ANESTHESIOLOGY

Postoperative Delirium and Postoperative Cognitive Dysfunction

Overlap and Divergence

Lori A. Daiello, Pharm.D., Sc.M., Annie M. Racine, Ph.D., Ray Yun Gou, Ph.D., Edward R. Marcantonio, M.D., Zhongcong Xie, M.D., Ph.D., Lisa J. Kunze, M.D., Kamen V. Vlassakov, M.D., Sharon K. Inouye, M.D., Richard N. Jones, Sc.D., for the SAGES Study Group*

ANESTHESIOLOGY 2019; 131:477–91

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Postoperative delirium and postoperative cognitive dysfunction both occur in a substantial number of older surgical patients
- Postoperative delirium and postoperative cognitive dysfunction share risk factors and may co-occur, although their relationship is unclear

What This Article Tells Us That Is New

- Postoperative delirium increased the risk of postoperative cognitive dysfunction at 1 month postoperatively but there was no association between postoperative delirium and cognitive dysfunction at 2 and 6 months after major noncardiac surgery
- Postoperative delirium and longer-term postoperative cognitive dysfunction may be different disorders

ABSTRACT

Background: Postoperative delirium and postoperative cognitive dysfunction share risk factors and may co-occur, but their relationship is not well established. The primary goals of this study were to describe the prevalence of postoperative cognitive dysfunction and to investigate its association with in-hospital delirium. The authors hypothesized that delirium would be a significant risk factor for postoperative cognitive dysfunction during follow-up.

Methods: This study used data from an observational study of cognitive outcomes after major noncardiac surgery, the Successful Aging after Elective Surgery study. Postoperative delirium was evaluated each hospital day with confusion assessment method–based interviews supplemented by chart reviews. Postoperative cognitive dysfunction was determined using methods adapted from the International Study of Postoperative Cognitive Dysfunction. Associations between delirium and postoperative cognitive dysfunction were examined at 1, 2, and 6 months.

Results: One hundred thirty-four of 560 participants (24%) developed delirium during hospitalization. Slightly fewer than half (47%, 256 of 548) met the International Study of Postoperative Cognitive Dysfunction-defined threshold for postoperative cognitive dysfunction at 1 month, but this proportion decreased at 2 months (23%, 123 of 536) and 6 months (16%, 85 of 528). At each follow-up, the level of agreement between delirium and postoperative cognitive dysfunction was poor (kappa less than .08) and correlations were small (r less than .16). The relative risk of postoperative cognitive dysfunction was significantly elevated for patients with a history of postoperative delirium at 1 month (relative risk = 1.34; 95% CI, 1.07–1.67), but not 2 months (relative risk = 1.08; 95% CI, 0.72–1.64), or 6 months (relative risk = 1.21; 95% CI, 0.71–2.09).

Conclusions: Delirium significantly increased the risk of postoperative cognitive dysfunction in the first postoperative month; this relationship did not hold in longer-term follow-up. At each evaluation, postoperative cognitive dysfunction was more common among patients without delirium. Postoperative delirium and postoperative cognitive dysfunction may be distinct manifestations of perioperative neurocognitive deficits.

(ANESTHESIOLOGY 2019; 131:477–91)

Older adults represent a large and increasing proportion of surgical patients in the United States; although adults 65 yr and older comprised only 14% of the general population in 2014, they underwent more than one-third of all inpatient surgical procedures.[1,2] Advances in surgical and anesthesia techniques, coupled with better preoperative risk assessment, have resulted in safer operations and lower rates of some serious complications (*e.g.*, infections)[3]; however, much less is known about effectively safeguarding the aging brain from perioperative stress.

Perioperative disturbances of cognition may occur acutely, in the form of postoperative delirium,[4] or after hospital discharge, as postoperative cognitive dysfunction.[5] The

This article is featured in "This Month in Anesthesiology," page 1A. This article is accompanied by an editorial on p. 456. This article has an audio podcast. This article has a visual abstract available in the online version. For a downloadable PPT slide containing this article's citation information, please visit https://anesthesiology.pubs.asahq.org/ss/downloadable_slide.aspx. This work was presented in part at the Alzheimer's Association International Conference, London, United Kingdom (July 15, 2017). S.K.I. and R.N.J. contributed equally to this article.

Submitted for publication May 25, 2018. Accepted for publication February 28, 2019. From the Alzheimer's Disease and Memory Disorders Center, Rhode Island Hospital, Providence, Rhode Island (L.A.D.); Institute for Aging Research, Hebrew SeniorLife, Boston, Massachusetts (A.M.R., R.Y.G., S.K.I.); Harvard Medical School, Boston, Massachusetts (A.M.R., E.R.M., Z.X., L.J.K., K.V.V., S.K.I.); Departments of Medicine (E.R.M., S.K.I.) and Anesthesia and Critical Care (L.J.K.), Beth Israel Deaconess Medical Center, Boston, Massachusetts; Department of Anesthesia, Massachusetts General Hospital, Boston, Massachusetts (Z.X.); Department of Anesthesiology, Perioperative, and Pain Medicine, Brigham and Women's Hospital, Boston, Massachusetts (K.V.V.); Departments of Psychiatry and Human Behavior (R.N.J.) and Neurology (L.A.D., R.N.J.), Brown University Warren Alpert Medical School, Providence, Rhode Island.

*Members of the Successful Aging after Elective Surgery (SAGES) Study Group are listed in appendix 1.

 Anesthesiology 2019; 131:477–91. DOI: 10.1097/ALN.0000000000002729

<zdoi;10.1097/ALN.0000000000002729>

incidence of postoperative delirium is 20 to 45% among older adult surgery patients[4,6]; postoperative cognitive dysfunction is experienced by 20 to 50% of older patients three months after cardiac surgery[7,8] and in 5 to 55% of those undergoing other major surgeries.[9,10] In general, higher rates have been reported in studies that defined postoperative cognitive dysfunction using less stringent statistical thresholds, and conversely, studies using more stringent statistical methods have found lower rates of postoperative cognitive dysfunction. This point is nontrivial because unlike delirium, postoperative cognitive dysfunction is not a clinical diagnosis but rather a variably operationalized concept defined by decline in postoperative cognitive performance as measured by a neuropsychologic tests.[5,11,12]

At present, little is known about how to effectively prevent postoperative cognitive dysfunction, or how to successfully treat either postoperative delirium or postoperative cognitive dysfunction. Neither condition is benign. Delirium is linked with persistent impairments in brain function, including cognitive decline,[13–15] and increased risk of dementia,[13,16] as well as numerous negative outcomes, including longer hospitalizations, decline in physical functioning,[17] increased risk of institutionalization, and death.[21,22] postoperative cognitive dysfunction has been associated with delay in returning to work and premature retirement, as well as increased mortality.[9,23,24]

That delirium has been linked to cognitive decline after delirium[13,15,18] raises the question of whether postoperative delirium and postoperative cognitive dysfunction are distinct disorders or overlapping conditions on a continuum of neurocognitive deficits.[19,20] Previous observations that postoperative delirium and postoperative cognitive dysfunction sometimes occur in the same individuals with overlapping risk factors have resulted in the suggestion of a common underlying neuropathogenesis.[21,22]

Considering this, we hypothesized that delirium is an independent risk factor for postoperative cognitive dysfunction. Thus, the goals of this study were to (1) investigate the incidence of postoperative cognitive dysfunction up to 6 months after surgery and (2) evaluate relationships between postoperative delirium and subsequent development of postoperative cognitive dysfunction during follow-up among older adults undergoing major noncardiac surgery in the Successful Aging after Elective Surgery cohort.

Materials and Methods

Data Source and Participants

Data for this retrospective cohort study were obtained from the Successful Aging after Elective Surgery study, an ongoing observational study of older adults undergoing major elective surgery.[22,23] The study design and methods have been detailed previously.[22,23] Eligible participants were age 70 yr and older, English-speaking and able to communicate verbally, scheduled to undergo elective surgery at two Harvard-affiliated academic medical centers with an anticipated length of stay of at least 3 days, and available for in-person follow-up interviews. Qualifying surgical procedures were total hip or knee replacement, lumbar, cervical, or sacral laminectomy, lower extremity arterial bypass surgery, open abdominal aortic aneurysm repair, and open or laparoscopic colectomy. Exclusion criteria were delirium, previous hospitalization within 3 months, legal blindness, severe deafness, terminal condition, history of schizophrenia or psychosis, history of alcohol abuse or withdrawal, and evidence of dementia at the presurgery assessment. Dementia diagnosis was determined through a rigorous process fulfilling the National Institute on Aging–Alzheimer's Association criteria that included case review by an expert consensus panel but did not include biomarker data.[24,25]

In addition to the surgical patients, 118 patients without dementia were recruited in primary care clinics at the Beth Israel Deaconess Medical Center to serve as a nonsurgical control for measurement of practice effects associated with serial cognitive testing.[26] The nonsurgical control group met the same inclusion and exclusion criteria as the Successful Aging after Elective Surgery sample, other than undergoing major surgery, and were assessed with the same neuropsychologic test battery, administered at identical intervals as the surgical sample. Written informed consent was obtained according to procedures approved by the institutional review boards of Beth Israel Deaconess Medical Center and Brigham and Women's Hospital, the two study hospitals, and Hebrew SeniorLife, the study coordinating center, all located in Boston, Massachusetts.

Data Collection

Baseline interviews were performed on average within 2 weeks (mean 13 ± 15 days) before surgery and assessed demographics, cognition (Modified Mini-Mental State),[25] comorbidities, and daily living activities. Participants were evaluated for postoperative delirium daily (described in the Assessment of Delirium section below). The Successful Aging after Elective Surgery neuropsychologic test battery was administered to participants upon study entry, at 1 and 2 months after hospital discharge, and every 6 months thereafter, up to 36 months. Separate teams conducted inpatient and outpatient assessments so that the research staff assessing postoperative cognitive decline were blinded to the participants' delirium status.

Assessment of Delirium

Delirium assessment was conducted at the presurgical baseline visit (as an exclusionary factor), then daily during hospitalization until discharge. The initial delirium assessment was conducted on postoperative day 1 after transfer to the surgical floor; emergence delirium was not evaluated. Assessments included a brief cognitive screen (orientation, short-term recall, attention testing with Digit Span), the Delirium Symptom Interview,[27] and interviews with family

members and hospital staff.[28] This information was used to score the Confusion Assessment Method, which has been demonstrated to be highly sensitive (94%; 95% CI, 91–97) and specific (89%; 95% CI, 85–94) for detection of delirium compared with reference standard ratings.[29] Participants were determined to have incident postoperative delirium by a positive Confusion Assessment Method rating or by validated chart review evidence of delirium recorded at any time prior to hospital discharge.[28,30]

Assessment of Cognitive Function

The Successful Aging after Elective Surgery neuropsychologic test battery consists of the Hopkins Verbal Learning Test,[31] Digit Span Forwards and Backwards,[32,33] Phonemic (F-A-S) and Categorical (Supermarket) Fluency Tasks,[34] Boston Naming Test,[35] Visual Search and Attention Test,[36] Trail Making Test (A and B),[37] and the Digit Symbol Test.[38] Overall performance was summarized with the General Cognitive Performance, a weighted composite measure derived following standard procedures, and calibrated to a nationally representative sample of older adults to yield a mean score of 50 and SD of 10.[39,40]

Postoperative Cognitive Dysfunction

There is considerable variability in the measurement and definition of postoperative cognitive dysfunction.[11] To operationalize postoperative cognitive dysfunction, we adapted methods used in the International Study of Postoperative Cognitive Dysfunction, a landmark study of postoperative cognitive change.[5] The International Study of Postoperative Cognitive Dysfunction battery consisted of a total of seven test variables: the Rey Visual Verbal Learning Test[41] (number of words, delayed recall), the Concept Shifting Test[42] (time, number of errors), the Stroop Color-Word Test[43] (time, number of errors), and Letter-Digit Substitution[44] (number of correct responses). Postoperative cognitive dysfunction was defined based on change from baseline; a composite z score of at least 1.96 across all tests, or z scores for two or more tests scores at least 1.96.

The Successful Aging after Elective Surgery and International Study of Postoperative Cognitive Dysfunction neuropsychologic test batteries are not identical in the number and type of cognitive test variables; therefore, we developed an approach to defining postoperative cognitive dysfunction in the Successful Aging after Elective Surgery dataset that was consistent with the International Study of Postoperative Cognitive Dysfunction methods and accommodated differences in cognitive assessments between the two studies. First, we matched similar tests in the International Study of Postoperative Cognitive Dysfunction and Successful Aging after Elective Surgery batteries. Three of the eight Successful Aging after Elective Surgery neuropsychologic tests (Hopkins Verbal Learning Test, Trail-Making, Repeatable Battery for the Assessment of Neuropsychological Status) directly matched the International Study of Postoperative Cognitive Dysfunction tests by both content and cognitive domain to yield a core set of five component test variables (table 1).

Next, we repeatedly selected two of the remaining five unmatched tests from the Successful Aging after Elective Surgery battery (Digit Span Forwards and Backwards, Category Fluency, Phonemic Fluency, Boston Naming Test, Visual Search and Attention Test) and sequentially added these pairs to the set of five International Study of Postoperative Cognitive Dysfunction-matched tests. This process yielded a total of ten unique Successful Aging after Elective Surgery postoperative cognitive dysfunction test batteries, each with seven component variables that provided the same number of tests used in the International Study of Postoperative Cognitive Dysfunction.

We then applied the approach used in the International Study of Postoperative Cognitive Dysfunction to identify the prevalence of postoperative cognitive dysfunction in the surgical cohort at each follow-up. Neuropsychologic test results

Table 1. Crosswalk of Neuropsychologic Tests Used in the Successful Aging after Elective Surgery and International Study of Postoperative Cognitive Dysfunction Studies

Cognitive Domain	SAGES Tests	ISPOCD Tests
Verbal episodic memory	HVLT-R, sum of trials	Visual Verbal Learning, cumulative number of words
	HVLT-R, delayed recall	Visual Verbal Learning, delayed recall
Executive, visuospatial	DKEFS Trail Making, Part B time	Concept Shifting test, part C, time
	DKEFS Trail Making, Part B, number of errors	Concept Shifting Test, part C, number of errors
	RBANS Digit Symbol, Errors, time	Letter Digit Coding, Errors, time
	Visual Search and Attention Test*	
Confrontation naming, language	Boston Naming Test*	
Attention	WAIS Digit Span Forward and Backward*	
Executive, semantic memory, language	Category Fluency,* Phonemic Fluency*	
Executive, selective attention	NA	Stroop, errors
		Stroop, time

*Two tests from this group of five were selected at random to construct all 10 possible 7-test battery combinations—see Postoperative Cognitive Dysfunction section for details.

DKEFS, Delis–Kaplan Executive Function System; HVLT-R, Hopkins Verbal Learning, Revised; ISPOCD, International Study of Postoperative Cognitive Dysfunction; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SAGES, Successful Aging after Elective Surgery; WAIS, Wechsler Adult Intelligence Scale.

from the nonsurgical control group were used in the calculation of z scores to account for practice (and retest) effects across repeated cognitive testing sessions. Individual z scores were computed for each test, by subtracting the mean change score in the nonsurgical control group from the change score between baseline and follow-up for that test in the surgical patients. This result was then divided by the SD of the mean change score in the nonsurgical control group to obtain the individual cognitive test z scores. The z score for each test at baseline was then subtracted from the z score at each follow-up visit, and the individual test z scores were summed across all tests to create a composite z score. Postoperative cognitive dysfunction was defined as (1) z scores for two or more individual tests at or below −1.96 or (2) the sum of the seven z scores (composite z score) at or below −1.96.[45] Cohort members meeting neither criterion were considered not to have experienced postoperative cognitive dysfunction.

Statistical Analysis

For the primary analysis, we evaluated the prevalence of postoperative delirium and postoperative cognitive dysfunction for all participants with available data at 1, 2, and 6 months and assessed the correlation between postoperative delirium and postoperative cognitive dysfunction at each timepoint. No power calculation was performed for this retrospective study because the sample size was predetermined by the number of patients with available data at each follow-up.

For each patient, ten possible definitions of postoperative cognitive dysfunction were generated from the Successful Aging after Elective Surgery cognitive tests, as described in the Postoperative Cognitive Dysfunction section. The different postoperative cognitive dysfunction definitions were combined into a single analysis treating each definition as one of ten multiply-imputed outcomes. Multiple imputation is a statistical technique for analyzing incomplete data in which missing information is replaced with plausible values to create multiple complete datasets.[46] The imputed datasets are analyzed individually, and then the results are combined. We adapted this method by treating each of the 10 unique Successful Aging after Elective Surgery postoperative cognitive dysfunction test batteries (each with seven component variables) as a multiply imputed dataset which was then combined into a single multiply imputed definition of postoperative cognitive dysfunction. This approach gives equal weight to each of the 10 possible combinations and limits the number of multiple comparisons.

We calculated the prevalence of postoperative cognitive dysfunction, correlations (tetrachoric) and kappa coefficients for agreement between postoperative delirium and postoperative cognitive dysfunction, and relative risk estimates with 95% CI to compare the risk of subsequent postoperative cognitive dysfunction when postoperative delirium was present during hospitalization, with the risk of postoperative cognitive dysfunction when postoperative delirium was not present. These calculations were performed for each of the 10 possible definitions of postoperative cognitive dysfunction, as well as the overall (multiply imputed) definition of postoperative cognitive dysfunction, which was used for our primary level of inference. In *post hoc* secondary analyses, we investigated the concordance (persistence) of postoperative cognitive dysfunction across timepoints. Generalized linear models for binomial outcomes were used to estimate associations between in-hospital delirium and persistent postoperative cognitive dysfunction at 2 and 6 months.

Sensitivity Analyses. The International Study of Postoperative Cognitive Dysfunction-defined threshold has been criticized as an overly conservative cut-off that may miss subtle, but clinically relevant, cognitive decline. Similarly, the 2018 Recommendations for the Nomenclature of Cognitive Change Associated with Anesthesia and Surgery criteria for postoperative mild neurocognitive disorder designate a threshold of 1 to 2 standard deviations below population norms or controls.[47] Therefore, we redefined postoperative cognitive dysfunction as (1) z scores for two or more individual tests at or below −1.0 or (2) the sum of the seven z scores at or below −1.0.

As described previously,[23] cognitive test and other data were subject to rigorous quality procedures to minimize missing data and evaluation of outliers. No observations were omitted on the basis of their relative distribution. All tests were two-tailed, and statistical significance was defined at the $P < .05$ level. Statistical analyses were performed using Stata version 14.1 (Stata Corp, USA).

Results

Study Population

Data were available for 98% (551 of 560) of Successful Aging after Elective Surgery participants at baseline. Figure A1 shows a participant flow diagram. For this study, we compared baseline cognitive performance to the postoperative test results at 1 month (median, 40 days; interquartile range, 34 to 45), 2 months (86 days; interquartile range, 74 to 103), and 6 months (210 days; interquartile range, 192 to 245).

The surgical cohort was predominantly female (58%, 320 of 551), with an average age (mean ± SD) of 77 ± 5 years (table 2). Characteristics of the nonsurgical control group, including their relatively stable cognitive trajectories more than 6 months, have been described.[15,26] In summary, both groups were comparable at baseline in age and measures of cognitive performance; however, the proportion of men was greater in the control group (nonsurgical control [56%, 67 of 119] *vs.* surgical [42%, 236 of 551]; table A1 in appendix 2).[15]

The majority of surgical patients entered the study without cognitive impairment (*e.g.*, Modified Mini-Mental State score 93.6 ± 5.3), and none met criteria for dementia. Among the surgical procedures, orthopedic surgeries were most frequent (81%, 444 of 551), followed by gastrointestinal (13%, 71 of 551)

Table 2. Sociodemographic and Clinical Characteristics

Characteristics	Total Study Sample*	Stratified by POD and POCD at 2 Months (N = 536)			
		POD– POCD–	POD+ POCD–	POD– POCD+	POD+ POCD+
Number of observations, N (%)	551	319	95	91	31
Age (yr), mean ± SD	77 ± 5	76 ± 5	77 ± 5	77 ± 5	78 ± 5
Sex, n (%)					
Men	231 (42)	129 (40)	37 (39)	47 (52)	13 (42)
Women	320 (58)	190 (60)	58 (61)	44 (48)	18 (58)
Race, n (%)					
White	510 (93)	298 (93)	84 (88)	85 (93)	29 (94)
All other race and ethnicity groups	41 (7)	21 (7)	12 (13)	6 (6)	1 (4)
Education (years), mean ± SD	15 ± 3	15 ± 3	15 ± 3	14 ± 3	14 ± 2
3MS Score, mean ± SD	93.6 ± 5.3	94.5 ± 4.8	91.6 ± 5.7	92.7 ± 5.8	92.5 ± 5.9
General cognitive performance, (GCP), mean ± SD	57.7 ± 7.2	58.9 ± 7.2	54.7 ± 6.3	57.5 ± 7.4	55.6 ± 6.7
Proxy IQCODE, mean ± SD	3.1 ± 0.2	3.1 ± 0.2	3.2 ± 0.3	3.1 ± 0.2	3.3 ± 0.3
Charlson Comorbidity Index, [mean ± SD]	1.02 ± 1.3	0.90 ± 1.2	1.29 ± 1.3	1.14 ± 1.3	1.10 ± 1.4
Surgery type, n (%)					
Orthopedic	446 (81)	265 (83)	74 (78)	72 (79)	24 (77)
Vascular	34 (6)	13 (4)	8.5 (9)	8.7 (10)	1.5 (5)
Gastrointestinal	71 (13)	41 (13)	13 (14)	10 (11)	5.2 (17)
Anesthesia type, n (%)					
General	455 (85)	265 (84)	83 (87)	78 (86)	29 (97)
Spinal	77 (14)	52 (16)	12 (13)	12 (13)	1 (3)
General & Spinal	4 (1)	2 (1)	0 (0)	1 (1)	0 (0)
Duration of surgery (minutes), mean ± SD	144 ± 77	133 ± 67	166 ± 88	153 ± 87	157 ± 79
Duration of anesthesia (minutes), mean ± SD	193 ± 81	182 ± 73	219 ± 96	202 ± 85	204 ± 77

*N = 551, baseline characteristics, excludes those who had died or were lost to follow-up at 2 months. Proportion with POCD was estimated from multiply-imputed data for all participants with complete neuropsychiatric data at Month 2.

3MS, Modified Mini-Mental State; POCD, postoperative cognitive dysfunction; POD, postoperative delirium.

and vascular surgeries (6%, 34 of 551). The majority of surgeries (85%, 455 of 551) were performed under general anesthesia.

Postoperative Neurocognitive Change

Delirium occurred in nearly a quarter (24%, 134/560; 95% CI, 21–28) of the surgical patients while hospitalized. On average, postoperative cognitive dysfunction was observed more frequently than postoperative delirium; slightly fewer than half of all patients (47%, 256/548; 95% CI, 43–51) met the International Study of Postoperative Cognitive Dysfunction-defined threshold for postoperative cognitive dysfunction at 1 month, but this proportion decreased at 2 months (23%, 123/536; 95% CI, 19–26) and 6 months (16%, 85/528; 95% CI, 13–19; table 3). Similarly, the proportion of those with postoperative delirium who subsequently met criteria for postoperative cognitive dysfunction during follow-up also declined: 1 month (14%, 75/548; 95% CI, 11–17), 2 months (6%, 31/536; 95% CI, 4–8), and 6 months (4%, 23/528; 95% CI, 3–6; table 3, fig. 1).

At each follow-up, the level of agreement between postoperative delirium and postoperative cognitive dysfunction was poor (kappa coefficient, κ = .02–.11)[48] and the tetrachoric correlations (r) were small (r = .04–.21), with the strongest associations at 1 month. The risk for postoperative cognitive dysfunction was significantly elevated for patients with a history of postoperative delirium at 1 month (relative risk = 1.34; 95% CI, 1.07–1.67, P = .010) but not at 2 months (relative risk = 1.08; 95% CI, 0.720–1.63; P = .699) or 6 months (relative risk = 1.21; 95% CI, 0.70–2.09; P = .489; table 4).

Agreement, correlations, and relative risks varied by the subset of tests used to operationalize postoperative cognitive dysfunction, but the interpretation (*e.g.*, direction of effect and statistical significance) was generally consistent with the overall (multiply imputed) definition (table 3). For instance, the strength of the association of postoperative delirium as a risk factor for postoperative cognitive dysfunction at 1 month (relative risk) ranged from 1.22 to 1.47, and all but one subset was significant (P < .05).

Persistence of postoperative cognitive dysfunction across time points and its association with postoperative delirium was investigated in secondary analyses. Of the estimated 240 patients who were classified postoperative cognitive dysfunction+ at 1 month, 76 (32%) were postoperative cognitive dysfunction+ at month 2 and 30 (40%) were also postoperative cognitive dysfunction+ at month 6 (table A2). The estimated percentage of patients who had persistent postoperative cognitive dysfunction through month 2 (*e.g.*,

Table 3. Proportions of In-hospital POD and POCD during Follow-up*

	POCD		Total
In-hospital delirium and 1-month POCD (N = 548)			
In-hospital delirium, n (%)	No	Yes	
No	238 (43.4)	181 (33)	419 (76.4)
Yes	54 (9.9)	75 (13.7)	129 (23.5)
Total	292 (53.3)	256 (46.7)	548 (100)
In-hospital delirium and 2-month POCD (N = 536)			
In-hospital delirium	No	Yes	
No	318 (59.3)	92 (17.2)	410 (76.5)
Yes	95 (17.8)	31 (5.7)	126 (23.5)
Total	413 (77.1)	123 (22.9)	536 (100)
In-hospital delirium and 6-month POCD (N = 528)			
In-hospital delirium	No	Yes	
No	342 (64.8)	62 (11.7)	404 (76.5)
Yes	101 (19.1)	23 (4.4)	124 (23.5)
Total	443 (83.9)	85 (16.1)	528 (100)

*Proportion with POCD was estimated from multiply-imputed data for all participants with complete neuropsychiatric test data at each time point.
POCD, postoperative cognitive dysfunction; POD, postoperative delirium.

postoperative cognitive dysfunction+ at months 1 and 2) was 14% (76 of 535), and the estimated percent with persistent postoperative cognitive dysfunction through month 6 (*e.g.*, postoperative cognitive dysfunction+ at months 1, 2, and 6) was 6% (29 of 522). In-hospital delirium was weakly associated with increased risk of persistent postoperative cognitive dysfunction through month 2 (odds ratio = 1.30; 95% CI, 0.99–1.70; P =.062), but was not associated with having persistent postoperative cognitive dysfunction through month 6 (odds ratio = 1.07; 95% CI, 0.70–1.66; P =.744; table A3).

Sensitivity Analyses

Using the less stringent cut-off (z score 1.0) for postoperative cognitive dysfunction, 60% (324 of 540) of patients met criteria at 1 month, of which 27% (89 of 324) had a history of delirium. Consistent with the main results, the proportion of patients with postoperative cognitive dysfunction declined at each follow up: 2 months (36%, 192 of 535) and 6 months (27%, 141 of 522). Among patients with a history of postoperative delirium, the proportion with postoperative cognitive dysfunction declined to 8% (16 of 192) at 2

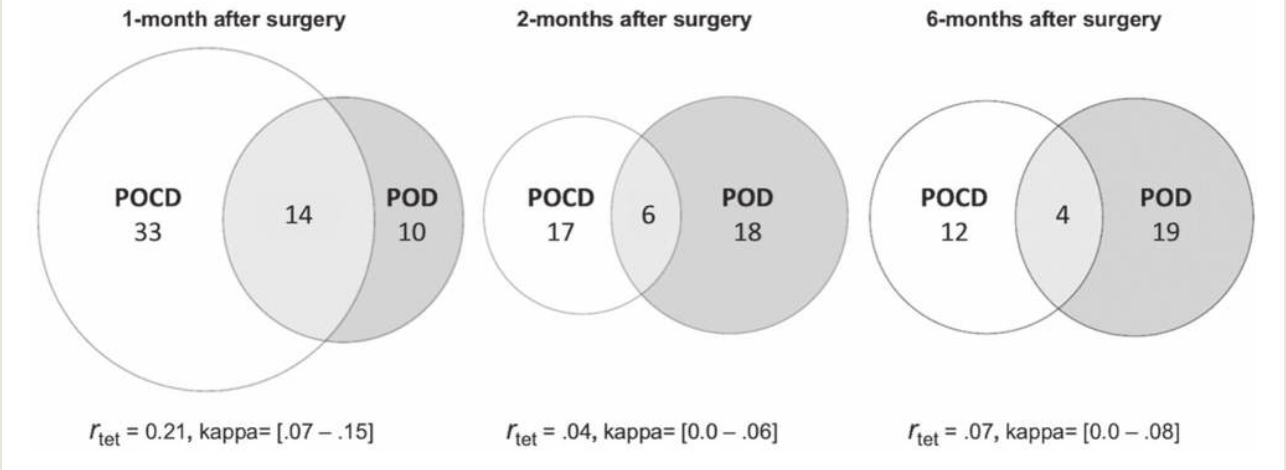

Fig. 1. Incidence of in-hospital postoperative delirium (POD) and postoperative cognitive dysfunction (POCD) during follow-up. Venn diagrams for overlap of POD and POCD at postoperative months 1 (*left*), 2 (*center*), and 6 (*right*). The three circles in each diagram illustrate the relative proportions of patients who (1) met criteria for POCD (*left*) at 1, 2, or 6 months after surgery, (2) developed POD while hospitalized (*right*), and (3) developed in-hospital POD and also met criteria for POCD (*center*) at each follow-up. Tetrachoric correlations (r_{tet}) and kappa coefficients are displayed for each month. Proportions estimated from multiply-imputed data.

Table 4. POCD Definitions and Summary Statistics for Associations with In-hospital POD during 6 Months of Postoperative Follow-up

Component Neuropsychologic Tests*	P(POCD)	*r*	κ	RR (95% CI)	*P*
Month 1					
BNT, Digit Span	0.43	0.13	0.07	1.22 (0.99, 1.50)	.058
Digit Span, Phonemic Fluency	0.49	0.20	0.10	1.30 (1.09, 1.55)	.003
Digit Span, Category Fluency	0.47	0.18	0.09	1.27 (1.06, 1.53)	.010
VSAT, Digit Span	0.46	0.20	0.10	1.32 (1.09, 1.59)	.004
BNT, Phonemic Fluency	0.48	0.20	0.10	1.30 (1.09, 1.56)	.004
Category Fluency, Phonemic Fluency	0.49	0.22	0.11	1.34 (1.13, 1.60)	.001
BNT, Category Fluency	0.43	0.23	0.12	1.39 (1.14, 1.69)	.001
VSAT, BNT	0.45	0.26	0.15	1.44 (1.20, 1.74)	<.001
VSAT, Category Fluency	0.46	0.29	0.15	1.47 (1.23, 1.76)	<.001
VSAT, Phonemic Fluency	0.51	0.24	0.11	1.34 (1.13, 1.58)	.001
Overall (Month 1)†	0.47	0.21	0.11	1.34 (1.08, 1.66)	.008
Month 2					
BNT, Digit Span	0.22	−0.02	−0.01	0.94 (0.65, 1.38)	.769
Digit Span, Phonemic Fluency	0.25	0.05	0.03	1.11 (0.79, 1.55)	.553
Digit Span, Category Fluency	0.24	0.04	0.02	1.08 (0.77, 1.53)	.646
VSAT, Digit Span	0.22	0.02	0.02	1.11 (0.77, 1.60)	.576
BNT, Phonemic Fluency	0.24	0.03	0.02	1.07 (0.76, 1.52)	.688
Category Fluency, Phonemic Fluency	0.24	−0.02	−0.01	0.97 (0.68, 1.38)	.851
BNT, Category Fluency	0.23	0.00	0.00	1.00 (0.70, 1.45)	.983
VSAT, BNT	0.20	0.04	0.02	1.10 (0.74, 1.62)	.636
VSAT, Category Fluency	0.22	0.09	0.05	1.21 (0.85,1.72)	.289
VSAT, Phonemic Fluency	0.22	0.11	0.06	1.29 (0.91, 1.81)	.151
Overall (Month 2)†	0.23	0.04	0.02	1.08 (0.72, 1.63)	.698
Month 6					
BNT, Digit Span	0.15	0.08	0.04	1.21 (0.78, 1.90)	.393
Digit Span, Phonemic Fluency	0.16	0.02	0.08	1.49 (0.98, 2.26)	.063
Digit Span, Category Fluency	0.18	0.04	0.02	1.10 (0.73, 1.67)	.650
VSAT, Digit Span	0.17	0.12	0.06	1.35 (0.91, 2.02)	.140
BNT, Phonemic Fluency	0.13	0.02	0.01	1.05 (0.63, 1.74)	.865
Category Fluency, Phonemic Fluency	0.16	0.15	0.07	1.46 (0.96, 2.22)	.075
BNT, Category Fluency	0.15	0.03	0.01	1.07 (0.67, 1.70)	.780
VSAT, BNT	0.15	−0.02	−0.01	0.95 (0.58, 1.54)	.822
VSAT, Category Fluency	0.18	0.07	0.04	1.20 (0.79, 1.81)	.391
VSAT, Phonemic Fluency	0.18	0.13	0.07	1.36 (0.92, 2.02)	.124
Overall (Month 6)†	0.16	0.07	0.04	1.21 (0.71, 2.08)	.486

Prevalence of POCD [P(POCD)], tetrachoric correlations (*r*), level of agreement, kappa (κ), relative risk (RR) for the association of POD as a risk factor for POCD, and significance level (*P*) for each of the 10 unique subsets of seven component neuropsychologic test variables used to define POCD at Months 1, 2, and 6. Neuropsychologic tests: Visual Search and Attention Test (VSAT); Boston Naming Test (BNT); Digit Symbol, Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Digit Symbol; Digit Span, Wechsler Adult Intelligence Scale (WAIS) Digit Span Forward and Backward; Category Fluency; Phonemic Fluency. POCD, postoperative cognitive dysfunction, proportions estimated from multiply-imputed data; POD, postoperative delirium.

*Each of the POCD definitions includes the following five test variables: Hopkins Verbal Learning Test, revised (HVLT-R), Sum of learning trials, HVLT-R Delayed Recall, Delis–Kaplan Executive Function System (D-KEFS) Trail Making Test (part B time), D-KEFS Trail Making Test (part B errors). †Overall refers to the definition of POCD at each time point estimated from multiply-imputed data.

months, and then remained relatively unchanged (7%, 10 of 140) at 6 months (table A4).

As before, the level of agreement between postoperative delirium and postoperative cognitive dysfunction was poor and correlations remained weak. The risk for postoperative cognitive dysfunction, when postoperative delirium was present, reached statistical significance only at 1 month (relative risk = 1.24; 95% CI, 1.06–1.45; $P = .007$). Results are reported in table A5.

Discussion

Postoperative delirium and postoperative cognitive dysfunction are neurocognitive complications with adverse consequences that may extend far beyond surgical recovery.[4,13] We found that postoperative delirium significantly increased the risk of postoperative cognitive dysfunction, but only in the first month; this relationship did not hold in longer-term follow-up. At each evaluation, postoperative cognitive dysfunction was more common among patients without delirium. These findings may suggest that postoperative delirium and postoperative cognitive dysfunction (variously defined) could be distinct manifestations of neurocognitive deficits, triggered by interactions between surgery, anesthesia, and one or more preoperative vulnerabilities (*e.g.*, inflammation, preclinical Alzheimer neuropathology, blood–brain barrier dysfunction).

The nature of the relationship between postoperative delirium and postoperative cognitive dysfunction is not well characterized.[49,50] Delirium is associated with long-term cognitive decline,[50] an observation that has been

taken to suggest a putative role for postoperative delirium in the pathogenesis of postoperative cognitive dysfunction. Furthermore, delirium has been associated with postoperative cognitive dysfunction in a number of previous studies of cognitive outcomes after noncardiac surgeries[9,51–59]; however, not all used rigorous delirium assessment, sensitive cognitive tests, and consideration of practice effects. A strength of this study is the Successful Aging after Elective Surgery data,[22] which is remarkable for its longitudinal follow-up of more than 500 surgical patients using well-validated delirium measures and a neuropsychologic test battery sensitive to global and domain-specific cognitive change.[60,61]

Others have also reported associations between postoperative delirium and postoperative cognitive dysfunction at hospital discharge or 1 month, but not at later follow-up.[9,57,58] Franck *et al.*[54] only found an association between postoperative delirium and postoperative cognitive dysfunction in a subgroup of participants, and concluded that there was no clear evidence that delirium is independently associated with postoperative cognitive dysfunction beyond 1 week after surgery. Our findings support those of others that suggest a link between postoperative delirium and postoperative cognitive dysfunction in early recovery. However, it is important to recognize that cognitive outcomes in the first postoperative month may be influenced by multiple factors, including waning effects of anesthesia, pain, sleep disturbance, and burden of sedative and analgesic medications.

Absence of associations between postoperative delirium and postoperative cognitive dysfunction beyond the first postoperative month does not contradict the growing appreciation of delirium as a neurotoxic event that precipitates a trajectory of cognitive deterioration. In fact, a number of studies have shown that postoperative delirium is a predictor of progression to dementia and cognitive decline years after surgery.[15,62–65] Moreover, it remains possible that the effects of postoperative delirium and postoperative cognitive dysfunction may converge after 6 months, whereby patients who developed both postoperative delirium and postoperative cognitive dysfunction may experience the greatest long-term cognitive decline.

Another consideration is a potential statistical issue that may have lessened the correlation between postoperative delirium and postoperative cognitive dysfunction. The finding that postoperative cognitive dysfunction and postoperative delirium would show a very low correlation could have been expected considering previous research and the definition of postoperative cognitive dysfunction. Specifically, we have shown that preoperative cognitive functioning is a moderately strong predictor of postoperative delirium and dominates all other risk factors for postoperative delirium with a strong negative polyserial correlation ($r = -.33$).[66] Thus, higher baseline cognitive performance scores are associated with lower risk of postoperative delirium. In contrast, the opposite association might be expected for postoperative cognitive dysfunction using the current definition (based on cognitive change scores) and the phenomena of regression to the mean,[67] which refers to the observation that higher baseline scores are frequently associated with larger (negative) change scores. Regression to the mean would imply, therefore, that high baseline cognitive scores should be associated with greater rates of postoperative cognitive dysfunction (*i.e.*, larger negative change scores) and low baseline cognitive scores should be associated with lower rates of postoperative cognitive dysfunction (*i.e.*, less negative change scores). Taking these observations together, a major risk factor for delirium (baseline cognitive ability) would potentially be inherently associated with lower rates of postoperative cognitive dysfunction (as defined by change scores). As a result, we might expect low or moderately low correlations between these two constructs, all other factors held constant. Our findings of low correlations between postoperative delirium and postoperative cognitive dysfunction may, therefore, reflect a statistical phenomenon rather than absence of an underlying biologic association. Thus, for future work and to advance the field, it may be important to consider alternative methods to defining postoperative cognitive dysfunction that do not induce a correlation between baseline cognitive performance and postoperative cognitive dysfunction (*e.g.*, residualizing follow-up cognitive performance for baseline cognitive performance, rather than computing difference or change scores). This or other more sophisticated methods for modeling change[68] might help to clarify relationships among variables rather than revealing potentially spurious correlations (or their lack thereof) induced by methodology.

We chose to adapt the statistical approach developed by the International Study of Postoperative Cognitive Dysfunction consortium to define postoperative cognitive dysfunction, because these methods (and their variations) have been extensively studied. The use of multiple imputation is an innovative modification that addressed differences in the number and types of cognitive tests used in the International Study of Postoperative Cognitive Dysfunction and Successful Aging after Elective Surgery studies. The number of cognitive test variables is an important determinant of postoperative cognitive dysfunction incidence (as well as the risk of Type 1 error), because the likelihood of detecting postoperative cognitive dysfunction increases with the number of individual tests. The demonstration of consistent associations between postoperative delirium and postoperative cognitive dysfunction at each postoperative timepoint indicates that our construct of postoperative cognitive dysfunction was relatively robust to different combinations of neuropsychologic tests. Furthermore, results of the sensitivity analyses (which used a more permissive postoperative cognitive dysfunction threshold) confirm that the generally weak associations between delirium and postoperative cognitive dysfunction beyond the first month were not a result of "setting the bar too high."

Variability in the timing of cognitive assessments across studies is another frequently cited methodologic challenge in postoperative cognitive dysfunction research; notably, most contemporary postoperative cognitive dysfunction studies have assessed cognition at 3 and 12 months after surgery. Using available data for the Successful Aging after Elective Surgery cohort, our findings (postoperative cognitive dysfunction prevalence: 47% at 1 month, 23% at 2 months, 15% at 6 months) are not inconsistent with those of the few previous studies that reported the incidence of postoperative cognitive dysfunction at one or more of these intervals (*e.g.*, 41% at 2 months, 36% at 3 months, and 24% at 6 months[69] and more recently, 72% at 6 days and 30% at 6 months[70]).

It is important to recognize the recent efforts by the International Perioperative Cognition Nomenclature Working Group to address these and other methodologic challenges, which resulted in a proposal to harmonize criteria for postoperative cognitive dysfunction and establish new nomenclature for conditions related to delayed postsurgical cognitive recovery (*e.g.*, postoperative delirium and postoperative cognitive dysfunction), now termed "postoperative neurocognitive disorders."[47] In many aspects, this study provides support for a number of recommendations in the report.

Several limitations deserve mention. First, we were unable to ascertain delirium that might have occurred, and subsequently resolved, during the interval between hospital discharge and one month. Second, this study was not designed to investigate associations between postoperative delirium, our construct of postoperative cognitive dysfunction, and long-term cognitive recovery. However, Inouye *et al.*[15] recently described the long-term consequences of postoperative delirium in the Successful Aging after Elective Surgery cohort and found that delirium was associated with a 2.8-fold increase in the rate of cognitive decline over three years.[17] Similarly, we were unable to investigate associations between potential risk factors (*e.g.*, age, education, surgery type, complications, delirium severity or subtype) and postoperative cognitive dysfunction incidence or severity; clarifying these complex relationships is an important area of future research. Third, Successful Aging after Elective Surgery participants were nearly a decade older (mean age, 77 yr) than those enrolled in the International Study of Postoperative Cognitive Dysfunction (mean age, 68 yr)[5] and subsequent postoperative cognitive dysfunction studies.[71] The cohort was also relatively cognitively and physically healthy, primarily white, and well-educated; thus, it is possible that our findings may not generalize to other populations. Fourth, it is possible that our negative findings were attributable in part to insufficient sample sizes, which may have limited our ability to detect small effects. However, *post hoc* simulation reveals that if a population correlation between postoperative cognitive dysfunction and postoperative delirium of $r = .50$ (25% shared variance in the tendency to satisfy postoperative cognitive dysfunction and postoperative delirium criteria) exists, the probability of observing a correlation of less than 0.1 in our sample is less than 1 in 10,000. If the association was more modest ($r = .20$, about 4% shared variance in the tendency to satisfy postoperative cognitive dysfunction and postoperative delirium criteria), there is about a 1 in 12 probability of observing a correlation less than $r = 0.1$, given our sample size. Finally, our results may differ from other postoperative cognitive dysfunction studies because we did not log-transform performance data from timed tests.

Delayed or incomplete cognitive recovery complicates recuperation from surgery for many older adults.[72,73] Our results provide evidence for considering postoperative delirium and postoperative cognitive dysfunction as distinct constructs. The finding that postoperative delirium is a significant risk factor for postoperative cognitive dysfunction at 1 month may have clinical implications. At least 40% of delirium cases may be avoidable[6]; consequently, interventions aimed at delirium prevention might also serve to decrease the risk of postoperative cognitive dysfunction. Because postoperative delirium and postoperative cognitive dysfunction may be more strongly related in subpopulations, such as those with multiple comorbidities or preoperative cognitive impairment, studies evaluating factors associated with vulnerabilities for postoperative cognitive dysfunction in the absence of postoperative delirium are needed. Finally, future research should investigate the effects of postoperative delirium, postoperative cognitive dysfunction, and their co-occurrence on functional decline, dementia, and mortality to better understand long-term prognosis for patients with either or both conditions.

Acknowledgments

The authors gratefully acknowledge the contributions of the patients, family members, nurses, physicians, staff members, and members of the Executive Committee who participated in the Successful Aging after Elective Surgery (SAGES) Study (see appendix 1). This work is dedicated to the memory of Joshua Bryan Inouye Helfand and Jane Ann McDowell, R.N., M.S.N.

Research Support

This work was supported by the National Institutes of Health (Bethesda, Maryland) grant Nos. P01AG031720 (to Dr. Inouye), K07AG041835 (to Dr. Inouye), R24AG054259 (to Dr. Inouye), R01AG044518 (to Drs. Inouye and Jones), R01AG030618 (to Dr. Marcantonio), K24AG035075 (to Dr. Marcantonio), and T32AG023480 (to Dr. Racine). Dr. Inouye holds the Milton and Shirley F. Levy Family Chair. The funding sources had no role in the design, conduct, or reporting of this study.

Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Daiello: Alzheimer's Disease and Memory Disorders Center, Rhode Island Hospital, 593 Eddy Street, Providence, Rhode Island 02903. lori_daiello@brown.edu. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

References

1. U.S. Census Bureau PD: Annual Estimates of the Resident Population for Selected Age Groups by Sex for the United States, States, Counties, and Puerto Rico Commonwealth and Municipios: April 1, 2010 to July 1, 2014
2. McDermott K FW, Elixhauser A: Overview of Operating Room Procedures During Inpatient Stays in US Hospitals, 2014: Statistical Brief# 233. In. Rockville, MD: Agency for Healthcare Research and Quality.
3. Kim S, Brooks AK, Groban L: Preoperative assessment of the older surgical patient: Honing in on geriatric syndromes. Clin Interv Aging 2015; 10:13–27
4. Rudolph JL, Marcantonio ER: Review articles: Postoperative delirium: Acute change with long-term implications. Anesth Analg 2011; 112:1202–11
5. Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, Rabbitt P, Jolles J, Larsen K, Hanning CD, Langeron O, Johnson T, Lauven PM, Kristensen PA, Biedler A, van Beem H, Fraidakis O, Silverstein JH, Beneken JE, Gravenstein JS: Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. Lancet 1998; 351:857–61
6. Inouye SK, Westendorp RG, Saczynski JS: Delirium in elderly people. Lancet 2014; 383:911–22
7. Evered L, Scott DA, Silbert B, Maruff P: Postoperative cognitive dysfunction is independent of type of surgery and anesthetic. Anesth Analg 2011; 112:1179–85
8. Meybohm P, Renner J, Broch O, Caliebe D, Albrecht M, Cremer J, Haake N, Scholz J, Zacharowski K, Bein B: Postoperative neurocognitive dysfunction in patients undergoing cardiac surgery after remote ischemic preconditioning: A double-blind randomized controlled pilot study. PLoS One 2013; 8:e64743
9. Monk TG, Weldon BC, Garvan CW, Dede DE, van der Aa MT, Heilman KM, Gravenstein JS: Predictors of cognitive dysfunction after major noncardiac surgery. Anesthesiology 2008; 108:18–30
10. McDonagh DL, Mathew JP, White WD, Phillips-Bute B, Laskowitz DT, Podgoreanu MV, Newman MF; Neurologic Outcome Research Group: Cognitive function after major noncardiac surgery, apolipoprotein E4 genotype, and biomarkers of brain injury. Anesthesiology 2010; 112:852–9
11. Rudolph JL, Schreiber KA, Culley DJ, McGlinchey RE, Crosby G, Levitsky S, Marcantonio ER: Measurement of post-operative cognitive dysfunction after cardiac surgery: A systematic review. Acta Anaesthesiol Scand 2010; 54:663–77
12. Funder KS, Steinmetz J, Rasmussen LS: Cognitive dysfunction after cardiovascular surgery. Minerva Anestesiol 2009; 75:329–32
13. Gross AL, Jones RN, Habtemariam DA, Fong TG, Tommet D, Quach L, Schmitt E, Yap L, Inouye SK: Delirium and long-term cognitive trajectory among persons with dementia. Arch Intern Med 2012; 172:1324–31
14. Saczynski JS, Marcantonio ER, Quach L, Fong TG, Gross A, Inouye SK, Jones RN: Cognitive trajectories after postoperative delirium. N Engl J Med 2012; 367:30–9
15. Inouye SK, Marcantonio ER, Kosar CM, Tommet D, Schmitt EM, Travison TG, Saczynski JS, Ngo LH, Alsop DC, Jones RN: The short-term and long-term relationship between delirium and cognitive trajectory in older surgical patients. Alzheimers Dement 2016; 12:766–75
16. Olofsson B, Persson M, Bellelli G, Morandi A, Gustafson Y, Stenvall M: Development of dementia in patients with femoral neck fracture who experience postoperative delirium: A three-year follow-up study. Int J Geriatr Psychiatry 2018; 33:623–32
17. Kiely DK, Jones RN, Bergmann MA, Murphy KM, Orav EJ, Marcantonio ER: Association between delirium resolution and functional recovery among newly admitted postacute facility patients. J Gerontol A Biol Sci Med Sci 2006; 61:204–8
18. Fong TG, Jones RN, Marcantonio ER, Tommet D, Gross AL, Habtemariam D, Schmitt E, Yap L, Inouye SK: Adverse outcomes after hospitalization and delirium in persons with Alzheimer disease. Ann Intern Med 2012; 156:848–56, W296
19. Devinney MJ, Mathew JP, Berger M: Postoperative delirium and postoperative cognitive dysfunction: Two sides of the same coin? Anesthesiology 2018; 129:389–91
20. Berger M, Terrando N, Smith SK, Browndyke JN, Newman MF, Mathew JP: Neurocognitive function after cardiac surgery: From phenotypes to mechanisms. Anesthesiology 2018; 129:829–51
21. Fong TG, Jones RN, Shi P, Marcantonio ER, Yap L, Rudolph JL, Yang FM, Kiely DK, Inouye SK: Delirium accelerates cognitive decline in Alzheimer disease. Neurology 2009; 72:1570–5
22. Schmitt EM, Marcantonio ER, Alsop DC, Jones RN, Rogers SO Jr, Fong TG, Metzger E, Inouye SK; SAGES Study Group: Novel risk markers and long-term outcomes of delirium: The successful aging after elective surgery (SAGES) study design and methods. J Am Med Dir Assoc 2012; 13:818.e1–10

23. Schmitt EM, Saczynski JS, Kosar CM, Jones RN, Alsop DC, Fong TG, Metzger E, Cooper Z, Marcantonio ER, Travison T, Inouye SK; SAGES Study Group: The Successful Aging after Elective Surgery (SAGES) study: Cohort description and data quality procedures. J Am Geriatr Soc 2015; 63:2463–71
24. Kimchi EY, Hshieh TT, Guo R, Wong B, O'Connor M, Marcantonio ER, Metzger ED, Strauss J, Arnold SE, Inouye SK, Fong TG: Consensus approaches to identify incident dementia in cohort studies: Systematic review and approach in the successful aging after elective surgery study. J Am Med Dir Assoc 2017; 18(12):1010–1018 e1011
25. Teng EL, Chui HC: The Modified Mini-Mental State (3MS) examination. J Clin Psychiatry 1987; 48:314–8
26. Racine AM, Gou Y, Fong TG, Marcantonio ER, Schmitt EM, Travison TG, Inouye SK, Jones RN: Correction for retest effects across repeated measures of cognitive functioning: A longitudinal cohort study of postoperative delirium. BMC Med Res Methodol 2018; 18:69
27. Albert MS, Levkoff SE, Reilly C, Liptzin B, Pilgrim D, Cleary PD, Evans D, Rowe JW: The delirium symptom interview: An interview for the detection of delirium symptoms in hospitalized patients. J Geriatr Psychiatry Neurol 1992; 5:14–21
28. Saczynski JS, Kosar CM, Xu G, Puelle MR, Schmitt E, Jones RN, Marcantonio ER, Wong B, Isaza I, Inouye SK: A tale of two methods: Chart and interview methods for identifying delirium. J Am Geriatr Soc 2014; 62:518–24
29. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI: Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med 1990; 113:941–8
30. Inouye SK, Leo-Summers L, Zhang Y, Bogardus ST Jr, Leslie DL, Agostini JV: A chart-based method for identification of delirium: validation compared with interviewer ratings using the confusion assessment method. J Am Geriatr Soc 2005; 53:312–8
31. Shapiro AM, Benedict RH, Schretlen D, Brandt J: Construct and concurrent validity of the Hopkins Verbal Learning Test-revised. Clin Neuropsychol 1999; 13:348–58
32. Wechsler DS: Manual for the Wechsler Adult Intelligence Scale —Revised. New York, Psychological Corporation, 1981
33. Benton A H, K. de S: Multilingual Aphasia Examination: Manual Instructions. Iowa City, University of Iowa, 1989
34. Benton AL: Differential behavioural effects in frontal lobe disease Neuropsychologica. 1968; 6:53–60
35. Goodglass HK: The Assessment of Aphasia and Related Disorders. 2nd edition. Philadelphia, Lea & Febiger, 1983
36. Trenerry MR, Crosson B, DeBoe J, Leber WR: Visual Search and Attention Test. Odessa, FL, Psychological Assessment Resources, 1990
37. Delis DC, Kaplan E, Kramer JH: Delis-Kaplan Executive Function System. San Antonio, TX, The Psychological Corporation, 2001
38. Randolph C, Tierney MC, Mohr E, Chase TN: The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): Preliminary clinical validity. J Clin Exp Neuropsychol 1998; 20:310–9
39. Jones RN, Rudolph JL, Inouye SK, Yang FM, Fong TG, Milberg WP, Tommet D, Metzger ED, Cupples LA, Marcantonio ER: Development of a unidimensional composite measure of neuropsychological functioning in older cardiac surgery patients with good measurement precision. J Clin Exp Neuropsychol 2010; 32(10):1041–9
40. Gross AL, Jones RN, Fong TG, Tommet D, Inouye SK: Calibration and validation of an innovative approach for estimating general cognitive performance. Neuroepidemiology 2014; 42:144–53
41. Rey A: Psychological examination in cases of traumatic encephalopathy [in French]. Archives de Psychologie 1941; 28:215–85
42. Reitan RM: The relation of the trail making test to organic brain damage. J Consult Psychol 1955; 19:393–4
43. Bohnen N, Twijnstra A, Jolles J: Performance in the Stroop color word test in relationship to the persistence of symptoms following mild head injury. Acta Neurol Scand 1992; 85:116–21
44. Lezak M: Neuropsychological Assessment. 3rd edition. New York, Oxford University Press, 1995
45. Krenk L, Rasmussen LS, Siersma VD, Kehlet H: Short-term practice effects and variability in cognitive testing in a healthy elderly population. Exp Gerontol 2012; 47:432–6
46. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, Wood AM, Carpenter JR: Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 2009; 338:b2393
47. Evered L, Silbert B, Knopman DS, Scott DA, DeKosky ST, Rasmussen LS, Oh ES, Crosby G, Berger M, Eckenhoff RG; Nomenclature Consensus Working Group: Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery-2018. Br J Anaesth 2018; 121:1005–12
48. Fleiss J: Statistical Methods for Rates and Proportions. New York, John Wiley & Sons, 2000
49. Silverstein JH, Deiner SG: Perioperative delirium and its relationship to dementia. Prog Neuropsychopharmacol Biol Psychiatry 2013; 43:108–15
50. MacLullich AM, Beaglehole A, Hall RJ, Meagher DJ: Delirium and long-term cognitive impairment. Int Rev Psychiatry 2009; 21:30–42
51. Beishuizen SJE, van Munster BC, de Jonghe A, Abu-Hanna A, Buurman BM, de Rooij SE: Distinct

cognitive trajectories in the first year after hip fracture. J Am Geriatr Soc 2017; 65:1034–42
52. Bryson GL, Wyand A, Wozny D, Rees L, Taljaard M, Nathan H: A prospective cohort study evaluating associations among delirium, postoperative cognitive dysfunction, and apolipoprotein E genotype following open aortic repair. Can J Anaesth 2011; 58:246–55
53. Benoit AG, Campbell BI, Tanner JR, Staley JD, Wallbridge HR, Biehl DR, Bradley BD, Louridas G, Guzman RP, Fromm RA: Risk factors and prevalence of perioperative cognitive dysfunction in abdominal aneurysm patients. J Vasc Surg 2005; 42:884–90
54. Franck M, Nerlich K, Neuner B, Schlattmann P, Brockhaus WR, Spies CD, Radtke FM: No convincing association between post-operative delirium and post-operative cognitive dysfunction: A secondary analysis. Acta Anaesthesiol Scand 2016; 60:1404–14
55. Neufeld KJ, Leoutsakos JM, Sieber FE, Wanamaker BL, Gibson Chambers JJ, Rao V, Schretlen DJ, Needham DM: Outcomes of early delirium diagnosis after general anesthesia in the elderly. Anesth Analg 2013; 117:471–8
56. Radtke FM, Franck M, Lendner J, Krüger S, Wernecke KD, Spies CD: Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction. Br J Anaesth 2013; 110 Suppl 1:i98–105
57. Rudolph JL, Marcantonio ER, Culley DJ, Silverstein JH, Rasmussen LS, Crosby GJ, Inouye SK: Delirium is associated with early postoperative cognitive dysfunction. Anaesthesia 2008; 63:941–7
58. Sauër AC, Veldhuijzen DS, Ottens TH, Slooter AJC, Kalkman CJ, van Dijk D: Association between delirium and cognitive change after cardiac surgery. Br J Anaesth 2017; 119:308–15
59. Krogseth M, Watne LO, Juliebø V, Skovlund E, Engedal K, Frihagen F, Wyller TB: Delirium is a risk factor for further cognitive decline in cognitively impaired hip fracture patients. Arch Gerontol Geriatr 2016; 64:38–44
60. Price CC, Garvan CW, Monk TG: Type and severity of cognitive decline in older adults after noncardiac surgery. Anesthesiology 2008; 108:8–17
61. Price CC, Tanner JJ, Schmalfuss I, Garvan CW, Gearen P, Dickey D, Heilman K, McDonagh DL, Libon DJ, Leonard C, Bowers D, Monk TG: A pilot study evaluating presurgery neuroanatomical biomarkers for postoperative cognitive decline after total knee arthroplasty in older adults. Anesthesiology 2014; 120:601–13
62. Fong TG, Davis D, Growdon ME, Albuquerque A, Inouye SK: The interface between delirium and dementia in elderly adults. Lancet Neurol 2015; 14:823–32
63. Davis DH, Muniz-Terrera G, Keage HA, Stephan BC, Fleming J, Ince PG, Matthews FE, Cunningham C, Ely EW, MacLullich AM, Brayne C; Epidemiological Clinicopathological Studies in Europe (EClipSE) Collaborative Members: Association of delirium with cognitive decline in late life: A neuropathologic study of 3 population-based cohort studies. JAMA Psychiatry 2017; 74:244–51
64. Devore EE, Fong TG, Marcantonio ER, Schmitt EM, Travison TG, Jones RN, Inouye SK: Prediction of long-term cognitive decline following postoperative delirium in older adults. J Gerontol A Biol Sci Med Sci 2017; 72:1697–702
65. Kat MG, Vreeswijk R, de Jonghe JF, van der Ploeg T, van Gool WA, Eikelenboom P, Kalisvaart KJ: Long-term cognitive outcome of delirium in elderly hip surgery patients: A prospective matched controlled study over two and a half years. Dement Geriatr Cogn Disord 2008; 26:1–8
66. Jones RN, Marcantonio ER, Saczynski JS, Tommet D, Gross AL, Travison TG, Alsop DC, Schmitt EM, Fong TG, Cizginer S, Shafi MM, Pascual-Leone A, Inouye SK: Preoperative cognitive performance dominates risk for delirium among older adults. J Geriatr Psychiatry Neurol 2016; 29:320–7
67. Rogosa D: Myths about longitudinal research, Methodological Issues in Aging Research. Edited by Schaie KC, Meredith, W, Rawlings, S. New York, Springer Publishing Company, 1988, pp 177–209
68. Castro-Schilo L G, K. J: Using residualized change versus difference scores for longitudinal research. Journal of Social and Personal Relationships 2018;35(1):32–58
69. Abildstrom H, Christiansen M, Siersma VD, Rasmussen LS; ISPOCD2 Investigators: Apolipoprotein E genotype and cognitive dysfunction after noncardiac surgery. Anesthesiology 2004; 101:855–61
70. Deo H, West G, Butcher C, Lewis P: The prevalence of cognitive dysfunction after conventional and computer-assisted total knee replacement. Knee 2011; 18:117–20
71. Paredes S, Cortínez L, Contreras V, Silbert B: Postoperative cognitive dysfunction at 3 months in adults after non-cardiac surgery: A qualitative systematic review. Acta Anaesthesiol Scand 2016; 60:1043–58
72. Gleason LJ, Schmitt EM, Kosar CM, Tabloski P, Saczynski JS, Robinson T, Cooper Z, Rogers SO Jr, Jones RN, Marcantonio ER, Inouye SK: Effect of delirium and other major complications on outcomes after elective surgery in older adults. JAMA Surg 2015; 150:1134–40
73. Berger M, Nadler JW, Browndyke J, Terrando N, Ponnusamy V, Cohen HJ, Whitson HE, Mathew JP: Postoperative cognitive dysfunction: Minding the gaps in our knowledge of a common postoperative complication in the elderly. Anesthesiol Clin 2015; 33:517–50

Appendix 1: The Successful Aging after Elective Surgery (SAGES) Study Group

Overall Principal Investigator: Sharon K. Inouye, M.D., M.P.H.
Project and Core Leaders: David Alsop, Ph.D.; Richard Jones; Thomas Travison, Ph.D.; Edward R. Marcantonio, M.D., S.M.
Executive Committee: Steven Arnold, M.D.; Zara Cooper, M.D., M.Sc.; Bradford Dickerson, M.D.; Tamara Fong, M.D., Ph.D.; Eran Metzger, M.D.; Alvaro Pascual-Leone, M.D.; Eva M. Schmitt, Ph.D.; Mouhsin Shafi, M.D.
Other Co-investigators: Michele Cavallari, M.D., Ph.D.; Weiying Dai, Ph.D.; Simon T. Dillon, Ph.D.; Janet McElhaney, M.D.; Charles Guttmann, M.D.; Tammy Hshieh, M.D.; George Kuchel, M.D., F.R.C.P.; Towia Libermann, Ph.D.; Long Ngo, Ph.D.; Daniel Press, M.D.; Jane Saczynski, Ph.D.; Sarinnapha Vasunilashorn, Ph.D.
Clinical Consensus Panel: Margaret O'Connor, Ph.D.; Eyal Kimchi, M.D., Jason Strauss, M.D.; Bonnie Wong, Ph.D.
Surgical Leaders: Michael Belkin, M.D.; Douglas Ayres, M.D.; Mark Callery, M.D.; Frank Pomposelli, M.D.; John Wright, M.D.; Marc Schermerhorn, M.D.
Epidemiology Core: Tatiana Abrantes; Asha Albuquerque; Sylvie Bertrand; Amanda Brown, M.Ed.; Amy Callahan; Madeline D'Aquila, B.S.; Sarah Dowal, M.S.W., L.C.S.W., M.P.H.; Meaghan Fox, B.S.; Jacqueline Gallagher, M.S.; Rebecca Anna Gersten, M.D.; Ariel Hodara, R.N.; Ben Helfand, M.P.H.; Jennifer Inloes, B.S.; Jennifer Kettell; Aleksandra Kuczmarska, A.B.; Jacqueline Nee, B.A.; Emese Nemeth, B.S.; Lisa Ochsner; Kerry Palihnich, B.A.; Katelyn Parisi, B.A.; Margaret Puelle, M.D.; Sarah Rastegar, MA; Margaret Vella, B.S., Guoquan Xu, M.D., Ph.D.
Data Management and Statistical Analysis Core: Margaret Bryan, B.A.; Jamey Guess, M.S.; Dee Enghorn; Alden Gross, Ph.D., M.H.S.; Yun Gou, M.A.; Daniel Habtemariam, B.A.; Ilean Isaza, Ph.D.; Cyrus Kosar, M.A.; Christopher Rockett, Ph.D.; Douglas Tommet, M.P.H.
Fiscal Management Committee: Ted Gruen, B.A., M.B.A.; Meg Ross; Katherine Tasker, B.A.
Scientific Advisory Board: James Gee, Ph.D.; Ann Kolanowski, Ph.D., R.N., F.A.A.N.; Margaret Pisani, M.D., M.P.H.; Sophia de Rooij, M.D., Ph.D.; Selwyn Rogers, M.D., M.P.H.; Stephanie Studenski, M.D.; Yaakov Stern, Ph.D.; Anthony Whittemore, M.D.
Internal Advisory Board: Gary Gottlieb, M.D., M.B.A.; John Orav, Ph.D.; Reisa Sperling, M.D., M.M.Sc.

Appendix 2

The information below is provided for transparency about study participants both in the primary cohort study, Successful Aging after Elective Surgery (figure A1, table A1), and a nonsurgical comparison cohort that was recruited for assessment of retest and practice effects (table A1). Table A2 describes results from the secondary analysis of postoperative cognitive dysfunction concordance across timepoints. Association of in-hospital postoperative delirium with persistent postoperative cognitive dysfunction is shown in table A3. Detailed results of sensitivity analyses in which the threshold for postoperative cognitive dysfunction was redefined as (1) z scores for two or more individual tests at or below −1.0 or (2) the sum of the seven z scores at or below −1.0 are presented in tables A3 and A4.

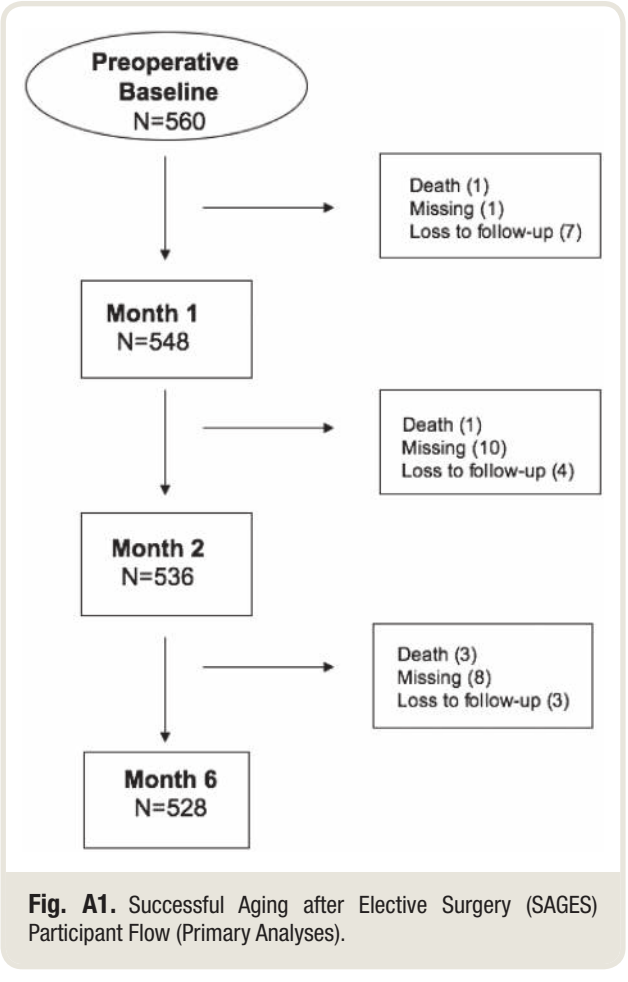

Fig. A1. Successful Aging after Elective Surgery (SAGES) Participant Flow (Primary Analyses).

Table A1. Selected Baseline Characteristics of the Successful Aging after Elective Surgery Surgical Patients and Nonsurgical Control Group

Characteristic	Full SAGES (Surgical) Sample N = 560	Nonsurgical Control Group N = 118
Age, mean yr ± SD	77 ± 5	77 ± 5
Female, n (%)	326 (58)	52 (44)
Nonwhite, n (%)	42 (8)	16 (13)
Education, mean yr ± SD	15 ± 3	16 ± 3
GCP score, mean ± SD	57.6 ± 7.3	58.0 ± 9.8
3MS score, mean ± SD	93.5 ± 5.4	93.8 ± 5.4

GCP, General Cognitive Performance; 3MS, Modified Mini-Mental State Exam, range (0–100), lower scores indicate greater impairment; SAGES, Successful Aging after Elective Surgery.

Table A3. Association of In-hospital POD with Persistent POCD*

	POCD at 1 & 2 months (N = 535)		
POD, n (%)	No POCD	POCD	Total
No POD	308 (57.5)	48 (9.0)	356 (66.5)
POD	151 (28.3)	28 (5.2)	179 (33.5)
Total	459 (85.8)	76 (14.2)	535 (100)
	OR = 1.30; 95% CI, 0.99–1.70; $p = .062$		

	POCD at 1, 2 & 6 months (N = 522)		
POD	No POCD	POCD	Total
No POD	327 (62.6)	19 (3.7)	346 (66.3)
POD	166 (31.8)	10 (1.9)	176 (33.7)
Total	493 (94.4)	29 (5.6)	522 (100)
	OR = 1.08; 95% CI, 0.70–1.66; $p = .744$		

*Proportion with POCD was estimated from multiply-imputed data for all participants with complete neuropsychologic test data at each time point

OR, odds ratio; POCD, postoperative cognitive dysfunction; POD, postoperative delirium.

Table A2. Concordance of POCD across Timepoints

	POCD at 2 months (N = 535)		
POCD at 1 month, n (%)	No POCD	POCD	Total
No POCD	265 (49.5)	30 (5.6)	295 (55.1)
POCD	164 (30.7)	76 (14.2)	240 (44.9)
Total	429 (80.2)	106 (19.8)	535 (100)

	POCD at 6 months (N = 525)		
POCD at 1 month	No POCD	POCD	Total
No POCD	268 (51.1)	23 (4.3)	291 (55.4)
POCD	177 (33.7)	57 (10.9)	234 (44.6)
Total	445 (84.8)	80 (15.2)	525 (100)

	POCD at 6 months (N = 523)		
POCD at 2 months	No POCD	POCD	Total
No POCD	381 (72.9)	42 (8.0)	423 (80.9)
POCD	62 (11.8)	38 (7.3)	100 (19.1)
Total	443 (84.7)	80 (15.3)	523 (100)

	POCD at 6 months (N = 522)		
POCD at 1 and 2 months	No POCD	POCD	Total
No POCD	398 (76.3)	51 (9.7)	449 (86.0)
POCD	44 (8.4)	29 (5.6)	73 (14.0)
Total	442 (84.7)	80 (15.3)	522 (100)

POCD, postoperative cognitive dysfunction.

Table A4. Proportions of In-hospital POD and POCD during Follow-up* Using Threshold of 1 SD Decline to Define POCD

	POCD		Total
In-hospital delirium and 1-month POCD (N = 548)			
In-hospital delirium, n (%)	No	Yes	
No	181 (33.1)	238 (43.5)	419 (76.6)
Yes	38 (6.9)	90 (16.5)	128 (23.4)
Total	219 (40.0)	328 (60.0)	547 (100)
In-hospital delirium and 2-month POCD (N = 536)			
In-hospital delirium	No	Yes	
No	262 (48.8)	149 (27.7)	411 (76.5)
Yes	82 (15.3)	43 (8.2)	125 (23.5)
Total	344 (64.1)	192 (35.9)	536 (100)
In-hospital delirium and 6-month POCD (N = 528)			
In-hospital delirium	No	Yes	
No	302 (57.1)	103 (19.6)	405 (76.7)
Yes	84 (16)	39 (7.3)	123 (23.3)
Total	386 (73.1)	142 (26.9)	528 (100)

*Proportion with POCD was estimated from multiply-imputed data for all participants with complete neuropsychologic test data at each time point.

POCD, postoperative cognitive dysfunction; POD, postoperative delirium.

Table A5. POCD Definitions and Summary Statistics for Associations with In-hospital POD during 6 Months of Postoperative Follow-up, Using Threshold of 1 SD Decline to Define POCD

Component Neuropsychologic Tests*	P(POCD)	*r*	κ	RR (95% CI)	*P*
Month 1					
BNT, Digit Span	0.58	0.16	0.07	1.19 (1.02–1.39)	0.025
Digit Span, Phonemic Fluency	0.62	0.20	0.08	1.21 (1.06–1.38)	0.006
Digit Span, Category Fluency	0.59	0.21	0.09	1.24 (1.07–1.43)	0.003
VSAT, Digit Span	0.61	0.19	0.08	1.22 (1.06–1.40)	0.006
BNT, Phonemic Fluency	0.60	0.23	0.10	1.27 (1.10–1.46)	0.001
Category Fluency, Phonemic Fluency	0.63	0.22	0.09	1.24 (1.08–1.41)	0.002
BNT, Category Fluency	0.56	0.17	0.07	1.21 (1.03–1.41)	0.018
VSAT, BNT	0.58	0.26	0.11	1.32 (1.14–1.51)	0.000
VSAT, Category Fluency	0.59	0.27	0.11	1.32 (1.15–1.52)	0.000
VSAT, Phonemic Fluency	0.65	0.22	0.08	1.22 (1.08–1.39)	0.002
Overall (Month 1)†	0.60	0.21	0.09	1.24 (1.06–1.45)	0.007
Month 2					
BNT, Digit Span	0.35	–0.06	–0.03	0.90 (0.68–1.19)	0.443
Digit Span, Phonemic Fluency	0.38	–0.06	–0.03	0.91 (0.68–1.18)	0.471
Digit Span, Category Fluency	0.38	–0.07	–0.04	0.89 (0.67–1.16)	0.381
VSAT, Digit Span	0.34	–0.07	–0.04	0.88 (0.65–1.17)	0.371
BNT, Phonemic Fluency	0.36	–0.01	–0.01	0.97 (0.74–1.28)	0.849
Category Fluency, Phonemic Fluency	0.39	0.00	0.00	1.00 (0.78–1.29)	0.983
BNT, Category Fluency	0.36	–0.04	–0.02	0.93 (0.70–1.22)	0.586
VSAT, BNT	0.33	0.00	0.00	1.00 (0.75–1.33)	0.976
VSAT, Category Fluency	0.36	0.05	0.03	1.09 (0.84–1.42)	0.505
VSAT, Phonemic Fluency	0.35	0.07	0.04	1.14 (0.88–1.47)	0.321
Overall (Month 2)†	0.36	–0.02	–0.01	0.97 (0.69–1.34)	0.835
Month 6					
BNT, Digit Span	0.26	0.11	0.06	1.25 (0.91–1.71)	0.167
Digit Span, Phonemic Fluency	0.28	0.08	0.04	1.17 (0.86–1.59)	0.331
Digit Span, Category Fluency	0.28	0.03	0.01	1.06 (0.77–1.45)	0.737
VSAT, Digit Span	0.27	0.08	0.04	1.17 (0.85–1.60)	0.335
BNT, Phonemic Fluency	0.25	0.14	0.08	1.34 (0.98–1.85)	0.071
Category Fluency, Phonemic Fluency	0.28	0.05	0.03	1.11 (0.81–1.53)	0.497
BNT, Category Fluency	0.27	0.13	0.07	1.31 (0.97–1.77)	0.081
VSAT, BNT	0.26	0.18	0.10	1.43 (1.05–1.95)	0.022
VSAT, Category Fluency	0.27	0.10	0.05	1.22 (0.90–1.66)	0.205
VSAT, Phonemic Fluency	0.28	0.15	0.08	1.34 (1.00–1.80)	0.054
Overall (Month 6)†	0.27	0.11	0.05	1.23 (0.86–1.78)	0.259

Prevalence of POCD [P(POCD)], tetrachoric correlations (*r*), level of agreement, kappa (κ), relative risk (RR) for the association of POD as a risk factor for POCD, and significance level (*P*) for each of the unique subsets of seven component neuropsychologic test variables used to define POCD in the SAGES cohort. Neuropsychologic tests: Visual Search and Attention Test (VSAT); Boston Naming Test (BNT); Digit Symbol, Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Digit Symbol; Digit Span, Wechsler Adult Intelligence Scale (WAIS) Digit Span Forward and Backward; Category Fluency; Phonemic Fluency. POCD, postoperative cognitive dysfunction, proportions estimated from multiply-imputed data; POD, postoperative delirium; SAGES, Successful Aging after Elective Surgery.

*Each of the ten POCD definitions includes the following five test variables: Hopkins Verbal Learning Test, revised (HVLT-R) Sum of learning trials, HVLT-R Delayed Recall, Delis–Kaplan Executive Function System (D-KEFS) Trail Making Test (part B time), D-KEFS Trail Making Test (part B errors). †Overall refers to the definition of POCD at each time point estimated from multiply-imputed data.