac surgery patients that did find an association with dementia. However, a much larger subsequent Canadian population-based longitudinal study did not replicate this finding. Several population epidemiological studies have recently been published, yielding conflicting and provocative results. Two Taiwanese studies drawn from national databases and a large French population study have all found a link between surgery or anaesthesia and subsequent incident dementia. On the other hand, another epidemiological study from the Mayo clinic found no independent association between surgery or anaesthesia and subsequent dementia. Without well-designed prospective research, the controversy surrounding the hypothetical causal link between surgery coupled with anaesthesia and subsequent dementia will be difficult to resolve. It is currently unknown whether patients who are cognitively normal, but have brain pathology consistent with subsequent clinical dementia onset within the next 20 yr, are at increased risk of POCD or accelerated dementia after surgery. In a similar vein, whether genetic risk factors for POCD overlap with those for neurodegenerative disorders, such as Alzheimer’s disease, has been the subject of some investigation; however, no associations between genetic factors such as the apolipoprotein E gene and POCD have thus far been observed.

**Preoperative cognitive trajectory**

Support for the ‘cognitive reserve’ hypothesis is that higher education status is suggested to protect against cognitive...
perioperative cognitive trajectory

In contrast, a major risk factor for POCD is preoperative cognitive impairment and decline. Therefore, it remains likely that the preoperative cognitive trajectory is an important determinant of the postoperative trajectory. If there is a postoperative change, it remains ambiguous whether the cognitive trajectory is transiently altered (e.g. for up to 3 months) or irreversibly altered.

Evidence based on patients with MCI who have undergone surgery is conflicting in this regard. Kline and colleagues examined data from the Alzheimer Disease Neuroimaging Initiative (ADNI); patients who underwent surgical procedures (n=41) and a group of propensity-matched controls who did not undergo surgery (n=123) were included. The investigators found that patients with MCI or early dementia before surgery experienced POCD within the first few months of operation while individuals with normal preoperative cognitive function did not. On structural magnetic resonance imaging, surgical patients demonstrated evidence of postoperative atrophy in the cortex and hippocampus at the first follow-up visit, ~6 months after surgery. Interestingly, both the cognitive decline and the brain atrophy were subsequently reversed in many subjects suggesting a return towards the preoperative cognitive trajectory. The findings of this small study challenge the current paradigm and reinforce new hypotheses about lifelong neuroplasticity and the brain’s capacity for adaptive reorganization.

Modifiable factors

Inflammation and resolution of inflammation

Systemic inflammation is known to carry a cognitive burden, which has been documented in both surgical and non-surgical patients. Studies have demonstrated a link between neuroinflammation and the development of Alzheimer’s disease. Anti-inflammatory drugs might even provide protection against age-related loss of brain volume, which could potentially protect patients from subsequent cognitive dysfunction. The trauma of surgery induces substantial acute inflammation via activation of the innate immune system. Preclinical data show that surgery induces the release of proinflammatory cytokines capable of disrupting hippocampal long-term potentiation, a neurobiological correlate of learning and memory formation. The inflammation generates lethargy, anorexia, fever, and cognitive dysfunction, all of which promote rest and allow wound healing to proceed. During the healing phase, the immune system should be switched to a healing mode with curtailment of the initial innate inflammatory response. The marked systemic inflammation in the immediate postoperative period probably contributes to postoperative delirium or early POCD, but may produce a longer-term injury in certain vulnerable patients. Cardiac surgery, both with and without cardiopulmonary bypass, induces a widespread systemic inflammatory response that has been associated with delirium and early POCD. Small doses of ketamine have been found to reduce the incidence of delirium and POCD after on-pump CABG, possibly through its effects on the inflammatory system. The systemic inflammatory response has also been documented in non-cardiac surgeries, such as arthroplasty, and an increased proinflammatory response was associated with higher rates of postoperative delirium. In some vulnerable patients, such as those with metabolic syndrome, regulation of inflammatory processes may be dysfunctional or the effects on neuronal function may be more profound and may lead to a later cognitive decline. After the acute systemic inflammatory response, a shift towards resolution of inflammation should occur. In patients with chronic pain, or inflammatory conditions driving the need for surgery, postoperative inflammation may be reduced to below preoperative levels. Such patients could conceivably experience POCD after a period of recovery from successful surgery.

Pain and decrease in pain

Though often occurring simultaneously, the effects of pain and inflammation are likely to have separate mechanisms by which they affect cognitive function. Neuroimaging studies have generally shown that patients with chronic pain have evidence of a decrease in grey matter in particular regions that function as multi-integrative structures during the experience and the anticipation of pain, most notably the anterior cingulate cortex, insula, and dorsolateral prefrontal cortex. Although the mechanism of the structural changes have yet to be determined, it has been hypothesized that these morphological changes may be driven by prolonged nociceptive input in pain-transmitting regions of the brain.

Acute pain in the immediate postoperative period can probably cause delirium and POCD. However, after a period of recovery and resolution of pain, many patients should return to baseline cognition or may experience POCD. In fact, there is evidence that patients who undergo surgeries that decrease pain and inflammation, such as CABG surgery and joint replacement surgery, benefit from improved quality-of-life and persistent cognitive improvement. Prospective studies combining neuroimaging, pain, and functional assessments have shown that when surgery successfully treats chronic pain (e.g. back surgery or hip replacement surgery), grey matter increases in multiple areas including the dorsolateral prefrontal cortex, the anterior cingulate cortex, and the amygdala, and cognition improves. Thus, the changes seen in grey matter volume with chronic pain are often reversible and successful treatment of chronic pain, whether by medical or surgical means, could restore cognitive function in patients. For many patients who have chronic pain, successful treatment could conceivably lead to cognitive improvement from their preoperative baseline.

Intraoperative techniques

There is a suggestion that general anaesthesia independent of surgery could cause POCD and Alzheimer’s disease, but there is scant evidence supporting this. Meta-analytic review of studies that randomized patients to regional or general anaesthesia did not find that general anaesthesia was associated with
persistent POCD in adults.\textsuperscript{128,129} If general anaesthesia does independently contribute to POCD, any contribution is likely to be minor. Interestingly, hypoxia or hypotension was not associated with POCD at 1 week and 3 months in the ISPOCD study.\textsuperscript{24} While it is plausible that hypotension contributes to POCD, evidence for a contribution remains lacking. Intraoperative cerebral hyperfusion could lead to neurological injury and POCD especially in patients with hypertension and vascular disease, who have impaired cerebral autoregulation.\textsuperscript{127} A recent study of 70 patients found a 10% incidence of covert stroke (ischaemic brain damage identified on magnetic resonance imaging but without clinical neurologic changes) after non-cardiac surgery,\textsuperscript{128} if validated in larger studies, the contribution of intraoperative management and the impact of covert stroke on POCD will need to be evaluated. A small randomized controlled study suggested that guiding anaesthetic management with a processed electroencephalogram monitor and cerebral oximetry might lead to a lower incidence of POCD at 1 yr.\textsuperscript{80} The investigators suggest that avoiding unnecessarily deep anaesthesia and maintaining adequate cerebral oxygen supply could be important approaches to protecting the brain from subtle damage during surgery.

Cardiopulmonary bypass

A strong perception remains that heart surgery, especially with cardiopulmonary bypass, is causally associated with a high risk of POCD. Interestingly, a meta-analysis of the clinical trials that have randomized patients to cardiac surgery with or without cardiopulmonary bypass found no difference in postoperative cognitive trajectories between groups.\textsuperscript{84} While cognitive decline might occur after cardiac surgery, it is difficult to dissociate any surgery-related decline from decline attributable to other factors such as vascular disease. Studies comparing patients who underwent cardiac surgery with non-surgical control patients with and without vascular disease suggest the underlying vascular disease, not the surgery, is the relevant factor.\textsuperscript{35,36} There was no difference in the rate of cognitive decline among those with vascular disease who underwent heart surgery and those that were not treated surgically; however, the control group without vascular disease did not have the same rate of cognitive decline. The investigators hypothesized that generalized vascular disease might be a more potent risk factor for cognitive decline than coronary surgery.\textsuperscript{35,36} With one of their aims of providing information about the effects of cardiac surgery with general anaesthesia on cognitive function, several studies have randomized patients with coronary artery disease to receive either surgery or percutaneous coronary intervention.\textsuperscript{34,42,47} These trials have not demonstrated worse cognitive outcomes in patients randomized to surgical treatment. Furthermore, quality-of-life was improved by either intervention.\textsuperscript{47} The meta-analysis by Cormack and colleagues\textsuperscript{82} reinforced these results; they concluded that persistent cognitive decline is probably not as common as previously reported after heart surgery and alternatively, there may be an improvement in overall cognitive function in the first year after CABG surgery.

Vascular risk factors and changes in cerebral blood flow

Vascular risk factors, such as hypertension, smoking, and atherosclerosis, are strongly associated with cognitive decline in the general population.\textsuperscript{71,76} Chronic vascular disease is also likely to be an important risk factor for perioperative cognitive decline.\textsuperscript{77} Acute alterations in cerebral blood flow and oxygenation acutely affect cognition; thus, it can be hypothesized that long-term changes in cerebral blood flow may contribute to long-term cognitive alterations as well. Perioperative cerebral oxygen desaturation may be associated with postoperative delirium or early POCD,\textsuperscript{129,130} but the effects on persistent cognitive changes are unknown. Based on the ‘cognitive reserve’ hypothesis, it is possible that periods of hypoperfusion have more profound effects on vulnerable patients.\textsuperscript{130} Conversely, it may be hypothesized that if cerebral blood flow is ultimately improved after surgery, such as in carotid revascularization procedures,\textsuperscript{52} or placement of ventricular assist devices,\textsuperscript{131–133} patients may experience POCD. A recent study using proton magnetic resonance spectroscopy to study preoperative and postoperative cerebral metabolism in patients undergoing CEA found that the ratios of particular cerebral metabolites associated with cognitive function were higher in patients with POCD and lower in patients with POCD when compared with patients whose postoperative cognition was unchanged.\textsuperscript{134} While the relationship of cerebral metabolites to cognitive alterations is not well defined, it is possible that improved cerebral metabolism is related to improvement in cerebral haemodynamics after CEA.\textsuperscript{134}

A meta-analysis of 32 studies published before 2006 studying the cognitive outcomes after CEA or CAS reported conflicting results with evidence of both cognitive impairment and improvement, and because of the methodological differences of the included studies, determined the results to be inconclusive.\textsuperscript{135} Several recent small studies of patients undergoing carotid revascularization continue to demonstrate that the majority of patients remain unchanged, a subset of patients decline, and a relatively equal subset of patients show improvement in multiple cognitive domains.\textsuperscript{52,134,136–138} Despite methodological weaknesses, these findings suggest that those patients who do not experience surgical complications (e.g. microemboli or prolonged hypoperfusion) should recover to baseline or better over time. Successful surgery to treat conditions that are themselves associated with cognitive dysfunction (e.g. vascular disease) may help to improve a patient’s long-term cognitive trajectory.

Postoperative delirium

The association between postoperative delirium and long-term decline is unclear, with findings conflicting among studies. For example, postoperative delirium has been associated with early POCD lasting weeks to months,\textsuperscript{20,100,139} but other studies have not found an association.\textsuperscript{140,141} A recent study that followed patients after heart surgery showed that patients with delirium had early POCD, which in some patients appeared to persist for up to 6 months; nonetheless, these patients appeared to return to baseline cognition within the
first postoperative year. Although POCD associated with postoperative delirium has generally been shown to resolve, research has also shown that patients who experience postoperative delirium are at increased risk of subsequent cognitive decline, incident dementia, and severe dependency in activities of daily living measured 2–3 yr after surgery. These findings could be consistent with postoperative delirium occurring in patients who have brain pathology but have not yet manifested clinical evidence of dementia; surgery and anaesthesia might unmask the underlying pathology. If this were true, postoperative delirium could be a marker of brain pathology, decreased cognitive reserve, and a harbinger of future cognitive decline and dementia. Conceptually, major surgery and general anaesthesia could be thought of as a stress test for the brain, with postoperative delirium as a ‘positive’ result of the test, revealing brain vulnerability.

Critical illness
Mounting evidence suggests that pathological processes associated with critical illness and intensive care hospitalizations may be modifiers of cognitive function. Studies of hospitalized patients show an association between acute illness and cognitive dysfunction with the severity of illness being an independent predictor of cognitive dysfunction. Potential associated factors may include severity of hypoxia, hypotension, infection or sepsis, and systemic inflammatory response syndrome. Studies of patients with acute respiratory distress syndrome have shown evidence of cognitive impairment and long-term brain atrophy suggestive of permanent dysfunction, however, other studies have suggested that this cognitive dysfunction is reversible. Given the potential for reversibility, further investigation into the causes of cognitive dysfunction after critical illness is warranted.

Quality-of-life and mood
Quality-of-life and mental health are potentially important factors regarding cognitive function. Evidence suggests that the effects of increased cortisol on the hippocampus may cause difficulty with learning and memory; other studies have suggested that mood disorders, such as anxiety or depression, affect cognition as well, and thus, Murkin and colleagues recommended that mood state assessments be performed concurrently with cognitive assessments in their consensus statement regarding neuropsychological testing in cardiac surgery patients. Reviews of the literature have generally found that after successful surgery, quality-of-life improves for the majority of patients, conceivably because of improved physical and functional status. For those patients who report improved quality-of-life, POCD is unlikely; patients with subjective improved quality-of-life are more likely to be at their baseline cognitive status or better.

Conclusion
The key factors that are most likely to affect the postoperative cognitive trajectory are the preoperative cognitive trajectory, the success of the surgery, and events in the perioperative period. After early POCD lasting up to 3 months, most patients probably return to their preoperative cognitive trajectories. Depending on vulnerabilities, stressors, and surgical outcomes, different patient subsets might experience persistent POCD or POCI. In view of the misconceptions that have arisen with methodologically limited research in this field, future studies seeking to clarify factors impacting on postoperative cognition should adopt scrupulous methods, which we have attempted to highlight in this review (Table 1). For example, the methodology of future research may be improved by establishing a preoperative cognitive trajectory and by assessing cognitive change over time with a statistical approach that accounts for repeated measures within patients at variable time points. Including healthy elders and patients with MCI or early dementia and using appropriate, age-matched controls with similar comorbidities and characteristics in a homogeneous surgical population may address challenges based on patient factors. Furthermore, future research may aim to improve the interpretation of cognitive outcomes by following patients for at least 1 yr after surgery and evaluating cognition in the context of surgical outcomes, postoperative functional status, and quality-of-life. Additionally, future studies should consider cognitive decline and cognitive improvement as plausible postoperative outcomes. The goal for the majority of surgical patients should be quality-of-life improvement, with stable or improved cognition.

Authors’ contributions
M.R.N. contributed to the writing, editing, and the final approval of this manuscript. R.D.S. contributed to the conceptualization of this review, writing of all drafts of manuscript, and the final approval of this manuscript. M.S.A. contributed to the conceptualization of this review, writing of all drafts of manuscript, and the final approval of this manuscript.

Declaration of interest
M.R.N. declares no interest in commercial organizations, consultancy/board activity, or personal gain. R.D.S. declares the following interests: commercial organizations and consultancy/board activity: R.D.S. has acted as a consultant for Air Liquide, Paris, France, concerning the development of medical gases and has received speaker fees from Orion, Turku, Finland, and Hospira, Chicago, IL, USA. R.D.S. declares no interest in personal gain. M.S.A. declares no interest in commercial organizations, consultancy/board activity, or personal gain.

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