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Cognitive and Cerebrospinal Fluid Alzheimer's Disease–related Biomarker Trajectories in Older Surgical Patients and Matched Nonsurgical Controls

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ABSTRACT

Background: Anesthesia and/or surgery accelerate Alzheimer's disease pathology and cause memory deficits in animal models, yet there is a lack of prospective data comparing cerebrospinal fluid (CSF) Alzheimer's disease–related biomarker and cognitive trajectories in older adults who underwent surgery *versus* those who have not. Thus, the objective here was to better understand whether anesthesia and/or surgery contribute to cognitive decline or an acceleration of Alzheimer's disease–related pathology in older adults.

Methods: The authors enrolled 140 patients 60 yr or older undergoing major nonneurologic surgery and 51 nonsurgical controls *via* strata-based matching on age, sex, and years of education. CSF amyloid β (Aβ) 42, tau, and p-tau-181p levels and cognitive function were measured before and after surgery, and at the same time intervals in controls.

Results: The groups were well matched on 25 of 31 baseline characteristics. There was no effect of group or interaction of group by time for baseline to 24-hr or 6-week postoperative changes in CSF Aβ, tau, or p-tau levels, or tau/Aβ or p-tau/Aβ ratios (Bonferroni $P > 0.05$ for all) and no difference between groups in these CSF markers at 1 yr ($P > 0.05$ for all). Nonsurgical controls did not differ from surgical patients in baseline cognition (mean difference, 0.19 [95% CI, –0.06 to 0.43]; $P = 0.132$), yet had greater cognitive decline than the surgical patients 1 yr later (β, –0.31 [95% CI, –0.45 to –0.17]; $P < 0.001$) even when controlling for baseline differences between groups. However, there was no difference between nonsurgical and surgical groups in 1-yr postoperative cognitive change in models that used imputation or inverse probability weighting for cognitive data to account for loss to follow up.

Conclusions: During a 1-yr time period, as compared to matched nonsurgical controls, the study found no evidence that older patients who underwent anesthesia and noncardiac, nonneurologic surgery had accelerated CSF Alzheimer's disease–related biomarker (tau, p-tau, and Aβ) changes or greater cognitive decline.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Anesthesia and surgery have been associated with increases in Alzheimer's disease pathology and memory deficits in animal models
- It is unclear whether anesthesia and surgery are associated with increases in Alzheimer's disease pathology and memory deficits in humans

What This Article Tells Us That Is New

- In this prospective matched cohort study, there is no conclusive evidence that anesthesia and surgery are associated with increases in Alzheimer's disease pathology or cognitive deficits in humans

Some older patients have lasting cognitive impairment after anesthesia and surgery, but it remains unclear to what extent this cognitive decline is caused by anesthesia and/or surgery *versus* the extent to which it reflects their natural cognitive trajectory (see review[1]). Postoperative

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cognitive dysfunction[2] and postoperative neurocognitive disorder[3] are both characterized by objectively measured cognitive decline within 1 to 12 months after surgery; postoperative neurocognitive disorder also requires the presence of subjective cognitive complaints. Since postoperative neurocognitive disorder is a relatively new term, its incidence is not yet well defined; postoperative cognitive dysfunction (as defined by a 1 SD or greater decrease in one or more cognitive domains at 6 weeks after surgery) has been reported in up to 41% of surgical patients above age 60 yr.[4] Postoperative cognitive dysfunction is associated with decreased quality of life, increased workforce attrition, and increased postoperative mortality.[5]

One theory for perioperative neurocognitive disorders suggests surgical trauma/stress and anesthetic drugs accelerate Alzheimer's disease pathology, which then disrupts brain function and results in postoperative cognitive dysfunction and/or neurocognitive disorder. This theory is supported by work demonstrating that inhaled anesthetics promote amyloid β (Aβ) oligomerization[6] *in vitro*, and tau phosphorylation and aggregation[7] in mice. In humans, 24-h postoperative cerebrospinal fluid (CSF) tau levels increase after a variety of surgical procedures and anesthetic techniques.[8–13] However, the largest postoperative increases in CSF tau levels have been observed after neurosurgical and otolaryngology procedures, which involve direct surgical manipulation of the brain and/or dura.[9,13] Further, the absence of a nonsurgical control group in these studies makes it unclear to what extent these postoperative CSF Alzheimer's disease biomarker changes were due to anesthesia and/or surgery *versus* the passage of time or other factors, such as inflammation due to repeated lumbar punctures.[14,15]

To better understand whether anesthesia and surgery contribute to cognitive decline and/or an acceleration of Alzheimer's disease–related pathology in older adults, we compared changes in cognition and CSF Alzheimer's disease–related biomarkers from before to after surgery between older surgical patients and demographically matched nonsurgical controls who underwent identical assessments over the same time intervals as the surgical patients. This builds upon our previous work[16] to determine whether surgical patients had significantly more abnormal cognitive scores or CSF Alzheimer's disease–related biomarkers than nonsurgical community-dwelling older adults across a 1-yr study period.

Materials and Methods

This is a secondary analysis of data from Markers of Alzheimer's Disease and neuroCognitive Outcomes after Perioperative Care (MADCO-PC), an observational cohort study registered with clinicaltrials.gov (NCT01993836) in November 2013, and approved by the Duke University institutional review board.[16] The primary aim of MADCO-PC was to examine the extent to which there is a correlation between postoperative changes in both cognition and CSF Alzheimer's disease–related biomarkers in older surgical patients, which was published last year.[16] Our previous report[16] included only surgical patients who returned for 6-week follow-up (n = 110), while the current study included all surgical patients who completed baseline cognitive testing (n = 137).

MADCO-PC study participants provided informed consent before enrollment. Patients were prospectively

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screened (and enrolled if willing) if they were 60 yr or older undergoing noncardiac, nonneurologic surgery under general anesthesia for 2 h or more, and lived within a 60-mile radius (to help ensure that transportation to the hospital for study visits would not be an issue). For additional inclusion or exclusion criteria, see the supplemental methods (https://links.lww.com/ALN/D457).

Upon receipt of additional funding, enrollment of an approximately 50-participant matched nonsurgical group began in February 2016, after surgical enrollment was complete; the nonsurgical controls underwent the same assessments as the surgical patients at the same time intervals. We used strata-based enrollment to recruit nonsurgical controls who, at a group level, matched the surgical cohort based on age, sex, and years of education (see Supplemental Table 1 for additional details, https://links.lww.com/ALN/D457). This strategy necessitated enrolling the nonsurgical controls after the demographics of the surgical patients were known; thus, surgical patients were enrolled from 2013 to 2016 (with 1-yr follow-ups completed in 2017), and nonsurgical controls were enrolled from 2016 to 2018 (with 1-yr follow-ups completed in 2019).

For strata-based matching, age was divided into four strata of 60 to 64, 65 to 69, 70 to 74, and more than 75 yr. Years of education (total years of complete schooling) was divided into four strata of less than 12 (less than high school), 12 (high school), 13 to 15 (partial college or associate's degree), and more than 16 yr (college degree or more). Two sex strata by four age strata by four education strata produced 32 different groups ($2 \times 4 \times 4 = 32$). Into these 32 bins, we then sorted the 110 surgical patients who returned for the 6-week follow-up. We then recruited a targeted number of nonsurgical participants within each of these strata groups, such that the surgical and nonsurgical groups would be matched overall on these baseline characteristics, even though the groups differed in size (n = 110 surgical patients and n = 51 nonsurgical controls). Nonsurgical controls were recruited from research subject registries from the Duke Center for the Study of Aging (n = 32) and the Duke Bryan Alzheimer's Disease Research Center (n = 7), or *via* advertising at Duke Hospital and public locations within an approximately 60-mile radius (n = 12), the same area in which surgical patients had to live to participate.

APOE genotyping was performed as described.[9] Mild cognitive impairment and Alzheimer's disease diagnoses were based on International Classification of Diseases, Tenth Revision, codes in patients' medical records at the time of study entry.

Cognitive Testing and Analysis

At preoperative, 6-week postoperative, and 1-yr postoperative visits (and the same intervals in controls), participants completed a cognitive test battery as previously described (Supplemental Digital Content, https://links.lww.com/ALN/D457).[17] Factor analysis of these tests produced four cognitive domains: verbal memory, visual memory, executive function, and attention/concentration (see Supplemental Digital Content for details, https://links.lww.com/ALN/D457).[16] The continuous cognitive index was defined as the average of these four cognitive domain scores and represents a sensitive global measure of cognition that our group has used in multiple studies for more than 20 yr.[17,18] Patients also completed questionnaires to assess perceived physical function, general health, instrumental activities of daily living, depression and anxiety symptoms, social support, and cognitive difficulties (Supplemental Digital Content, https://links.lww.com/ALN/D457). Patients also completed the Mini-Mental State Examination. Mild and major postoperative neurocognitive disorder were defined as previously described (see Supplemental Digital Content for details, https://links.lww.com/ALN/D457).[3] Postoperative delirium assessments in these patients are described in the Supplemental Digital Content (https://links.lww.com/ALN/D457).

CSF Sampling and Alzheimer's Disease Biomarker Assays

CSF samples (10 to 12 ml each) were obtained at preoperative baseline, and 24 h, 6 weeks, and 1 yr after surgery, and the same time intervals in nonsurgical controls. Aβ, tau, and p-tau-181p were measured *via* AlzBio3 assays (Innogenetics; Ghent, Belgium).[16] The AlzBio3 assay was no longer in production by the time 1-yr CSF sample collection was complete, so CSF Aβ, tau, and p-tau-181p were measured in 1-yr samples with the Fujirebio Lumipulse platform (USA; see Supplemental Digital Content for details, https://links.lww.com/ALN/D457).

Statistical Analysis

We previously observed baseline to 24-h postoperative CSF tau level increases of 87 pg/ml.[9] Based on this, we calculated that 85 or more surgical and 42 or more nonsurgical participants would provide 80% power with $\alpha = 0.05$ to detect a 65-pg/ml smaller increase in 24-h CSF tau change among nonsurgical controls *versus* surgical patients (*i.e.*, a 75% smaller increase in CSF tau levels among controls than surgical patients). Based on previous work,[17] this sample size also provides 80% or greater power to detect a 0.15 or greater unit difference in continuous cognitive index change (a moderate Cohen's d effect size of 0.55) from before to 6 weeks or 1 yr later between surgical patients and nonsurgical controls, which is even smaller than the difference in continuous cognitive index change seen between patients with *versus* without postoperative cognitive dysfunction in a previous study.[19] Given the 51 to 53% rate of loss to follow-up observed in previous studies with multiple lumbar punctures,[10,20] we enrolled 140 surgical and 51 nonsurgical participants to ensure sufficient sample size after loss to follow-up; see the supplemental methods for details (https://links.lww.com/ALN/D457).

CSF Alzheimer's disease–related biomarker trajectories (from baseline to the 24-h and 6-week time points) were compared with nonparametric longitudinal models in R version 4.2.0 (https://www.R-project.org/, accessed December 11, 2023).[21] CSF biomarker data at the 1 yr time point were analyzed using Wilcoxon rank sum tests. To reduce type I error, the 5 CSF biomarker models were Bonferroni-corrected. Hodges–Lehmann group median difference estimates were used to calculate 95% CI for all nonparametric variables, including CSF biomarkers; Hodges–Lehmann estimates do not match the absolute differences between groups because these are nonparametric, rank-based calculations.

Mild and major postoperative neurocognitive disorder rates were compared using chi-square or Fisher exact tests. A multivariable linear regression model was used to assess group differences in 1-yr continuous cognitive index change, with multivariable adjustment for baseline cognition and statistically significant baseline differences between groups. Multiple imputation and inverse probability weighting were applied to address missing data. A tipping point approach was utilized to address the possibility that the overall results may have differed if 1-yr cognitive scores were not missing at random (Supplemental Digital Content, https://links.lww.com/ALN/D457). Finally, we examined the effect on the overall study findings if we substituted the worst possible 1-yr cognitive test scores for surgical patients who died before the 1-yr visit, were institutionalized (*e.g.*, in a nursing home), or were too sick to return for 1-yr cognitive testing.

We also performed a series of *post hoc* sensitivity analyses and investigated the impact of four alternative modeling approaches on our findings for cognitive function. Specifically, first, we compared cognitive outcomes between recruitment sources (for nonsurgical controls) *via t* test to address the possibility of confounding if nonsurgical controls recruited *via* aging or Alzheimer's disease–related research registries were at higher long-term cognitive decline risk *versus* nonsurgical controls recruited by public flyers. Second, we used baseline attention/concentration instead of the overall continuous cognitive index in the linear regression model, given that surgical patients and nonsurgical controls trended toward a difference in this cognitive domain (table 1). Third, since different statistical modeling techniques can yield divergent results when applied to the same data,[22] we also analyzed cognition as a 1-yr follow-up score rather than baseline to 1-yr change score to investigate the impact of this parameterization. Fourth, we also included a longitudinal mixed model of baseline, 6-week, and 1-yr cognitive function with time interaction terms for group and covariates that had significant main effects.

Next, we examined the possibility that a subgroup of surgical patients, such as those with postoperative delirium, would have worse cognitive dysfunction at the 1-yr time point than the other groups (surgical patients without postoperative delirium, nonsurgical controls). A Fisher exact test was used to compare the fraction of patients within each group with an overall cognitive index at least one unit below the sample mean at the 1-yr time point. Last, we analyzed a longitudinal mixed model of group (surgical patients with postoperative delirium, surgical patients without postoperative delirium, nonsurgical controls), time (baseline, 6 weeks, 1 yr), and a group-by-time interaction to determine whether surgical patients with postoperative delirium had worse cognitive scores than the other subgroups at baseline or over time. Unless otherwise specified, all statistical analyses were performed in SAS v9.4 (SAS Institute Inc., USA; see Supplemental Methods, https://links.lww.com/ALN/D457).

Results

Figure 1 shows participant enrollment flow; model-specific sample sizes are described in the Supplemental Digital Content (https://links.lww.com/ALN/D457). Intraoperative factors in the surgical cohort are described in Supplemental Table 2 (https://links.lww.com/ALN/D457). Of 31 measured baseline characteristics, 25 did not differ between surgical patients and nonsurgical controls (table 1), including the three characteristics the groups were matched upon (age, sex, and years of education). However, as compared to nonsurgical controls, surgical patients had more hypertension (absolute difference in rates between surgical and nonsurgical groups, 25.5% [95% CI, 8.38 to 42.5%]; $P = 0.004$), lower self-reported physical functional capacity (Hodges–Lehmann group median difference estimate, –8.00 [95% CI, –15.2 to –1.00]; $P = 0.012$), worse subjective health scores on the Medical Outcomes Study 36-Item Short Form Health Survey General Health Perceptions questionnaire (Hodges–Lehmann group median difference estimate, 1.00 [95% CI, 0.00 to 1.00]; $P = 0.001$), and worse scores on the Social Activities (Hodges–Lehmann group median difference estimate, 2.00 [95% CI, 0.00 to 3.00]; $P = 0.016$) and Symptom Limitations scales (Hodges–Lehmann group median difference estimate, 1.14 [95% CI, 0.00 to 2.29]; $P = 0.045$). However, a higher proportion of the nonsurgical cohort had baseline CSF Aβ levels less than 250 pg/ml and/or CSF tau levels greater than 93 pg/ml (indicators of brain Aβ and tau pathology, respectively)[23,24] than were seen in the surgical group (difference, 22.9% [95% CI, 6.77 to 39.1%]; $P = 0.004$). Among 185 participants with complete baseline cognitive data, no surgical patients or nonsurgical controls had a diagnosis of mild cognitive impairment or Alzheimer's disease, although 13% of the surgical cohort and 10% of the nonsurgical controls had Mini-Mental State Examination scores less than 27 (which has been shown to have 87% specificity for mild cognitive impairment).[25]

Figure 2 shows median CSF biomarker levels in the surgical and nonsurgical cohorts at baseline, 24 h, and 6 weeks (from the AlzBio3 assay) and at 1 yr after surgery (from the Fujirebio Lumipulse platform). There were no significant

Table 1. Baseline Demographics, Cognitive Function, and Cerebrospinal Fluid Biomarkers in Surgical Patients, Strata-matched Nonsurgical Controls

	Surgical Patients (n = 137)	Nonsurgical Controls (n = 48)	*P* Value
Baseline patient demographics			
Age*	68 [64, 73]	68 [64, 74.5]	0.626†
Non-White race*	17 (12.78%)	11 (22.92%)	0.096‡
Male sex*	79 (59.40%)	28 (58.33%)	0.898‡
Years of education§	15.25 [12.5, 18]	16 [13.5, 18]	0.193†
Baseline comorbidities			
Cerebrovascular disease‖	6 (4.51%)	0 (0.00%)	0.338#
Parkinson's disease‖	1 (0.75%)	0 (0.00%)	1.000#
Hypertension‖	89 (66.92%)	17 (41.46%)	0.004‡
Heart disease‖	32 (24.06%)	8 (19.51%)	0.545‡
Diabetes‖	40 (30.08%)	8 (19.51%)	0.186‡
Renal disease‖	14 (10.53%)	2 (4.88%)	0.365#
Chronic lung disease‖	16 (12.03%)	3 (7.32%)	0.569#
Thyroid disease‖	20 (15.04%)	7 (17.07%)	0.753‡
Baseline cognitive performance			
Mini-Mental State Examination	29 [28, 29]	29 [27, 30]	0.560†
Mini-Mental State Examination < 25	7 (5.11%)	1 (2.08%)	0.682#
Continuous cognitive index	0.05 ± 0.75	0.24 ± 0.73	0.132**
Verbal memory	0.42 ± 0.91	0.61 ± 1.13	0.233**
Visual memory	–0.12 ± 0.97	0.06 ± 0.87	0.254**
Executive function	0.05 ± 1.09	0.14 ± 0.93	0.610**
Attention/concentration	–0.14 ± 0.84	0.15 ± 1.02	0.057**
APOE4 genotypes and baseline Alzheimer's disease–related biomarkers			
APOE4-positive	39 (28.47%)	15 (31.25%)	0.715‡
Amyloid β, tau classification††			0.002#
$A^+ \mid T^+$	2 (2.04%)	3 (6.52%)	
$A^+ \mid T^-$	15 (15.31%)	10 (21.74%)	
$A^- \mid T^+$	1 (1.02%)	6 (13.04%)	
$A^- \mid T^-$	80 (81.63%)	27 (58.70%)	
Baseline mental and physical health, activities, and quality of life measures			
Center for Epidemiologic Studies Depression Scale depression symptoms (–)‡‡	8 [3.16, 15]	7 [4.5, 12.5]	0.617†
State-Trait Anxiety Inventory anxiety symptoms (–)§§	28.5 [23, 37]	27 [23, 32.5]	0.400†
Duke Activity Status Index perceived physical function (+)§§	21.1 [10, 40.2]	32.58 [18.7, 50.7]	0.012†
Medical Outcomes Study 36-Item Short Form Health Survey General Health Perceptions (–)‡‡	3 [2, 3]	2 [1, 3]	0.001†
Medical Outcomes Study 36-Item Short Form Health Survey Work Activities (–)*	7 [4, 10]	6 [4.5, 7.5]	0.103†
Instrumental Activities of Daily Living (–)*	6 [6, 6]	6 [6, 6]	0.575†
Cognitive difficulties (–)§§	77 [64, 93.39]	79.01 [66.5, 88]	0.978†
Social activities (–)‡‡	16 [13, 19.2]	13.5 [11, 18]	0.016†
Social support (+)§§	86.28 [73, 93]	82 [63.5, 93]	0.259†
Symptom limitations (–)§§	12.57 [9.14, 16]	10.29 [9, 14.86]	0.045†

Values represent mean ± SD, medians [quartile 1, quartile 3], or n (%). A minus sign (–) indicates that a lower score is better; a positive sign (+) indicates that a higher score is better.
*Missing for four surgical patients. †Wilcoxon test. ‡Chi-square test. §Missing for one surgical patient. ‖Missing for four surgical patients and seven nonsurgical controls. #Fisher exact test. **_t_ Test. ††A small number of participants had missing cerebrospinal fluid samples due to refusal of or inability to perform the lumbar puncture, thus excluding n = 9, 17, and 13 surgical participants and n = 0, 4, and 10 nonsurgical controls from baseline, 24 h, and 6-week cerebrospinal fluid Alzheimer's disease biomarker analyses, respectively. ‡‡Missing for two surgical patients. §§Missing for three surgical patients.

differences in CSF tau, p-tau-181p, or Aβ levels or the tau/Aβ or p-tau-181p/Aβ ratios between groups, and no effects of time or group-by-time interactions for any of the CSF Alzheimer's disease–related biomarkers measured at baseline, 24 h, or 6 weeks ($P > 0.05$ for all after Bonferroni correction; Supplemental Table 3, https://links.lww.com/ALN/D457; fig. 2). In a separate analysis of 1-yr CSF biomarker values, there were no significant differences between groups for Aβ (Hodges–Lehmann group median difference estimate, –72 [95% CI, –224 to 75]; $P > 0.999$), tau (2 [95% CI, –69 to 75]; $P > 0.999$), p-tau-181p (4.5 [95% CI, –4.2 to 16]; $P > 0.999$), tau/Aβ (0.03 [95% CI, –0.03 to 0.10]; $P > 0.999$), or p-tau-181p/Aβ (0.006 [95% CI, –0.001 to 0.014]; $P = 0.400$) after Bonferroni correction (fig. 2).

Supplemental Table 4 (https://links.lww.com/ALN/D457) summarizes scores on each cognitive test at baseline, 6 weeks later, and 1 yr later in the surgical and nonsurgical cohorts; the continuous cognitive index and cognitive domain data in both groups over time are shown in figure 3 with statistics for group, time, and group-by-time effects. There was no significant difference between surgical patients and nonsurgical controls in the rate of mild postoperative neurocognitive

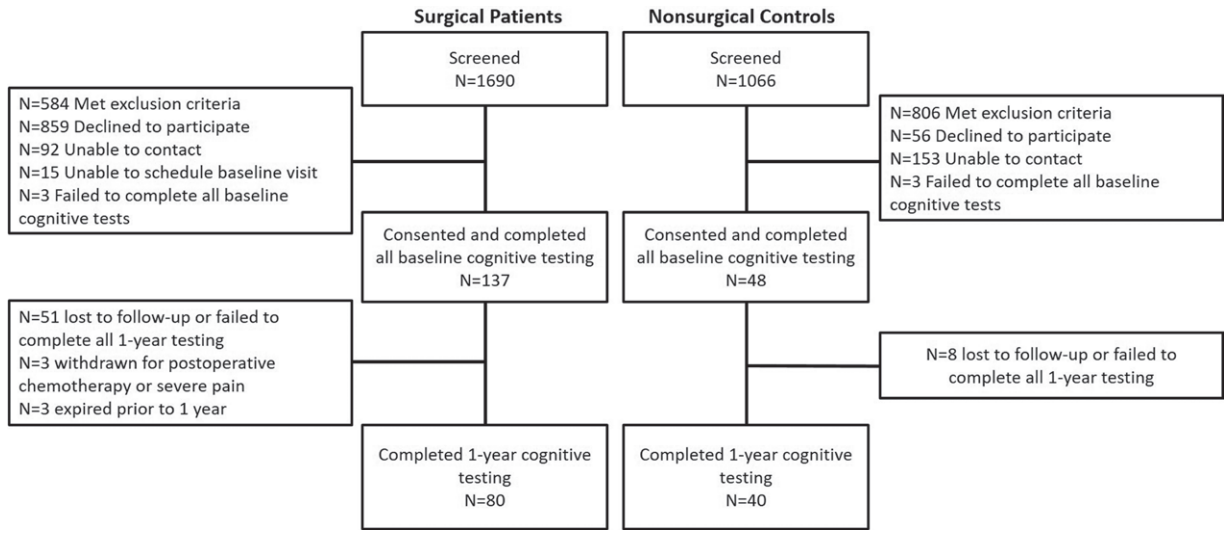

Fig. 1. Participant consort diagram. Surgical patients (*left*) and nonsurgical controls (*right*).

disorder (n = 25 of 105 surgical patients, 18 of 46 nonsurgical controls; absolute difference in rate between groups, –15.3% [95% CI, –31.6 to 0.97%]; $P = 0.110$) or major postoperative neurocognitive disorder (n = 1 of 103 surgical patients, 0 of 46 nonsurgical controls; 0.97% [95% CI, –0.92 to 2.86%]; $P > 0.999$) between groups at 6 weeks after Bonferroni correction. Similarly, there was no group difference in rates of mild or major neurocognitive disorder at 1 yr after Bonferroni correction (mild: n = 32 of 80 surgical patients, 19 of 40 nonsurgical controls; absolute difference in rate between groups, –7.50% [95% CI, –26.3 to 11.3%]; $P = 0.883$; major: n = 0 of 79 surgical patients, 2 of 40 nonsurgical controls; –5.00% [95% CI, –11.75 to 1.75%]; $P = 0.222$).

In a linear regression model for cognitive change controlling for the baseline differences observed between groups in table 1, the nonsurgical controls still had greater cognitive decline from baseline to 1 yr than the surgical patients (β, –0.31 [95% CI, –0.45 to –0.17]; $P < 0.001$; table 2). To address the possibility of greater loss to follow up among patients who may have been more likely to experience cognitive decline, we repeated this analysis on 1-yr cognitive data using inverse probability weighting and multiple imputation. Inverse probability weighting showed similar results to the observed data model, in which nonsurgical controls had greater 1-yr cognitive decline than surgical patients (β, –0.33 [95% CI, –0.47 to 0.18]; $P < 0.001$; Supplemental Table 5, https://links.lww.com/ALN/D457). Although no longer significant when using imputed data, there was a potential trend toward greater 1-yr cognitive decline in the nonsurgical controls *versus* surgical patients (β, –0.16 [95% CI, –0.32 to 0.01]; $P = 0.071$; Supplemental Table 6, https://links.lww.com/ALN/D457).

To address the potential for data missing not at random, we used a tipping point approach to calculate the shift in imputed 1-yr cognitive decline scores of surgical patients who did not return for 1-yr follow-up, which would be required in order to conclude that surgical patients had significantly greater cognitive decline at 1 yr than nonsurgical controls. The imputed mean 1-yr continuous cognitive index change among surgical patients lost to follow-up was –0.22, while the actual 1-yr continuous cognitive index change among surgical patients who returned for follow-up was –0.03. Thus, based on the tipping point analysis, in order for the surgical group as a whole to have had greater cognitive decline than the nonsurgical controls at 1 yr, every surgical patient lost to follow-up at 1 yr would have to have experienced a –1.08 further shift in their mean imputed 1-yr cognitive decline scores (*i.e.*, beyond –0.22). This means that the surgical patients lost to follow-up would have had a mean 1-yr cognitive change of -1.30 ± 0.62, which would be approximately 4 SDs below the actual observed 1-yr cognitive change among surgical patients who did return for follow-up (mean ± SD, -0.03 ± 0.33). This equates to a Cohen's *d* effect size of 2.69, which is implausibly large compared to, for instance, the Cohen's *d* of 1.38 previously observed between cognitively normal *versus* mild cognitive impairment patients.[26] While theoretically possible, it is highly unlikely that we would have observed nearly double this magnitude of an effect (*i.e.*, a Cohen's *d* of 2.69) between surgical patients who did *versus* did not return for 1-yr cognitive testing.

Of the 57 surgical patients who did not return for 1-yr cognitive testing (of the 137 who completed the baseline study visit), 4 passed away before the 1-yr time point, and 6 others were too ill to return at the 1-yr time point or were unable to return because they were living in nursing homes or other assisted living facilities. Hence, we examined the effect on the 1-yr cognitive change analysis of imputing

the worst possible cognitive test values for these 10 surgical patients at the 1-yr time point (*i.e.*, if they had gotten the worst score on every individual test at the 1-yr time point). For this analysis, we used the previously imputed scores for the nonsurgical and other 47 surgical patients who did not return for 1-yr follow-up, since they were still alive and living independently, and many simply did not want to return for the 1-yr study visit due to other obligations. When using this approach, the mean 1-yr cognitive change in the surgical patients was still not significantly worse than the mean 1-yr cognitive change in the nonsurgical controls (β for nonsurgical controls *versus* surgical controls, 0.03 [95% CI, –0.27 to 0.33]; $P = 0.843$; Supplemental Table 7, https://links.lww.com/ALN/D457).

Further, we performed six additional analyses to ensure that our findings were robust to possible confounding. First, we checked whether there was a confounding effect of nonsurgical control recruitment source (public flyers *vs.* aging-related research registries) on baseline to 1-yr changes in cognition. The recruitment source for nonsurgical controls (*i.e.*, public flyers *vs.* registries) was not associated with 6-week (mean difference, 0.09 [95% CI, –0.12 to 0.30]; $P = 0.391$) or 1-yr cognitive change (0.23 [95% CI, –0.02 to 0.47]; $P = 0.069$), although we may have been underpowered to detect effect sizes in these ranges given the small sample sizes (at baseline, 12 patients recruited from flyers *vs.* 39 patients recruited from aging/Alzheimer's disease registries).

Second, there remained a significant worsening of cognition in the nonsurgical group even if we included baseline attention/concentration (rather than baseline continuous cognitive index) in our linear regression model for cognitive change (β, –0.30 [95% CI, –0.44 to –0.16]; $P < 0.001$; Supplemental Table 8, https://links.lww.com/ALN/D457). Third, our alternative model of 1-yr cognitive index scores (rather than change in cognitive index values from before to 1 yr after surgery) also showed similar results (*i.e.*, the surgical patients did not have worse cognition at the 1-yr time point than nonsurgical controls; in fact, the nonsurgical controls had worse cognition at 1 yr than the surgical patients; β, –0.31 [95% CI, –0.45 to –0.17]; $P < 0.001$; Supplemental Table 9, https://links.lww.com/ALN/D457). Fourth, a longitudinal mixed model for cognitive function showed a significant interaction between group and time for continuous cognitive index change from baseline to 1-yr follow-up. In this model, as in the primary linear regression model, the nonsurgical controls again had greater cognitive decline at 1 yr (β, –0.30 [95% CI, –0.43 to –0.18]; $P < 0.001$; Supplemental Table 10, Supplemental Figure 1, https://links.lww.com/ALN/D457).

Fifth, we explored the possibility that although there was a lack of evidence that the surgical group had worse cognitive decline than the nonsurgical group overall, there may have been a subgroup of surgical patients with worse cognitive dysfunction (such as those who developed postoperative delirium) than both the rest of the surgical group and the nonsurgical group. Indeed, in this exploratory analysis, the percentage of each group with an overall cognitive index at least one unit below the sample mean in this cohort (*i.e.*, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, objective criteria for mild neurocognitive disorder[27]) at the 1-yr time point was 42.9% (3 of 7) among surgical patients with postoperative delirium, 6.85% (5 of 73) among surgical patients without postoperative delirium, and 7.5% (3 of 40) among the nonsurgical controls (overall $P = 0.037$). Sixth, we explored whether surgical patients with *versus* without postoperative delirium had different cognitive trajectories than nonsurgical controls. This model suggested that surgical patients who later developed postoperative delirium (n = 7) started with a lower cognitive baseline than both the surgical patients who did not develop postoperative delirium (n = 73; β, –0.42 [95% CI, –0.83 to –0.01]; $P = 0.047$) and the nonsurgical controls (n = 40; β, –0.49 [95% CI, –0.92 to –0.05]; $P = 0.029$; Supplemental Figure 2, https://links.lww.com/ALN/D457). Additionally, the surgical patients who developed postoperative delirium had steeper trajectories of baseline to 1-yr cognitive decline than surgical patients who did not develop postoperative delirium (β, –0.28 [95% CI, –0.50 to –0.05]; $P = 0.017$). However, the surgical patients who developed postoperative delirium did not have steeper trajectories of baseline to 1-yr cognitive decline than nonsurgical controls (β, 0.01 [95% CI, –0.23 to 0.24]; $P = 0.948$). It is important to note that only seven surgical patients who developed postoperative delirium returned for 1-yr follow-up, so these conclusions are likely underpowered. The small number of patients with postoperative delirium emphasizes the need for caution in concluding that patients with delirium have greater cognitive decline than patients without delirium from these data.

Discussion

In this prospective cohort study, with strata-based matching of nonsurgical controls to the surgical patient group based on age, sex, and education, there was no difference between groups in CSF Aβ, tau, or p-tau-181p levels at 24 h, 6 weeks, or 1 yr. Further, as compared to nonsurgical controls, the surgical patients did not have a greater incidence of postoperative neurocognitive disorder from baseline to 6 weeks or 1 yr later. In a multivariable analysis, contrary to the hypothesis that surgery would lead to long-term cognitive decline, the nonsurgical controls had greater cognitive decline than surgical patients during the next 1 yr. Further, when using imputation, inverse probability weighting, or worst-case scores for data lost to follow-up as well as other alternative modeling strategies, there remained no evidence of greater 1-yr cognitive decline in surgical *versus* nonsurgical participants. Additionally, a tipping point analysis showed that, in order to flip our conclusions, the required shift observed

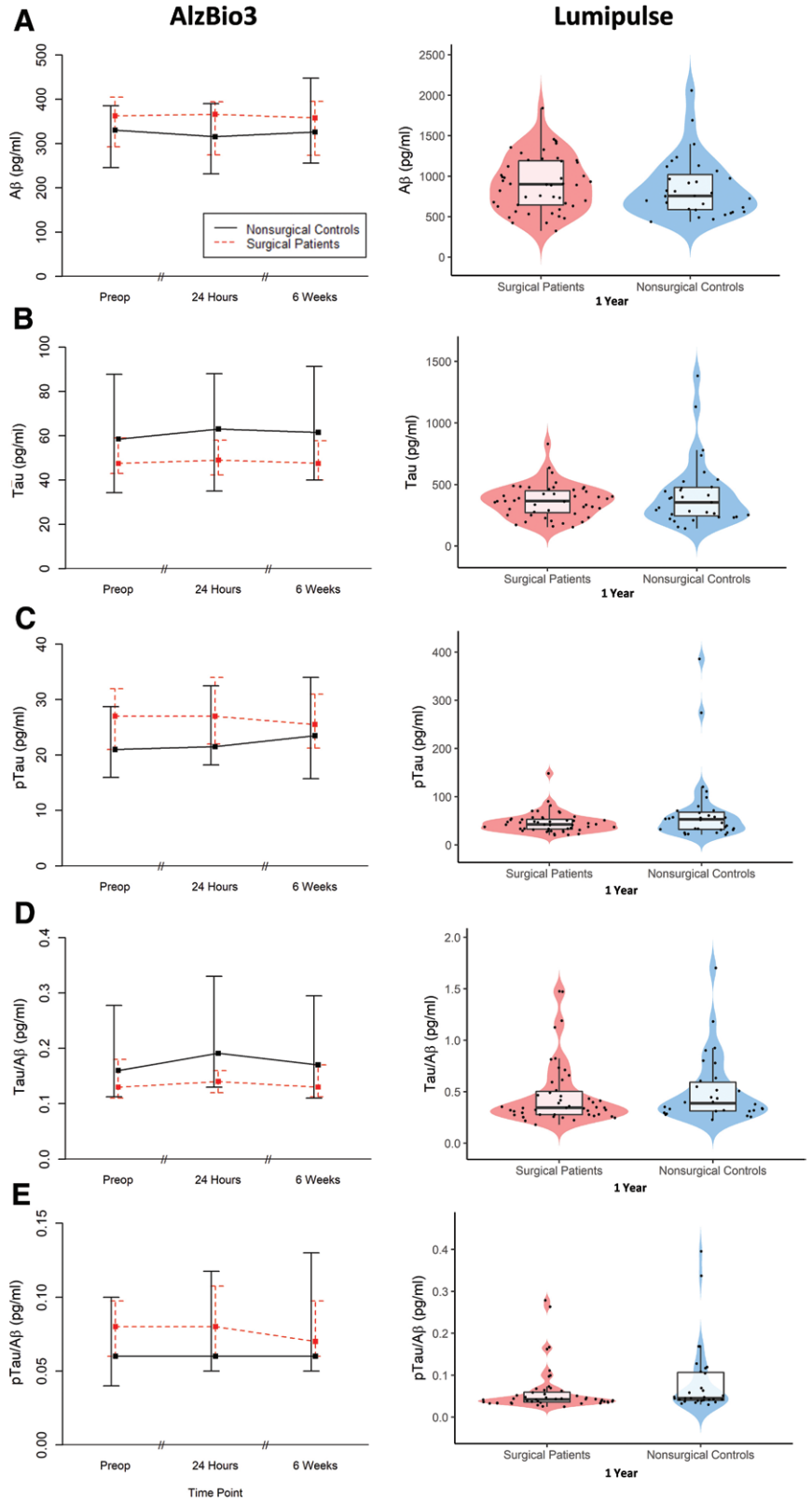

Fig. 2. Cerebrospinal fluid levels of (*A*) amyloid β (Aβ), (*B*) tau, (*C*) p-tau-181p, (*D*) tau/Aβ, and (*E*) p-tau-181p/Aβ in surgical patients and nonsurgical controls. The first column represents baseline, 24-h, and 6-week data from the AlzBio3 assay platform *(Continued)*

among surgical patients who did not return for 1-yr follow-up would have been approximately 4 SDs larger than the mean 1-yr cognitive decline among observed surgical patients at the 1-yr time point, which equates to an effect size nearly double what has previously been observed between memory composite scores of cognitively normal *versus* mild cognitive impairment groups.[26]

These results stand in contrast to findings from animal studies in which anesthesia and/or surgery led to increased Alzheimer's disease–related pathology and memory deficits,[6,7,28] yet they are broadly consistent with previous work that showed delirium and critical illness (but not anesthesia and/or surgery *per se*) were associated with 1-yr cognitive decline.[29] These results are also consistent with previous work from our group: the rate of mild and major postoperative neurocognitive disorder in the surgical patients at the 1-yr time point in this study was 40%, which is similar to the 46% rate of postoperative cognitive dysfunction (defined as a 1 SD or greater drop in one or more cognitive domains) seen previously in a similar noncardiac surgery cohort at our institution.[17]

However, few previous studies have directly compared cognitive data in surgical patients to those in a matched nonsurgical control group. Thus, the lack of greater cognitive decline in the surgical patients (than nonsurgical controls) seen here can be interpreted in two ways. First, these data could reflect a true lack of greater cognitive decline in older surgical patients *versus* nonsurgical controls among the range of noncardiac, nonneurologic surgeries studied here, which could be explained by three factors. First, some major surgeries can lead to postoperative cognitive improvement rather than cognitive decline, especially if the surgery treats underlying medical problems that caused cognitive dysfunction.[5,30–32] Second, many patients in this study underwent minimally invasive procedures such as thyroidectomies,[33] which cause less tissue trauma and may have fewer detrimental cognitive effects than longer or more invasive procedures like cardiac surgery.[2,18] Consistent with this idea, the postoperative delirium rate in this surgical cohort (8.8% or 7 of the 80 surgical patients who returned for 1-yr cognitive testing) was lower than that seen in studies of more invasive procedures such as cardiac surgery, in which postoperative delirium rates as high as 73% have been seen.[34] Third, improvements in surgical care that occurred by the time this study was conducted, such as widespread use of continuous nerve blocks,[35] epidurals, and enhanced recovery protocols,[36] may have improved cognitive outcomes, although this seems unlikely in light of the fact that the rate of longer-term cognitive decline seen here is similar to that seen in a previous study from our group conducted from 2000 to 2005.[17] Further, prospective randomized studies have not found lower delirium rates after regional *versus* general anesthesia for hip fracture repair,[37,38] although less is known about the effects of nerve blocks and enhanced recovery protocols on cognitive dysfunction between 6 weeks and 1 yr after other types of noncardiac surgery.

Second, the lack of greater cognitive decline in the surgical patients (*vs.* the nonsurgical controls) could reflect unmeasured baseline differences between groups that may have led to greater 1-yr cognitive decline in the nonsurgical group. Indeed, although the groups were matched on 25 of 31 baseline characteristics, there were baseline differences between them in attention/concentration, Aβ and/or tau pathology, self-perceived physical function, general health, social activities, and symptom limitations. However, the surgical patients did not have greater cognitive decline in our models even when accounting for these baseline differences, suggesting that the greater cognitive decline in the nonsurgical group was not due to these baseline differences. However, it remains possible that other unmeasured baseline differences between groups may have confounded the results.

Additionally, since the majority of the surgical participants who had Aβ | tau pathology in this cohort were exclusively $A\beta^+$ and tau^- (n = 15 of the 18 with any Aβ | tau pathology), the lack of correlation between amyloid deposition and cognitive function in the Alzheimer's literature may partially explain why baseline differences in Aβ | tau pathology between the surgical patients and nonsurgical controls in this cohort did not account for their group differences in cognitive function through 1 yr.[39] Future studies are needed to determine the extent to which Aβ and tau pathologies separately influence surgical *versus* nonsurgical cognitive trajectories over time.[40] Prospective matched cohort study designs (as used here) are considered an inferior form of evidence compared to randomized controlled trials,[41] since there is always a possibility of unmeasured confounding between matched cohort groups. However, studies examining cognitive change after anesthesia and/or surgery are often restricted to sampling nonsurgical controls matched to surgical patients based on demographics, because it is usually neither ethical nor practical to randomize patients to

Fig. 2. *(Continued)* (Innogenetics; Ghent, Belgium). *Error bars* represent the 25th and 75th percentiles of the data. The second column represents 1-yr cerebrospinal fluid Alzheimer's disease biomarker levels in surgical patients (*red*) and nonsurgical controls (*blue*) from the Fujirebio Lumipulse (USA) assay platform; 1-yr data were log-transformed to reduce skew. Each *dot* represents data from an individual patient at a single time point; the *width of the colored area* indicates the data distribution. Within the boxplots, the *middle line* shows the median of the data, and the *upper and lower edges* show the interquartile range. There were no significant group differences (see the main text for analysis details). Missingness: 98 surgical patients had cerebrospinal fluid data at baseline, 90 at 24 h, 94 at 6 weeks, and 48 at 1 yr. One additional surgical patient was missing tau data at 1 yr due to assay artifact. A total of 46 nonsurgical controls had cerebrospinal fluid data at baseline, 42 at 24 h, 36 at 6 weeks, and 32 at 1 yr. One additional control was missing tau data at 24 h; two other controls were missing Aβ and tau data at 1 yr, respectively, due to assay artifact.

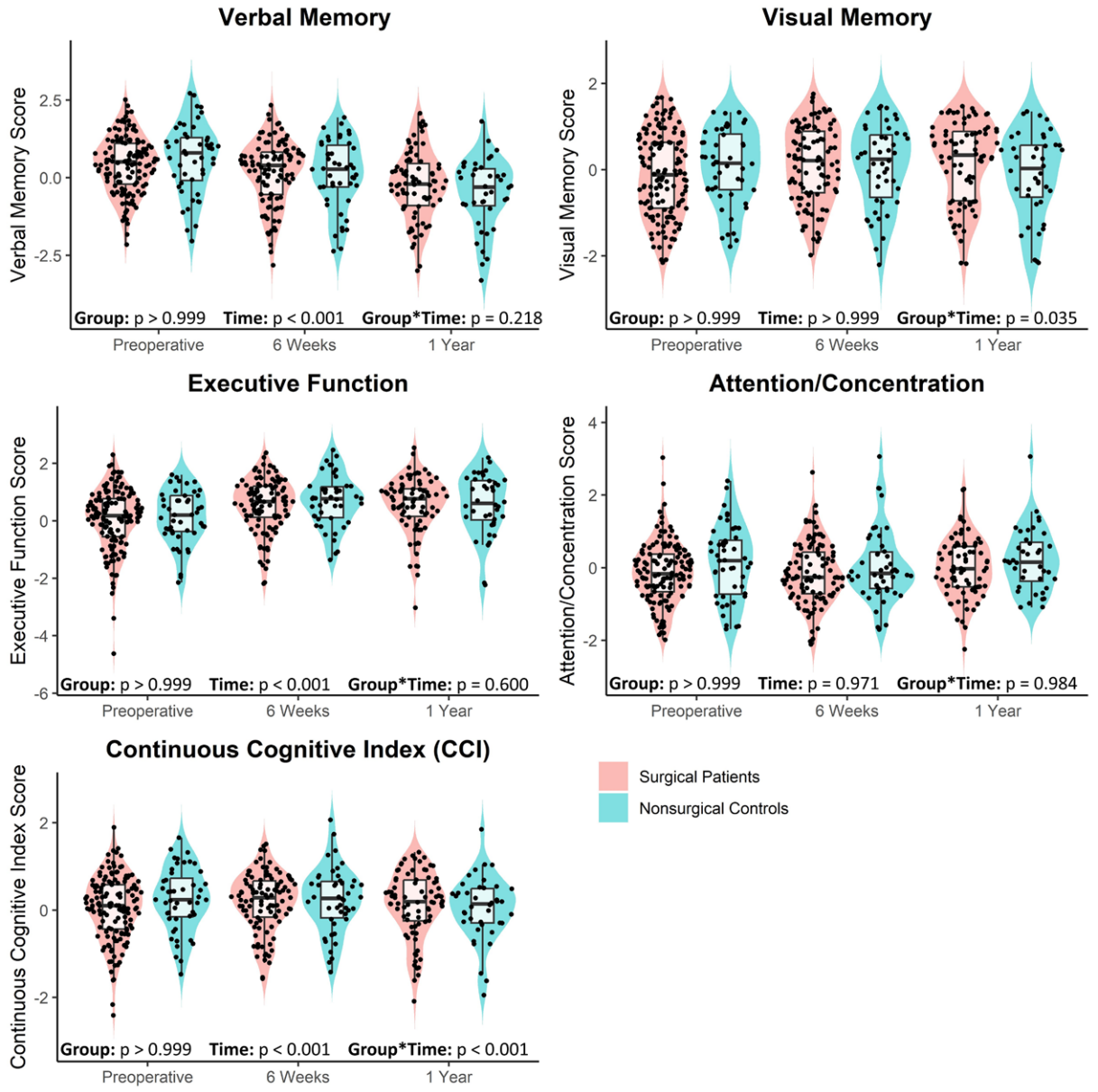

Fig. 3. Cognitive function by domains and overall continuous cognitive index (the average of the four domain scores) over time, in surgical patients (*red*) and nonsurgical controls (*turquoise*). Each *dot* represents data from an individual patient at a single time point; the *width of the colored area* indicates the data distribution. Within the boxplots, the *middle line* shows the median of the data, and the *upper and lower edges* show the interquartile range (see table 2 for statistical comparisons). *P* values are Bonferroni corrected for the five cognitive models.

surgery *versus* nonoperative management.[4,42–51] Our results suggest the need for careful consideration for minimizing potential confounders when using matched nonsurgical control groups for analyses such as reliable change index calculations, which present data on cognitive dysfunction solely in the surgical cohort (indexed to cognitive data from the nonsurgical group),[40,52,53] since the two cohorts may not be fully matched on baseline characteristics related to cognitive function (as seen here). These imbalances could confound cognitive comparisons between groups. Thus, while variables such as baseline CSF Alzheimer's disease biomarkers, hypertension, and *APOE4* genotypes may be challenging to include as part of the matching process, thorough reporting of variables that may impact cognition is crucially important for both minimizing unmeasured confounding and enabling better comparisons in studies with matched surgical and nonsurgical groups.

This study has limitations. First, this was a single-center study at a tertiary academic medical center, which may limit generalizability. Second, selection bias may have been

Table 2. Multivariable Linear Regression Model for Continuous Cognitive Index Change from Baseline to 1 Year after Surgery with Observed Baseline Data for All Variables Listed Below (n = 72 Surgical Patients, 35 Nonsurgical Controls)

Factor	β (95% CI)	*P* Value
Baseline continuous cognitive index	–0.03 (–0.14 to 0.07)	0.513
Nonsurgical controls	–0.31 (–0.45 to –0.17)	< 0.001
Amyloid β|tau pathology	–0.02 (–0.17 to 0.13)	0.778
Hypertension	0.02 (–0.11 to 0.15)	0.735
Duke Activity Status Index	0.00 (–0.00 to 0.01)	0.249
Medical Outcomes Study 36-Item Short Form Health Survey General Health Perceptions	–0.10 (–0.18 to –0.02)	0.015
Social activities	–0.00 (–0.02 to 0.01)	0.625
Symptom limitations	0.02 (–0.01 to 0.04)	0.178

The reference groups for categorical variables were as follows: surgical patient group, baseline time, amyloid β-|tau- classification status, and no hypertension.

present among nonsurgical controls recruited from aging and Alzheimer's disease research subject registries, since individuals may have enrolled in these registries due to a family history of dementia or personal memory concerns. While we found no difference in 6-week or 1-yr cognitive change among nonsurgical controls recruited from these registries *versus* public flyers, we may have been underpowered to detect this difference. Future studies should aim to recruit nonsurgical controls outside of aging or Alzheimer's disease registries to minimize this potential for bias. For example, instead of recruiting from aging or Alzheimer's disease registries, nonsurgical controls could be recruited from patients seen in surgery clinics who did not elect to have surgery.

Third, the control cohort size was modest relative to other postoperative cognitive dysfunction or neurocognitive disorder studies with greater than 100 controls.[54,55] Of the 185 patients who completed baseline testing (table 1), 80 surgical patients and 40 nonsurgical controls completed 1-yr cognitive testing, a 35% rate of loss to follow-up. Nonetheless, this is actually smaller than the 51 to 53% loss to follow-up rates seen in similar previous studies with repeated lumbar punctures in older patients.[10,20] Lower baseline continuous cognitive index and attention or concentration were each associated with loss to follow-up in the nonsurgical controls but not in the surgical patients (table 3), yet controlling for these factors did not account for the group difference in cognitive decline at 1 yr (table 2; Supplemental Table 7, https://links.lww.com/ALN/D457). Further, our results remained similar regardless of whether we utilized inverse probability weighting or multiple imputation for data lost to follow-up.

Fourth, the possibility that cognitive scores in the surgical patients who did not return for 1-yr follow-up were not missing at random is an important and prominent limitation of this study. However, our tipping point analysis suggested that the mean 1-yr cognitive change scores among unobserved surgical patients would need to have been nearly 4 SD beyond the mean cognitive change scores among observed surgical patients (nearly double the effect size seen in a previous study of normal cognitive function *vs.* MCI[26]) in order to reverse our conclusions at 1 yr. While theoretically possible, this is highly unlikely to have occurred.

Fifth, unlike previous studies,[6,13,42,56] here anesthesia and surgery was not associated with a detrimental change in CSF Alzheimer's disease–related biomarkers or cognition. However, cognitive decline in Alzheimer's disease typically occurs over years to decades. This study was limited to 1 yr after surgery, so it is possible there could be greater differences in Alzheimer's disease biomarkers or cognitive change between patients who do *versus* do not undergo surgery over longer time periods. However, large retrospective studies have found only small surgery-related differences in long-term cognitive decline at a group level.[57,58] No previous prospective study has examined CSF Alzheimer's disease biomarker trajectories in both surgical patients and nonsurgical controls during the 1-yr time period studied here, although animal studies have found acute (not chronic) effects of anesthetics and/or surgery on Alzheimer's disease pathology.[59]

Sixth, neither retrospective studies[57,58] nor the prospective data reported here rule out the presence of smaller patient subgroups who may have significant cognitive decline after surgery, such as *APOE4* allele carriers or others who may be more sensitive to the detrimental effects of postoperative inflammation on cognition.[60–62] This may include patients who experienced postoperative delirium, whom we found had an increased incidence of cognitive dysfunction at the 1-yr time point, although this result should be interpreted cautiously given the small total number of patients with postoperative delirium here. Indeed, there were only seven patients with postoperative delirium, three of whom had cognitive deficits more than 1 unit below the sample mean at 1 yr (the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, objective criteria for mild neurocognitive disorder), although four of these seven patients with delirium did not meet this threshold at 1 yr. These small numbers and the fact that four of the seven surgical patients with postoperative delirium did not meet Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, objective criteria for mild neurocognitive disorder at 1 yr emphasize the need for caution in concluding from these data that patients with delirium have greater cognitive decline, although the idea that patients with postoperative delirium have worse cognitive decline is consistent with numerous other studies.[63–66]

In fact, the small number of patients with postoperative delirium in this cohort may suggest that this overall sample may have been more resilient and/or have

Table 3. Baseline Demographics, Cognitive Function, and Cerebrospinal Fluid Biomarkers between Individuals Who Subsequently Remained in the Study *versus* Those Lost to Follow-up at 1 Year

	Surgical Patients		Nonsurgical Controls		
	Not Lost to Follow-up (n = 80)	Lost to Follow-up (n = 57)	Not Lost to Follow-up (n = 40)	Lost to Follow-up (n = 8)	*P* Value
Baseline patient demographics					
Age*	68.5 [64, 72]	68 [65, 73]	68 [64, 74.5]	68 [64, 76]	0.726
White/Caucasian race*	73 (91.25%)†	43 (81.13%)	32 (80.00%)	5 (62.50%)	0.991
Male sex*	46 (57.50%)	33 (62.26%)	24 (60.00%)	4 (50.00%)	0.481
Years of education‡	15.5 [12, 17]	14.75 [13, 18]	16 [14, 18.5]†	13 [12, 16]†	0.068
Baseline cognitive measures					
Mini-Mental State Examination	29 [28, 29]	28 [28, 29]	29 [28, 30]	28 [26, 30]	0.503
Mini-Mental State Examination < 25	3 (3.75%)	4 (7.02%)	0 (0.00%)	1 (12.50%)	0.978
Continuous cognitive index	0.15 ± 0.67	–0.08 ± 0.82	0.34 ± 0.71†	–0.25 ± 0.60†	0.234
Verbal memory	0.50 ± 0.88	0.30 ± 0.95	0.61 ± 1.17	0.65 ± 0.99	0.477
Visual memory	–0.02 ± 0.93	–0.26 ± 1.02	0.07 ± 0.89	–0.01 ± 0.82	0.759
Executive function	0.20 ± 0.96	–0.15 ± 1.24	0.31 ± 0.90†	–0.71 ± 0.61†	0.069
Attention/concentration	–0.08 ± 0.83	–0.22 ± 0.85	0.36 ± 0.88†	–0.93 ± 1.03†	0.018
Baseline Alzheimer's disease and dementia-related measures					
APOE4-positive	23 (28.75%)	16 (28.07%)	13 (32.50%)	2 (25.00%)	0.729
Amyloid β, tau classification§					
$A^+ \mid T^+$	1 (1.37%)	1 (4.00%)	2 (5.00%)	1 (16.67%)	0.998
$A^+ \mid T^-$	12 (16.44%)	3 (12.00%)	8 (20.00%)	2 (33.33%)	0.996
$A^- \mid T^+$	1 (1.37%)	0 (0.00%)	6 (15.00%)	0 (0.00%)	0.999
$A^- \mid T^-$	59 (80.82%)	21 (84.00%)	24 (60.00%)	3 (50.00%)	—
Baseline quality of life, mental health, and physical function measures					
Center for Epidemiologic Studies Depression Scale (–)‖	8 [4, 15]	9 [2, 16]	7 [4, 11.5]	10.5 [5.5, 17.5]	0.257
State-Trait Anxiety Inventory (–)#	28 [23.5, 37.5]	29 [22, 37]	27 [22.5, 32.5]	27 [23, 38.06]	0.440
Duke Activity Status Index (+)#	23.2 [10, 40.2]	18.95 [8.95, 40.95]	31.83 [18.70, 50.70]	35.95 [21.075, 48.075]	0.766
Medical Outcomes Study 36-Item Short Form Health Survey General Health Perceptions (–)‖	2.5 [2, 3]	3 [2, 4]	2 [1, 3]	2 [1.5, 3]	0.668
Medical Outcomes Study 36-Item Short Form Health Survey Work Activities (–)*	7 [5, 9]	6 [4, 11]	6 [5, 8]	5 [4, 6.5]	0.107
Instrumental Activities of Daily Living (–)*	6 [6, 6]	6 [6, 7]	6 [6, 6]	6 [6, 7.7]	0.366
Cognitive difficulties (–)#	79 [64, 95]	74 [61.58, 88]	77 [65, 88]	82.05 [76.50, 87.50]	0.277
Social activities (–)‖	16 [13, 19]	16 [12, 20]	13.5 [11, 18.5]	13 [11.5, 15]	0.507
Social support (+)#	86.56 [73.00, 94.00]	86 [74, 92]	82 [63.5, 93]	87.5 [57.25, 92.39]	0.976
Symptom limitations (–)#	12.57 [9.14, 16.00]	13.71 [9.14, 16.00]	10.29 [9.00, 15.43]	10.71 [8.57, 11.71]	0.247

Values represent mean ± SD, medians [quartile 1, quartile 3], or n (%). *P* value column to the right reflects whether the distribution of a variable between lost to follow-up *versus* not lost to follow-up patients differs among surgical and nonsurgical groups. A minus sign in parentheses (–) indicates a measure for which lower scores are better (*i.e.*, more healthy); a plus sign in parentheses (+) indicates a measure for which higher scores are better (*i.e.*, more healthy).

*Missing for four surgical patients. †$P < 0.05$ for lost to follow-up *versus* not lost to follow-up within a given group (*i.e.*, surgical or nonsurgical). ‡Missing for one surgical patient. §Missing for 39 surgical patients and 2 nonsurgical controls. ||Missing for two surgical patients. #Missing for three surgical patients.

experienced relatively milder surgical trauma than seen in other delirium studies in intensive care unit and/or cardiac surgery patients,[34,67] which may explain why we found no evidence for greater cognitive decline in surgical patients *versus* nonsurgical controls in this cohort. Further, our exploratory subgroup analysis of cognition among surgical patients with *versus* without postoperative delirium (and compared to nonsurgical controls) suggested that the subgroup of patients who developed postoperative delirium experienced greater 1-yr cognitive decline after surgery than the surgical patients who did not develop postoperative delirium. Given the small sample size of this subgroup analysis in this cohort, appropriately powered future studies should compare cognition and Alzheimer's disease–type biomarkers in these subgroups (*i.e.*, surgical patients with postoperative delirium, surgical patients without postoperative delirium, and nonsurgical controls) at baseline and over time.

Seventh, the 1-yr CSF Alzheimer's disease–related biomarker data came from a different assay than that used for the earlier time points, since the AlzBio3 assay was no longer being manufactured by the time all 1-yr samples were collected here. This limits the ability to draw conclusions about CSF Alzheimer's disease–related biomarker changes through 1 yr in this study. However, our repeated-measures analyses from baseline, 24 h, and 6 weeks did not show group differences in postoperative CSF biomarkers between surgical patients and nonsurgical controls, and

neither did a cross-sectional comparison of group differences in biomarker levels at 1 yr.

Conclusions

These data represent the first prospective comparison of cognitive and CSF Alzheimer's disease–related biomarker trajectories among older surgical patients and matched nonsurgical controls. Although matched cohort designs cannot exclude possible selection bias and/or unmeasured confounders, the data showed no difference between groups in CSF Alzheimer's disease–related biomarker changes or increased cognitive decline among surgical patients greater than 1 yr. These conclusions held after accounting for missingness among patients lost to follow-up and controlling for baseline group differences. Thus, despite the limitations discussed, the findings from this cohort do not support the hypothesis that anesthesia and noncardiac, nonneurologic surgery in older adults are associated with accelerated Alzheimer's disease pathology or cognitive decline over the next year.

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Competing Interests

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Supplemental Digital Content

Supplemental descriptions, tables, and figures: https://links.lww.com/ALN/D457

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Appendix

The Markers of Alzheimer's Disease and neuroCognitive Outcomes after Perioperative Care (MADCO-PC) Investigators also include C. L. Amundsen, S. Bengali, E. Bennett, M. F. Berry, D. G. Blazer, M. P. Bolognesi, R. Brassard, B. E. Brigman, M. Bullock, J. Carter, J. Chapman, B. Colin, T. A. D'Amico, J. K. DeOrio, D. Erdmann, R. M. Esclamado, M. Ferrandino, B. Funk, J. Gadsden, J. Gardner, G. Garrigues, C. Giattino, D. T. Gold, S. Grant, J. Guercio, D. K. Gupta, A. Habib, D. H. Harpole, S. M. Harris, M. G. Hartwig, S. T. Hollenbeck, J. Hu, E. Iboaya, B. A. Inman, D. W. Jang, J. Kaisen, A. Khan, S. Lagoo-Deenadayalan, D. T. Laskowitz, P. S. Lee, W. T. Lee, J. Lemm, H. Levinson, M. E. Lipkin, C. R. Mantyh, D. L. McDonagh, J. Migaly, S. K. Mithani, P. Mosca, J. Moul, M. F. Newman, K. Ni, B. Ohlendorf, M. W. Onaitis, T. N. Pappas, A. N. Perez, A. C. Peterson, T. J. Polascik, A. Podgoreanu, G. M. Preminger, Q. Quinones, E. N. Rampersaud, A. Ray, K. Roberts, C. N. Robertson, S. A. 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, J. Whittle, M. Woldorff, N. Waldron, D. S. Warner, X. Wang, S. S. Wellman, T. Wickenheisser, C. Young, and S. Zani.