




RESEARCH ARTICLE

Postoperative changes in cognition and cerebrospinal fluid neurodegenerative disease biomarkers

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Abstract

Objective: Numerous investigators have theorized that postoperative changes in Alzheimer's disease neuropathology may underlie postoperative neurocognitive disorders. Thus, we determined the relationship between postoperative changes in cognition and cerebrospinal (CSF) tau, p-tau-181p, or A β levels after non-cardiac, non-neurologic surgery in older adults. **Methods:** Participants underwent cognitive testing before and 6 weeks after surgery, and lumbar punctures before, 24 h after, and 6 weeks after surgery. Cognitive scores were combined via factor analysis into an overall cognitive index. In total, 110 patients returned for 6-week postoperative testing and were included in the analysis. **Results:** There was no significant change from before to 24 h or 6 weeks following surgery in CSF tau (median [median absolute deviation] change before to 24 h: 0.00 [4.36] pg/mL, $p = 0.853$; change before to 6 weeks: -1.21 [3.98] pg/mL, $p = 0.827$). There were also no significant changes in CSF p-tau-181p or A β over this period. There was no change in cognitive index (mean [95% CI] 0.040 [−0.018, 0.098], $p = 0.175$) from before to 6 weeks after surgery, although there were postoperative declines in verbal memory (-0.346 [−0.523, -0.170], $p = 0.003$) and improvements in executive function (0.394, [0.310, 0.479], $p < 0.001$). There were no significant correlations between preoperative to 6-week postoperative changes in cognition and CSF tau, p-tau-181p, or A β 42 changes over this interval ($p > 0.05$ for each). **Interpretation:** Neurocognitive changes after non-cardiac, non-neurologic surgery in the majority of cognitively healthy, community-dwelling older adults are unlikely to be related to postoperative changes in AD neuropathology (as assessed by CSF A β , tau or p-tau-181p levels or the p-tau-181p/A β or tau/A β ratios). Trial Registration: clinicaltrials.gov (NCT01993836).

Introduction

One of the largest controversies in perioperative medicine over the last quarter century has been whether anesthesia and surgery contribute to long-term cognitive decline and/or the development of dementia in older adults. This question has major public health implications, since approximately half of adults over 65 will undergo at least one surgery, and over 120,000 Americans will die of Alzheimer's disease (AD) per year.^{1,2} Thus, if anesthesia and surgery make even a small contribution to long-term cognitive decline or increased AD risk, this would have significant population-level implications.

Four lines of evidence raise the possibility that anesthesia and surgery may accelerate cognitive decline and/or the underlying neuropathologic processes associated with AD. First, the two largest epidemiologic studies on this topic have found increased dementia rates in people who underwent surgery versus those who did not, though these studies were retrospective^{3,4} and smaller studies have not replicated these associations.^{5–9}

Second, cognitive decline occurs in many older adults within months after anesthesia and surgery.¹⁰ This early cognitive decline, typically termed postoperative cognitive dysfunction or neurocognitive disorder postoperative¹¹ when accompanied by subjective cognitive complaints, has been associated with long-term cognitive decline 5 years later.¹² Similarly, postoperative delirium has been associated with greater cognitive decline 3 years later.¹³ However, in both cases, it remains unclear to what extent this long-term cognitive decline reflects an effect of anesthesia and surgery (or other aspects of perioperative care such as sleep disruption, pain, or inflammation) versus confounding due to underlying surgical disease processes or medical comorbidities (e.g., cardiovascular disease).^{14,15} Nonetheless, cognitive decline within 1–3 months after surgery has been associated with functional brain connectivity changes similar to those seen in early mild cognitive impairment and dementia due to AD.^{16–18} Postoperative cortical thinning has also been observed within brain regions that show atrophy in AD,¹⁹ and patients with MCI show greater hippocampal volume loss after surgery than those who are cognitively normal.²⁰

Third, in mouse models and in vitro systems, anesthetic drugs and surgical stress promote many key pathophysiologic processes involved in AD such as amyloid beta (A β) plaque formation^{21,22} and tau phosphorylation.^{23–26} Blocking these processes in mouse models improves memory following surgery.^{27,28} Fourth, we and others have found postoperative increases in CSF tau levels into the range seen in AD.^{29–33} However, CSF tau level increases are seen in multiple neurologic disorders aside from AD; tau is best considered a pan-neuronal injury marker.^{34,35} Based on

these four lines of evidence, we undertook this prospective cohort study to determine the relationship between postoperative changes in both cognition and CSF A β , tau, and p-tau-181p levels in older surgical patients.

Methods

Study participants

Markers of Alzheimer's Disease and neuroCognitive Outcomes after Perioperative Care (MADCO-PC) was an IRB-approved observational cohort study with a nested randomized controlled trial, in which all cohort study patients were also randomized to isoflurane versus propofol for anesthetic maintenance. We designed the study this way since virtually all patients currently undergoing general anesthesia receive either an inhaled anesthetic (with isoflurane being the most common at our institution) or propofol, both of which are considered standard of care. Thus, randomizing the parent cohort study patients to isoflurane versus propofol does not expose these patients to any drug outside the current standard of care. Further, randomizing patients to isoflurane versus propofol reduces other factors that could bias which drug a patient receives, thus allowing for an unbiased comparison of the effects of these two drugs on cognition and CSF AD-related biomarkers in older surgical patients.

The prespecified primary study outcome was on the relationship between cognitive and CSF tau change over the interval from before to 6 weeks after surgery in the full observational cohort. The effect of intraoperative anesthetic randomization (i.e., in the nested RCT) is a secondary outcome described in a separate manuscript now under preparation. MADCO-PC was conducted at Duke University Medical Center (Durham, NC), and registered with clinicaltrials.gov (NCT01993836). Eligibility criteria were age ≥ 60 years, undergoing major non-cardiac, non-neurologic surgery (i.e., under general anesthesia for a planned intraoperative duration of >2 h and an expected hospital stay of ≥ 1 night), English-speaking, and ability to give informed consent. Patients were excluded if they were an inmate of a correctional facility, pregnant, had a family or personal history of malignant hyperthermia, were unable to receive propofol/isoflurane due to allergy or other specific contraindication, or were taking anticoagulants that would preclude safe lumbar puncture.^{36,37} Patients who received systemic chemotherapy between preoperative and 6-week postoperative cognitive testing were also excluded to avoid confounding effects on cognition. There were no exclusions for preoperative/baseline cognitive status.

The Duke Hospital electronic surgery schedule was screened for patients potentially eligible for the study,

who were then contacted by phone. Patients who agreed to participate were scheduled for a baseline study visit <1 month before surgery and gave written informed consent before engaging in study activities. Study recruitment began in November 2013 and follow-up visits were completed in December 2017.

Patient and surgical characteristics are described using mean (standard deviation) or median (interquartile range) for numeric variables and *N* (%) for categorical variables.

Intraoperative management

All study patients received general anesthesia with an inhaled anesthetic (i.e., isoflurane) or an intravenous propofol infusion. Anesthetic administration was titrated to maintain bispectral index processed EEG values between 40 and 60. There were no restrictions on regional or neuraxial blocks (e.g., spinal or epidural anesthesia), adjunct anesthetic drugs, or surgical technique, other than the exclusion of cardiac and neurosurgical patients.

CSF sample collection, biomarker measurements, and APOE genotyping

CSF samples were collected before and 24 h and 6 weeks after surgery using a 25-g pencil-point needle by aspiration with a 10-mL polypropylene syringe, using our established protocol.³⁷ CSF samples were then aliquoted into Sarstedt 1.5-mL polypropylene microcentrifuge tubes (VWR; Radnor, PA) and frozen at -80°C within 1 h. CSF samples were maintained at -80°C without any freeze/thaw cycles until they were thawed together for batched analysis. One hundred and five (95%) patients contributed CSF data to the analysis, and 86 (78%) had a complete dataset of CSF biomarker data at all three time points. CSF tau, p-tau-181p and A β 42 measurements were performed using the AlzBio3 platform.³⁰ Multiple imputation methods were used for missing data in patients with incomplete CSF sample data. Since these biomarker data were not normally distributed, change values are reported as medians with median absolute deviations (MAD, i.e., the nonparametric equivalent of a standard deviation). CSF A β 42 and tau results were classified as pathologic based on cutoffs of <250 and >93 pg/mL, respectively.³⁸ APOE genotyping was performed as described.³⁰

CSF biomarker metrics

We defined two change scores of interest in our analysis. Our primary biomarker change of interest was the change from baseline to 24 h and from baseline to 6 weeks in tau concentrations, defined as the 24-h concentration minus

the baseline level, and 6-week concentration minus the baseline level. For secondary analysis, we defined the 24-h and 6-week CSF change scores for p-tau-181p, A β , and the ratios of tau and p-tau-181p to A β in the same way. Additionally, we considered the trajectory of CSF concentrations over time to investigate if there was change across the study period.

CSF imputation strategy

We included all patients that returned for follow-up cognitive testing in our primary analysis cohort. One hundred and five (95%) patients contributed CSF data to the analysis, and 86 (78%) had a complete dataset at all three time points. In order to include patients with incomplete data in the analysis, we pursued multiple imputation using SRCWare software v0.2 based on all known patient and surgical factors as well as observed cognitive test scores and CSF concentrations. SRCWare employs multivariate sequential regression to replace missing data within a plausible range to represent uncertainty in the true value. This yields multiple imputed datasets, which are analyzed in the same manner as the rest of the data. The analyses are then pooled to produce results that properly reflect uncertainty resulting from the missing data points.³⁹ We created 10 imputation datasets and used standard methods to pool across imputed sets. Sensitivity analysis was conducted on patients with complete data (i.e., excluding patients with imputed data) to ensure all conclusions were robust to this imputation technique.

Cognitive testing

Patients completed cognitive tests at both the preoperative and 6-week postoperative study visits. Individual tests are listed in Table 2. To characterize cognitive function over time while minimizing potential redundancy in the cognitive measures, a factor analysis with oblique rotation was performed on 10 of the cognitive test scores administered in this study. Scoring coefficients (weights) of each test on each factor were determined using the rotated factor solution from the factor analysis conducted on baseline scores among 389 non-cardiac patients in a prior study.⁴⁰ Factor scores of each subject in our cohort were computed for all time points using the same scoring coefficients, so that the cognitive domain structure remained consistent and comparable over time. Factor analysis suggested a four-factor solution, which accounts for 87% of the variability in the original test scores and represents four cognitive domains: (1) unstructured verbal memory (i.e., the ability to remember from a narrative); (2) visual memory; (3) executive function; and (4) attention and concentration. We defined continuous cognitive outcome measures for each

cognitive domain as the change in cognitive score calculated by subtracting the baseline from the follow-up domain score (a change score of 0 indicates no change from baseline, while a negative score indicates cognitive decline, and a positive score indicates cognitive improvement). We also defined a global cognitive index outcome as the average of the four domain change scores, with global cognitive change obtained by subtracting the baseline from the follow-up average of the four domain scores. We tabulated the cohort performance on the battery of cognitive tests administered, with mean scores, standard deviations, and score ranges at baseline and 6 weeks.

Analysis of association between cognitive change and CSF biomarker change

All patients who returned for 6-week postoperative cognitive testing were included in the primary analysis. To investigate the association of preoperative to 6-week postoperative changes (a subtraction of baseline from follow-up) in CSF biomarkers and cognition, we used Spearman’s correlation coefficients (r_s), as postoperative CSF biomarker data were not normally distributed.³⁰ We used multivariable analyses to account for potential confounders of relationships between postoperative changes

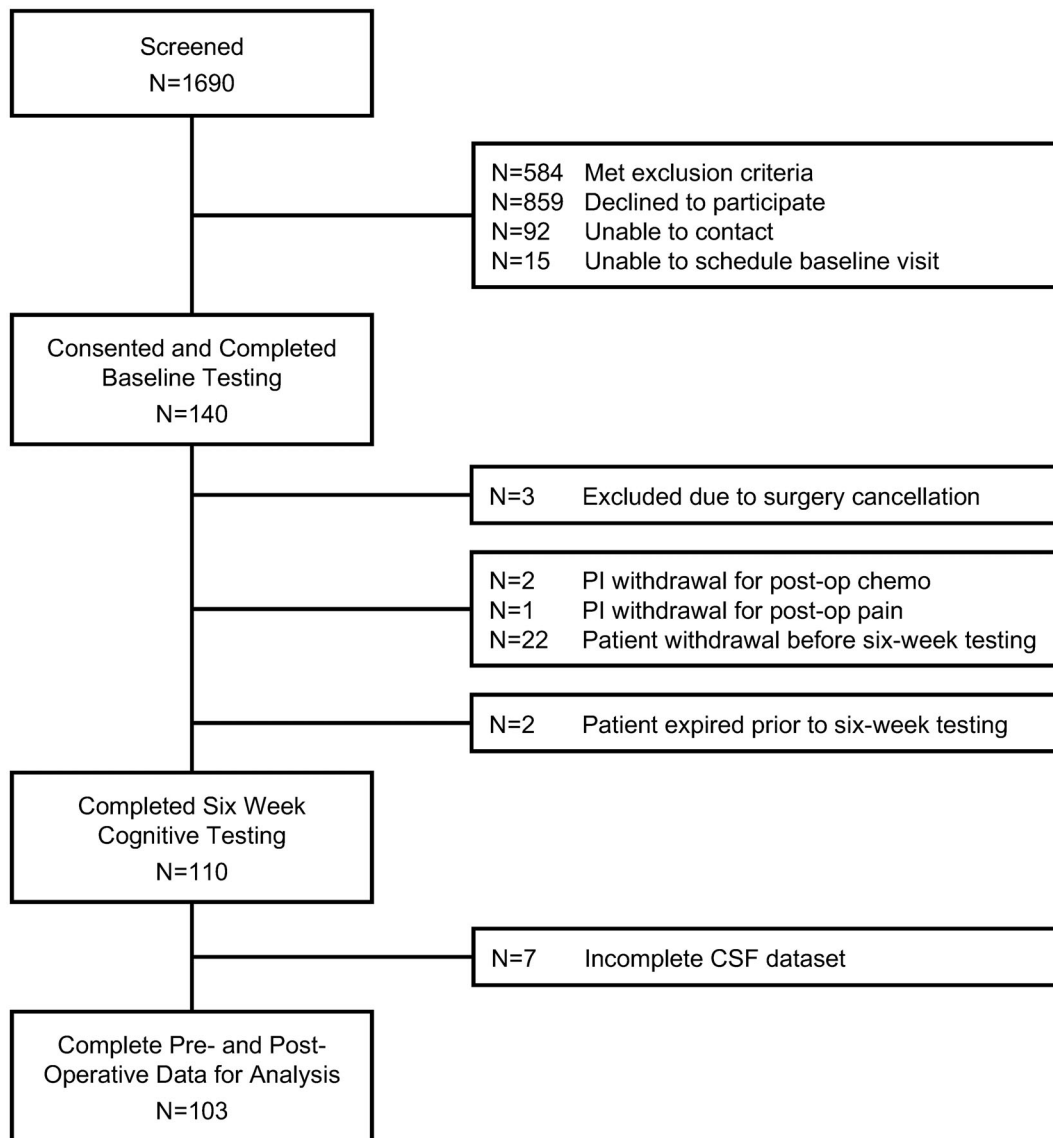


Figure 1. MADCO-PC study flow diagram. Out of 140 patients who consented to and enrolled in the study and underwent baseline testing, 110 patients returned for cognitive testing at 6 weeks after surgery. These 110 patients were used in the final data analysis.

in CSF biomarkers and cognition, including age, years of education, baseline cognitive index, and *APOE4* allele carrier status. To assess CSF biomarker changes over time, we used Friedman's test. Analyses were performed in SAS v9.4 (SAS Inc., Cary, NC, USA). Values of *p* are reported with a Benjamini–Hochberg false discovery rate correction at $\alpha = 0.05$, unless otherwise indicated.⁴¹

Sample size and power analysis

Based on prior work,³⁰ we calculated that $N = 108$ patients would provide >80% power to detect a Spearman correlation of ≥ 0.3 between preoperative to 6-week postoperative changes in the continuous cognitive index score and CSF tau level changes. We enrolled 140 patients to ensure that ≥ 108 patients would return for 6-week postoperative follow-up.

Results

Patient demographics and baseline neurocognitive and intraoperative characteristics

Study subject enrollment is depicted in Figure 1; baseline and intraoperative characteristics are listed in Table 1. The mean age was ~69 years (SD = 6.5 years). One patient had a clinical diagnosis of mild cognitive impairment; none of the patients had a clinical diagnosis of AD or related dementias. Consistent with this, the median preoperative Mini-Mental State Examination score was 29, and ~94% of patients had a score of 25 or higher. Over 95% of patients underwent thoracic, orthopedic, ENT, urologic, or general surgery; typical surgery duration was roughly 2 h. Most patients (>85%) did not receive an epidural or peripheral nerve block. Roughly half of the patients received inhaled anesthesia with isoflurane, and roughly half received propofol-based total intravenous anesthesia. Based on NIA-AA AD stage classifications^{42–44} and AD pathology threshold values,³⁸ ~83% ($N = 91$) of this cohort would be classified as $A\beta^-tau^-$ (i.e., normal), ~14% ($N = 15$) would be $A\beta^+tau^-$ (i.e., likely preclinical AD), ~1% ($N = 1$) would be $A\beta^-tau^+$ (suspected non-AD pathophysiology), and ~3% ($N = 3$) would be classified as $A\beta^+tau^+$ (likely either preclinical AD, MCI, or dementia due to AD; percentages add to more than 100 due to rounding).

Pre- to postoperative CSF biomarker trajectories

No significant changes were found in CSF tau or $A\beta$ levels from before to 24 h (median [MAD] tau change:

Table 1. Baseline demographic and intraoperative characteristics.

| | Total (N = 110) |
|---|------------------------|
| Age (years) (SD) | 69.2 (6.5) |
| Race (%) | |
| Black or African American | 10 (9.1) |
| Caucasian/White | 99 (90.0) |
| Not reported/declined | 1 (0.9) |
| Gender (male) (%) | 69 (62.7) |
| Height (cm) (Q1, Q3) | 171.9 (10.7) |
| Weight (kg) (SD) | 85.7 (18.8) |
| BMI (kg/m ²) [Q1, Q3] | 28.6 [24.5, 32.0] |
| Years of education [Q1, Q3] | 16.0 [12.0, 18.0] |
| MMSE total score [Q1, Q3] | 29.0 [28.0, 29.0] |
| MMSE category (%) | |
| <20 | 1 (0.9) |
| 20–24 | 6 (5.5) |
| 25–30 | 103 (93.6) |
| Mean Baseline Cognitive Index (SD) | 0.074 (0.74) |
| Median baseline $A\beta$ (MAD) | 360.1 (51.4) |
| Median baseline p-tau (MAD) | 27.0 (6.2) |
| Median baseline p-tau/ $A\beta$ (MAD) | 0.076 (0.018) |
| Median baseline tau (MAD) | 47.6 (8.2) |
| Median baseline tau/ $A\beta$ (MAD) | 0.135 (0.026) |
| <i>APOE4</i> positive | 35 (32.4) |
| ASA physical status classification (%) | |
| 1 | 1 (0.9) |
| 2 | 23 (20.9) |
| 3 | 84 (76.4) |
| 4 | 2 (1.8) |
| Surgery type (%) | |
| Thoracic | 11 (10.0) |
| General | 31 (28.2) |
| Gynecologic | 2 (1.8) |
| Orthopedic | 21 (19.1) |
| Otolaryngology head and neck | 2 (1.8) |
| Plastic | 3 (2.7) |
| Urologic | 40 (36.4) |
| Nerve block type (%) | |
| None | 94 (85.5) |
| Peripheral nerve block | 15 (13.6) |
| Epidural block | 1 (0.9) |
| Surgery duration (minute) [Q1, Q3] | 140.0 [100.0, 199.0] |
| Case average BIS [Q1, Q3] ¹ | 46.1 [41.9, 51.5] |
| Received inhaled anesthetic for >50% of case | 56 (50.9) |
| Case average aaMAC [Q1, Q3] ² | 0.7 [0.7, 0.8] |
| aaMAC hours [Q1, Q3] ² | 1.6 [1.3, 2.7] |
| Received intraoperative dexmedetomidine (%) | 13 (11.8) |
| Received intraoperative ketamine (%) | 23 (20.9) |
| Received intraoperative propofol >400 mg (%) | 55 (50.0) |
| Intraoperative propofol dose (mg) (Q1, Q3) ³ | 1357.0 [975.5, 2536.8] |
| Hospital LOS (days) [Q1, Q3] | 2.0 [1.0, 3.0] |

aaMAC, age-adjusted minimum alveolar concentration for inhaled anesthetics; BIS, Bispectral Index (processed EEG value); LOS, length of stay; MAD, median absolute deviation; MMSE, Mini-Mental State Examination; SD, standard deviation.

¹Among those who had BIS values for >50% of the case.

²Among those who received inhaled anesthetic for >50% of the case.

³Among those who received >400 mg intraoperative propofol.

0.00 [4.36] pg/mL, $p = 0.853$; A β : -0.88 [22.75] pg/mL, $p = 0.871$) or from before to 6 weeks (-1.21 [3.98] pg/mL, $p = 0.827$; A β : -5.09 [24.40] pg/mL, $p = 0.827$) after surgery (Fig. 2). There was also no significant change in the tau/A β ratio from before to 24 h after anesthesia (median [MAD] tau/A β ratio: -0.001 [0.018], $p = 0.864$) or from before to 6 weeks after anesthesia (0.001 [0.014], $p = 0.879$; Fig. 2).

Similarly, there was no significant group change in CSF p-tau-181p from before to 24 h after surgery (median [MAD] p-tau-181p change: 1.10 [5.01] pg/mL, $p = 0.771$) or from before to 6 weeks after surgery (-0.44 [5.90] pg/mL, $p = 0.871$; Fig. 2). All nine patients had CSF p-tau-181p levels that were >1.5 times the interquartile range at one or more time points (Fig. 2C). All these nine patients had a CSF p-tau-181p increase from before to 6 weeks after surgery, and two of them had a ~ 2 - to 3-fold increase in CSF p-tau-181p over this interval. At a group level, there was no significant change in the p-tau-181p/A β ratio from before to 24 h after anesthesia (median [MAD] p-tau-181p/A β ratio change: 0.002 [0.014], $p = 0.814$) or from before to 6 weeks after anesthesia (0.002 [0.018], $p = 0.830$; Fig. 2). Yet, 14 patients had a p-tau-181p/A β ratio >1.5 times the interquartile range at one or more time points (Fig. 2E), including two patients whose p-tau-181p/A β ratios increased by ~ 2 -fold from before to 6 weeks after surgery—the same two patients who had a ~ 2 - to 3-fold increase in p-tau-181p levels over this interval in Figure 2C. Additionally, we observed no effect of surgery type (i.e., urologic, general/abdominal, thoracic, orthopedic, or other) on preoperative to 6-week postoperative change in CSF tau, p-tau-181p or A β levels or the p-tau-181p/A β or tau/A β ratios (data not shown).

Pre- to postoperative cognitive trajectories

Cognitive domain and overall cognitive index scores before and 6 weeks after surgery are shown in Figure 3. There was a significant postoperative decline in verbal memory across all patients (mean [95% CI]: -0.346

[-0.523 , -0.170], $p = 0.003$). Yet, there was a significant improvement in executive function from before to 6 weeks after surgery (Table 2; mean [95% CI]: 0.394 [0.310, 0.479], $p = <0.001$). There was no significant change in attention/concentration (Table 2; mean [95% CI]: -0.012 [-0.114 , 0.090], $p = 0.822$) or in visual memory (Table 2; mean [95% CI]: 0.123 [0.003, 0.244], $p = 0.060$). There was no significant change in overall cognitive index (the average of the four cognitive domain scores) from before to 6 weeks after surgery (mean [95% CI]: 0.040 [-0.018 , 0.098], $p = 0.175$). There was no difference in overall cognitive index change from before to 6 weeks after surgery as a function of surgery type (i.e., orthopedic, thoracic, general or other), or as a function of surgery duration (Table 4). Approximately 27% of patients had a ≥ 1 standard deviation decline and 26% had a ≥ 1 standard deviation increase in at least one cognitive domain from before to after surgery.

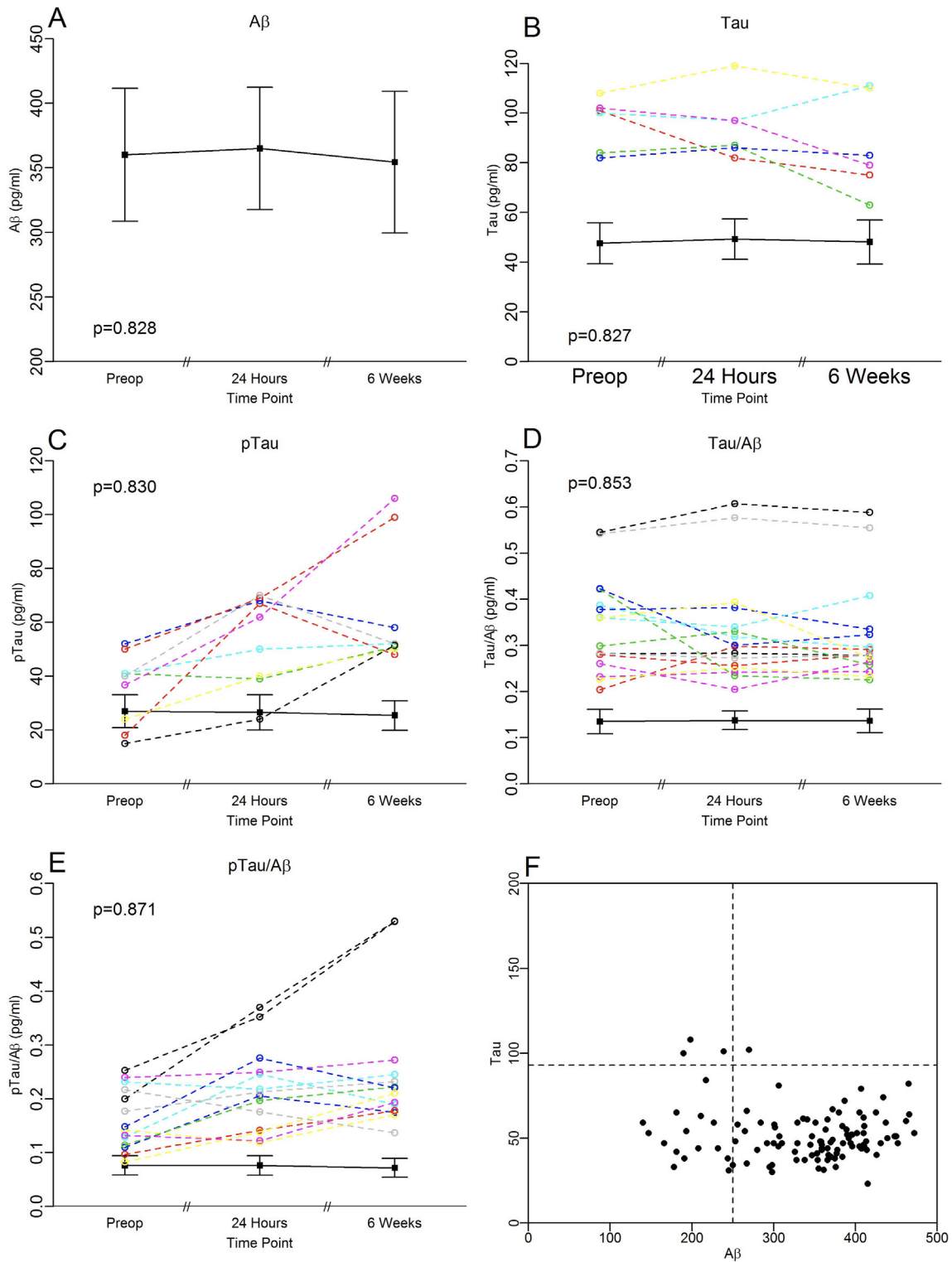
Relationships between pre- to postoperative changes in CSF biomarkers and cognition

Next, we evaluated potential associations between individual patient CSF biomarker (Fig. 2) and cognitive trajectories (Fig. 3) from before to 6 weeks after anesthesia/surgery. No correlation was observed between the continuous cognitive change index and 24-h or 6-week changes in CSF tau (24-h change: $r_s = -0.01$, 95% CI = [-0.21 , 0.19], $p = 0.966$; 6-week change: $r_s = -0.03$, 95% CI = [-0.23 , 0.18], $p = 0.879$; or CSF A β (24-h change: $r_s = 0.03$, 95% CI = [-0.17 , 0.24], $p = 0.871$; 6-week change: $r_s = -0.08$, 95% CI = [-0.29 , 0.13], $p = 0.830$). There was also no significant correlation between the continuous cognitive change index and 24-h or 6-week changes in CSF tau/A β (24-h change: $r_s = -0.05$, 95% CI = [-0.25 , 0.15], $p = 0.853$; 6-week change: $r_s = 0.02$, 95% CI = [-0.19 , 0.22], $p = 0.902$). Similarly, there was no significant correlation between the continuous cognitive change index and 24-h or 6-week change in CSF p-tau-181p levels (24-h change: $r_s = 0.16$,

Figure 2. CSF biomarkers in MADCO-PC surgical patients before, 24 h after, and 6 weeks after anesthesia and surgery. In (A–F) black lines represent the group medians, error bars represent MADs. Colored lines in (A–E) represent biomarker trajectories for individual patients who had values >1.5 the interquartile range from the median (a standard statistical definition for outliers⁷⁵) at any time point. (A) CSF A β levels. CSF A β 42 levels were within 1.5 times the IQR from the group median at all three time points in all patients. (B) CSF tau levels. Six patients had CSF tau levels >1.5 times the IQR from the group median at one or more time points. (C) CSF p-tau-181p levels. Nine patients had CSF p-tau-181p levels >1.5 times the IQR from the group median at one or more time points. In one of the two patients with p-tau-181p levels >90 at the 6-week time point, CSF samples were unavailable at the preoperative and 24 h time points, so these values were imputed (see Methods section). (D) CSF tau/A β ratio. Sixteen patients had CSF tau/A β 42 ratios >1.5 times the IQR from the group median at one or more time points. (E) CSF p-tau-181p/A β ratio. 14 patients had CSF p-tau-181p/A β 42 ratios >1.5 times the IQR from the group median at one or more time points. In one of the two patients with a p-tau-181p/A β ratio >0.5 at the 6-week time point, CSF samples were unavailable at the preoperative and 24 h time points, so these values were imputed (see Methods section). (F) CSF tau versus A β plot in MADCO-PC patients, with dashed lines representing the cutoffs for pathological A β and tau levels.

95% CI = [-0.05, 0.37], $p = 0.721$; 6-week change: $r_s = 0.12$, 95% CI = [-0.08, 0.32], $p = 0.814$) or the CSF p-tau-181p/A β ratio (24-h change: $r_s = 0.12$, 95%

CI = [-0.10, 0.33], $p = 0.827$; 6-week change: $r_s = 0.16$, 95% CI = [-0.05, 0.34], $p = 0.721$) after anesthesia/surgery (Fig. 4). There were also no significant



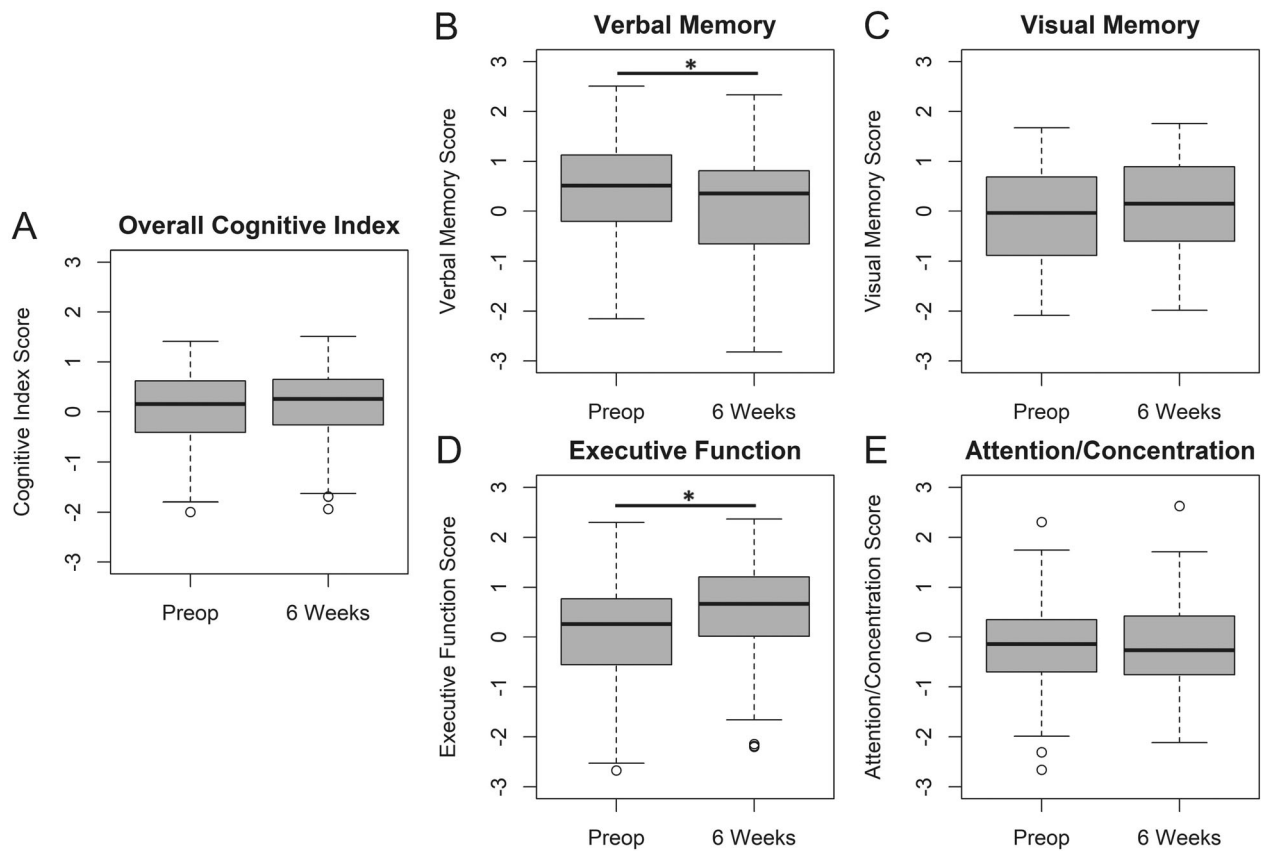


Figure 3. Cognitive results before and 6 weeks after surgery. (A) overall cognitive index; (B) verbal memory; (C) visual memory; (D) executive function; (E) attention/concentration. A positive score on the y-axis represents an improvement in cognitive score from before to after surgery, and vice versa. * indicates a significant difference between the preoperative and 6-week timepoints at $p < 0.05$.

correlations between changes from before to either 24 h or 6 weeks after surgery in any of the aforementioned CSF biomarkers, and changes from before to 6 weeks after surgery in any of the four individual cognitive domains (Table 3). There were no significant differences in the change in any of these CSF biomarkers from before to either 24 h or 6 weeks after surgery between patients who did versus those who did not have a ≥ 1 SD decrease in ≥ 1 cognitive domains from before to 6 weeks after surgery ($p > 0.05$ for each).

In multivariable models adjusting for age, years of education, *APOE4* genotype, and baseline preoperative cognitive index, there were no significant associations between postoperative changes in tau (24-h change: $\hat{\beta}=0.003$, 95% CI = [-0.005, 0.011], $p = 0.483$; 6-week change: $\hat{\beta}= -0.001$, 95% CI = [-0.010, 0.007], $p = 0.738$) or tau/A β (24-h change: $\hat{\beta}=0.054$, 95% CI = [-1.547, 1.656], $p = 0.946$; 6-week change: $\hat{\beta}=0.381$, 95% CI = [-1.295, 2.056], $p = 0.652$) and 6-week postoperative cognitive change (Table 4). Similarly, in a model containing surgery type, there was also no significant

relationship between 6-week postoperative changes in tau and cognition, nor was there any association between surgery type and 6-week postoperative cognitive change. There was also no correlation between postoperative changes in overall cognitive index and CSF tau levels or the tau/A β ratio in a sensitivity analysis excluding imputed data, $p > 0.05$ for each comparison).

Discussion

These data demonstrate no significant association between preoperative to 24-h or 6-week postoperative changes in CSF tau (or p-tau-181p, A β , and the tau/A β and p-tau-181p/A β ratios) and cognitive change from before to 6 weeks after non-cardiac, non-neurologic surgery in older adults. Most patients showed no clinically significant change in CSF A β , tau, or p-tau-181p levels from before to after surgery.⁴⁵ There was no change in overall cognition from before to 6 weeks after surgery, though this was likely due to opposing decreases in verbal memory and increases in executive function.

Table 2. Cognitive assessment data.

| Cognitive domains and tests | Baseline preoperative testing | 6-week postoperative follow-up | Tests for change in domains | |
|--|-------------------------------|--------------------------------|-----------------------------|--------|
| Verbal memory domain | 0.46 (0.89) | 0.12 (1.05) | 0.003 | |
| Immediate RANDT gist | 7.20 (1.47) 4–10 | 6.72 (1.75) 2–9 | | |
| Immediate RANDT verbatim | 10.54 (3.03) 4–18 | 9.83 (3.39) 2–18 | | |
| Delay RANDT gist | 6.60 (1.86) 0–10 | 6.21 (2.21) 0–10 | | |
| Delay RANDT verbatim | 8.92 (3.25) 4–18 | 7.99 (3.47) 0–17 | | |
| Hopkins Verbal Learning Initial (3 Trial Sum) ¹ | 23.90 (5.98) 7–35 | 24.37 (5.79) 8–35 | | |
| Hopkins delayed recall ¹ | 7.87 (3.59) 0–12 | 7.94 (3.46) 0–12 | | |
| Hopkins delayed recognition ¹ | 10.32 (1.90) 3–12 | 10.08 (1.97) 2–12 | | |
| Visual memory domain | –0.07 (0.97) | 0.06 (0.93) | | 0.060 |
| Wechsler reproduction immediate (3 trial sum) | 6.27 (2.83) 0–11 | 6.85 (2.71) 1–11 | | |
| Wechsler reproduction delay (3 trial sum) | 5.65 (2.93) 0–11 | 5.82 (2.90) 0–11 | | |
| Executive function domain | 0.08 (1.07) | 0.47 (1.01) | | <0.001 |
| Digit symbol | 43.15 (11.74) 10–69 | 46.10 (12.15) 0–67 | | |
| Trails Making Test Part A ¹ | 45.32 (96.04) 16–1028 | 39.20 (42.84) 16–450 | | |
| Trails Making Test Part B | 126.86 (105.17) 32–600 | 98.88 (90.24) 26–514 | | |
| Attention/concentration domain | –0.18 (0.86) | –0.19 (0.86) | 0.822 | |
| Digit span repeat forwards | 7.36 (2.03) 2–12 | 7.62 (2.15) 3–14 | | |
| Digit span repeat backwards | 6.10 (2.34) 0–14 | 5.77 (2.21) 1–12 | | |
| Cognitive Index Score | 0.07 (0.74) | 0.11 (0.75) | 0.175 | |

Values are given as mean (SD). One hundred and ten patients completed each test at each time point, with the following exceptions due to test administration deviations or the inability of some patients to complete certain tests: Hopkins Delayed Recognition ($N = 109$ at pre-operative testing), Digit Symbol ($N = 109$ at preoperative testing), and Trails Making test Part B ($N = 107$ at preoperative testing, $N = 108$ at 6-week postoperative testing). The domain and cognitive index scores are based on the factor solution from a previous study by McDonagh et al and include multiply imputed values for the four patients with unobserved test values.

¹Not included in the prior study test battery from which factor weights were derived, so not included in cognitive factor analysis.

The finding of no significant group-level changes in CSF tau, p-tau-181p, or A β levels or their ratios from before to 24 h or to 6 weeks after surgery contrasts with prior reports from both our group and others of significant 24-h postoperative increases in CSF and plasma tau levels.^{29,30,46,47} These differences are notable given that CSF biomarker measurements in these prior studies were obtained using the same assay as used here for CSF biomarkers, in the same laboratory used here.^{29,30} However, all patients in these prior CSF studies underwent neurosurgical or ENT procedures that involved manipulation of their brain and/or dura,^{29,30} whereas none of the

patients in this study did. Another recent report found that CSF tau levels increased linearly from before to 48 h after surgery, although this study obtained CSF via intrathecal catheters.⁴⁸ Intrathecal catheters themselves can cause neuroinflammation and neurologic symptoms.^{49–51} Thus, the most parsimonious interpretation of these data is that while surgery on the central nervous system leads to CSF tau increases 24 h later, non-neurologic surgery and general anesthesia are not associated with a significant change in CSF biomarkers of amyloid or tau pathology 1 day or 6 weeks later in most older adults.

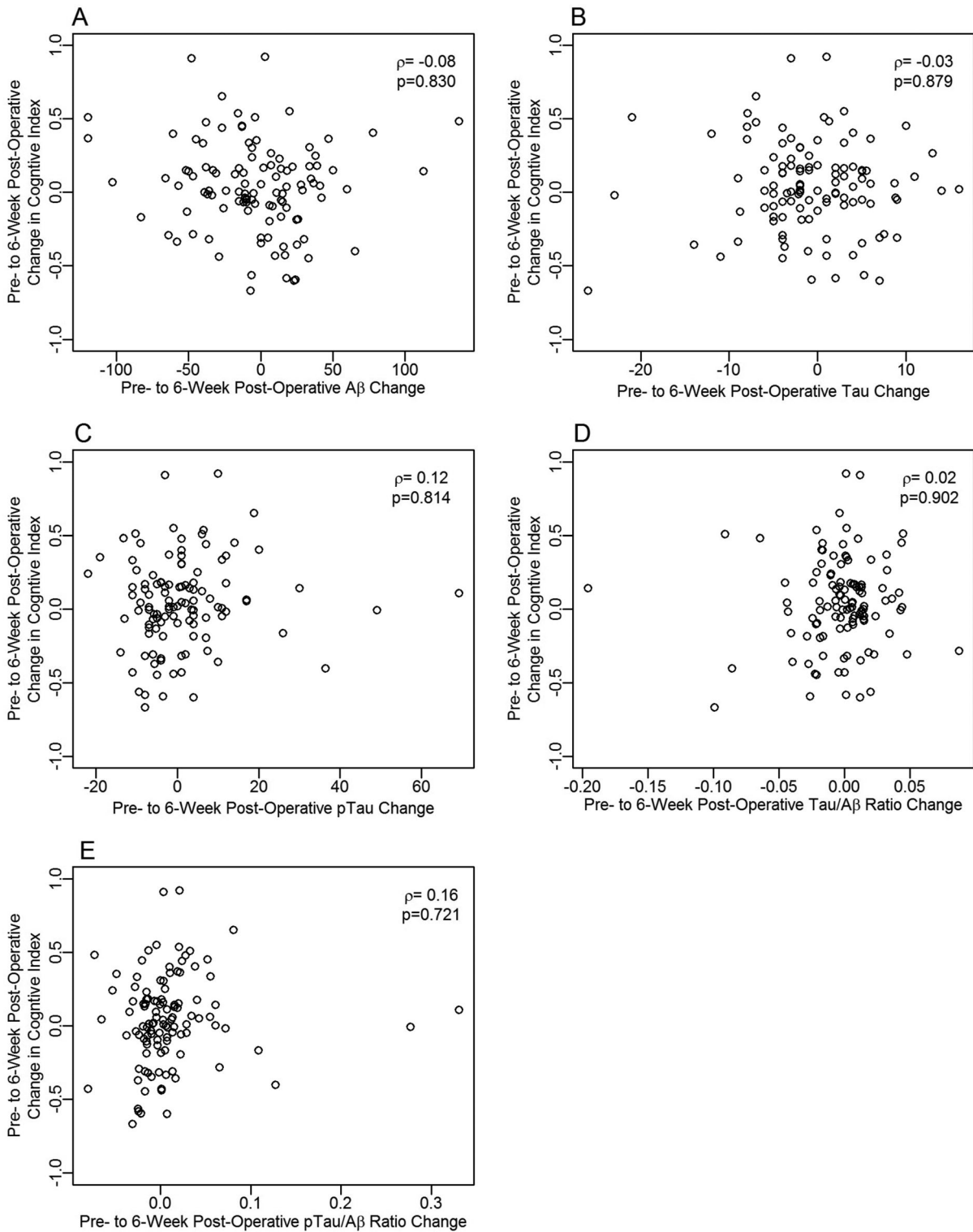


Figure 4. Correlation between changes in CSF biomarkers and overall cognitive index change from before to 6 weeks after surgery and anesthesia. (A) CSF A β ; (B) CSF tau; (C) CSF p-tau-181p; (D) tau/A β ratio; (E) p-tau-181p/A β ratio. A positive score on the x- or y-axis represents an improvement in cognitive score or an increase in the indicated biomarker from before to after surgery, respectively, and vice versa.

Table 3. Correlations between preoperative to 24-h postoperative CSF biomarker changes and preoperative to 6-week postoperative across cognitive domain score change.

| | Verbal domain | | Figural domain | | Attention/concentration | | Executive function | |
|-------------------|---------------------|---------|---------------------|---------|-------------------------|---------|---------------------|---------|
| | Spearman's rho | p-value | Spearman's rho | p-value | Spearman's rho | p-value | Spearman's rho | p-value |
| 24-h CSF change | | | | | | | | |
| A β | 0.04 (–0.16, 0.24) | 0.853 | –0.07 (–0.30, 0.17) | 0.853 | 0.06 (–0.15, 0.27) | 0.853 | –0.08 (–0.28, 0.13) | 0.830 |
| p-Tau | 0.13 (–0.07, 0.31) | 0.814 | 0.10 (–0.11, 0.31) | 0.827 | –0.10 (–0.30, 0.11) | 0.827 | 0.06 (–0.16, 0.27) | 0.853 |
| Tau | –0.05 (–0.25, 0.16) | 0.853 | 0.05 (–0.16, 0.26) | 0.853 | –0.03 (–0.26, 0.19) | 0.871 | 0.05 (–0.16, 0.26) | 0.853 |
| p-Tau/A β | 0.10 (–0.11, 0.29) | 0.827 | 0.12 (–0.10, 0.32) | 0.827 | –0.10 (–0.29, 0.10) | 0.827 | 0.05 (–0.17, 0.27) | 0.853 |
| Tau/A β | –0.08 (–0.28, 0.12) | 0.83 | 0.12 (–0.08, 0.31) | 0.814 | –0.06 (–0.28, 0.16) | 0.853 | 0.05 (–0.17, 0.26) | 0.853 |
| 6-week CSF change | | | | | | | | |
| A β | –0.09 (–0.29, 0.12) | 0.830 | –0.01 (–0.22, 0.21) | 0.981 | 0.10 (–0.11, 0.30) | 0.827 | –0.13 (–0.32, 0.08) | 0.814 |
| p-Tau | 0.11 (–0.09, 0.31) | 0.827 | 0.09 (–0.13, 0.30) | 0.83 | 0.08 (–0.12, 0.28) | 0.830 | 0.02 (–0.18, 0.21) | 0.902 |
| Tau | –0.13 (–0.33, 0.08) | 0.814 | 0.11 (–0.10, 0.32) | 0.827 | 0.00 (–0.20, 0.21) | 0.992 | –0.00 (–0.21, 0.20) | 0.992 |
| p-Tau/A β | 0.15 (–0.06, 0.34) | 0.792 | 0.06 (–0.15, 0.26) | 0.853 | 0.06 (–0.13, 0.25) | 0.851 | 0.06 (–0.14, 0.26) | 0.853 |
| Tau/A β | –0.04 (–0.24, 0.16) | 0.864 | 0.05 (–0.15, 0.24) | 0.853 | –0.07 (–0.26, 0.14) | 0.851 | 0.08 (–0.15, 0.29) | 0.841 |

The lack of postoperative change in CSF A β and tau levels reported here also differ with data from mouse models^{22–24} and in vitro^{25,26} systems demonstrating that anesthetic drugs and surgical stress promote A β and tau pathology. The discrepancy between these human data versus basic laboratory studies may be explained by species differences between humans and mice, or by differences in physiologic management between human anesthetic cases versus mouse studies, as many of these mouse model studies did not report intraoperative blood pressure, heart rate, oxygenation, and/or temperature data.^{23–25} Further, A β , tau, and p-tau-181p levels were measured here in human CSF, whereas many rodent studies examined these proteins in brain tissue sections^{22–24}; the differing results could reflect differences in the specimen types studied (i.e., human CSF versus mouse brain tissue).

The postoperative cognitive change data are reported here as group means and 95% confidence intervals. Most patients had a decrease in verbal memory from before to 6 weeks after surgery, yet an improvement in executive function over this period. These data are consistent with prior work demonstrating that most patients show improved executive function at 6 weeks after surgery.¹² To our knowledge, prior studies have not shown a verbal memory decline in the majority of older adults at 6 weeks after major surgery, although many prior studies simply reported the number or percentage of patients who met a specific decline threshold rather than providing mean verbal memory score values across all patients before and after surgery.^{12,52} Overall, since the average patient in this study had no significant change in overall cognitive function from before to 6 weeks after surgery, the cognitive data presented here offer a reassuring conclusion to older surgical patients.

Although average cognitive index and CSF biomarker levels did not significantly change from before to 6 weeks after surgery, there was significant variation among individual patients in these measures over time. This wide variation in postoperative changes in cognition and CSF biomarker levels among individual patients thus emphasizes the question this study was designed to address: Is there a relationship between postoperative changes in CSF biomarkers associated with AD and postoperative changes in cognition?

At a group level, this study provides a clear negative answer: there was no significant correlation between postoperative changes in overall cognition and CSF A β , tau, or p-tau-181p levels or their ratios (Fig. 4). Further, aside from the lack of statistical significance, the relatively small correlation coefficient values observed between postoperative changes in cognition and CSF biomarkers strongly suggest that even a much larger study would be unlikely to find a significant or clinically meaningful correlation between these variables.

This study has several limitations. First, the vast majority of the patients in this study were cognitively normal (median Mini-Mental State Examination [MMSE] = 29), none had a clinical diagnosis of AD or other dementia, only one had a diagnosis of MCI, only 16 had low CSF A β or high CSF tau levels (i.e., A + T– or A–T+), and only three patients had low CSF A β and high CSF p-tau-181p levels (i.e., A + T+). Thus, these data may have limited generalizability to older surgical patients with baseline amyloid and tau pathology, and those with baseline dementia or MCI, who may be at higher risk of cognitive decline after surgery.²⁰ The extent to which anesthesia and surgery accelerate amyloid and/or tau pathology and/or cognitive decline in patients who already have

Table 4. Multivariable linear regression models for the association of tau or tau/ β change from preop to either 24 h or 6 weeks after surgery, with cognitive change from preop to 6 weeks after surgery.

| Parameter | Estimate (95% CI) | <i>p</i> -value |
|---|----------------------|-----------------|
| Model 1—Association of preop to 24-h CSF tau change, preop to 6-week postop cognitive change | | |
| Intercept | 0.37 (−0.35, 1.1) | 0.307 |
| Baseline Cognitive Index | −0.14 (−0.24, −0.05) | 0.003 |
| Age (per year) | −0.01 (−0.02, 0.00) | 0.072 |
| Years of education | 0.02 (0.00, 0.04) | 0.100 |
| <i>APOE4</i> carrier versus non-carrier | −0.05 (−0.17, 0.08) | 0.465 |
| Surgery duration (per 30 min) | 0.01 (−0.01, 0.02) | 0.348 |
| Tau change 24 h | 0.00 (−0.01, 0.01) | 0.521 |
| Model 2—Association of preop to 24-h CSF tau/ $A\beta$ change, preop to 6-week postop cognitive change | | |
| Intercept | 0.36 (−0.36, 1.09) | 0.324 |
| Baseline Cognitive Index | −0.14 (−0.24, −0.05) | 0.004 |
| Age (per year) | −0.01 (−0.02, 0.00) | 0.078 |
| Years of education | 0.02 (0.00, 0.04) | 0.010 |
| <i>APOE4</i> carrier versus non-carrier | −0.04 (−0.17, 0.08) | 0.474 |
| Surgery duration (per 30 min) | 0.01 (−0.01, 0.03) | 0.326 |
| Tau/ $A\beta$ change 24 h | −0.01 (−1.6, 1.59) | 0.995 |
| Model 3—Association of preop to 6-week postop CSF tau change, preop to 6-week postop cognitive change | | |
| Intercept | 0.36 (−0.37, 1.08) | 0.330 |
| Baseline Cognitive Index | −0.14 (−0.24, −0.05) | 0.004 |
| Age (per year) | −0.01 (−0.02, 0.00) | 0.079 |
| Years of education | 0.02 (0.00, 0.04) | 0.101 |
| <i>APOE4</i> carrier versus non-carrier | −0.04 (−0.17, 0.08) | 0.505 |
| Surgery duration (per 30 min) | 0.01 (−0.01, 0.02) | 0.334 |
| Tau change 6-week | 0.00 (−0.01, 0.01) | 0.799 |
| Model 4—Association of preop to 6-week postop CSF tau/ $A\beta$ change, preop to 6-week postop cognitive change | | |
| Intercept | 0.36 (−0.36, 1.09) | 0.321 |
| Baseline Cognitive Index | −0.14 (−0.24, −0.05) | 0.004 |
| Age (per year) | −0.01 (−0.02, 0) | 0.075 |
| Years of education | 0.02 (0, 0.04) | 0.094 |
| <i>APOE4</i> carrier versus non-carrier | −0.05 (−0.17, 0.08) | 0.442 |
| Surgery duration (per 30 min) | 0.01 (−0.01, 0.02) | 0.323 |
| Tau/ $A\beta$ change 6-week | 0.36 (−1.32, 2.05) | 0.667 |

p-values are uncorrected for multiple comparisons.

significant levels of amyloid and tau pathology remains an important question for future study.

Second, these data do not show a correlation between AD-related CSF biomarker change and cognitive change from before to 6 weeks after surgery, a time interval during which cognitive deficits have been detected after anesthesia and surgery in numerous prior studies.^{10–12,16,17,40,53–70} Yet, this does not exclude the possibility that such a correlation exists over a longer postoperative follow-up period. However, with longer time intervals postsurgery, it becomes less clear that any changes in CSF biomarkers or cognition are directly related to the surgery; this is partly why the perioperative neurocognitive

disorders nomenclature¹¹ does not use the modifier “perioperative” for cognitive dysfunction occurring >1-year postsurgery. Nonetheless, since cognitive decline in AD typically occurs over 8–10 years,⁷¹ future studies should examine whether there are correlations between cognitive and CSF AD-related biomarker changes over longer periods after surgery.

Third, 30 of the original 140 patients enrolled were lost to follow-up prior to the 6-week follow-up visit. This rate of loss to follow-up is not surprising in studies like this that involve invasive procedures in older patients following major surgery. Yet, the loss to follow-up was not entirely random; patients lost to follow-up were significantly more likely to be African American, a challenge that other aging researchers have described and for which new strategies are being discussed to improve equity in subject representation for future studies.^{72,73} Patients lost to follow-up were also more likely to have a lower baseline cognitive index value, and had slightly lower aaMAC values (−0.08 aaMAC units lower, *p* = 0.0086; Table S1). Nonetheless, with 110 patients who returned for 6-week follow-up, this study still had >80% power to detect a Spearman $r_s \geq 0.3$ for the correlation between postoperative CSF tau change and preoperative to 6-week postoperative cognitive change, and no such correlation was seen. Further, a group of patients with complete 6-week follow-up data that matched key demographics (race, baseline cognition, gender, and surgical aaMAC) of the 30 patients lost to follow-up also showed no significant correlations between postoperative changes in CSF AD-related biomarkers and cognition (Tables S2–S5). Thus, even if the patients lost to follow-up had returned for the 6-week postoperative visit and contributed data to the study, it would still be highly unlikely that there would have been a significant correlation between postoperative CSF AD-related biomarker and cognitive changes.

Fourth, the cognitive data were not adjusted for practice or learning effects by comparison to a nonsurgical control group using reliable change index (RCI) or other regression methods.⁷⁴ We did not analyze the data this way, because our goal was simply to examine potential correlations between changes in CSF biomarkers and cognition from before to after surgery. The purpose of this study was not to determine how much of the cognitive change in individual patients was due to anesthesia/surgery versus practice or learning effects, or other potential causes of cognitive change after anesthesia/surgery (i.e., sleep disruption, pain, changes in ambulation, etc.).

To our knowledge, this study represents the largest cohort of older surgical patients to undergo cognitive testing and CSF biomarker measurements before and after surgery. The lack of significant changes in CSF $A\beta$, tau,

and p-tau-181p levels after surgery observed here suggest that the wide variety of non-cardiac, non-neurologic surgical procedures and anesthetic techniques studied here are unlikely to cause a significant acceleration of amyloid or tau neuropathology in the vast majority of community dwelling, cognitively normal older adults. The lack of association between postoperative changes in cognition and CSF biomarkers observed here also suggests that postoperative changes in cognition are unlikely to be related to changes in A β or tau pathology within 1–2 months after non-cardiac, non-neurologic surgery in cognitively older adults. Taken together, these results should thus provide reassurance that anesthesia and surgery are unlikely to accelerate amyloid or tau related neuropathological processes associated with AD in the 6 weeks after surgery in community-dwelling older adults.

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Author Contributions

M. B., J. N. B., M. C. W., C. N., M. R., and J. P. M. contributed to writing of the manuscript. M. C. W. and M. R. performed statistical analysis. All authors contributed to analyzing and interpreting the data. M. B., B. J. C., M. J. D., E. W. M., J. W. M., B. O., D. T. L., L. M. S., H. E. W. and H. J. C. contributed to patient recruitment, study design. M. B. obtained funding for this work with input from J. P. M., J. N. B., M. C. W., H. E. W., and H. J. C.

Conflicts of Interest

M. B. has received material support (i.e., EEG monitor loan) for a postoperative recovery study in older adults

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Appendix

The MADCO-PC (Markers of Alzheimer's Disease and neuroCognitive Outcomes after Perioperative Care) Investigators also include: C. L. Amundsen, R. Beach, E. Bennett, D. G. Blazer, M. P. Bolognesi, R. Brassard, B. E. Brigman, T. Bunning, J. Carter, J. Chapman, V. Cheong, T. A. D'Amico, J. K. DeOrto, T. Ellett, D. Erdmann, R. M. Esclamado, M. N. Ferrandino, B. Funk, J. C. Gadsden, S. Grant, G. E. Garrigues, J. R. Guercio, A. S. Habib, R. K. Hallows, D. H. Harpole, M. G. Hartwig, S. T. Hollenbeck, J. Hu, R. Huang, E. Iboaya, B. A. Inman, D. W. Jang, J. Kaisen, A. Khan, S. Lagoo-Deenadayalan, P. S. Lee, W. T. Lee, J. Lemm, H. Levinson, M. E. Lipkin, C. R. Mantyh, K. T. Martucci, D. L. McDonagh, J. Migaly, S. K. Mithani, P. Mosca, M. F. Newman, K. Ni, T. Novick, T. N. Pappas, A. N. Perez, A. C. Peterson, T. J. Polascik, A. Podgoreanu, G. M. Preminger, Q. J. Quinones, E. N. Rampersaud, A. Ray, K. Roberts, C. N. Robertson, S. Roman, S. Runyon, A. Sandler, F. Sbahi, C. D. Scales, R. P. Scheri, S. K. Smith, L. Talbot, J. K. M. Thacker, J. Thomas, B. C. Tong, Y. Toulgoat-Dubois, A. Tu, S. N. Vaslef, N. Waldron, D. S. Warner, X. Wang, S. S. Wellman, T. Wickenheisser, M. Woldorff, C. Young, S. Zani.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Demographics of lost to follow-up (LTFU) cohort compared to returning cohort at 6 weeks.

Table S2. Comparison of cognitive trajectories between entire cohort who returned for 6-week follow-up, and a subset of $n = 26$ patients who returned for 6-week follow-up yet who had baseline characteristics similar to the patients lost to follow-up prior to the 6-week postoperative study visit.

Table S3. Correlations between preoperative CSF biomarker levels and preoperative to 6-week postoperative cognitive change, in the entire cohort who returned for 6-week follow-up, and in a subset of $n = 26$ patients who returned for 6-week follow-up yet who had baseline characteristics similar to the patients lost to follow-up prior to the 6-week postoperative study visit.

Table S4. Correlations between preoperative to 24-h postoperative CSF biomarker change and preoperative to 6-week postoperative cognitive change, in the entire cohort who returned for 6-week follow-up, and in a subset of $n = 26$ patients who returned for 6-week follow-up yet who had baseline characteristics similar to the patients lost to follow-up prior to the 6-week postoperative study visit.

Table S5. Correlations between preoperative to 6-week postoperative CSF biomarker changes and preoperative to 6-week postoperative cognitive change, in the entire cohort who returned for 6-week follow-up, and in a subset of $n = 26$ patients who returned for 6-week follow-up yet who had baseline characteristics similar to the patients lost to follow-up prior to the 6-week postoperative study visit.