

Preexisting Cognitive Impairment Is Associated with Postoperative Cognitive Dysfunction after Hip Joint Replacement Surgery

Brendan Silbert, M.B., B.S., F.A.N.Z.C.A., Lisbeth Evered, B.Sc., M.Biostat., Ph.D., David A. Scott, M.B., B.S., F.A.N.Z.C.A., Ph.D., Stephen McMahon, M.B.B.S., F.R.A.C.S.(Orth), F.A.(Orth), Peter Choong, M.B., B.S., M.D., F.R.A.C.S., David Ames, B.A., M.D., F.R.C.Psych., F.R.A.N.Z.C.P., Paul Maruff, Ph.D., Konrad Jamrozik, Ph.D.†

ABSTRACT

Background: This study investigated the prevalence of cognitive impairment in elderly noncardiac surgery patients and any association between preoperative cognitive impairment and postoperative cognitive dysfunction (POCD). Additionally, the incidence of cognitive decline at 12 months after surgery was identified.

Methods: Three hundred patients for hip joint replacement and 51 nonsurgical controls aged 60 yr or older were studied in a prospective observational clinical trial. All study participants and controls completed a battery of eight neuropsychological tests before surgery and at 7 days, 3 months, and 12 months afterwards. Preoperative cognitive status was assessed using preexisting cognitive impairment (PreCI) defined as a decline of at least 2 SD on two or more of seven neuropsychological tests compared to population norms. POCD and cognitive decline were assessed using the reliable change index utilizing the results of the control group.

Results: PreCI was classified in 96 of 300 (32%) patients (95% CI, 23 to 43%). After surgery, 49 of 286 (17%) patients (95% CI, 13 to 22%) and 27 of 284 (10%) patients (95% CI, 6 to 13%) demonstrated POCD at 7 days and 3 months, respectively, while 7 of 271 (3%) patients (95% CI, 1 to 4%) demonstrated cognitive decline at 12 months. Patients with PreCI had a significantly increased incidence of POCD at 7 days and 3 months and cognitive decline at 12 months.

Conclusions: Patients with PreCI have an increased incidence of POCD and cognitive decline. PreCI is a good predictor of subsequent POCD and cognitive decline. The incidence of cognitive decline after 12 months in this group of patients is low.

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POSTOPERATIVE cognitive dysfunction (POCD) refers to an objectively measured decrease in cognition after anesthesia and surgery. Although originally described after cardiac surgery,¹ POCD has also been well documented after noncardiac surgery. Following noncardiac surgery, the International Study of Postoperative Cognitive Dysfunction (ISPOCD) reported an incidence of POCD 25.8% at 1 week and 9.9% at 3 months in patients older than 60 yr.² Monk *et al.*³ studied POCD in 355 patients older than 60 yr undergoing noncardiac surgery and found an incidence of 41.4% at discharge and 12.7% at 3 months.

Although POCD has been well described following anesthesia and surgery in the elderly, a key issue still to be resolved is whether the level of cognitive function preoperatively is associated with POCD. This is important because in the general population, subtle impairment of cognition

What We Already Know about This Topic

- Postoperative cognitive dysfunction has been identified in patients undergoing noncardiac surgery 3 months after surgery. Whether preexisting cognitive dysfunction contributes to postoperative cognitive decline is not clear.
- Cognitive function was evaluated prior to, and 7 days, 3 months, and 12 months postoperatively in patients who underwent hip arthroplasty. Control group subjects underwent cognitive assessment but did not undergo surgery.

What This Article Tells Us That Is New

- Preexisting cognitive dysfunction was identified in approximately a third of the patients prior to surgery.
- Preexisting cognitive dysfunction is a good predictor of cognitive dysfunction 3 months and 1 yr after surgery.
- However, there is no evidence that anesthesia and surgery *per se* contribute to cognitive dysfunction 1 yr after surgery.

† Deceased.

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Submitted for publication April 16, 2014. Accepted for publication February 10, 2015. From the Centre for Anaesthesia and Cognitive Function, Department of Anaesthesia, St. Vincent's Hospital, Melbourne, Victoria, Australia (B.S., L.E., D.A.S.); Anaesthesia, Perioperative and Pain Medicine Unit, Melbourne Medical School, University of Melbourne, Melbourne, Victoria, Australia (B.S., L.E., D.A.S.); Department of Surgery, Monash University, Melbourne, Victoria, Australia (S.M.); Malabar Orthopaedic Clinic, Windsor, Victoria, Australia (S.M.); Department of Surgery, University of Melbourne, Melbourne, Victoria, Australia (P.C.); Department of Orthopaedics, St. Vincent's Hospital, Melbourne, Victoria, Australia (P.C.); Academic Unit for Psychiatry of Old Age, Department of Psychiatry, University of Melbourne, Parkville, Victoria, Australia (D.A.); National Aging Research Institute, Parkville, Victoria, Australia (D.A.); Florey Institute for Neuroscience and Mental Health, Parkville, Victoria, Australia (P.M.); and School of Population Health, University of Adelaide, Adelaide, South Australia, Australia (K.J.).

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is known to precede dementia. Determining whether preoperative cognitive function increases the risk of POCD will help in understanding the etiology of POCD and provide a marker of risk when surgery is contemplated.

Only one group has examined relationships between preoperative cognitive impairment and POCD. The ISPOCD group retrospectively analyzed preoperative Visual Verbal Learning tasks to identify individuals with decreased memory function preoperatively but were unable to find any association.⁴ Monk *et al.*³ used MiniMental State Examination (MMSE) to measure preoperative cognition and were unable to identify any association with POCD; they stressed that the MMSE is a screening tool and called for the use of an appropriate measure of preoperative cognition to be used.

While POCD in the immediate postoperative period might impact on recovery and length of hospital stay,⁵ it is also associated with increased 1-yr mortality,³ decreased quality of life,⁶ and poorer social outcomes.⁷ Therefore, understanding the relationship between preoperative cognitive impairment and POCD is important.

A second issue of importance is measuring the incidence of cognitive decline at 1 yr after anesthesia and surgery. The ISPOCD group analyzed a subset of 336 patients 1 yr after surgery and found that the incidence of POCD was 10.4%, and this was similar to the incidence in a nonsurgical control group of 10.6%.⁸ We could not find any other studies that had tracked cognition more than 6 months after noncardiac surgery. Although the term "POCD" has been used to describe cognitive decline at time points greater than 3 months, we will use the more general term "cognitive decline" for 1-yr test results (both are calculated using the same method), to indicate that change in cognition may not be directly attributable to the prior anesthesia and surgery.

A recent review highlighted the methodological issues in POCD research including lack of suitable control groups, dissociation of cognitive outcomes from surgical outcomes, suboptimal statistical techniques, and absence of longitudinal preoperative cognitive assessments.⁹

The primary aim of the study was to identify the prevalence of preexisting cognitive impairment (PreCI) in elderly noncardiac surgery patients and any association between PreCI and POCD. The secondary aim was to identify the incidence of cognitive decline at 1 yr.

Materials and Methods

Subjects and Study Design

This investigation was a prospective observational clinical trial to identify the prevalence of PreCI and relate this to the incidence of POCD at 7 days and 3 months and cognitive decline at 12 months following noncardiac surgery. We studied 300 patients and 51 nonsurgical controls. The trial was registered with the Australian Clinical Trials Registry (ACTRN12607000049471; registered January 16, 2007; Principal Investigator: B.S.). Patients were recruited

between August 1, 2007, and May 31, 2011. Controls were recruited between June 2009 and November 2011. The first 164 patients have been previously published to 3-month assessment using the first 34 controls.¹⁰ The current article is the first publication of the entire cohort of the study of 300 patients and 51 controls. This is not an interim analysis for a larger study, although the patients enrolled continue to be assessed for follow-on studies up to 5 yr postoperatively.

Eligible patients were 60 yr or older scheduled to undergo elective first-time total hip replacement for osteoarthritis. Patients were recruited from the waiting lists at three large hospitals. These waiting lists were sufficiently long for identification, contact, consent and enrolment, and baseline neuropsychological testing of consented patients in the week before their surgery. All participants gave written informed consent, and the study was approved by the Institutional Ethics Review Boards at the relevant hospitals (Ethics Committee at St. Vincent's Hospital, St. Vincent's Private Hospital, and the Avenue Hospital, Victoria, Australia). Additional inclusion criteria were that the participants must reside in accessible proximity to the hospital to enable investigators to administer neuropsychological testing in their homes. Patients were excluded if they had preexisting neurological or clinically evident neurovascular disease (*e.g.*, stroke); MMSE less than 26 or Clinical Dementia Scale more than 1 (*i.e.*, excluded dementia); anticipated difficulty with neuropsychological assessment, such as English not being the prime language, blindness, and deafness; associated medical problems that may lead to significant complications and subsequent loss to follow-up (American Society Anesthesiologists Physical Status IV or higher); and geographical remoteness that may make it difficult to test patients at home.

In order to determine POCD and cognitive decline, it is necessary to use a nonsurgical control group.¹¹ We used an age- and gender-matched control group consisting of patients with osteoarthritis not scheduled for surgery. They were recruited from advertisements in appropriate newsletters and senior citizens centers. We believe that this control group was more appropriately matched to the study group than using a healthy control group.¹² The control group underwent neuropsychological testing at time points corresponding to assessments in the patients undergoing surgery.

Neuropsychological Testing

All study participants and controls completed a battery of eight neuropsychological tests administered by a trained interviewer. This was done on four occasions:

1. Baseline tests: during the week before surgery
2. Early postoperative tests: day 7 after surgery
3. Intermediate postoperative tests: 3 months after surgery
4. Late postoperative tests: 12 months after surgery

The neuropsychological tests were selected because they have been used commonly and recommended in an expert consensus statement.¹³ The test battery consisted of the Consortium

to Establish a Registry in Alzheimer Disease (CERAD) Auditory Verbal Learning Test, Trail Making Test Parts A and B, Digit Symbol Substitution Test, Controlled Oral Word Association Test, CERAD Semantic Fluency Test (animals), and the Grooved Pegboard Test (dominant and nondominant hands). All of these tests have been described elsewhere.⁵

All tests were used for assessment of POCD and cognitive decline.

Preexisting cognitive impairment (PreCI), which is a measure of cognition (*vide infra*), was calculated using all cognitive tests except the Digit Symbol Substitution Test, which was excluded because we did not have access to appropriate population norms.

Visual analog scales were used to assess anxiety and depression at each time of testing. These are especially suitable for this situation because they offer simple, reliable, and valid techniques for measuring anxiety and depression while placing minimal demands on patients.^{14,15} Patients were asked to mark an ungraded line (10 cm in length) anchored by 0 and 100 at either end.

Absolute test scores were reversed for timed tasks so that a decrease implied cognitive decline for every test.

Parallel forms were administered for the CERAD Auditory Verbal Learning Test, and all the tests were administered in the same order at all time points. The National Adult Reading Test was used to estimate intelligence quotient¹⁶ and was administered at the baseline assessment.

Calculation of Preoperative Cognitive Status

We used a measure of preoperative cognitive status commonly used in the anesthetic literature known as PreCI.^{17,18} This is defined as a decline of at least 2 SD on two or more of seven neuropsychological tests compared to the population or healthy matched control group.^{17,19} We used population norms to calculate PreCI.

Calculation of POCD and Cognitive Decline

Postoperative cognitive dysfunction (7 days and 3 months) and Cognitive Decline (12 months) were calculated using the reliable change index (RCI).²⁰ RCIs were determined by subtracting the preoperative score (X_1) from the postoperative score (X_2), giving Δ_X for each individual participant for a given task. The mean change for the controls Δ_{Xc} , calculated in the same way, was then subtracted from this, removing any practice effect. This score was then divided by the SD for the change in test results of the control group $SD(\Delta_{Xc})$, controlling for the expected variability. These scores were then used to create a combined test score (Z_{combined}) using the sum of Z scores for each test ($\sum Z_{a,b,c,d,etc.}$) divided by the SD of this summation in the control group [$SD(\sum Z_{\text{control}})$]. POCD and cognitive decline were defined in an individual when their RCI score was less than -1.96 on at least 2 tests, and/or their combined Z score was less than -1.96 . This classifies POCD or cognitive decline on the basis of a substantial failure on two or more tests or a more pervasive subtle decline across the neuropsychological test battery.

Surgery and Anesthesia

All clinical care followed recognized clinical practice. An anterolateral or posterior approach to the hip was used, followed by a standard femoral neck osteotomy. The acetabular component was then inserted (cementless or cemented). The intramedullary canal was prepared in the standard fashion before insertion of the femoral prosthesis. Postoperative management followed standard practice, including deep vein thrombosis prophylaxis.

To ensure all patients were under similar levels of anesthesia, the protocol required that the bispectral index be maintained below 60. Apart from this requirement, individual anesthesiologists were free to choose anesthetic agents. Spinal anesthesia (0.5% bupivacaine either isobaric or heavy) was used in the majority of patients. This was accompanied by intravenous midazolam and fentanyl followed by volatile (sevoflurane) or intravenous (propofol) anesthesia. A laryngeal mask was the most common form of airway maintenance. Hypotension was treated as clinically appropriate with intravenous metaraminol or ephedrine. Postoperative pain was most commonly treated with patient controlled analgesia using either morphine or fentanyl in the initial period followed by oral oxycodone. All aspects of clinical care were documented in case report forms.

Statistical Analysis

Sample size was based on a preoperative prevalence of cognitive impairment in patients aged 65 yr or more of 25% (a lower estimate than in cardiac patients). Assuming the relative risk of POCD in these patients was increased six-fold (based on a conservative increased risk of progression to dementia in patients with mild cognitive impairment [MCI] of 15% over 12 months) and the incidence of POCD at 3 months postoperatively is 14% (12% in those with baseline cognitive impairment and 2% in those with normal baseline cognition), we would require 300 patients to identify this difference (power of 90%, and $\alpha = 0.05$, two-tailed). The control number was based on previous studies where the number of participants is convenience but large enough to reduce variability and allow matching.

Group comparisons were made using independent t tests for continuous variables, Mann-Whitney U test for ranked data, and chi-square or Fisher exact test for dichotomous data. All hypothesis testing was two-tailed. A P value of less than 0.05 was taken to indicate significance. Odds ratios and 95% CIs were determined for individual tests and combined outcomes. Tests were performed using STATA (Ver 12.0; Stata Corporation, USA)

Results

We recruited 300 patients. The trial profile is shown in figure 1. There were no significant differences in demographic or comorbidities between 271 patients followed for 12 months and 29 patients not assessed (appendix 1).

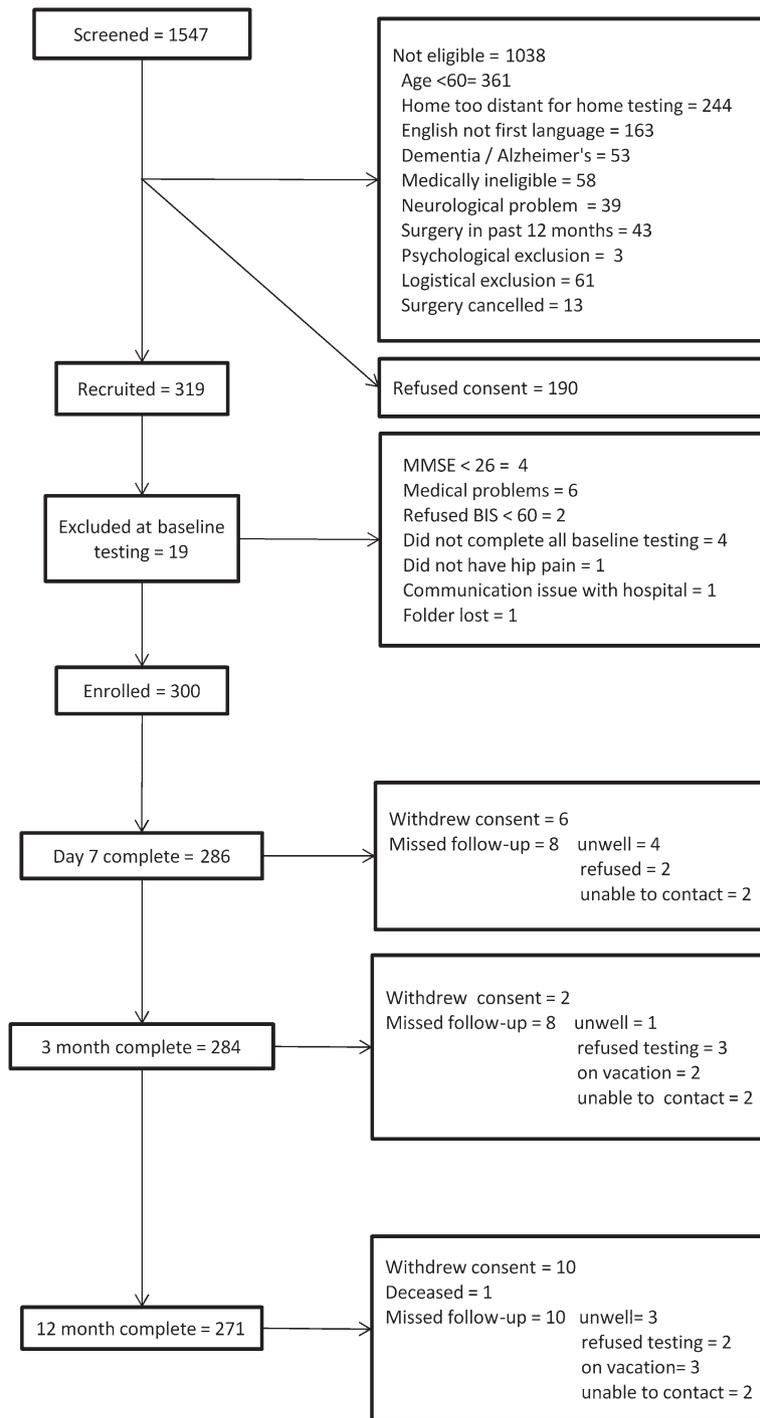


Fig. 1. Trial profile. BIS = bispectral index; MMSE = MiniMental State Examination.

Patient and control baseline characteristics, including medical history and medications, are shown in table 1. We recruited 65 control participants in total (appendix 2). We excluded four control participants due to surgery during the course of the study, four with baseline dementia (according to baseline study neuropsychological assessment), one withdrew after baseline testing, and five for age matching, resulting in 51 age-matched controls for the purpose of calculating

POCD. Fifty were assessed at day 7, 48 at 3 months, and 38 at 12 months. There were no significant differences between baseline characteristics for patients and controls, except estimated intelligence quotient was higher in controls.

The mean \pm SD time in days for testing was 8.7 ± 2.0 (range, 4 to 14), 95.1 ± 12.3 (range, 72 to 163), and 371 ± 18.4 (range, 336 to 435) for assessment at 7 days, 3 months, and 12 months, respectively (appendix 3).

Table 1. Patient and Control Demographics and Medical History

	Patients, n		Controls, n		P Value
Age, yr	300	70.1 (6.6)	51	72.0 (7.2)	0.06
Gender (male/female)	300	103/197	51	13/38	0.22
Height, cm	299	166.4 (9.4)	49	166.0 (8.6)	0.79
Weight, kg	300	78.5 (15.0)	50	75.3 (17.3)	0.17
Body mass index	299	28.3 (4.9)	49	27.2 (5.0)	0.12
Diabetes	296	26 (8.8)	50	6 (12)	0.47
Hypertension	299	160 (53.5)	51	34 (66.7)	0.08
Peripheral vascular disease	287	3 (1.0)	51	3 (5.9)	0.05
History of myocardial infarct	295	12 (4.1)	50	7 (14.0)	0.01
History of smoking	300	144 (48.0)	51	20 (39.2)	0.29
Hypercholesterolemia	297	115 (38.7)	51	26 (51.0)	0.12
Estimated intelligence quotient	270	111.0 (10.3)	48	115.4 (9.0)	<0.01
Prior general anesthesia	295	275 (93.2)	48	45 (93.8)	1.00
Preoperative medications					
Statins	300	99 (33.0)	47	21 (44.7)	0.14
β -blockers	300	39 (13.0)	47	6 (12.8)	1.00
Antidepressants	297	36 (12.1)	47	4 (8.5)	0.63
ACE inhibitors	300	63 (21.0)	47	11 (23.4)	0.70

Continuous variables presented as mean (SD) and categorical variables as number (%).

ACE = angiotensin-converting enzyme.

The results of neuropsychological testing of patients and controls at baseline are shown in table 2 with 286 patients being tested at 7 days, 284 at 3 months, and 271 at 12 months. Controls performed better on the Controlled Oral Word Association Test than patients at baseline, but there were no other significant differences between neuropsychological test results after allowing for multiple comparisons.

Preexisting cognitive impairment was classified in 96 of 300 (32%) patients (95% CI, 23 to 43%). Patients with PreCI had performed significantly worse on all tests at baseline, but scores were all adequate to avoid floor effects (appendix 4).

In the surgical group, 49 of 286 (17%) patients (95% CI, 13 to 22%) and 27 of 284 (10%) patients (95% CI, 6 to 13%) demonstrated POCD at 7 days and 3 months, while

7 of 271 (3%) patients (95% CI, 1 to 4%) demonstrated cognitive decline at 12 months. When the same criteria for calculating POCD were applied to the control group, the incidence of cognitive decline was 3 of 50 (6%) (95% CI, -1 to 13%) and 2 of 48 (4.2%) (95% CI, -2 to 10%) at 7 days and 3 months, while 3 of 38 (7.9%) (95% CI, -1 to 17%) demonstrated cognitive decline at 12 months.

When considering the surgical patients, those with PreCI had a significantly increased incidence of POCD compared with those without PreCI. At 7 days, the incidence of POCD was 25.3% versus 13.3%, and at 3 months, it was 14.9% versus 7.1%. Cognitive decline at 12 months was 9.4% in those with PreCI versus 1.1% in those without PreCI (table 3).

Univariable analysis was conducted at 3 months by assessing all demographic, perioperative, and comorbid factors,

Table 2. Test Score Results at Baseline

	Patients (n = 300)	Controls (n = 51)	P Value
MMSE	28.18 (1.23)	28.49 (1.19)	0.10
Estimated IQ	111.04 (10.32)	115.40 (8.99)	0.01
CERAD-AVLT, n	17.47 (3.80)	18.66 (3.93)	0.04
TMTA, s	51.66 (21.74)	43.12 (14.85)	0.01
TMTB, s	116.64 (59.12)	97.73 (55.41)	0.28
DSST, n	37.79 (10.86)	41.14 (11.26)	0.05
COWAT, n	35.18 (12.35)	42.90 (13.19)	<0.01
CERAD semantic fluency (animals), n	17.89 (4.61)	19.92 (4.79)	<0.01
GPBd, s	98.38 (36.96)	89.55 (23.52)	0.11
GPBnd, s	109.95 (52.10)	98.49 (25.55)	0.13

Test results are either number correct (n) or time taken (s). All data are presented as mean (SD).

AVLT = Auditory Verbal Learning Test; CERAD = Consortium to Establish a Registry for Alzheimer Disease; COWAT = Controlled Oral Word Association Test; DSST = Digit Symbol Substitution Test; GPBd = Grooved Pegboard Test dominant; GPBnd = Grooved Pegboard Test nondominant; IQ = intelligence quotient; MMSE = MiniMental State Examination; TMTA = Trail Making Test Part A; TMTB = Trail Making Test Part B.

Table 3. Prevalence of Preexisting Cognitive Impairment and Incidence of Postoperative Cognitive Dysfunction and Cognitive Decline

	PreCI (n = 96)	No PreCI (n = 204)	P Value	95% CI Difference
Day 7				
POCD	23/91 (25.3%)	26/195 (13.3%)	0.012	12% (2%, 22%)
95% CI	16.7%, 35.5%	8.9%, 18.9%		
3 months				
POCD	13/87 (14.9%)	14/197 (7.1%)	0.039	7.8% (1%, 16%)
95% CI	8.2%, 24.2%	3.9%, 11.6%		
12 months				
Cognitive decline	5/83 (9.4%)	2/188 (1.1%)	<0.001	8.3% (2%, 15%)
95% CI	2.0%, 13.5%	0.1%, 3.8%		

Data are presented as n (%), 95% CI in percent.

POCD = postoperative cognitive dysfunction; PreCI = preexisting cognitive impairment.

which demonstrated an association ($P < 0.2$) with the outcome (POCD at 3 months) (appendix 5). A classification of PreCI at baseline was associated with POCD at 3 months (table 4). In a final model, age and PreCI were both forced into a logistic regression model to examine the impact of PreCI on 3-month POCD after controlling for age.

Discussion

There is a paucity of evidence on the impact of preoperative cognitive status on postoperative cognitive change. We found a high prevalence of PreCI (32%) in older patients presenting for noncardiac surgery, and moreover, this was associated with subsequent POCD.

The term preexisting cognitive impairment (PreCI) has been used previously to define preoperative cognitive status. Hogue *et al.*¹⁷ defined PreCI as a test score more than 2 SD lower on two or more tests compared with cognitive test data obtained in controls. PreCI thus identifies individuals with impaired cognition, which may not only involve the memory domain but affect other domains, such as attention, concentration, and executive function. In fact, a more detailed analysis of the tests, which contribute to the classification of PreCI in our patients, shows that measures of complex and simple attentional function (*e.g.*, Trails Making Test B with 66% sensitivity and Trails Making Test A with 58% sensitivity) and motor function (Grooved Pegboard dominant with 52% sensitivity) were the most common contributor to the classification of PreCI. By comparison, impairment in memory (CERAD-Auditory Verbal Learning Test with 17% sensitivity) contributed less to the classification of the PreCI.

Population studies often use amnesic MCI, defined by an impairment in episodic memory (identified by performance on a test of memory that is less than 1.5 SD compared with norms) together with a subjective or informant report of memory loss.²¹ Silverstein *et al.*⁴ used a surrogate for MCI, which they called preoperative cognitive impairment (PCI). Their construct did not require a report of memory loss and was defined as a preoperative score of at least 1.5 SD below healthy controls in the Visual Verbal Learning Test in cumulated learning or in delayed recall. They found an incidence

of PCI of 74 of 1,185 (6.2%) in their study group before surgery. Our incidence of PreCI of 32% is higher than both the incidence of PCI observed by Silverstein *et al.*⁴ and that observed in large population studies that use MCI as a measure of subtle cognitive decline (14 to 18%).²¹

Preexisting cognitive impairment is both a broader index of cognition than MCI or PCI (because it incorporates multiple domains) and also a more conservative index because of the 2 SD criteria which identify individuals who lie in the bottom 2.28% of responses in two or more tests. In contrast, the objective component of both MCI and PCI use a cutoff of 1.5 SD, thus identifying individuals who lie in the lowest 6.68% in a memory test alone and is more specific because it assesses only one domain. Given the more rigorous objective requirements for PreCI, the higher prevalence of PreCI identified in our study must therefore be due to the wider range of cognitive tests used rather than the degree of cognitive impairment.

Previously, we have reported a prevalence of PreCI of 20% in 152 patients who comprised a substudy of the current investigation.¹⁸ Our current finding of 32% patients with PreCI is comparable with that reported before cardiac surgery of 25%,²² 35%,¹⁹ and 45%¹⁷ and underscores similarities in this area between patients presenting for cardiac and noncardiac surgeries.¹⁰

We found that patients with subtle cognitive impairment at baseline identified by PreCI had a significantly greater incidence of POCD than those without PreCI at 7 days and 3 months and a significantly greater incidence of cognitive decline at 12 months. This is consistent with current theories on cognitive decline in the elderly in population studies which link decreased cognitive status to future cognitive decline.²³

It has long been suspected that patients with impaired cognition may be susceptible to POCD, but direct evidence in support of this hypothesis has not been forthcoming. Silverstein *et al.*⁴ found no difference in the incidence of POCD in patients with or without cognitive impairment identified by PCI at either 7 days or 3 months.

Bekker *et al.*²⁴ undertook a retrospective analysis of community-dwelling volunteers. Individuals with MCI who

Table 4. Univariable and Multivariable Analysis

Predictor	POCD 3 Months			
	Univariable Analysis		Multivariable Analysis	
		P Value	Odds Ratio (95% CI)	P Value
Age	$t = -1.213$	0.23	1.04 (0.98, 1.10)	0.17
PreCI	$\chi = 4.307$	0.04	2.41 (1.06, 5.492)	0.04

POCD = postoperative cognitive dysfunction; PreCI = preexisting cognitive impairment.

underwent surgery had a greater decline in performance on the Digit Span Forward Test compared with those without MCI. They concluded that MCI patients declined in attention and concentration after surgery compared with normal individuals.

Bekker *et al.*²⁴ have noted the importance of identifying subgroups susceptible to POCD in order to target these individuals for treatment. The current findings suggest PreCI would be a useful tool in this regard.

Age has repeatedly been shown to be a predictor of POCD.²⁵ Increased age has been found to be associated with the incidence of POCD after both cardiac²⁶ and noncardiac surgery.³ We found no association between age and POCD at 3 months when the regression model included age and PreCI. That is, if PreCI was excluded from the regression model, age was significantly associated with POCD, whereas inclusion of PreCI removed the association of age with POCD at 3 months. This suggests that age may be acting as a surrogate for cognitive status in analyses for risk of POCD.

The long-term incidence of cognitive decline after noncardiac surgery is of interest. The incidence of cognitive decline after cardiac surgery has been followed for periods as long as 5 yr,²⁷ and there are reports of early postoperative improvements followed by decreases in cognitive function at 5 yr.²⁸ There is little information on the natural history of cognition after noncardiac surgery at time intervals greater than 12 months. In a substudy of the ISPOCD investigation, Abildstrom *et al.*⁸ determined the incidence of cognitive decline (using the same method as used to calculate POCD) 1 to 2 yr after noncardiac surgery using 336 patients and 47 controls. They identified cognitive decline in 10.4% of patients, but this did not differ significantly from the incidence in the control group of 10.6%. However, subjects were administered a battery of only four neuropsychological tests, from which seven parameters were derived to calculate cognitive decline, exposing the analysis to double counting (type 1 error). Our overall incidence of cognitive decline of 3% (95% CI, 1 to 6%) at 12 months is lower than Abildstrom *et al.*,⁸ but consistent with the incidence we found in our control group of 8%. Either way, both studies indicate that at 12 months, the incidence of cognitive decline does not differ from controls after noncardiac surgery. It should be noted that patients without PreCI had an even lower incidence of cognitive decline at 12 months (1.1%), which may reflect a level of cognitive impairment at baseline in both the patients and controls.

Our calculation of POCD and cognitive decline was based on a nonoperative control group suffering from osteoarthritis (who did not undergo surgery). The control group was more comparable with the study group than the use of healthy nonsurgical controls which have been used as a reference group in previous studies.²⁹ Since the use of our control group was more likely to be comparable in terms of ongoing pain, analgesics, and comorbidities than the use of a healthy control group, the calculated incidence of POCD and cognitive decline was likely to be less than in studies that have used healthy controls. The use of appropriate control groups has previously been advocated.⁸ When controls with cardiac disease (rather than healthy controls) were used to identify the incidence of cognitive decline after cardiac surgery, no significant difference was identified.³⁰

Identifying predictors of risk before surgery has the advantage that prospective decisions can be made. Population studies have consistently drawn a strong association between subtle cognitive impairment such as MCI and progressive cognitive decline over the following years. Our results show that PreCI strongly predicted POCD at 7 days and 3 months and cognitive decline at 12 months.

It has been suggested that the release of microemboli during hip arthroplasty may contribute to POCD compared with other noncardiac surgery.³¹ However, a recent review found no relationship between microembolic count and subsequent cognitive decline.³²

In summary, PreCI was identified in 32% of patients presenting for noncardiac surgery and is a predictor of subsequent POCD at 7 days and 3 months and cognitive decline at 12 months. Prospective longer term (more than 12 months) outcomes are required in the noncardiac surgical population to track the natural history of cognitive decline. This is especially pertinent as there is a suggestion that after cardiac surgery, improvement in the incidence of cognitive decline at 12 months is followed by subsequent decline.²⁸ Given that identifying early decline in cognitive function is now routine in geriatric care (*e.g.*, MCI) and is now an accepted mechanism for identifying future cognitive decline, the current findings suggest that PreCI may similarly predict cognitive decline following surgical intervention.

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Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Silbert: Department of Anaesthesia, St. Vincent's Hospital, PO Box 2900, Fitzroy, Victoria 3065, Australia. brendan.silbert@svhm.org.au. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

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Appendix 1. Baseline Characteristics between Patients Assessed and Not Assessed at 12 Months

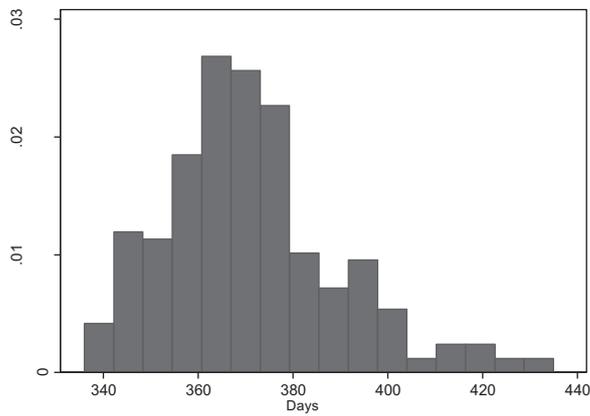
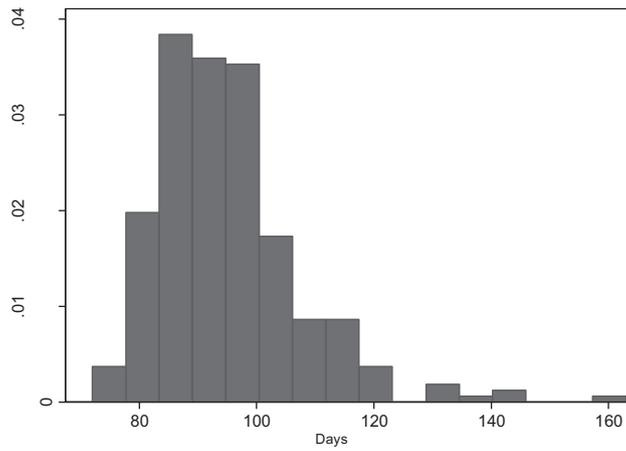
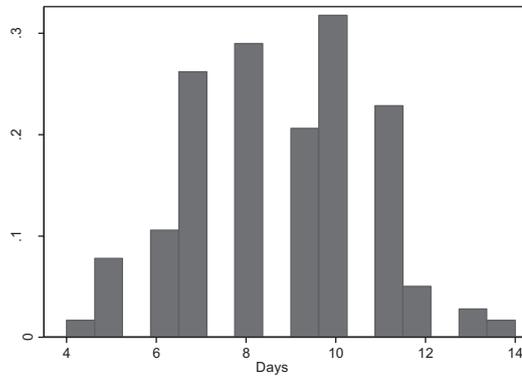
Characteristic	n = 271	n = 29	P Value
Age	69.9 (6.6)	71.6 (6.2)	0.19
Gender (male/female)	90/171	13/16	0.21
Height	166.2 (9.0)	167.7 (12.7)	0.42
Weight	78.6 (14.6)	77.6 (19.3)	0.73
Body mass index	28.4 (4.9)	27.3 (5.1)	0.23
Diabetes	24 (9.0)	2 (7.0)	0.75
History of or current smoking	129 (47.6)	15 (51.7)	0.67
Hypertension	147 (54.2)	13 (46.4)	0.43
Hypercholesterolemia	106 (39.4)	9 (32.1)	0.45
Peripheral vascular disease	3 (1.1)	0 (0)	0.57
History acute myocardial infarction	11 (4.1)	1 (3.7)	0.92
Estimated intelligent quotient	111.1 (10.3)	110.3 (11.0)	0.71
Apolipoprotein E4 positive	54 (25.1)	3 (17.6)	0.49
Prior general anesthetic	251 (94.0)	24 (85.7)	0.10
Statins	90 (33.2)	9 (31.0)	0.81
β-blockers	38 (14.0)	1 (3.4)	0.11
Antidepressants	35 (13.1)	1 (3.4)	0.13
Angiotensin-converting enzyme inhibitors	60 (22.1)	3 (10.3)	0.14

Appendix 2. Control Group: Mean (SD) for Each Test at Each Time Point

	Baseline	Day 7	3 Months	12 Months
CERAD-AVLT	18.7 (3.9)	19.9 (3.5)	19.6 (3.2)	19.4 (4.0)
TMTA	43.1 (14.8)	41.9 (19.3)	38.3 (12.3)	42.3 (21.1)
TMTB	97.7 (55.4)	92.0 (43.2)	83.5 (41.4)	89.6 (64.0)
DSST	41.1 (11.3)	44.9 (11.5)	46.1 (9.6)	47.1 (12.2)
COWAT	42.9 (13.2)	44.4 (16.4)	44.4 (14.7)	46.9 (14.8)
CERAD semantic fluency (animals)	19.9 (4.8)	20.1 (5.3)	21.1 (5.1)	21.2 (5.3)
GPBd	89.6 (23.5)	85.1 (18.0)	85.2 (16.7)	89.6 (28.2)
GPBnd	98.5 (25.5)	93.9 (22.3)	95.5 (21.8)	97.6 (28.9)

AVLT = Auditory Verbal Learning Test; CERAD = Consortium to Establish a Registry for Alzheimer Disease; COWAT = Controlled Oral Word Association Test; DSST = Digit Symbol Substitution Test; GPBd = Grooved Pegboard Test dominant; GPBnd = Grooved Pegboard Test nondominant; TMTA = Trail Making Test Part A; TMTB = Trail Making Test Part B.

Appendix 3: Density Distribution of Time of Testing at Each 7 Days, 3 Months, and 12 Months



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Appendix 4. Comparison of Test Scores for Patients Classified as No Preexisting Cognitive Impairment and Preexisting Cognitive Impairment

Test	No Preexisting Cognitive Impairment	Preexisting Cognitive Impairment	P Value
CERAD-AVLT	18.3 (3.5)	15.8 (3.8)	<0.01
TMTA	44.1 (13.4)	67.6 (26.8)	<0.01
TMTB	97.6 (36.0)	156.4 (76.7)	<0.01
COWAT	36.8 (12.2)	31.8 (12.0)	<0.01
CERAD semantic fluency (animals)	18.5 (4.6)	16.6 (4.5)	<0.01
GPBd	87.2 (17.7)	122.5 (52.9)	<0.01
GPBnd	95.6 (19.5)	141.0 (80.0)	<0.01

AVLT = Auditory Verbal Learning Test; CERAD = Consortium to Establish a Registry for Alzheimer Disease; COWAT = Controlled Oral Word Association Test; GPBd = Grooved Pegboard Test dominant; GPBnd = Grooved Pegboard Test nondominant; TMTA = Trail Making Test Part A; TMTB = Trail Making Test Part B.

Appendix 5. Univariable Analysis Was Undertaken to Assess Associations between the Outcome (Postoperative Cognitive Dysfunction at 3 Months) and All Demographic, Comorbid, and Perioperative Variables

Univariable Parameter	Met Inclusion for Entry to Multivariable
Baseline	3 months
Age	Known association, $P = 0.23$
Gender	
Height	
Weight	
Body mass index	
Obesity*	$P = 0.15$
Education	
Estimate intelligent quotient	
Alcohol consumption	
History of or current smoking*	
Hypertension*	
Hypercholesterolemia*	
History of acute myocardial infarction*	
Diabetes*	
Peripheral vascular disease*	
Cancer	
History transient ischemic attack	
Epilepsy	
Prior general anesthetic	
Lung disease	
Apolipoprotein E4 positive	
Treatment with analgesics	
Nonsteroidal antiinflammatory drugs	
β -blockers	
Angiotensin-converting enzyme inhibitors	
Benzodiazepines	
Antidepressant medication	
Statins	
Cardiovascular risk factor†	
Visual analog scale (anxiety)	
Visual analog scale (depression)	
Visual analog scale (fatigue)	
Visual analog scale (pain)	
Preexisting cognitive impairment	$P = 0.04$

(Continued)

Appendix 5. Continued

Univariable Parameter	Met Inclusion for Entry to Multivariable
Perioperative	
Dose of midazolam	
Dose of fentanyl	
Sevoflurane	$P = 0.19$
Desflurane	
Total propofol dose	
Type of airway	
Mean bispectral index level	
Use of antiemetic	
Patient controlled analgesia dose	
Postoperative nonsteroidal antiinflammatory drugs	
Transfusion	
Time to test for each assessment	
Length of hospital stay	$P = 0.16$
Quality of recovery score	
Complications	

Multivariable analysis was then conducted including variables that yielded $P < 0.02$ on univariable analysis and then modeled according to best fit. All hypothesis testing was two-tailed.

* Ranked variable 0 to 7; † sum of seven variables.