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Predictors of Cognitive Dysfunction after Major Noncardiac Surgery

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Background: **The authors designed a prospective longitudinal study to investigate the hypothesis that advancing age is a risk factor for postoperative cognitive dysfunction (POCD) after major noncardiac surgery and the impact of POCD on mortality in the first year after surgery.**

Methods: **One thousand sixty-four patients aged 18 yr or older completed neuropsychological tests before surgery, at hospital discharge, and 3 months after surgery. Patients were categorized as young (18–39 yr), middle-aged (40–59 yr), or elderly (60 yr or older). At 1 yr after surgery, patients were contacted to determine their survival status.**

Results: **At hospital discharge, POCD was present in 117 (36.6%) young, 112 (30.4%) middle-aged, and 138 (41.4%) elderly patients. There was a significant difference between all age groups and the age-matched control subjects ($P < 0.001$). At 3 months after surgery, POCD was present in 16 (5.7%) young, 19 (5.6%) middle-aged, and 39 (12.7%) elderly patients. At this time point, the prevalence of cognitive dysfunction was similar between age-matched controls and young and middle-aged patients but significantly higher in elderly patients compared to elderly control subjects ($P < 0.001$). The independent risk factors for POCD at 3 months after surgery were increasing age, lower educational level, a history of previous cerebral vascular accident with no residual impairment, and POCD at hospital discharge. Patients with POCD at hospital discharge were more likely to die in the first 3 months after surgery ($P = 0.02$). Likewise, patients who had POCD at both hospital discharge and 3 months after surgery were more likely to die in the first year after surgery ($P = 0.02$).**

Conclusions: **Cognitive dysfunction is common in adult patients of all ages at hospital discharge after major noncardiac surgery, but only the elderly (aged 60 yr or older) are at significant risk for long-term cognitive problems. Patients with POCD are at an increased risk of death in the first year after surgery.**

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POSTOPERATIVE cognitive dysfunction (POCD) is often associated with cardiac surgery, but less is known about the prevalence of this problem after other types of surgery.[1,2] In 1998, the International Study of Postoperative Cognitive Dysfunction (ISPOCD1) evaluated cognitive decline in 1,218 elderly patients, aged 60 yr or older, who had undergone major noncardiac surgery, and found that cognitive dysfunction was present in 26% of older patients 1 week after surgery and in 10% 3 months after surgery.[3] However, this study had significant differences in the incidence of early POCD at the 13 participating hospitals, placing this finding in question.

Research evaluating cognitive decline after cardiac and noncardiac surgery has primarily focused on older patients, who might have an increased vulnerability to neurologic deterioration.[1,3,4] However, the cognitive effects of surgery and anesthesia in younger adults are poorly understood, making it difficult to determine whether advancing age is the primary risk factor for this complication. Studies on normal aging have shown that abrupt declines in cognitive function in older adults are associated with early death.[5,6] The relation between POCD and mortality has not been reported.

To investigate the hypothesis that advancing age is a risk factor for POCD, we designed a prospective cohort study evaluating the incidence of early (hospital discharge) and late (3 months after surgery) cognitive dysfunction in adults of all ages undergoing elective, major noncardiac surgery. This study used the same neuropsychological methodology as the ISPOCD1 study in an attempt to replicate its results at a single institution.[3] Patients were also followed to determine the impact of POCD on survival in the first year after major surgery. A companion article analyzes the type and severity of cognitive impairment in the elderly patients in this study.[7]

Materials and Methods

Subject Enrollment

After approval by the institutional review board, 1,064 patients undergoing major, noncardiac surgery at Shands Hospital at the University of Florida (Gainesville, Florida) gave their written informed consent and were enrolled in the study between February 1, 1999, and January 31,

2002. Inclusion criteria included adult patients who were aged 18 yr or older and scheduled to be admitted to the hospital as an inpatient for a minimum of 2 days after surgery. Additional inclusion criteria were surgery scheduled under general anesthesia that was expected to last 2 h or longer, fluency in English, ability to read, and the absence of serious hearing or vision impairment that would preclude neuropsychological testing. Patients were excluded if they were scheduled to undergo cardiac, carotid, or intracranial procedures or were not expected to be alive or available to complete testing at 3 months after surgery. Additional exclusion criteria included a score of 23 or less on the Mini-Mental State Examination (MMSE)[8] before surgery; a history of dementia or any disease of the central nervous system, including previous cerebral vascular accident with residual deficit; current use of tranquilizers or antidepressants; a current or past history of psychiatric illness; and alcoholism or drug dependence. Patients could not be included twice, even if they had an unrelated second procedure.

Previous studies have suggested that repeated neuropsychological testing may result in an improvement in test performance, or a practice effect.[9,10] To estimate the magnitude of this practice effect for the neuropsychological tests used in this study, we enrolled a group of 210 control subjects. These subjects were recruited from primary family members (spouses, siblings, or children) of patients enrolled in the study. With the exception of the surgically related items, inclusion and exclusion criteria for the patients and control subjects were identical. The control group underwent neuropsychological testing at the same time intervals as the patients. Control subjects did not undergo surgery or anesthesia during the study period.

Preoperative Evaluation and Perioperative Management

The preoperative evaluation was performed within 14 days of surgery. Information about the patients' demographic status, medical history, physical examination, education, and employment status were recorded. Current medications, alcohol use, smoking history, and previous surgical history were also recorded. The Charlson comorbidity score,[11] a weighted index that includes both the number and seriousness of comorbid medical conditions, was computed for all patients at hospital admission. The anesthesia provider also rated the patient's presurgical comorbidity with the American Society of Anesthesiologists physical status.[12]

All surgery was performed with general anesthesia, and there were no restrictions on the type of anesthesia or postoperative analgesia. All patients were visited daily during their hospital stay, and the medical records were reviewed for complications. At 1 yr after surgery, patients or their families were contacted *via* telephone to determine their survival status.

Neuropsychological Assessment

A brief battery of neuropsychological tests was administered before surgery (within 14 days of surgery), on the day of hospital discharge (or at 1 week after surgery if still hospitalized), and 3 months after surgery. The neuropsychological assessment was performed in a quiet room with only the patient and the psychometrician present. If a patient had a second operation during the study period, he or she remained in the study, and the neuropsychological test results were included in the final analysis. The occurrence of a second operation in the first 3 months after surgery (before the 3-month neurocognitive testing) was captured as a variable and included in the analysis of factors predicting POCD.

Each examiner was trained on psychometric test administration and relevant interview techniques by the neuropsychologist (D.E.D.) involved in the protocol. All measures were administered and scored in a standardized manner to minimize differences between test administrators. Project investigators trained in neuropsychological assessment completed all data scoring and interpretation.

The neuropsychological test battery included the tests used to evaluate patients for POCD in the ISPOCD1 and 2 studies.[3,13] Three parallel forms of the tests were used in a sequence using a full Latin square design for tests other than the Stroop test. Patient assignment to one of six possible sequences was random. These tests primarily focus on memory and executive functions and evaluate the following:

1. Word learning: Visual Verbal Learning Test[14] based on the Rey's Auditory Recall of words
2. Word recall: the number or words recalled from Visual Verbal Learning trials after a 20-min delay
3. Cognitive flexibility: Concept Shifting Test,[15] part C, based on the Trail Making Test
4. Distractibility: Stroop Color Word Interference Test[16]
5. Working memory: Letter–Digit Coding[17] based on the Symbol Digit Substitution Test from the Wechsler Adult Intelligence Scale III, 3rd edition

Mood and pain assessment measures included the following:

1. Beck Depression Inventory[18]: This assessment screens for the presence and degree of depression in adults. It has been found to have high reliability and validity for identifying depressed patients across age groups, sexes, and cultures.
2. State Trait Anxiety Inventory[19]: This inventory has two separate scales for measuring state and trait anxiety. The state anxiety scale consists of 20 statements that evaluate how the respondent feels at the present

time. The trait anxiety scale consists of 20 statements that assess how the respondent generally feels.

3. Numerical rating scale[20] for pain: 0 indicates no pain, and 10 indicates severe pain.

For the first 3 days after surgery, patients were visited by a member of the study team, and delirium was assessed using the confusion assessment method.[21] A patient was considered delirious if the confusion assessment method was positive on any one of these days. If a patient exhibited delirium at a testing time, the neuropsychological test battery was not performed.

During the preoperative visit and the 3-month postoperative testing visit, the patient's functional status was estimated by the administration of the instrumental activities of daily living questionnaire,[22] which contained seven questions related to use of the telephone, shopping, domestic work, preparation of meals, and related activities. This questionnaire was completed by both the patient and an informant (a member of the patient's immediate family). If a patient could do the activity without assistance, the question received a score of 0; if some assistance from other people was needed to do the activity, the score was 1; and if the patient could not do the activity, the score was 2 (scores ranged from 0 to 14).[22] Higher scores indicate increasing difficulty in engaging in daily activities.

Statistical Analysis

The primary expected outcome of concern for the study was the occurrence of cognitive decline 3 months after surgery. To determine the presence of cognitive decline, we used the same definition of POCD that was used in the ISPOCD1 and ISPOCD2 studies.[3,13] To quantify the practice effect, we compared the average amount of change in performance for control subjects in each age group (18–39 yr, 40–59 yr, and ≥60 yr) for each measure between baseline and subsequent tests 1 week and 3 months later. For patients, we compared baseline (preoperative) scores with the 1-week and 3-month postoperative test results, subtracted the age-appropriate average practice effect from these scores, and divided the result by the age-appropriate control group SD to obtain a Z score for each individual test. This technique identifies patients with POCD by comparing the changes in test scores of an individual patient undergoing surgery with changes in the test scores of the age-matched control group over the same interval. The sign is adjusted so that positive Z scores indicate deterioration from the baseline test.[3,10]

The Z score for all tests can be summarized as a composite Z score.[3] The composite score is calculated as the sum of the Z scores for an individual patient divided by the SD for the sum of the Z scores for the age-matched control group. A patient was classified as exhibiting POCD if the Z scores on two individual tests or the combined Z score was 1.96 or greater. This definition identifies patients with general deterioration in all tests or substantial deterioration on only some tests.

We used chi-square or Fisher exact test for bivariate analyses of categorical data (*e.g.*, testing association of POCD and age group) and nonparametric tests (*i.e.*, Wilcoxon signed-rank tests, Kruskal-Wallis, Spearman correlations) for analysis of numerical data. We modeled the binary outcome of POCD in a logistic regression to determine which demographic and perioperative factors were associated with cognitive decline at 3 months after surgery after adjusting for other factors. All factors that were significant in bivariate analyses were included in the logistic regression model. We used SAS software version 9.1 (SAS Institute Inc., Cary, NC) for all analyses.

Sample Size Calculation

The sample size in this study was determined for the purpose of analyzing the difference between POCD in elderly (60 yr or older) *versus* middle-aged (40–59 yr) and younger (18–39 yr) patients. We choose these age classifications because the ISPOCD1 study evaluating POCD in the elderly included patients aged 60 yr or older and the ISPOCD2 study evaluating POCD in middle-aged patients included patients aged 40–59 yr.[3,13] The ISPOCD1 study[3] used Z score calculations and found that elderly patients had a 10% incidence of POCD at 3 months after major, noncardiac surgery. For the sample size calculation, we assumed that the incidence of cognitive decline at 3 months after surgery would be 5% for middle-aged patients and 3% for young patients. Using logistic regression to test for the presence of a linear trend that a patient would demonstrate a cognitive deficit at 3 months after surgery, we calculated that 375 patients per group would provide 80% power to see this difference based on a two-tailed significance level of 0.05. The sample size calculation was performed using the SIZ sample size and power module contained in the EGRET epidemiologic statistics software package (Cytel Software Corp., Cambridge, MA). This calculation determined that a sample size of 375 patients in each of the three age groups would allow us to estimate the incidence of POCD after 3 months in young, middle-aged, and elderly surgical populations with 2.9, 3.3, and 4.2% margins of error, respectively, when constructing 95% confidence intervals (CIs). We included approximately 70 control subjects in each age group who were not undergoing surgery so we could calculate the practice effect of repeated neuropsychological testing.

Results

A total of 1,496 patients were assessed for eligibility in the study; 267 refused to participate and 165 did not meet the inclusion criteria. Therefore, a total of 1,064

Table 1. Baseline Characteristics of the Patients

	Young (n = 331)	Middle-aged (n = 378)	Elderly (n = 355)	*P* Value
Age, yr	30.51 ± 6.01	49.89 ± 5.64	69.95 ± 6.8	<0.0001
Sex, %				
Male	30	35	44	0.0006
Female	70	65	56	
Years of education	13.38 ± 2.33	13.63 ± 2.76	13.43 ± 2.79	0.5632
Beck Depression Inventory score	7.09 ± 6.98	7.66 ± 7.25	5.87 ± 5.08	0.0103
State Trait Anxiety Index				
Trait anxiety	34.05 ± 9.97	32.76 ± 9.89	30.03 ± 8.35	<0.0001
State anxiety	38.37 ± 12.20	37.31 ± 11.73	33.44 ± 11.25	<0.0001
Mini-Mental State Examination	29.33 ± 1.05	29.16 ± 1.17	28.72 ± 1.45	<0.0001
Numerical rating scale for pain	2.14 ± 2.98	2.59 ± 3.11	2.46 ± 3.07	0.0728
ASA physical status, %				
I	25	10	5	<0.001
II	56	53	47	
III	17	35	44	
IV	2	2	4	
Charlson Comorbidity Index	0.99 ± 1.59	1.49 ± 1.86	2.14 ± 2.19	<0.0001

Plus–minus values are mean ± SD.

ASA = American Society of Anesthesiologists.

patients were enrolled, with 331 (31%) patients in the young (18–39 yr), 378 (36%) in the middle-aged (40–59 yr), and 355 (33%) in the elderly (≥ 60 yr) group. Of the original 1,064 patients, 1,021 (96%) were available for testing at hospital discharge, and 926 (87%) were available for follow-up at 3 months after surgery. At the late test time, the dropout rate was evenly distributed among the age groups; 50 patients in the young, 42 in the middle-aged, and 46 in the elderly group. The reasons for loss to follow-up were death (26%), too ill to complete testing (6%), too depressed to complete testing (5%), patient refusal (18%), moved out of state (15%), and inability to contact the patients (30%). During the same time period, 210 control subjects were enrolled (74 young, 74 middle-aged, 62 elderly). Twenty-eight (13%) of the control subjects dropped out before the final testing period (10 young, 12 middle-aged, 6 elderly). Data from 49 of the patients and 5 control subjects in the middle-aged group were included in the ISPOCD2 article describing POCD in middle-aged patients.[13]

The baseline characteristics of the patients included in the study are listed in table 1 and were similar to those individuals who declined to participate in the study. There were more women in the young age group compared with the elderly group. Elderly patients had more comorbid conditions than younger patients, and this was a reflected in higher baseline American Society of Anesthesiologists physical status and Charlson comorbidity scores. Education levels (median educational level was 13 yr for all age groups) and preoperative pain scores were similar among the groups. Older patients had baseline MMSE scores, anxiety scores, and depression levels that were statistically lower than the other two groups. Characteristics of the surgical procedures and hospital stay are included in table 2.

Patients and their age-matched controls were similar with respect to age, sex, educational level, and preoperative MMSE and State Trait Anxiety Inventory scores (table 3). Young and middle-aged patients had significantly greater levels of depression on the Beck Depression Inventory than age-matched controls, whereas there was no difference in depression scores between elderly patients and their controls.

The mean scores for the neuropsychological tests at baseline and 3 months after surgery are presented in table 4. The incidence of POCD at hospital discharge and

Table 2. Characteristics of the Surgical Procedure and Hospital Stay

	Young (n = 331)	Middle-aged (n = 378)	Elderly (n = 355)	*P* Value
Type of surgery, %				
Minimally invasive*	28	14	14	
Intraabdominal/thoracic	57	63	47	<0.0001
Orthopedic	15	23	39	
Duration of anesthesia, min	208 ± 108	217 ± 101	217 ± 113	0.2500
ICU stay, % of total number of patients in each age group	8	10	20	<0.0001
Duration of hospital stay, days	4.95 ± 8.27	6.26 ± 15.95	6.22 ± 8.66	<0.0001

Plus–minus values are mean ± SD.

* Minimally invasive surgery included laparoscopic surgery and superficial reconstructive surgery.

ICU = intensive care unit.

Table 3. Baseline Characteristics of the Patients and Control Subjects

	Young, 18–39 yr			Middle-aged, 40–59 yr			Elderly, ≥ 60 yr		
	Patients (n = 331)	Controls (n = 74)	*P* Value	Patients (n = 378)	Controls (n = 74)	*P* Value	Patients (n = 355)	Controls (n = 62)	*P* Value
Age, yr	30.5 ± 6.0	30.1 ± 6.3	0.6263	49.9 ± 5.6	49.6 ± 6.0	0.7222	69.9 ± 6.8	68.5 ± 5.2	0.1996
Sex, %									
Male	30	42	0.0556	35	27	0.2263	44	42	0.7830
Female	70	58		65	73		56	58	
Years of education	13.4 ± 2.3	13.9 ± 2.8	0.3367	13.6 ± 2.8	13.3 ± 2.7	0.2340	13.4 ± 2.8	13.7 ± 2.7	0.4537
BDI score	7.1 ± 7.0	5.0 ± 5.8*	0.0107	7.7 ± 7.3	5.12 ± 6.1*	0.0004	5.9 ± 5.1	6.2 ± 5.5	0.7446
STAI score									
Trait scale	34.1 ± 10.0	33.8 ± 10.0	0.7884	32.8 ± 9.9	32.1 ± 9.6	0.5955	30.0 ± 8.3	31.9 ± 8.2	0.0614
State scale	38.4 ± 12.2	38.0 ± 13.6	0.6779	37.3 ± 11.7	36.0 ± 12.2	0.3121	33.4 ± 11.3	36.7 ± 12.9	0.0791
MMSE score	29.3 ± 1.1	29.6 ± 0.8	0.0704	29.2 ± 1.2	29.3 ± 1.2	0.2617	28.7 ± 1.5	29.0 ± 1.4	0.0979

Plus–minus values are mean ± SD.

* Significant difference between patients and controls.

BDI = Beck Depression Inventory; MMSE = Mini-Mental State Examination; STAI = State Trait Anxiety Inventory.

the 3-month test session are presented in figure 1 and table 5. There were 367 patients with POCD at hospital discharge, and the incidence of cognitive dysfunction ranged from 30% to 41%. There were no statistically significant differences in POCD between the young group and either the middle-aged or elderly group; however, the elderly patients had a higher incidence of POCD than the middle-aged patients ($P = 0.01$). The prevalence of cognitive decline at hospital discharge was similar for control subjects of all age groups at this testing session (4.1% [95% CI, 0.9–11.5%] in the young, 2.8% [95% CI, 0.3–9.6%] in the middle-aged, and 5.1% [95% CI, 1.1–14.2%] in the elderly group). Cognitive impairment was significantly higher in age-matched patients compared with age-matched control subjects in all three groups at hospital discharge ($P < 0.001$; fig. 1). Because there was no statistical difference in the incidence of cognitive decline among the control groups at either testing time, the mean incidence for the control groups is illustrated in figure 1.

At 3 months after surgery, cognitive deficits occurred in 12.7% of elderly patients, which was significantly greater than the incidence in young (5.7%) or middle-aged patients (5.6%) ($P = 0.001$; fig. 1 and table 5). The incidence of cognitive decline in the control subjects was similar for all age groups at the 3-month testing interval and was 6.3% (95% CI, 1.7–15.2%) in the young, 4.8% (95% CI, 1.0–13.5%) in the middle-aged, and 1.8% (95% CI, 0.0–9.6%) in the elderly group. At 3 months after surgery, when the prevalence of cognitive deficits in the young and middle-aged patient groups were compared with their age matched control groups, there were no significant differences. However, when the elderly patients' cognitive abilities at 3 months after surgery

Table 4. Neuropsychological Test Results for the Patients at Baseline and 3 Months after Surgery

	Young Patients Baseline (n = 331)	Young Patients 3 Months after Surgery (n = 282)	Middle-aged Patients Baseline (n = 378)	Middle-aged Patients 3 Months after Surgery (n = 336)	Elderly Patients Baseline (n = 355)	Elderly Patients 3 Months after Surgery (n = 308)
Cumulative learning, number of words	30.4 ± 5.6	31.0 ± 6.2	29.2 ± 6.1	30.4 ± 6.4	25.5 ± 6.0	26.4 ± 6.1
Delayed verbal recall, number of words	10.4 ± 2.9	10.7 ± 2.9	10.1 ± 2.9	10.2 ± 3.2	8.3 ± 3.1	8.4 ± 3.1
Concept Shifting Test, part C, time in seconds	26.7 ± 9.3	25.1 ± 8.9	32.7 ± 15.2	30.4 ± 11.5	41.8 ± 19.1	40.0 ± 17.4
Concept Shifting Test, part C, number of errors	0.5 ± 1.1	0.6 ± 1.4	0.6 ± 1.4	0.7 ± 1.8	0.5 ± 1.1	0.8 ± 1.8
Stroop test, part 3, time in seconds	39.1 ± 10.6	35.1 ± 10.2	47.4 ± 12.7	42.9 ± 12.2	56.5 ± 16.1	53.4 ± 16.9
Stroop test, part 3, number of errors	1.0 ± 1.8	0.6 ± 1.9	1.4 ± 2.5	0.8 ± 1.9	2.5 ± 4.3	1.7 ± 3.2
Letter–Digit Coding, number of correct answers	39.4 ± 7.7	40.7 ± 7.6	34.2 ± 6.9	35.8 ± 7.1	28.9 ± 7.3	30.3 ± 7.2

Values are mean ± SD.

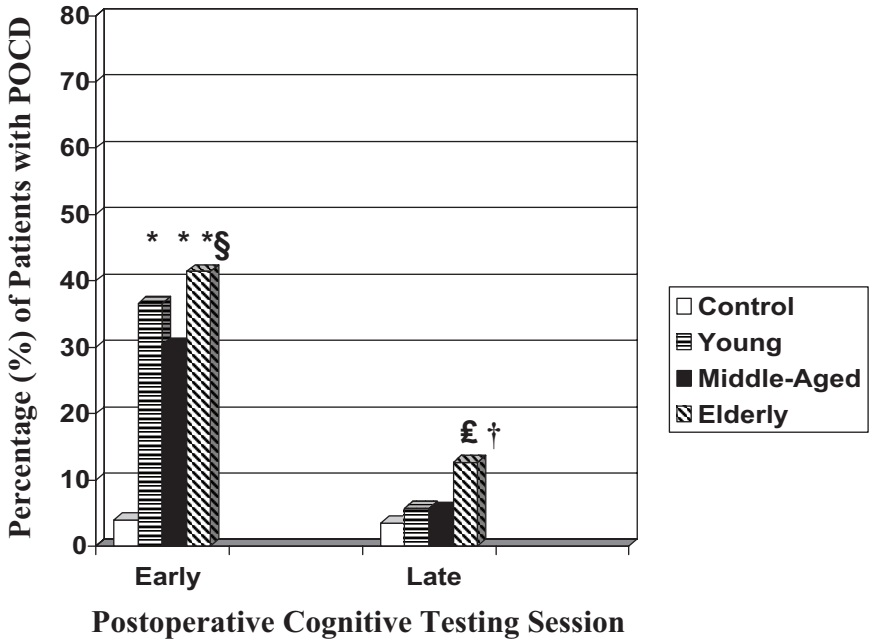

Fig. 1. Percentage of control subjects and patients (young [18–39 yr], middle-aged [40–59 yr], and elderly [60 yr and older]) experiencing postoperative cognitive dysfunction (POCD) at early (hospital discharge) and late (3 months after surgery) testing sessions. * Patient group significantly different from age-matched control subjects, $P < 0.001$ for all age groups. § Elderly group significantly different from middle-aged group, $P = 0.01$. † Elderly patient group significantly different from both young and middle-aged patient groups, $P = 0.001$. £ Elderly patient group significantly different from elderly control subjects, $P < 0.001$.

were compared with their age-matched controls, there was a significantly higher prevalence of cognitive decline in this elderly patient group ($P < 0.001$; fig. 1).

Predictors of POCD at hospital discharge are shown in table 6. During hospitalization, 35 of the 1,064 patients (3.3%) enrolled in the study experienced delirium, with 4 (1.2%) young, 8 (2.1%) middle-aged, and 23 (6.5%) elderly patients ($P = 0.003$). Only 26 of these 35 patients (74.3%) were able to be tested at hospital discharge. Delirium during the hospital stay was associated with POCD at hospital discharge ($P = 0.046$), but not with POCD at 3 months after surgery (tables 6 and 7).

Forty-six patients (4.3%) had a second operation during the study period, with 13 patients undergoing the second operation before the hospital discharge testing and 33 patients between hospital discharge and the 3-month testing time. A second operation before hospital discharge was not associated with POCD at hospital discharge. Similarly, a second operation at any time after the initial surgery was not associated with POCD at 3 months after surgery (table 7).

Forty-seven (63%) of the 74 patients with cognitive decline at 3 months after surgery also had POCD at hospital discharge, whereas the other 27 patients (36%) did not have cognitive decline at hospital discharge (table 8). Cognitive dysfunction at hospital discharge was an independent predictor of POCD at 3 months after surgery ($P = 0.0001$; table 7).

Independent predictors of cognitive decline at 3 months after surgery are included in table 7. Of the significant bivariate predictive factors for POCD at 3 months after surgery, increasing age, history of cerebral vascular accident with no residual impairment, years of education, and POCD at hospital discharge remained significant in the multiple logistic regression analysis.

At 1 yr after surgery, we were able to contact 914 of the 926 patients (99%) (or their families) who had completed neuropsychological testing at 3 months after surgery. A total of 58 patients (5.5%) died within 1 yr of surgery, with 16 dying during the first week, 20 dying in the 1-week to 3-month testing interval, and 22 dying after the 3-month testing session. There were 8 deaths in

Table 5. Proportion of Patients with Postoperative Cognitive Dysfunction at Hospital Discharge and 3 Months after Surgery

	Hospital Discharge			3 Months after Surgery		
	Number of Patients	Number of Days Testing Occurred after Surgery, Mean ± SD; Median	Patients with POCD, n (%) [95% CI]	Number of Patients	Number of Days Testing Occurred after Surgery, Mean ± SD; Median	Patients with POCD, n (%) [95% CI]
Young,18–39 yr	320	6.4 ± 8.1; 3.0	117 (36.6) [31.3–41.8%]	282	113.2 ± 70.0; 97	16 (5.7) [3.0–8.5%]
Middle-aged, 40–59 yr	368	5.9 ± 7.1; 4.0	112 (30.4) [25.7–37.1%]	336	117.8 ± 73.3; 92	19 (5.6) [3.2–8.1%]
Elderly, ≥60 yr	333	5.7 ± 6.0; 4.0	138 (41.4)* [36.2–46.7%]	308	103.9 ± 58.6; 93	39 (12.7)† [8.9–16.4%]

* Significantly different from middle-aged patients, $P = 0.01$. † Significantly different from both middle-aged and younger patients, $P = 0.001$.
CI = confidence interval; POCD = postoperative cognitive dysfunction.

Table 6. Summary Statistics for the Predictors of Cognitive Decline at Hospital Discharge

Predictor	POCD (n = 367)	No POCD (n = 654)	*P* Value
Age, yr	51.9 ± 17.3	49.4 ± 16.5	0.027
Years of education	13.2 ± 2.4	13.7 ± 2.8	0.013
ASA physical status			0.020
I	31 (3)	102 (10)	
II	194 (19)	337 (33)	
III	132 (13)	204 (20)	
IV	10 (1)	11 (1)	
Surgery category			0.001
Minimally invasive*	40 (4)	347 (34)	
Intraabdominal/thoracic	214 (21)	143 (14)	
Orthopedic	113 (11)	164 (16)	
Duration of hospital stay, days	6.6 ± 16.3	4.8 ± 5.9	0.0003
Delirium during hospital stay	15 (1.5)	11 (1.1)	0.046
Opioid use <24 h before test	324 (32)	265 (26)	0.010

Values are mean ± SD, or number of patients (% of all patients tested).

* Minimally invasive surgery included laparoscopic surgery and superficial reconstructive surgery.

ASA = American Society of Anesthesiologists; POCD = postoperative cognitive dysfunction.

the young, 16 deaths in the middle-aged, and 34 deaths in the elderly group. Patients with POCD at hospital discharge were more likely to die before the 3-month testing time (6.5%) compared with patients without POCD (3.4%) ($P = 0.02$). Likewise, patients who exhibited POCD at both hospital discharge and 3 months after surgery were more likely to die in the first year after surgery (10.6%) compared with patients with no POCD (2.1%), cognitive decline only at hospital discharge (2.86%), or cognitive decline only at 3 months after surgery (3.9%) ($P = 0.02$; fig. 2).

Discussion

This is the first prospective longitudinal study to simultaneously investigate postoperative cognitive changes after major noncardiac surgery in adult patients of all ages. Our findings indicate that 30–41% of all adult patients experience POCD at hospital discharge. Patients in all age groups have improvement in cognitive function by 3 months after surgery, but the prevalence of late POCD was significantly higher in the elderly than in the young or middle-aged patients. Our study confirms the findings of ISPOCD1, which found that advancing age and lower educational levels are risk factors for the development of cognitive decline after noncardiac surgery.[3] In addition, we found that asymptomatic patients with a history of stroke and those with POCD at hospital discharge had a higher incidence of late (3 months after surgery) POCD.

There were baseline differences among the groups, but advancing age is responsible for the majority of these differences (table 1). Depression and anxiety were less common in elderly patients. These finding are consistent with previous research, which indicates that younger individuals in a community population experience a higher prevalence of depression.[23] Despite the statistical differences in depression scores, the mean values for all groups were well below the cutoff of 14, which is needed to diagnose depression with the Beck Depression Inventory.[18] Normative samples of young, middle-aged, and older adults have also found that mean anxiety scores were similar in the two younger groups and somewhat higher than those of the elderly group.[19] As expected, elderly patients had more comorbid conditions than patients in the young and middle-aged groups, and this was reflected in higher baseline American Society of Anesthesiologists physical status and Charlson comorbidity scores. Older patients had baseline MMSE scores that were statistically lower than the other two groups. However, these differences were minimal and not likely to be clinically significant.[24]

POCD at Hospital Discharge

The high rates of POCD (30–41%) at hospital discharge in our study were associated with multiple factors (table 6) and are in agreement with the high rates of early POCD found in the ISPOCD 1 and 2 studies.[3,13] Older patients with less education, higher American Society of Anesthesiologists physical status, more complicated surgery, and longer hospital stays were also more likely to exhibit POCD at hospital discharge. Age has repeatedly been identified as a risk factor and predictor of early POCD after cardiac and noncardiac surgeries.[1,3] The ISPOCD1 study also found that lower educational level predicted cognitive decline at hospital discharge after noncardiac surgery.[3]

It was surprising that early POCD was significantly higher in elderly *versus* middle-aged patients, but there was no statistical difference between elderly and young patients (table 5 and fig. 1). The majority of the younger patients were tested 1 day earlier than the other two groups (median, 3 days after surgery compared with 4 days for the middle-aged and elderly groups; table 5). It

Table 7. Predictors of Cognitive Decline at 3 Months after Surgery

Predictor	Bivariate Analyses*		Multiple Logistic Regression Analysis†	
	Summary Statistics‡	*P* Value	Odds Ratio (95% CI)§	*P* Value
Age, yr				
No POCD	50.0 ± 16.4	<0.0001	1.02 (1.01–1.04)	0.0109
POCD	58.2 ± 16.8			
Sex			—	—
Female	7.5	0.4121		
Male	9.0			
Years of education		0.0002		
No POCD	13.7 ± 2.6		0.84 (0.76–0.93)	0.0031
POCD	12.5 ± 3.0			
Baseline Beck Depression Inventory, symptoms of depression		0.7081	—	—
No POCD	6.7 ± 6.6			
POCD	7.3 ± 7.2			
Baseline State Trait Anxiety Inventory, state anxiety		0.9109	—	—
No POCD	35.9 ± 1.6			
POCD	35.7 ± 1.6			
Baseline State Trait Anxiety Inventory, trait anxiety		0.3743	—	—
No POCD	32.0 ± 9.4			
POCD	32.8 ± 9.2			
Baseline MMSE		0.0643	—	—
No POCD	29.1 ± 1.2			
POCD	28.8 ± 1.6			
Baseline instrumental activities of daily living, by patient				
No POCD	0.5 ± 1.2	0.0033		0.0885
POCD	0.9 ± 1.6			
Change in instrumental activities of daily living from baseline to 3 mo after surgery, by patient			—	—
No POCD‖	−0.4 ± 1.5	0.4372		
POCD	−0.8 ± 2.5			
Baseline numerical rating scale for pain		0.3083	—	—
No POCD	2.4 ± 3.0			
POCD	2.9 ± 3.5			
ASA physical status		0.0293		0.7982
I POCD#	2.6			
II POCD	7.3		2.19 (0.64–7.46)	
III POCD	11.0		2.11 (0.59–7.48)	
IV POCD	11.8		2.00 (0.25–15.81)	
Charlson comorbidity index		0.0639	—	—
No POCD	1.4 ± 1.8			
POCD	2.0 ± 2.3			
Surgery category		0.1869	—	—
Minimally invasive	4.7			
Intraabdominal/ thoracic	8.5			
Orthopedic	9.4			
Duration of anesthesia, min		0.5216	—	—
No POCD	211.5 ± 103.2			
POCD	215.0 ± 92.8			
Duration of hospital stay, days		0.0173	1.03 (1.00–1.05)	
No POCD	5.0 ± 6.3			0.2479
POCD	7.2 ± 13.6			
ICU stay		0.9236	—	—
Not admitted to ICU	8.0			
Admitted to ICU	7.8			
Delirium during hospital stay		0.3730	—	—
No	5.6			
Yes	6.7			
POCD at hospital discharge		<0.0001		<0.0001
No	4.4		0.32 (0.19–0.54)	
Yes	14.4			
Second operation at any time after the initial surgery		0.0863	—	—
No	7.6			
Yes	8.6			

(*continued*)

Table 7. Continued

Predictor	Bivariate Analyses* Summary Statistics‡	Bivariate Analyses* *P* Value	Multiple Logistic Regression Analysis† Odds Ratio (95% CI)§	Multiple Logistic Regression Analysis† *P* Value
History of hypertension		0.2652	—	—
No	7.3			
Yes	9.4			
History of myocardial infarction		0.0195	1.53 (0.62–3.78)	0.2679
No	7.5			
Yes	17.0			
History of CVA with no residual damage		0.0005	3.14 (1.23–8.02)	0.0298
No	7.4			
Yes	24.2			
NYHA functional classification		0.0472		0.2301
1#	6.6			
2	12.3		1.58 (0.93–2.71)	
3	5.9		0.59 (0.19–1.82)	
4	11.1		0.91 (0.09–9.35)	
Opioid use <24 h before 3-month test		0.7461	—	—
No	7.93			
Yes	8.55			

* Postoperative cognitive dysfunction (POCD) at 3 months was modeled as a function of a single predictor. † POCD at 3 months was modeled as a function of all predictors that were significant in the bivariate analyses. ‡ Values are mean ± SD or percentage with POCD. § A dash indicates that the variable was not included in the multiple logistic regression analysis. ‖ A negative value indicates a decline from baseline scores. # Reference value for odds ratio.

ASA = American Society of Anesthesiologists; CI = confidence interval; CVA = cerebrovascular accident; ICE = intensive care unit; MMSE = Mini-Mental State Examination; NYHA = New York Heart Association Functional Classification for cardiac risk.

is possible that younger patients had a higher incidence of early POCD than middle-aged patients because they had less time to recover from the effects of anesthesia and surgery before testing.

Patients with POCD at hospital discharge had a higher rate of opioid analgesic use than those with no cognitive impairment. Opioids have sedative effects that likely have a detrimental influence on patients' performance on neuropsychological tests. Alternatively, patients still receiving opioids at hospital discharge may have been experiencing significant pain that would also detract from their test performance.[25,26]

Our study is one of the few investigations of postoperative cognitive function that includes younger patients. We found a low incidence of delirium in all age groups in our study, but still demonstrated that elderly patients are much more likely to develop postoperative delirium than younger patients. Our study only included patients with a preoperative MMSE score of 24 or greater, and the relatively low incidence of postoperative delirium in our elderly patients is similar to that previously reported for elders with preoperative MMSE scores of 25 or greater undergoing hip surgery.[27] Investigations reporting higher incidences of delirium often include patients with lower preoperative MMSE scores.[27]

Patients in the current study who developed postoperative delirium were more likely to have POCD when tested at hospital discharge but not at 3 months. It is unclear whether this relation represents a continuum of disease between delirium and POCD or whether the existence of the former simply confounds the sensitive neurocognitive tests used to diagnose POCD. None of the patients were delirious when tested; however, it is possible that some of the patients had subclinical delirium not detected by the confusion assessment method at the time of testing. Delirious patients have difficulty concentrating, distractibility, and a diminished attention span and have been shown to score lower on neurocognitive tests.[28]

Table 8. Proportion of Patients with Postoperative Cognitive Dysfunction at Each Testing Point*

	Number of Patients	No POCD at Either Test Point	POCD at Hospital Discharge Only	POCD at 3 Months Only	POCD at Both Hospital Discharge and 3 Months	*P* Value
Young, 18–39 yr	275	170 (61.8) [55.8–67.6%]	89 (32.4) [26.9–38.3%]	4 (1.5) [0.4–3.7%]	12 (4.4) [2.3–7.5%]	
Middle-aged, 40–59 yr	336	226 (67.3) [62.0–72.3%]	92 (27.4) [22.7–32.5%]	9 (2.7) [1.2–5.0%]	9 (2.7) [1.2–5.0%]	0.0015
Elderly, ≥60 yr	303	165 (54.5) [48.7–60.2%]	99 (32.7) [27.4–38.3%]	13 (4.3) [2.3–7.2%]	26 (8.6) [5.7–12.3%]	

Data are n (%) [95% confidence interval].

* Patients needed both discharge and 3-month data to be included in this analysis. Four young, one middle-aged, and five elderly patients had missing data.

POCD = postoperative cognitive dysfunction.

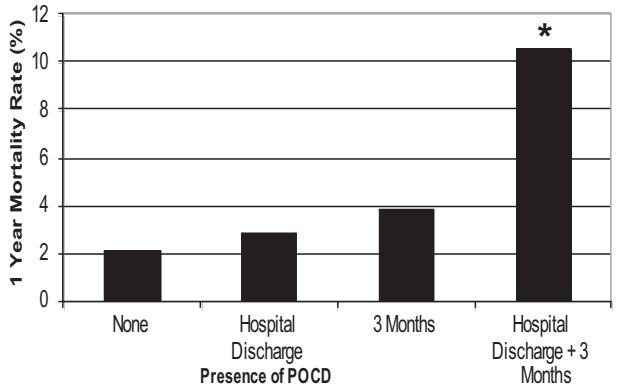

Fig. 2. Relation between the presence of postoperative cognitive dysfunction (POCD) and the percentage of patients who died in the first year after surgery. This figure includes only patients who survived to test at the 3-month (late) test time. The figure includes the following four groups: none (patients who did not experience POCD at either of the testing times), hospital discharge (patients who had POCD only at hospital discharge), 3 months (patients who had POCD only at the late [3 months postoperative] testing session), and hospital discharge + 3 months (patients who had POCD at both hospital discharge and the late testing sessions). * Hospital discharge + 3 month group was significantly different than the other three groups, $P = 0.02$.

There are other potential etiologic factors of early POCD that we did not examine and are unable to confirm with this study. Disturbed cortisol secretion[29,30] and the release of proinflammatory mediators,[31] both of which are a part of the physiologic stress response to major surgery, have been implicated in cognitive decline in humans. Lingering anesthetic effects in the form of central anticholinergic or anticatecholeminergic[32,33] activity and sleep deprivation associated with hospitalization[34] may also have had deleterious effects on our patients' neurocognitive test performance at hospital discharge.

The multiple factors that affect cognitive testing at hospital discharge make it difficult to determine whether patients who decline on neurocognitive tests at this time point have POCD or whether the declines are secondary to other factors. Hospital discharge may be too early to test for cognitive changes and postoperative testing should be delayed until patients have recovered from the effects of sleep deprivation, anesthetics, and opioid agents.

POCD at 3 Months after Surgery

Cognitive performance improved for impaired patients in all age groups after hospital discharge, but approximately 13% in the elderly group demonstrated cognitive dysfunction at 3 months after surgery. This is in agreement with the findings of ISPOCD1, which reported that 10% of patients 60 yr or older had prolonged cognitive dysfunction 3 months after surgery.[3] Approximately 6% of middle-aged patients in our study exhibited POCD at 3 months after surgery, which is similar to the prevalence found in middle-aged patients at the same time point in the ISPOCD2 study.[13] Multiple logistic regression analysis of prolonged POCD identified four independent factors: advanced age, lower educational level, previous stroke with no residual impairment, and POCD at hospital discharge.

Our study provides further evidence that the elderly are at particular risk of prolonged POCD. Although it is well known that there is a gradual decline in cognitive function during normal aging, some elders seem to be at greater risk than others for the development of dementia[35] and progress rapidly to a diagnosis of Alzheimer disease.[36] Our elderly group could have included subjects with mild preexisting cognitive deficits that were not detected by the screening MMSE. It is possible that perioperative events may have hastened or unmasked ongoing cognitive decline in some of these patients.

We found that lower educational level was associated with prolonged cognitive decline as previously reported by the ISPOCD1 investigators and others.[1,3,37] Previous studies have shown that a larger cognitive reserve capacity is protective in the development of dementia in the elderly[38,39] and is associated with better functional status after traumatic brain injury[40] and cerebral infarction.[41] Our results are consistent with a study in a normal aging population that demonstrated protective effects of higher educational level or better intellectual endowment against the development of cognitive decline.[42]

We were unable to demonstrate a relation between baseline cognitive function as measured by the MMSE and the development of POCD at 3 months after surgery (table 7). The MMSE is fundamentally a screening test, and it may not be sensitive enough to detect subtle degrees of neurocognitive impairment. The authors of a widely used compendium of neuropsychological tests state that the "presence and nature of cognitive impairment should not be diagnosed on the basis of MMSE alone."[43] Future studies should determine whether more sensitive neuropsychological tests can be used to identify subtle cognitive impairment before surgery.

Patients with lower instrumental activities of daily living scores before surgery (*i.e.*, needed more assistance with activities before surgery) were more likely to develop POCD at 3 months after surgery ($P = 0.0033$; table 7). Our investigation did not demonstrate a correlation between a decline in instrumental activities of daily living scores and the occurrence of POCD at 3 months after surgery. This finding is in contrast to the results of the ISPOCD1 study, which demonstrated a significant correlation between declines in instrumental activities of daily living scores and cognitive dysfunction at 3 months after surgery.[3] Because 136 patients in our study were not available for testing at this time point (51 of these patients [36%] were unavailable secondary to death, severe depression, or illness), it is possible that we excluded the patients who had the greatest decline in functional status. However, a companion article evaluating the subtypes of cognitive impairment in the el-

derly patients in this study found that impairment in instrumental activities of daily living scores were related to the type of postoperative cognitive impairment.[7] We did, however, find a significant correlation between POCD and mortality which is of even greater clinical significance.

The finding that asymptomatic patients with a history of stroke had an increased incidence of prolonged POCD may also be related to the concept of cognitive reserve. Despite having no residual neurologic deficits at the time of surgery, these patients may have lost critical neural mass with their stroke, leading to a decrease in their cognitive reserve and an increased susceptibility to POCD. Preexisting brain dysfunction is a well-known risk factor for postoperative delirium in the elderly.[44] Our results support the conclusions of two previous studies that described the role of preexisting brain injury/dysfunction as a risk factor for POCD. Goto *et al.*[45] reported that patients about to undergo coronary artery bypass grafting who had multiple cerebral infarctions on magnetic resonance imaging had an incidence of early postoperative cognitive decline three times that of patients with no infarctions. In this study, nearly two thirds of patients with preoperative magnetic resonance imaging findings of stroke were asymptomatic.[45] In a study of 140 elderly patients undergoing noncardiac surgery, French investigators found that preoperative cognitive impairment was a risk factor for prolonged POCD.[37]

Patients experiencing cognitive decline at hospital discharge were at higher risk for late POCD when tested at 3 months postoperatively. Of the patients with POCD at 3 months, 65% were considered to have persistent POCD from their hospital discharge testing period. Two previous studies have demonstrated an association between POCD at 1 week and very long-term POCD (1–5 yr) after both cardiac[1] and noncardiac surgery.[46] The existence of persistent POCD suggests a perioperative injury to the brain resulting in prolonged problems with cognition. The nature of such an injury can only be speculated upon but could involve some of the proposed mechanisms for early POCD alone or in combination with other factors (*i.e.*, paradoxical embolization during orthopedic surgery or an underlying genetic or neurologic predisposition to brain injury).

It is unclear why some patients developed POCD between the assessment at hospital discharge and 3 months (table 8). One possible explanation for this delayed POCD might be that these patients experienced a progression of their underlying medical comorbidities or that they acquired new medical problems in the interval between testing sessions. Likewise, patients who developed clinical depression after their surgery might perform more poorly on the 3-month postoperative neuropsychological test battery. Stockton *et al.*[47] reported that elderly patients who developed depression or new onset medical illness during the 12 months after surgery were more likely to manifest cognitive decline as the study progressed. The cause of cognitive decline in our delayed POCD group may be different than in patients with persistent POCD as reflected by significantly different 1-yr mortality rates in these two groups of patients. If the etiology of delayed POCD is not related to surgery, it might be more appropriate to refer to this problem as cognitive dysfunction and not delayed POCD.

POCD and Mortality

This study is the first to report an association between the occurrence of POCD and increased mortality in the first year after major noncardiac surgery. Patients with POCD at hospital discharge were more likely to die before the 3-month testing time. Likewise, patients with POCD that persisted for the initial 3 months after surgery were at a significantly higher risk of death in the first postoperative year.

Our observation of an association between POCD and postoperative mortality is in agreement with numerous population-based studies reporting an increased risk of early mortality in elderly individuals who experience cognitive decline.[5,6,48–50] These studies have shown that diminishing cognitive performance over long intervals (7–9 yr)[5,48] or shorter intervals of time ($\leq$ 2 yr)[6,49,50] is predictive of early death. It seems that the rate of cognitive decline is positively correlated with the risk of mortality, with rapid decline associated with the highest death rates.[5,6] The rate of cognitive decline in our postoperative patients could accurately be described as "precipitous" in comparison with that found in patients in these population-based studies. Moreover, there is evidence that a rapid decline in cognitive function has a significantly greater effect on mortality rates among the "young elderly" (<75 yr) than the "old elderly" (>75 yr).[6,49,50] Our elderly age group consisted predominantly of young elderly individuals (mean age, 70 yr) who may have been particularly vulnerable to the abrupt onset of cognitive dysfunction they experienced in the postoperative period.

It is unclear whether there is a causal link between POCD and mortality or if these outcomes are solely related to the patient's underlying medical condition. In a previous publication based on the same study population, we reported that preoperative comorbidity was the major predictor of mortality after noncardiac surgery.[51] Patients in this current report who developed POCD were more likely to be older and to have a history of stroke—both conditions that are associated with greater comorbidity. Population-based studies are providing a growing body of evidence that cognitive decline may itself be a reliable indicator of the rate of aging and the risk of impending mortality.[6] Patients with prolonged POCD might be less adherent to medication or physical therapy regimens or may not recognize the need for medical follow-up if they experience symptoms of com-

plications. These and other behaviors may result in suboptimal medical care and increase the patient's risk of dying in the postoperative period. Patients' perceptions of their own loss of intellectual function and reduced physical capacity may contribute to postoperative depression. Clinical depression is reported to be an independent and additive cofactor with cognitive impairment in determining the risk of mortality in the elderly.[52]

Our previous publication focused on the evaluation of preoperative predictors and intraoperative predictors of postoperative outcomes.[51] The intention of this study was to find variables that could predict long-term outcome or whose modification could potentially improve outcome. A surprising finding in that publication was that cumulative deep hypnotic time increased the risk of death in the first year after surgery. POCD was not included in that analysis because it is a postoperative complication. We performed a *post hoc* analysis on a composite bivariate endpoint, positive values of which indicated patients who either died within 1 yr of surgery or exhibited POCD at 3 months or both. In this analysis, the cumulative deep hypnotic time trended toward significance ($P = 0.08$). Future studies enrolling a larger number of patients are needed to determine whether cumulative deep hypnotic time is related to the occurrence of POCD.

Limitations of the Study

A major limitation of all studies investigating POCD is that there are major differences in research methodologies, including the neuropsychological test batteries, the interval between testing sessions, the definition of POCD, and the statistical methods used to analyze the data.[10] These differences make it impossible to compare the magnitude of cognitive change in our patients with patients in other studies. However, our investigation used a robust study design consistent with recent guidelines and the methodology of the ISPOCD1 and ISPOCD2 studies, allowing us to compare our findings with the findings of these multinational studies.[3,13] The ISPOCD studies use age- and ability-matched control groups studied at the same intervals as patients to compensate for learning effects, and we followed these guidelines in our study.[3,13] The incidence of late POCD in the control subjects in our study was 1.8% in the elderly, 4.8% in the middle-aged, and 6.3% in the young. In contrast to expectation, the prevalence of POCD was lower in elders in our control group. However, the prevalence rates were not significantly different among the age groups and are in agreement with the POCD rates seen in controls in the ISPOCD studies (2.8% in the elderly and 4.1% in the middle-aged studies).[3,13] Clearly, these differences warrant further exploration.

The early testing point was to be completed at hospital discharge or 7 days after surgery, but some of the patients were too ill to be tested at 1 week, so they were tested as late as 1 month after surgery. The late testing point in this study was designed to occur at 3 months after surgery. Because many of the patients in our study lived long distances from the hospital, the late testing window was extended to 6 months after surgery, resulting in large SDs in the testing time (table 5). It is possible that additional cognitive improvement occurred in patients who were tested later than 1 week or 3 months after surgery, resulting in an underestimation of the prevalence of POCD. However, the median times of testing in our study were similar to the testing times for the elderly patients in the ISPOCD1[3] and the middle-aged patients in the ISPOCD2 studies,[13] making the results of these studies comparable.

In conclusion, we found that increasing age, lower educational level, a history of previous cerebral vascular accident without residual impairment, and POCD at hospital discharge were independent risk factors for cognitive decline at 3 months after major noncardiac surgery. Although large numbers of patients of all ages were discharged from the hospital with POCD, only the elderly went on to have late cognitive decline. Of considerable concern, patients who experienced POCD at hospital discharge and at 3 months after surgery were more likely to die in the first year after surgery.

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