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Surgery and Anesthesia Exposure Is Not a Risk Factor for Cognitive Impairment After Major Noncardiac Surgery and Critical Illness

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Abstract

Objective—The aim of this study was to determine whether surgery and anesthesia exposure is an independent risk factor for cognitive impairment after major noncardiac surgery associated with critical illness.

Summary of Background Data—Postoperative cognitive impairment is a prevalent individual and public health problem. Data are inconclusive as to whether this impairment is attributable to surgery and anesthesia exposure versus patients' baseline factors and hospital course.

Methods—In a multicenter prospective cohort study, we enrolled ICU patients with major noncardiac surgery during hospital admission and with nonsurgical medical illness. At 3 and 12 months, we assessed survivors' global cognitive function with the Repeatable Battery for the Assessment of Neuropsychological Status and executive function with the Trail Making Test, Part B. We performed multivariable linear regression to study the independent association of surgery/anesthesia exposure with cognitive outcomes, adjusting initially for baseline covariates and subsequently for in-hospital covariates.

Results—We enrolled 1040 patients, 402 (39%) with surgery/anesthesia exposure. Median global cognition scores were similar in patients with surgery/anesthesia exposure compared with those without exposure at 3 months (79 vs 80) and 12 months (82 vs 82). Median executive function scores were also similar at 3 months (41 vs 40) and 12 months (43 vs 42). Surgery/anesthesia exposure was not associated with worse global cognition or executive function at 3 or 12 months in models incorporating baseline or in-hospital covariates ($P > 0.2$). Higher baseline education level was associated with better global cognition at 3 and 12 months ($P < 0.001$), and longer in-hospital delirium duration was associated with worse global cognition ($P < 0.02$) and executive function ($P < 0.01$) at 3 and 12 months.

Conclusions—Cognitive impairment after major noncardiac surgery and critical illness is not associated with the surgery and anesthesia exposure but is predicted by baseline education level and in-hospital delirium.

Keywords

anesthesia; cognition; delirium; executive function; surgery

Cognitive impairment after surgery and anesthesia—termed postoperative cognitive dysfunction (POCD)—is an individual and public health problem associated with increased mortality and decreased employment.^{1–8} Nevertheless, the characteristics and the magnitude of this cognitive impairment have been difficult to describe given the varied neuropsychological tests used in prior studies. Moreover, the lack of comparative cognitive outcomes data from patients who undergo surgery compared with those who do not, as well as to those with disease states such as traumatic brain injury (TBI), vascular dementia, and Alzheimer disease (AD), prevents placing this cognitive impairment after surgery and anesthesia into clinical context.

Age, education level, and pre-existing cognitive deficits have been shown to be associated with cognitive impairment after anesthesia and surgery,^{6,9,10} and some studies have shown that surgical and anesthetic factors may also play a role.^{6,11,12} Additional studies, however, have called this into question. For instance, cognitive outcomes are similar after invasive surgery requiring general anesthesia versus those performed under regional anesthesia^{8,13,14} or even percutaneous procedures requiring moderate sedation.^{15–17} Cognitive outcomes after coronary artery bypass grafting are similar to or improved from baseline¹⁸ and similar to those with coronary artery disease managed medically.¹⁹ Furthermore, reducing depth of anesthesia does not affect the incidence of cognitive impairment after surgery.²⁰ Thus, it is unclear whether exposure to surgery and anesthesia plays an independent role or whether this cognitive impairment is secondary to preexisting patient comorbidities or events during the hospital course. Most studies to date have focused on cardiac or elective joint replacement surgeries, have not utilized medical illness comparator groups, or have not examined significant postoperative factors such as delirium, which was recently shown to be associated with worse cognitive impairment up to a year after cardiac surgery.²¹

We hypothesized that exposure to surgery and anesthesia would not be associated with cognitive impairment in patients undergoing major noncardiac surgery. We performed a prospective cohort study of patients admitted to the intensive care unit (ICU) who underwent major noncardiac surgical procedures during their hospital admission and patients admitted to the ICU with nonsurgical medical illness, evaluating them for cognitive impairment 3 and 12 months after discharge. We tested the independent associations of exposure to surgery and anesthesia (yes/no) and increasing level of that exposure with cognitive impairment, adjusting for baseline and in-hospital factors.

METHODS

Study Design and Population

This prospective cohort study is a combined investigation of the MIND-ICU Study: Delirium and Dementia in Veterans Surviving ICU Care study (NCT00400062) conducted at the Tennessee Valley Healthcare System (Nashville, TN), George E. Wahlen Department of

VA Medical Center in VA Salt Lake City Health Care System (Salt Lake City, UT), and Seattle Division of the VA Puget Sound Health Care System (Seattle, WA) and the parallel (identical protocol) Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors (BRAIN-ICU)²² study (NCT00392795) conducted at Vanderbilt University Medical Center and Saint Thomas Hospital (both Nashville, TN). Results from the BRAIN-ICU study have been previously reported.^{22,23} The hypotheses tested in this larger combined cohort are original and have not been previously published.

The study protocol was approved by each institution's review board. We enrolled adult patients in respiratory failure or shock, including after major surgical procedures and nonsurgical medical illnesses, as previously described.^{22,23} We excluded patients with recent critical illness, moribund state, inability to perform delirium assessments, high likelihood of preexisting cognitive deficits, admission for stroke or neurological surgery, limited outpatient follow-up opportunity, and inability to obtain informed consent. See Supplemental Digital Content, <http://links.lww.com/SLA/B51> for further details.

Exposures

Our primary independent variable was surgery requiring general anesthesia in an operating room, which was determined by daily review of the medical record and prospectively collected. As general anesthesia and surgery occur together, we labeled the independent variable as "surgery/anesthesia exposure." Patients who had surgery with general anesthesia at any point during their current hospital admission before enrollment or within any time between enrollment and 30 days postenrollment were considered to have surgery/anesthesia exposure, irrespective of whether they were admitted to a medical or surgical ICU. In a subset of patients with surgery/anesthesia exposure, more robust data were obtained, including number of surgeries (total trips to the operating room while in the hospital), emergent surgery (yes/no), and total duration of anesthesia (sum of individual anesthetic exposures if more than 1) in order to test the relationship between increasing surgery/anesthesia exposure and outcomes.

Outcomes

At 3 and 12 months after hospital discharge, trained psychology professionals who were blinded to hospital course and surgery status assessed patients' global cognitive function with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS),²⁴ a validated neuropsychometric battery that measures domains of memory (immediate and delayed), visuospatial construction, language, and attention. The RBANS has a mean (standard deviation) population age-adjusted score of 100 ± 15 with lower scores indicating worse global cognitive function. The RBANS has also been validated in patients with TBI²⁵ and mild AD,²⁴ with mean scores of 78 and 70 in these populations, respectively. The RBANS domain scores have further been validated to differentiate between cortical dementias (such as AD) and subcortical dementias (vascular dementias, Huntington dementia), acknowledging the potential limitations of such a categorization approach.^{24,26,27} A single cortical-subcortical deviation score is calculated by subtracting the mean of the delayed memory index and the language index from the mean of the attention index and the visuospatial constructional index.^{24,26,27} Patients with cognitive impairment and a score >0

are considered to have cortical dementias, and those patients with a score <0 have subcortical dementias. In addition to global cognitive function, executive function was assessed with the Trail Making Test, Part B (Trails B),²⁸ a validated tool that examines cognitive flexibility and set shifting. The Trails B has an age-, sex-, and education- adjusted mean score of 50 ± 10 with lower scores indicating worse executive function.

Confounders

We collected demographic data upon enrollment and hospital course data from admission to 30 days after enrollment. We chose a priori potential confounders of the association between surgery/ anesthesia exposure and cognitive impairment on the basis of previous research and clinical judgment. Baseline confounders included age, years of education, comorbid disease burden with the Charlson comorbidity index, cerebrovascular disease with the Framingham stroke risk score, and pre-existing cognitive deficit with the Short Form Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE-SF)²⁹ score. The IQCODE-SF has a sensitivity >0.80 to identify mild cognitive impairment^{30,31} and >0.90 to identify adults at risk of dementia, including in the hospital.³² In-hospital confounders included duration of coma, duration of delirium, duration of severe sepsis, duration of hypoxemia, severity of illness with the Sequential Organ Failure Assessment Score, analgesic exposure, sedative exposure, and antipsychotic exposure. See Supplemental Digital Content, <http://links.lww.com/SLA/B51> for further details.

Statistical Analysis

We used multivariable linear regression to determine whether surgery/anesthesia exposure (yes/no) was independently associated with the primary outcome variables (RBANS and Trails B scores at 3 and 12 months). Among our entire cohort, we first evaluated surgery/ anesthesia exposure (yes/no) on cognitive outcomes adjusting for baseline covariates alone. We then performed linear regression analysis that included in-hospital covariates in addition to baseline covariates to determine the predictors of cognitive impairment. We included pre-defined interactions between surgery/anesthesia exposure and education and duration of delirium as well as an interaction between durations of delirium and coma. Finally, in the subset of surgical patients with robust details regarding their surgery/anesthesia exposure, we performed multivariable regression to examine whether having a higher number of surgeries, emergent surgery, and/or a longer total duration of anesthesia was associated with cognitive outcomes, accounting for baseline covariates.

In all models, continuous variables were modeled with the use of restricted cubic splines to allow for nonlinear associations (with the exception of dexmedetomidine and haloperidol doses; due to infrequent use of these medications, there were too few unique doses to allow splines). In order to reduce bias from missing data, we used multiple imputation in our analyses to include in our analyses any patient who had some missing covariates or who had at least partially completed cognitive assessments. No imputations were performed for completely missing cognitive assessments. Overall, imputed data were utilized in $<7\%$ of subjects at 3 months and $<5\%$ of subjects at 12 months (see Supplemental Digital Content, <http://links.lww.com/SLA/B51>). We used R version 3.1.2 (<https://www.r-project.org/>) for all

statistical analyses and considered $P < 0.05$ as statistical significance for independent variables.

RESULTS

Between March 2007 and May 2010, we enrolled 1046 patients (Supplemental Figure 1, <http://links.lww.com/SLA/B51>); 6 patients withdrew consent and requested data destruction. Thus, we included 1040 patients with a median (interquartile range) age of 62 (53 to 72) years and a high severity of illness (Table 1), 402 (39%) with surgery/anesthesia exposure, and 638 without exposure. After accounting for death, loss to follow-up, and withdrawal, 534 patients had cognitive testing at 3 and/or 12 months (Supplemental Figure 1, <http://links.lww.com/SLA/B51>), 219 (41%) with surgery/anesthesia exposure, and 315 without exposure.

Median RBANS global cognition scores were similar among patients with surgery/anesthesia exposure and among those without exposure [79 (71, 86) vs 80 (70, 87) at 3 months; 82 (72, 90) vs 82 (73, 90) at 12 months], approximately 1.5 standard deviations below adjusted population mean, a level indicative of significant cognitive impairment (Fig. 1). Among the patients with surgery/anesthesia exposure, 44% and 35% earned scores below those typical of patients with TBI at 3 and 12 months, respectively (39% and 35% in the group without exposure). Furthermore, 24% and 23% scored below those typical of patients with AD at 3 and 12 months (25% and 21% in those without exposure). Among all patients with scores indicative of cognitive impairment (< 78 on RBANS; 1.5 standard deviation below population mean), cortical-subcortical deviation score distribution was similar in patients with surgery/anesthesia exposure and in those without exposure (73% vs 74% had RBANS cortical-subcortical deviation scores < 0 , displaying a subcortical pattern as seen in vascular dementia, at 3 months; 69% vs 63% had scores indicative of a subcortical pattern at 12 months). Median Trails B executive function scores were also similar among patients with surgery/anesthesia exposure and among those without exposure [41 (33, 48) vs 40 (33, 48) at 3 months; 43 (37, 52) vs 42 (35, 49) at 12 months], approximately 1 standard deviation below adjusted population mean (Fig. 1).

In models incorporating only baseline covariates (Table 2), surgery/anesthesia exposure (yes/no) was not associated with RBANS global cognition or Trails B executive function scores at 3 or 12 months ($P > 0.2$). Pre-existing cognitive deficit as indicated by lower scores on the IQCODE-SF was associated with worse RBANS global cognition scores at 3 and 12 months ($P < 0.001$; $P = 0.04$), and higher years of education was associated with better scores ($P < 0.001$; $P < 0.001$). Pre-existing cognitive deficit by the IQCODE-SF was the only variable associated with lower Trails B executive function scores at 3 and 12 months ($P = 0.03$; $P < 0.001$). In the subset of 233 surgical patients with additional analyses, neither higher number of surgeries, emergent surgery, nor longer total duration of general anesthesia was associated with worse RBANS global cognition or Trails B executive function scores at 3 or 12 months ($P > 0.06$; Table 3). See Supplemental Table 1, <http://links.lww.com/SLA/B51> for details on the surgical and anesthesia characteristics.

In models incorporating baseline and in-hospital covariates (Table 4), surgery/anesthesia exposure (yes/no) remained unassociated with RBANS global cognition or Trails B executive function scores at 3 or 12 months ($P > 0.3$). At both 3 and 12 months, increasing age ($P < 0.001$; $P = 0.01$) and longer delirium duration ($P = 0.01$; $P = 0.003$) were associated with worse RBANS global cognition scores, and higher years of education was associated with better scores ($P < 0.001$; $P < 0.001$). Longer delirium duration was associated with lower Trails B executive function scores at both 3 and 12 months ($P = 0.01$; $P < 0.001$). We did not detect any statistically significant interactions between surgery/anesthesia exposure and education or duration of delirium.

DISCUSSION

In this multicenter prospective cohort study involving patients with surgical and nonsurgical critical illness at academic, community, and Veterans Affairs hospitals, we found that surgery/anesthesia exposure was not a risk factor for long-term global cognitive function or executive function impairment after major noncardiac surgery. In addition, increasing level of exposure as measured by number of surgeries, emergent surgery, and duration of anesthesia was not associated with worse global cognition or executive function. Cognitive impairment was highly prevalent at 3 and 12 months after hospital discharge and affected patients who were exposed to general anesthesia and surgery at rates similar to those who did not undergo a surgical procedure. This impairment was associated with pre-existing cognitive deficits and level of education; longer delirium duration was the only identified in-hospital risk factor for worse cognitive outcomes in our cohort. Over one-third of patients and approximately one quarter of patients scored at levels comparable to or worse than individuals with TBI and AD, respectively. The impairment we observed did not appear to be primarily of an Alzheimer type, as reflected in the subcortical (eg, vascular dementia) rather than cortical nature of deficits.

Our results complement and build upon the results of earlier cohort studies that have identified significant cognitive impairment in hospitalized and postsurgical patients,^{2,4,6,7,21,22,33,34} but our work has unique characteristics. First, we enrolled surgical and medical patients from civilian and veteran populations from across the United States and had high follow-up rates for assessments after discharge, making our cohort generalizable to a broad group of patients and allowing the patients without surgery/anesthesia exposure to serve as a medical comparator group often lacking in previous studies. Second, we obtained detailed hospital-course data and performed daily acute brain dysfunction assessments, allowing us to examine in-hospital factors that are almost never included in prior before-after studies of perioperative cognitive trajectory. Third, we performed extensive inperson assessments with the validated RBANS battery and Trails B test and demonstrated that a significant number of surgical patients have levels of impairment similar to or worse than TBI or AD. The impairment in our patients was predominantly subcortical in nature, similar to vascular dementia as opposed to AD. For instance, our patients were relatively more likely to demonstrate deficits in domains of attention and visuo-spatial construction than in domains of language and delayed memory, although neuropsychological deficits were common across virtually all domains. Many previous studies assessed cognition with abbreviated screening tools or failed to compare impairment seen after surgery with those

seen in reference populations such as TBI or AD. Our findings, therefore, provide a better appreciation of the range and magnitude of deficits and the possible societal implications that these may have.

Our results support the increasing evidence that preoperative and postoperative factors are the most important determinants of postoperative cognitive trajectory, not the operative event itself.^{10,21,35,36} By initially analyzing only surgery/anesthesia exposure and baseline factors (eg, age, education level, pre-existing deficits, stroke risk) in this mixed population, we were able to characterize better the associations between preexisting comorbidities and cognitive outcomes distinctly from the subsequent events of the hospital course. We then investigated the role of the hospital course on cognitive outcomes and examined a large number of potential clinical and pathophysiologic risk factors, including duration of delirium and coma, sepsis, hypoxemia, severity of illness, and sedative exposure, which are often inadequately characterized or not studied due to lack of robust data collection and statistical power. In both analyses, we did not find a significant independent association between surgery/anesthesia exposure and cognitive outcomes at 3 or 12 months. Furthermore, given the small effect size estimates and confidence intervals associated with surgery/anesthesia exposure, it is unlikely that there would be more than a 2.5 unit decrease in the RBANS based on the largest estimated upper confidence limit for the effect. This extent of change is not clinically significant,³⁷ and we can safely rule out an effect of that magnitude, if any at all, from surgery/anesthesia exposure.

Although we cannot exclude the possibility that some mild degree of dysfunction might occur from the surgery/anesthesia exposure, any contribution from this exposure, if present, would be far less than the contribution of baseline and in-hospital factors for this critically ill cohort. These results are consistent with a recent study of over 8000 twins that found no significant association of major surgery and anesthesia with long-term cognitive dysfunction.³⁶ Importantly, our study examined a void in the current literature—high-risk major noncardiac surgical patients with extensively analyzed postoperative courses—but our findings may not be applicable to noncritically ill patients exposed to lower acuity surgery or regional anesthesia techniques with less resulting cognitive impairment. Prior studies, however, support the lack of association in these populations as well.^{8,13–15,17,20} In addition, we did not find an association between surgery/anesthesia exposure and outcomes in our analyses when including baseline covariates only, thus excluding critical illness factors.

Of the risk factors examined, longer duration of delirium was the only potentially modifiable in-hospital factor that was associated with worse global cognitive function and executive function at 3 or 12 months. This association is consistent with recent results in both surgical and medical patients demonstrating that delirium during a hospitalization may portend worse long-term outcomes, including greater risk of cognitive, physical, and social functioning decline and need for institutionalization.^{38–40} For example, cardiac surgery patients with delirium had a larger decrease in cognitive function measured by the Mini-Mental State Examination at both 1 month and 12 months than those without delirium²¹; furthermore, a higher percentage of patients with delirium did not return to baseline function than those without delirium at 6 and 12 months.²¹ This study also extends our BRAIN-ICU findings demonstrating that delirium was associated with worse cognitive testing scores 3 and 12

months after critical illness.²² Thus, delirium, as a manifestation of acute brain organ dysfunction in patients with surgical or medical illness, portends significant chronic brain dysfunction.

We found that higher education level was independently associated with better global cognitive function at 3 and 12 months, whereas pre-existing cognitive deficit was associated with worse global cognitive function. This is similar to findings in other disease states such as TBI and AD^{41,42} and supports the premise that cognitive reserve is protective of long-term impairment after acute insult. Patients with higher cognitive reserve likely possess increased capacity to maintain normal functioning in response to stress (eg, surgical or medical illness) and are, therefore, at a lower risk for subsequent impairment. Therapeutic approaches for improving cognitive reserve may present opportunities for reducing cognitive impairment after acute stressors, particularly elective surgeries with time available for prehabilitation.^{43,44}

Our study has many strengths as outlined above but has a few limitations that warrant discussion. We were unable to account for depth of anesthesia and extent of surgical tissue injury. We were also unable to account for past surgery/anesthesia exposure or for prior delirium episodes related to past hospitalizations that could have altered cognitive trajectories. Despite being unable to perform extensive cognitive testing before hospitalization, we did obtain information on patients' pre-existing cognitive functioning. The IQCODE-SF,²⁹ which has high sensitivity to identify mild cognitive impairment and dementia,^{30–32} was used to account for baseline cognitive deficits and was the same in patients with surgery/anesthesia exposure and in those without exposure. Furthermore, other demographic characteristics associated with baseline cognitive status (eg, age, education level, socioeconomic status, frailty, functional activity level, comorbidities) were collected and were also similar between groups. These findings indicate that both groups had similar pre-admission cognitive functioning. Delirium assessments were not coordinated with interruption of sedation; patients considered delirious in our cohort may have included patients with rapidly reversible sedation-related delirium (previously reported to affect 12% of patients in a study of 102 patients and not associated with worse outcomes),⁴⁵ potentially biasing our delirium results toward the null hypothesis. Finally, observational studies cannot prove causation and are subject to unmeasured confounders; however, we were able to adjust for a large number of confounders due to the size of the cohort, including baseline and in-hospital factors.

In conclusion, exposure to surgery and general anesthesia is not a significant risk factor for long-term cognitive impairment after major noncardiac surgery associated with critical illness. Cognitive impairment is prevalent at 3 and 12 months after hospital discharge and primarily associated with baseline education level and longer duration of delirium in the hospital.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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CGH, MBP, JCJ, TDG, NEB, KGM, EWE, and PPP developed the study concept and design. All authors were involved in data acquisition and interpretation. CGH, MBP, JCJ, EWE, and PPP had primary responsibility for writing of the manuscript with critical revision and final approval performed by all authors. JLT and RC completed all data analyses. CGH, EWE, and PPP obtained funding for the study, and CGH, JCJ, TDG, EWE, and PPP supervised the conduct of the study. CGH and PPP had full access to all of the data in the study, take responsibility for the integrity of the data and the accuracy of the data analysis, and had final responsibility for the decision to submit for publication.

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FIGURE 1.

Global cognition and executive function scores in patients with versus without surgery/anesthesia exposure. The RBANS²⁴ is a validated tool that examines global cognitive function and has a mean (standard deviation) population age-adjusted score of 100 ± 15 with lower scores indicating worse global cognitive function. The Trails B²⁸ is a validated tool that examines executive function and has an age-, sex-, and education-adjusted mean score of 50 ± 10 with lower scores indicating worse executive function. RBANS scores were similar in patients with surgery/anesthesia exposure versus those without exposure, approximately 1.5 standard deviations below adjusted mean. Likewise, Trails B scores were similar in patients with surgery/anesthesia exposure versus those without exposure, approximately 1 standard deviation below the adjusted mean. The horizontal bar indicates the median, the upper and lower limits of the boxes indicate the interquartile range, the ends of the whiskers indicate 1.5 times the interquartile range, and the black dots indicate outliers. The green dashed line indicates the adjusted population mean for normal adults, and the green band indicates the standard deviation. Also shown are the expected RBANS mean scores for traumatic brain injury and Alzheimer disease from other cohort studies (patients >65 years of age in Alzheimer disease).

TABLE 1**Demographic and Clinical Characteristics by Surgery Exposure**

Characteristics*	Surgery (N = 402)	No Surgery (N = 638)
Age at enrollment, yrs	63 (53–71)	62 (52–72)
White race, N (%)	373 (93%)	573 (90%)
Male sex, N (%)	242 (60%)	385 (60%)
Education, yrs	12 (12–14)	12 (12–14)
AHRQ Socioeconomic Status Index	49.9 (47.3–52.9)	49.6 (47.3–52.7)
IQCODE-SF at enrollment	3 (3.00–3.12)	3 (3.00–3.12)
Clinical Frailty Scale at enrollment, N (%)		
Very fit	8 (2%)	23 (4%)
Well	54 (13%)	79 (12%)
Well, treated comorbid disease	146 (36%)	209 (33%)
Apparently vulnerable	80 (20%)	134 (21%)
Mildly frail	55 (14%)	85 (13%)
Moderately frail	50 (12%)	85 (13%)
Severely frail	9 (2%)	23 (4%)
FAQ score at enrollment, N (%)		
No impairment (score 0–8)	351 (89%)	541 (87%)
Some impairment (score 9)	45 (11%)	80 (13%)
Charlson comorbidity index	2.0 (1.0–4.0)	2.0 (1.0–4.0)
Framingham stroke risk	10.0 (6.0–14.0)	10.0 (6.0–15.0)
SOFA score at enrollment	9.0 (7.0–12.0)	9.0 (7.0–11.0)
APACHE II at admission	25.0 (19.0–31.0)	23.0 (17.2–29.0)
Sepsis in the ICU, N (%)	272 (68%)	483 (77%)
Duration among exposed, d	8.0 (3.0–14.0)	4.0 (2.0–8.0)
Mechanical ventilation, N (%)	384 (96%)	539 (84%)
Duration among exposed, d	2.2 (0.37–8.06)	2.0 (0.89–4.96)
Delirium, N (%)	312 (78%)	428 (67%)
Duration among exposed, d	5.0 (2.0–10.0)	3.0 (2.0–6.0)
Coma, N (%)	255 (63%)	372 (58%)
Duration among exposed, days	4.0 (2.0–7.0)	3.0 (1.0–5.0)
Sedative or analgesic use, N (%)		
Benzodiazepine	279 (69%)	407 (67%)
Propofol	222 (55%)	299 (47%)
Dexmedetomidine	65 (16%)	63 (10%)
Opiate	378 (94%)	456 (71%)
ICU length of stay, d	6.9 (3.0–15.1)	4.8 (2.4–9.1)
Hospital length of stay, d	12.8 (7.1–22.0)	8.8 (5.2–14.1)
In-hospital mortality, N (%)	60 (15%)	137 (21%)
One-year mortality, N (%)	149 (37%)	269 (42%)

* Median (interquartile range) or N (percentage).

AHRQ indicates Agency for Healthcare Research and Quality; APACHE, Acute Physiology and Chronic Health Evaluation; FAQ, Functional Activities Questionnaire; ICU, intensive care unit; IQCODE-SF, Short Form Informant Questionnaire on Cognitive Decline in the Elderly; SOFA, Sequential Organ Failure Assessment.

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TABLE 2

Effect of Surgery and Baseline Factors on Global Cognition and Executive Function Scores

3-Month Follow-Up (N = 494)	Adjusted RBANS Difference*	P	Adjusted Trails B Difference*	P
Surgery/anesthesia exposure (yes/no)	-1.35 (-3.49 to 0.79)	0.217	-0.07 (-2.38 to 2.24)	0.951
Age at enrollment, yrs	-1.31 (-4.79 to 2.17)	0.001	-0.35 (-2.28 to 1.58)	0.724
Education, yrs	4.78 (2.58 to 6.98)	<0.001	0.17 (-0.78 to 1.12)	0.723
Charlson comorbidity index	-2.58 (-5.46 to 0.31)	0.270	-1.39 (-2.91 to 0.13)	0.073
Framingham stroke risk	0.60 (-2.78 to 3.98)	0.611	-1.03 (-3.11 to 1.05)	0.330
IQCODE-SF	-1.19 (-2.74 to 0.36)	<0.001	-0.59 (-1.12 to -0.06)	0.030

12-Month Follow-Up (N = 413)	Adjusted RBANS Difference*	P	Adjusted Trails B Difference*	P
Surgery/anesthesia exposure (yes/no)	-0.99 (-3.50 to 1.52)	0.436	1.49 (-0.90 to 3.89)	0.220
Age at enrollment, yrs	-0.90 (-4.98 to 3.18)	0.011	0.23 (-1.80 to 2.25)	0.826
Education, yrs	4.50 (1.99 to 7.01)	<0.001	0.40 (-0.59 to 1.40)	0.424
Charlson comorbidity index	-0.66 (-4.27 to 2.94)	0.450	-0.33 (-1.93 to 1.27)	0.687
Framingham stroke risk	0.41 (-3.79 to 4.61)	0.936	-1.48 (-3.69 to 0.73)	0.189
IQCODE-SF	0.69 (-1.31 to 2.69)	0.038	-1.12 (-1.64 to -0.59)	<0.001

* A negative value is indicative of worse global cognition (RBANS) or executive function (Trails B) scores. The RBANS has a mean (standard deviation) population age-adjusted score of 100 ± 15 ; the Trails B has an age-, sex-, and education-adjusted mean score of 50 ± 10 . We report effect size estimates with the adjusted outcome difference (95% confidence interval) from multivariable linear regression analyses for yes versus no for each dichotomous covariate and the cohort's 75th versus 25th percentile value for each continuous covariate. Continuous variables were modeled with the use of restricted cubic splines to allow for nonlinear associations between covariates and outcomes but require multiple beta coefficients to estimate the effect. The most appropriate *P* value is one that takes into consideration all beta coefficients. Although the *P* value may indicate significance (and is correct), the comparison of the 25th and 75th percentiles may yield a point estimate with a confidence interval that crosses zero, or vice versa.

IQCODE-SF indicates Short Form Informant Questionnaire on Cognitive Decline in the Elderly.

TABLE 3

Effect of Surgery, Anesthesia, and Baseline Factors on Global Cognition and Executive Function Scores in a Subset of Surgical Patients

3-Month Follow-Up (N = 127)	Adjusted RBANS Difference*	P	Adjusted Trails B Difference*	P
Number of surgeries	1.22 (−3.93 to 6.38)	0.285	−2.15 (−5.09 to 0.80)	0.151
Emergent surgery (yes/no)	2.47 (−1.98 to 6.93)	0.274	−1.60 (−7.10 to 3.89)	0.565
Total anesthesia duration, min	−0.01 (−3.96 to 3.93)	0.190	1.02 (−2.84 to 4.87)	0.603
Age at enrollment, yrs	−1.41 (−4.16 to 1.35)	0.081	−1.57 (−4.86 to 1.73)	0.348
Education, yrs	3.97 (2.09 to 5.84)	<0.001	1.02 (−0.99 to 3.04)	0.317
Charlson comorbidity index	−0.53 (−3.85 to 2.80)	0.889	−1.78 (−5.53 to 1.97)	0.348
IQCODE-SF	−2.28 (−4.92 to 0.35)	<0.001	−0.58 (−1.20 to 0.05)	0.071

12-Month Follow-Up (N = 111)	Adjusted RBANS Difference*	P	Adjusted Trails B Difference*	P
Number of surgeries	1.67 (−2.95 to 6.29)	0.072	−0.66 (−4.04 to 2.73)	0.702
Emergent surgery (yes/no)	3.47 (−1.82 to 8.76)	0.196	3.05 (−2.71 to 8.80)	0.296
Total anesthesia duration, min	−4.71 (−8.83 to −0.59)	0.066	−1.75 (−5.43 to 1.93)	0.347
Age at enrollment, yrs	−0.08 (−3.57 to 3.41)	0.125	−0.86 (−4.22 to 2.50)	0.614
Education, yrs	3.94 (1.63 to 6.24)	<0.001	0.50 (−1.48 to 2.47)	0.618
Charlson comorbidity index	−0.33 (−3.89 to 3.23)	0.963	−0.04 (−3.61 to 3.52)	0.980
IQCODE-SF	−1.41 (−4.97 to 2.15)	0.060	−0.99 (−1.61 to −0.37)	0.002

* A negative value is indicative of worse global cognition (RBANS) or executive function (Trails B) scores. The RBANS has a mean (standard deviation) population age-adjusted score of 100 ± 15 ; the Trails B has an age-, sex-, and education-adjusted mean score of 50 ± 10 . We report effect size estimates with the adjusted outcome difference (95% confidence interval) from multivariable linear regression analyses for yes versus no for each dichotomous covariate and the cohort's 75th versus 25th percentile value for each continuous covariate. Continuous variables were modeled with the use of restricted cubic splines to allow for nonlinear associations between covariates and outcomes but require multiple beta coefficients to estimate the effect. The most appropriate *P* value is one that takes into consideration all beta coefficients. Although the *P* value may indicate significance (and is correct), the comparison of the 25th and 75th percentiles may yield a point estimate with a confidence interval that crosses zero, or vice versa.

IQCODE-SF indicates Short Form Informant Questionnaire on Cognitive Decline in the Elderly.

TABLE 4

Effect of Surgery, Baseline, and In-Hospital Factors on Global Cognition and Executive Function Scores

3-Month Follow-Up (N = 494)	Adjusted RBANS Difference*	P	Adjusted Trails B Difference*	P
Surgery/anesthesia exposure (yes/no)	-1.04 (-3.48 to 1.40)	0.404	0.42 (-2.17 to 3.02)	0.749
Age at enrollment, yrs	-0.91 (-4.58 to 2.76)	<0.001	0.63 (-3.25 to 4.51)	0.230
Education, yrs	4.67 (2.43 to 6.90)	<0.001	-0.25 (-2.65 to 2.14)	0.894
Charlson comorbidity index	-2.52 (-5.57 to 0.54)	0.274	-3.77 (-7.10 to -0.43)	0.026
Framingham stroke risk	1.05 (-2.44 to 4.54)	0.547	1.37 (-2.32 to 5.06)	0.391
IQCODE-SF	-0.81 (-2.39 to 0.76)	<0.001	0.82 (-0.86 to 2.49)	0.100
Delirium duration, d	-5.43 (-8.82 to -2.03)	0.012	-3.55 (-7.84 to 0.74)	0.010
Coma duration, d	-1.47 (-4.73 to 1.78)	0.537	2.16 (-3.36 to 7.68)	0.148
Severe sepsis duration, d	2.10 (-0.84 to 5.03)	0.372	1.13 (-2.07 to 4.34)	0.767
Hypoxemia, 15 min intervals	0.70 (-1.84 to 3.23)	0.250	-2.11 (-4.85 to 0.62)	0.321
Mean SOFA score	1.15 (-1.83 to 4.14)	0.839	0.85 (-2.33 to 4.03)	0.886
Mean benzodiazepines [†]	0.57 (-2.55 to 3.69)	0.564	-3.03 (-6.40 to 0.34)	0.176
Mean propofol [†]	-0.65 (-3.60 to 2.29)	0.923	-3.31 (-6.42 to -0.21)	0.214
Mean dexmedetomidine [†]	-0.70 (-7.23 to 5.83)	0.433	-1.24 (-8.31 to 5.83)	0.731
Mean opiates [†]	2.60 (-0.97 to 6.17)	0.145	5.66 (1.79 to 9.54)	0.039
Mean haloperidol [†]	-2.44 (-8.54 to 3.66)	0.433	-0.33 (-6.22 to 6.89)	0.921
12-Month Follow-Up (N = 413)	Adjusted RBANS Difference*	P	Adjusted Trails B Difference*	P
Surgery/anesthesia exposure (yes/no)	-0.47 (-3.28 to 2.33)	0.741	1.35 (-1.23 to 3.93)	0.305
Age at enrollment, yrs	-2.38 (-6.67 to 1.91)	0.012	0.87 (-1.24 to 2.99)	0.417
Education, yrs	4.01 (1.48 to 6.54)	<0.001	0.46 (-0.54 to 1.46)	0.364
Charlson comorbidity index	0.66 (-3.12 to 4.44)	0.151	-0.54 (-2.19 to 1.11)	0.519
Framingham stroke risk	1.05 (-3.26 to 5.35)	0.888	-0.97 (-3.22 to 1.27)	0.393
IQCODE-SF	1.15 (-0.85 to 3.16)	0.073	-1.10 (-1.63 to -0.58)	<0.001
Delirium duration, d	-7.28 (-11.35 to -3.22)	0.003	-2.96 (-4.70 to -1.22)	<0.001
Coma duration, d	0.37 (-3.50 to 4.24)	0.518	0.34 (-1.27 to 1.96)	0.679
Severe sepsis duration, d	0.78 (-2.77 to 4.32)	0.726	0.71 (-0.86 to 2.28)	0.374
Hypoxemia, 15 min intervals	2.06 (0.39 to 3.73)	0.040	-0.09 (-0.40 to 0.21)	0.542
Mean SOFA score	-0.97 (-4.45 to 2.52)	0.587	0.70 (-1.04 to 2.44)	0.432
Mean benzodiazepines [†]	-0.59 (-4.27 to 3.10)	0.178	1.03 (-1.31 to 3.36)	0.387
Mean propofol [†]	-1.40 (-4.69 to 1.88)	0.666	-1.18 (-3.23 to 0.87)	0.259
Mean dexmedetomidine [†]	-4.38 (-12.08 to 3.32)	0.264	-2.43 (-9.44 to 4.59)	0.497
Mean opiates [†]	0.87 (-3.36 to 5.09)	0.036	1.88 (-0.65 to 4.41)	0.145
Mean haloperidol [†]	-3.28 (-10.21 to 3.65)	0.352	-0.64 (-7.26 to 5.99)	0.850

* A negative value is indicative of worse global cognition (RBANS) or executive function (Trails B) scores. The RBANS has a mean (standard deviation) population age-adjusted score of 100 ± 15 ; the Trails B has an age-, sex-, and education-adjusted mean score of 50 ± 10 . We report effect size estimates with the adjusted outcome difference (95% confidence interval) from multivariable linear regression analyses for yes versus no for each dichotomous covariate and the cohort's 75th versus 25th percentile value for each continuous covariate. Continuous variables were modeled with the use of restricted cubic splines to allow for nonlinear associations between covariates and outcomes but require multiple beta coefficients to

estimate the effect. The most appropriate P value is one that takes into consideration all beta coefficients. Although the P value may indicate significance (and is correct), the comparison of the 25th and 75th percentiles may yield a point estimate with a confidence interval that crosses zero, or vice versa.

[†] Mean 24-hour doses on days exposed, cube root transformed to minimize impact of outlier doses.

IQCODE-SF indicates Short-Form Informant Questionnaire on Cognitive Decline in the Elderly; SOFA, Sequential Organ Failure Assessment.

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