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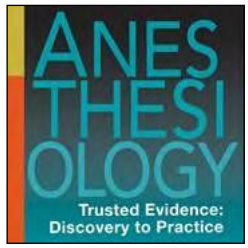

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Cognitive and cerebrospinal fluid Alzheimer's disease-related biomarker trajectories in older surgical patients and matched nonsurgical controls

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Author Contributions:

Study Concept: MB, JPM, HJC, HEW

Study Design: MB, JPM, HJC, HEW

Enrollment of patients, collection of baseline data and perioperative samples, administration of neuropsychological tests: MB, VC, JNB

Analysis and interpretation of data: MR, MCW, MB, MKW

Contribution to statistical analysis: MR, MCW

Drafting of the manuscript: MR, MKW, MCW, MB

Principal investigator and overall responsibility for this work: MB

All authors read and approved the final manuscript

ABSTRACT

Background: Anesthesia/surgery accelerate AD pathology and cause memory deficits in animal models, yet we lack prospective data comparing CSF AD-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/surgery contribute to cognitive decline or an acceleration of AD-related pathology in older adults.

Methods: We enrolled 140 patients age ≥ 60 undergoing major non-neurologic surgery and 51 nonsurgical controls via strata-based matching on age, sex, and years of education. CSF Aβ42, 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-year ($p>0.05$ for all). Nonsurgical controls did not differ from surgical patients in baseline cognition (mean difference [95% CI]: 0.19 [-0.06, 0.43], p=0.132), yet had greater cognitive decline than the surgical patients 1-year later (β [95% CI]: -0.31 [-0.45, -0.17], $p < 0.001$) even when controlling for baseline differences between groups. However, there was no difference between non-surgical and surgical groups in 1-year postoperative cognitive change in models which used imputation or inverse probability weighting for cognitive data to account for loss to follow up.

Conclusions: Over a 1-year time period, as compared to matched non-surgical controls, we found no evidence that older patients who underwent anesthesia and non-cardiac, non-neurologic surgery had accelerated CSF AD-related biomarker (tau, p-tau, and Aβ) changes or greater cognitive decline.

INTRODUCTION

Some older patients have lasting cognitive impairment after anesthesia/surgery, but it remains unclear to what extent this cognitive decline is caused by anesthesia/surgery vs the extent to which it reflects their natural cognitive trajectory (reviewed in[1]). Postoperative cognitive dysfunction (POCD)[2] and neurocognitive disorder, postoperative (NCD)[3] are both characterized by objectively measured cognitive decline within 1-12 months after surgery; postoperative NCD also requires the presence of subjective cognitive complaints. Since postoperative NCD is a relatively new term, its incidence is not yet well defined; POCD (as defined by a ≥ 1 SD decrease in ≥ 1 cognitive domain at 6 weeks after surgery) has been reported in up to 41% of surgical patients above age 60.[4] POCD 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 (AD) pathology, which then disrupts brain function and results in POCD and/or NCD. This theory is supported by work demonstrating that inhaled anesthetics promote amyloid beta (Aβ) oligomerization[6] *in vitro,* and tau phosphorylation and aggregation[7] in mice. In humans, 24 hour 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 AD biomarker changes were due to anesthesia/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 AD-related pathology in older adults, we compared changes in cognition and CSF AD-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 AD-related biomarkers than nonsurgical community-dwelling older adults across a 1-year study period.

METHODS

This is a secondary analysis of data from MADCO-PC, an observational cohort study registered with clinicaltrials.gov (NCT01993836) in November 2013, and approved by the Duke IRB.[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 AD-related biomarkers in older surgical patients, which was published last year.[16] Our prior report[16] included only surgical patients who returned for 6-week follow-up (N=110), while this paper included all surgical patients who completed baseline cognitive testing (N=137).

MADCO-PC study participants provided informed consent before enrollment. Patients were prospectively screened (and enrolled if willing) if they were ≥60 years old undergoing non-cardiac, non-neurologic surgery under general anesthesia for ≥2 hours, 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/exclusion criteria, see supplemental methods (https://links.lww.com/ALN/D457).

Upon receipt of additional funding, enrollment of a ~50 participant matched nonsurgical group began in February 2016, after surgical enrollment was complete; the non-surgical controls underwent the same assessments as the surgical patients at the same time intervals. We used strata-

based enrollment to recruit nonsurgical controls that, 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 2013-2016 (with 1-year follow-ups completed in 2017), and nonsurgical controls were enrolled from 2016-2018 (with 1-year follow-ups completed in 2019).

For strata-based matching, age was divided into 4 strata of 60-64, 65-69, 70-74, >75 years. Years of education (total years of complete schooling) was divided into 4 strata of <12 (less than high school), 12 (high school), 13-15 (partial college or associates degree), and >16 years (college degree or more). These 2 gender strata x 4 age strata x 4 education strata produced 32 different groups (2 x 4 x 4 = 32). Into these 32 bins we then sorted the 110 surgical patients who returned for 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 a ~60-mile radius (N=12), the same area in which surgical patients had to live to participate.

APOE genotyping was performed as described.[9] MCI and AD diagnoses were based on ICD-10 codes in patients' medical records at the time of study entry.

Cognitive Testing and Analysis

At preoperative, 6 week postoperative and 1-year postoperative visits (and the same intervals in controls), participants completed a cognitive test battery, as previously described (see Supplementary Materials, https://links.lww.com/ALN/D457).[17] Factor analysis of these tests

produced 4 cognitive domains: verbal memory, visual memory, executive function, and attention/concentration (see Supplementary Materials for details, https://links.lww.com/ALN/D457).[16] The continuous cognitive index (CCI) 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 over 20 years.[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 (see Supplementary Materials, https://links.lww.com/ALN/D457). Patients also completed the mini mental status exam (MMSE). Mild and major Postoperative NCD were defined as previously described (see Supplementary Materials for details, https://links.lww.com/ALN/D457).[3] Postoperative delirium (POD) assessments in these patients are described in the supplementary materials (https://links.lww.com/ALN/D457).

CSF Sampling and AD Biomarker Assays

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

Statistical Analysis

We previously observed baseline to 24-hr postoperative CSF tau level increases of 87 pg/ml.[9] Based on this, we calculated that ≥ 85 surgical and ≥ 42 nonsurgical participants would provide 80% power with $\alpha = 0.05$ to detect a 65 pg/ml smaller increase in 24-hour CSF tau change among non-surgical controls vs surgical patients (i.e. a 75% smaller increase in CSF tau levels

among controls than surgical patients). Based on prior work,[17] this sample size also provides ≥ 80% power to detect a ≥ 0.15 unit difference in CCI change (a moderate Cohen's d effect size of 0.55) from before to 6 weeks or 1 year later between surgical patients vs non-surgical controls, which is even smaller than the difference in CCI change seen between patients with vs without POCD in a prior study.[19] Given the 51-53% rate of loss to follow-up observed in prior 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 supplemental methods for details (https://links.lww.com/ALN/D457).

CSF AD-related biomarker trajectories (from baseline to the 24 hr and 6 wk time points) were compared with non-parametric longitudinal models in R version 4.2.0.[21] CSF biomarker data at the 1 year time point was 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% confidence intervals 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 NCD rates were compared using Chi-square or Fisher's Exact tests. A multivariable linear regression model was used to assess group differences in 1-year CCI 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-year cognitive scores were not missing at random (see Supplementary Materials for information, https://links.lww.com/ALN/D457). Finally, we examined the effect on the overall study findings if we substituted the worst possible 1-year

cognitive test scores for surgical patients who died before the 1-year visit, were institutionalized (eg, in a nursing home), or who were too sick to return for 1-year 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, we 1) compared cognitive outcomes between recruitment sources (for nonsurgical controls) via t-test to address the possibility of confounding if non-surgical controls recruited via aging or AD-related research registries were at higher long term cognitive-decline risk versus non-surgical controls recruited by public flyers. 2) 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 towards a difference in this cognitive domain (Table 1). 3) Since different statistical modeling techniques can yield divergent results when applied to the same data,[22] we also analyzed cognition as a 1-year follow-up score rather than baseline to 1-year change score to investigate the impact of this parameterization. 4) We also included a longitudinal mixed model of baseline, 6-week, and 1-year 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 (POD), would have worse cognitive dysfunction at the 1-year time point than the other groups (surgical patients without POD, nonsurgical controls). A Fisher's 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-year time point. Lastly, we analyzed a longitudinal mixed model of group (surgical patients with POD, surgical patients without POD, nonsurgical controls), time (baseline, 6 weeks, 1 year), and a group by time interaction to determine whether surgical patients with POD 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 (Cary, NC; see Supplemental Methods, https://links.lww.com/ALN/D457).

RESULTS

Figure 1 shows participant enrollment flow; model-specific sample sizes are described in the Supplementary Materials (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 non-surgical controls (Table 1), including the three characteristics the groups were matched upon (age, sex, and years of education). However, as compared to non-surgical controls, surgical patients had more hypertension (absolute difference in rates between surgical and nonsurgical groups [95% CI]: 25.5% [8.38%, 42.5%], p=0.004), lower self-reported physical functional capacity (Hodges-Lehmann group median difference estimate: -8.00 [-15.2, -1.00], p=0.012), worse subjective health scores on the SF-36 General Health Perceptions questionnaire (Hodges-Lehmann group median difference estimate [95% CI]: 1.00 [0.00, 1.00], p=0.001), and worse scores on the Social Activities (Hodges-Lehmann group median difference estimate [95% CI]: 2.00 [0.00, 3.00], p=0.016) and Symptom Limitations scales (Hodges-Lehmann group median difference estimate: 1.14 [0.00, 2.29], p=0.045). However, a higher proportion of the non-surgical cohort had baseline CSF Aβ levels < 250 pg/ml and/or CSF tau levels > 93 pg/ml (indicators of brain Aβ and tau pathology, respectively)[23,24] than was seen in the surgical group (difference [95% CI]: 22.9% [6.77%, 39.1%], p=0.004). Among 185 participants with complete baseline cognitive data, no surgical patients or non-surgical controls had a diagnosis of MCI or AD, although 13% of the surgical cohort and 10% of the non-surgical controls had MMSE scores below 27 (which has been shown to have 87% specificity for MCI).[25]

Figure 2 shows median CSF biomarker levels in the surgical and nonsurgical cohorts at baseline, 24-hours, and 6-weeks (from the AlzBio3 assay) and at 1-year after surgery (from the Fujirebio Lumipulse platform). There were no significant 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 AD-related biomarkers measured at baseline, 24-hours, or 6-weeks ($p > 0.05$ for all after Bonferroni correction; Supplemental Table 3, https://links.lww.com/ALN/D457, Figure 2). In a separate analysis of 1-year CSF biomarker values, there were no significant differences between groups for Aβ (Hodges-Lehmann group median difference estimate [95% CI]: -72 [-224, 75], p>0.999), tau (2 [-69, 75], p>0.999), p-tau-181p (4.5 [-4.2, 16], p>0.999), tau/Aβ (0.03 [-0.03, 0.10], p>0.999), or p-tau-181p/Aβ (0.006 [-0.001, 0.014], p=0.400) after Bonferroni correction (Figure 2).

Supplemental Table 4 (https://links.lww.com/ALN/D457) summarizes scores on each cognitive test at baseline, 6 weeks later and 1 year later in the surgical and nonsurgical cohorts; the CCI 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 NCD (N = 25 of 105 surgical patients, 18 of 46 nonsurgical controls; absolute difference in rate between groups [95% CI]: -15.3% [-31.6%, 0.97%], p = 0.110) or major postoperative NCD (N = 1 of 103 surgical patients, 0 of 46 nonsurgical controls; 0.97% [-0.92%, 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 NCD at 1 year (mild: N = 32 of 80 surgical patients, 19 of 40 nonsurgical controls, absolute difference in rate between groups [95% CI]: -7.50% [-26.3%, 11.3%], p = 0.867; major: N = 0 of 79 surgical patients, 2 of 40 nonsurgical controls, -5.00% [-11.75%, 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-year than the surgical patients (β [95% CI]: -0.31 [-0.45, -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-year 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-year cognitive decline than surgical patients (β [95% CI]: -0.33 [-0.47, 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 towards greater 1-year cognitive decline in the nonsurgical controls vs surgical patients (β [95% CI]: -0.16 [-0.32, 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-year cognitive decline scores of surgical patients who did not return for 1-year follow-up, which would be required in order to conclude that surgical patients had significantly greater cognitive decline at 1-year than nonsurgical controls. The imputed mean 1-year CCI change among surgical patients lost to follow-up was -0.22, while the actual 1-year CCI 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-year, every surgical patient lost to follow-up at 1 year would have to have experienced a -1.08 further shift in their mean imputed 1-year cognitive decline scores (ie, beyond -0.22). This means that the surgical patients lost to follow-up would have had a mean 1-year cognitive change of -1.30 (0.62), which would be ~4 SDs below the actual observed 1-year 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 vs MCI patients.[26] While theoretically possible, it is highly unlikely that we would have observed nearly double this magnitude of an effect (ie, a Cohen's d of 2.69) between surgical patients who did vs. did not return for 1-year cognitive testing.

Of the 57 surgical patients who did not return for 1-year cognitive testing (out of the 137 who completed the baseline study visit), four passed away before the 1-year time point, and 6 others were too ill to return at the 1-year 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-year cognitive change analysis of imputing the worst possible cognitive test values for these 10 surgical patients at the 1-year time point (ie if they had gotten the worst score on every individual test at the 1-year 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-year follow-up, since they were still alive and living independently and many simply did not want to return for the 1-year study visit due to other obligations. When using this approach, the mean 1-year cognitive change in the surgical patients was still not significantly worse than the mean 1-year cognitive change in the non-surgical controls (β [95% CI] for nonsurgical controls vs surgical controls: 0.03 [-0.27, 0.33], p=0.843; Supplemental Table 10, 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-year changes in cognition. The recruitment source for nonsurgical controls (i.e. public flyers vs registries) was not associated with 6-week (mean difference [95% CI]: 0.09 [-0.12, 0.30], p=0.391) or 1-year cognitive change (0.23 [-0.02, 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/AD 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 [95% CI]: -0.30 [-0.44, -0.16], $p < 0.001$; Supplemental Table 7, https://links.lww.com/ALN/D457). Third, our alternative model of 1-year cognitive index scores (rather than change in cognitive index values from before to 1-year after surgery) also showed similar results (i.e., the surgical patients did not have worse cognition at the 1 year time point than nonsurgical controls; in fact, the non-surgical controls had worse cognition at 1 year than the surgical patients (β [95% CI]: -0.31 [-0.45, -0.17], $p < 0.001$, Supplemental Table 8, https://links.lww.com/ALN/D457). Fourth, a longitudinal mixed model for cognitive function showed a significant interaction between group and time for CCI change from baseline to 1-year follow-up. In this model, as in the primary linear regression model, the nonsurgical controls again had greater cognitive decline over 1 year (β [95% CI]: -0.30 [-0.43, -0.18], $p<0.001$; Supplemental Table 9, 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 DSM-V objective criteria for mild neurocognitive disorder[27]) at the 1-year 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 vs without POD had different cognitive trajectories than nonsurgical controls. This model suggested that surgical patients who later developed POD (N=7) started with a lower cognitive baseline than both the surgical patients who did not develop POD (N=73) (β [95% CI]: -0.42 [-0.83, -0.01], p = 0.047) and the nonsurgical controls (N=40) (β [95% CI]: -0.49 [-0.92, -0.05], p = 0.029; Supplemental Figure 2, https://links.lww.com/ALN/D457). Additionally, the surgical patients who developed POD had steeper trajectories of baseline to 1-year cognitive decline than surgical patients who did not develop POD (β [95% CI]: -0.28 [-0.50, -0.05], p = 0.017). However, the surgical patients who developed POD did not have steeper trajectories of baseline to 1-year cognitive decline than nonsurgical controls (β [95% CI]: 0.01 [-0.23, 0.24], p = 0.948). It is important to note that only 7 surgical patients who developed POD returned for 1-year follow-up, so these conclusions are likely underpowered. The small number of patients with postoperative delirium emphasize 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-hours, 6-weeks, or 1-year. Further, as compared to non-surgical controls, the surgical patients did not have a greater incidence of postoperative NCD from baseline to 6-weeks or 1 year 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 over the following 1-year. 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-year cognitive decline in surgical vs nonsurgical participants. Additionally, a tipping point analysis showed that, in order to flip our

conclusions, the required shift that would had to have been observed among surgical patients who did not return for 1-year follow-up would have been ~ 4 standard deviations larger than the mean 1-year cognitive decline among observed surgical patients at the 1-year time point, which equates to an effect size nearly double what has previously been observed between memory composite scores of cognitively normal vs MCI groups.[26]

These results stand in contrast to findings from animal studies in which anesthesia/surgery led to increased AD-related pathology and memory deficits,[6,7,28] yet they are broadly consistent with prior work that showed delirium and critical illness (but not anesthesia/surgery per se) were associated with 1 year cognitive decline.[29] These results are also consistent with prior work from our group: the rate of mild and major postoperative NCD in the surgical patients at the 1 year time point in this study was 40%, which is similar to the 46% rate of POCD (defined as a $\geq$ 1 SD drop in $\geq$ 1 cognitive domains) seen previously in a similar non-cardiac surgery cohort at our institution.[17]

However, few prior 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 non-surgical 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 vs nonsurgical controls among the range of non-cardiac, non-neurologic surgeries studied here, which could be explained by three factors. 1) 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.[5,30,31,32] 2) 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/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-year 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] 3) 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, though 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 vs general anesthesia for hip fracture repair,[37,38] though less is known about the effects of nerve blocks and ERAS protocols on cognitive dysfunction between 6-weeks to 1-year after other types of non-cardiac surgery.

Second, the lack of greater cognitive decline in the surgical patients (vs the non-surgical controls) could reflect unmeasured baseline differences between groups that may have led to greater 1-year 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 Aβ+ and tau- (N=15 out 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 year.[39] Future studies are needed to determine the extent to which Aβ and tau pathologies separately influence surgical vs 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 (RCT),[41] since there is always a possibility of unmeasured confounding between matched cohort groups. However, studies examining cognitive change following anesthesia/surgery are often restricted to sampling nonsurgical controls matched to surgical patients based on demographics, because it is usually neither ethical or practical to randomize patients to surgery vs nonoperative management.[4,42-51] Our results suggest the need for careful consideration for minimizing potential confounders when using matched non-surgical control groups for analyses such as reliable change index (RCI) calculations, which present data on cognitive dysfunction solely in the surgical cohort (indexed to cognitive data from the non-surgical 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 AD 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 for enabling better comparisons in studies with matched surgical and non-surgical 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 present among nonsurgical controls recruited from Aging and AD 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-year cognitive change among

nonsurgical controls recruited from these registries vs. public flyers, we may have been underpowered to detect this difference. Future studies should aim to recruit nonsurgical controls outside of aging or AD registries to minimize this potential for bias. For example, instead of recruiting from aging or AD registries, non-surgical 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 POCD/NCD studies with over 100 controls.[54,55] Of the 185 patients who completed baseline testing (Table 1), 80 surgical patients and 40 nonsurgical controls completed 1-year cognitive testing, a 35% rate of loss to follow-up. Nonetheless, this is actually smaller than the 51-53% loss to follow up rates seen in similar prior studies with repeated lumbar punctures in older patients.[10,20] Lower baseline CCI and attention/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 year (Table 2; Supplemental Table 7, https://links.lww.com/ALN/D457). Further, our results remained similar regardless of whether or not 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-year 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-year 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 prior study of normal cognitive function vs MCI[26]) in order to reverse our conclusions at 1-year. While theoretically possible, this is highly unlikely to have occurred.

Fifth, unlike prior studies,[6,13,42,56] here anesthesia/surgery was not associated with a detrimental change in CSF AD-related biomarkers or cognition. However, cognitive decline in AD typically occurs over years to decades. This study was limited to 1-year post-surgery, so it's possible there could be greater differences in AD biomarkers or cognitive change between patients who do vs. 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 prior prospective study has examined CSF AD biomarker trajectories in both surgical patients and nonsurgical controls over the 1 year time period studied here, although animal studies have found acute (not chronic) effects of anesthetics/surgery on AD 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 following surgery, such as *APOE4* allele carriers or others who may be more sensitive to the detrimental effects of post-operative inflammation on cognition.[60,61,62] This may include patients who experienced POD, who we found had an increased incidence of cognitive dysfunction at the 1-year time point, though this result should be interpreted cautiously given the small total number of patients with POD here. Indeed, there were only 7 patients with postoperative delirium, 3 of whom had cognitive deficits > 1 unit below the sample mean at 1 year (the DSM-V objective criteria for mild neurocognitive disorder), though 4 of these 7 patients with delirium did not meet this threshold at 1 year. These small numbers and the fact that 4 of the 7 surgical patients with POD did not meet DSM-V objective criteria for mild neurocognitive disorder at 1 year emphasize the need for caution in concluding from these data that patients with delirium have greater cognitive decline, though this 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 POD in this cohort may suggest that this overall sample may have been more resilient and/or have experienced relatively milder surgical trauma than seen in other delirium studies in ICU and/or cardiac surgery patients,[34,67] which may explain why we found no evidence for greater cognitive decline in surgical patients vs nonsurgical controls in this cohort. Further, our exploratory subgroup analysis of cognition among surgical patients with vs without POD (and compared to nonsurgical controls) suggested that the subgroup of patients who developed POD experienced greater 1-year cognitive decline after surgery than the surgical patients who did not develop POD. Given the small sample size of this subgroup analysis in this cohort, appropriately powered future studies should compare cognition and AD-type biomarkers in these subgroups (ie surgical patients with POD, surgical patients without POD, and non-surgical controls) at baseline and over time.

Seventh, the 1-year CSF AD-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-year samples were collected here. This limits the ability to draw conclusions about CSF AD-related biomarker changes through 1-year in this study. However, our repeated measures analyses from baseline, 24 hours, 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-year.

Conclusions

These data represent the first prospective comparison of cognitive and CSF AD-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 AD-related biomarker changes nor increased cognitive decline among surgical patients over 1 year. These conclusions held after accounting for

missingness among patients lost to follow-up and controlling for baseline group differences. Thus, despite the limitations discussed above, the findings from this cohort do not support the hypothesis that anesthesia and non-cardiac, non-neurologic surgery in older adults are associated with accelerated AD pathology or cognitive decline over the following year.

Contributors:

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Supplemental Digital Content

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

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Table Legends

Table 1. Baseline (BL) demographics, cognitive function and CSF biomarkers in surgical patients, strata-matched nonsurgical controls. Values represent means (SD), medians [Q1, Q3], or N (%).

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

Table 3. Baseline (BL) demographics, cognitive function and CSF biomarkers between individuals who subsequently remained in the study vs those lost to follow-up (LTFU) at 1-year. Values represent means (SD), medians [Q1, Q3], or N (%). P-value column to the right reflects whether the distribution of a variable between LTFU vs not LTFU patients differs among surgical and nonsurgical groups. *indicates $p < 0.05$ for LTFU vs not LTFU within a given group (i.e., surgical or nonsurgical).

Figure Legends

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

Figure 2. CSF levels of (a) 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-hour, and 6-week data from the AlzBio3 assay platform. Error bars represent the 25^{th} and 75^{th} percentiles of the data. The second column represents 1-year CSF AD biomarker levels in surgical patients (red) and nonsurgical controls (blue) from the Fujirebio Lumipulse assay platform; 1-year data was 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 CSF data at baseline, 90 at 24-hours, 94 at 6 weeks, and 48 at 1 year. 1 additional surgical patient was missing tau data at 1 year due to assay artifact. 46 nonsurgical controls had CSF data at baseline, 42 at 24-hours, 36 at 6 weeks, and 32 at 1 year. 1 additional control was missing tau data at 24-hours; 2 other controls were missing Aβ and tau data at 1 year, respectively, due to assay artifact.

Figure 3. Cognitive function by domains and overall CCI (the average of the 4 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 5 cognitive models.

Table 1. Baseline (BL) demographics, cognitive function and CSF biomarkers in surgical patients, strata-matched nonsurgical controls. Values represent means (SD), medians [Q1, Q3], or N (%).

	Surgical Patients (N=137)	Nonsurgical Controls (N=48)	P-Value
Baseline Patient Demographics			
Age[a]	68 [64, 73]	68 [64, 74.5]	0.626[1]
Non-White Race[a]	17 (12.78%)	11 (22.92%)	0.096[2]
Male Sex[a]	79 (59.40%)	28 (58.33%)	0.898[2]
Years of Education[b]	15.25 [12.5, 18]	16 [13.5, 18]	0.193[1]
Baseline Comorbidities			
Cerebrovascular Disease[c]	6 (4.51%)	0 (0.00%)	0.338[3]
Parkinson's Disease[c]	1 (0.75%)	0 (0.00%)	1.000[3]
Hypertension[c]	89 (66.92%)	17 (41.46%)	0.004[2]
Heart Disease[c]	32 (24.06%)	8 (19.51%)	0.545[2]
Diabetes[c]	40 (30.08%)	8 (19.51%)	0.186[2]
Renal Disease[c]	14 (10.53%)	2 (4.88%)	0.365[3]
Chronic Lung Disease[c]	16 (12.03%)	3 (7.32%)	0.569[3]
Thyroid Disease[c]	20 (15.04%)	7 (17.07%)	0.753[2]
Baseline Cognitive Performance			
MMSE	29 [28, 29]	29 [27, 30]	0.560[1]
MMSE <25	7 (5.11%)	1 (2.08%)	0.682[3]
CCI	0.05 (0.75)	0.24 (0.73)	0.132[4]
Verbal Memory	0.42 (0.91)	0.61 (1.13)	0.233[4]
Visual Memory	-0.12 (0.97)	0.06 (0.87)	0.254[4]
Executive Function	0.05 (1.09)	0.14 (0.93)	0.610[4]
Attention/Concentration	-0.14 (0.84)	0.15 (1.02)	0.057[4]
APOE4 Genotypes and Baseline AD-related Biomarkers			
APOE4 Positive	39 (28.47%)	15 (31.25%)	0.715[2]
Aβ, Tau Classification[d]			0.002[3]
A+ | T+	2 (2.04%)	3 (6.52%)	
A+ | T-	15 (15.31%)	10 (21.74%)	
A- | T+	1 (1.02%)	6 (13.04%)	
A- | T-	80 (81.63%)	27 (58.70%)	
Baseline Mental and Physical Health, Activities, and Quality of Life Measures			
CESD depression symptoms (-)[e]	8 [3.16, 15]	7 [4.5, 12.5]	0.617[1]
STAI anxiety symptoms (-)[f]	28.5 [23, 37]	27 [23, 32.5]	0.400[1]
DASI perceived physical function (+)[f]	21.1 [10, 40.2]	32.58 [18.7, 50.7]	0.012[1]
SF-36 General Health Perception (-)[e]	3 [2, 3]	2 [1, 3]	0.001[1]

	Surgical Patients (N=137)	Nonsurgical Controls (N=48)	P-Value
Baseline Patient Demographics			
SF-36 Work Activities (-)[a]	7 [4, 10]	6 [4.5, 7.5]	0.103[1]
IADL (-)[a]	6 [6, 6]	6 [6, 6]	0.575[1]
Cognitive Difficulties (-)[f]	77 [64, 93.39]	79.01 [66.5, 88]	0.978[1]
Social Activities (-)[e]	16 [13, 19.2]	13.5 [11, 18]	0.016[1]
Social Support (+)[f]	86.28 [73, 93]	82 [63.5, 93]	0.259[1]
Symptom Limitations (-)[f]	12.57 [9.14, 16]	10.29 [9, 14.86]	0.045[1]

[1]Wilcoxon, [2]Chi-Square, [3]Fisher's Exact test, [4]T-test. [a]Missing for 4 surgical patients. [b]Missing for 1 surgical patient. [c]Missing for 4 surgical patients, 7 nonsurgical controls. [d]A small number of participants had missing CSF 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 hours, and 6-week CSF AD biomarker analyses, respectively. [e]Missing for 2 surgical patients. [f]Missing for 3 surgical patients. A minus sign (-) indicates that a lower score is better; a positive sign (+) indicates that a higher score is better. CCI – continuous cognitive index; CESD – Center for Epidemiologic Studies Depression Scale; DASI – Duke Activity Status Index; IADL – Instrumental Activities of Daily Living; STAI – State-Trait Anxiety Inventory; SF-36 – Medical Outcomes Study 36-Item Short Form Health Survey.

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

Factor	Beta (95% CI)	P-Value
Baseline Continuous Cognitive Index	-0.03 (-0.14, 0.07)	0.513
Nonsurgical Controls	-0.31 (-0.45, -0.17)	<0.001
Aβ|Tau Pathology	-0.02 (-0.17, 0.13)	0.778
Hypertension	0.02 (-0.11, 0.15)	0.735
DASI	0.00 (-0.00, 0.01)	0.249
SF-36 General Health Perceptions	-0.10 (-0.18, -0.02)	0.015
Social Activities	-0.00 (-0.02, 0.01)	0.625
Symptom Limitations	0.02 (-0.01, 0.04)	0.178

Table 3. Baseline (BL) demographics, cognitive function and CSF biomarkers between individuals who subsequently remained in the study vs those lost to follow-up (LTFU) at 1-year. Values represent means (SD), medians [Q1, Q3], or N (%). P-value column to the right reflects whether the distribution of a variable between LTFU vs not LTFU patients differs among surgical and nonsurgical groups. *indicates $p < 0.05$ for LTFU vs not LTFU within a given group (i.e., surgical or nonsurgical).

	Surgical Patients		**Nonsurgical Controls**		
	Not LTFU (N=80)	LTFU (N=57)	Not LTFU (N=40)	LTFU (N=8)	P-Value
Baseline Patient Demographics					
Age[a]	68.5 [64, 72]	68 [65, 73]	68 [64, 74.5]	68 [64, 76]	0.726
White/Caucasian Race[a]	73 (91.25%)*	43 (81.13%)	32 (80.00%)	5 (62.50%)	0.991
Male Sex[a]	46 (57.50%)	33 (62.26%)	24 (60.00%)	4 (50.00%)	0.481
Years of Education[b]	15.5 [12, 17]	14.75 [13, 18]	16 [14, 18.5]*	13 [12, 16]*	0.068
Baseline Cognitive Measures					
MMSE	29 [28, 29]	28 [28, 29]	29 [28, 30]	28 [26, 30]	0.503
MMSE <25	3 (3.75%)	4 (7.02%)	0 (0.00%)	1 (12.50%)	0.978
CCI	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 ADRD-related Measures					
APOE4 Positive	23 (28.75%)	16 (28.07%)	13 (32.50%)	2 (25.00%)	0.729
Aβ, Tau Classification[c]					
A+ | T+	1 (1.37%)	1 (4.00%)	2 (5.00%)	1 (16.67%)	0.998
A+ | T-	12 (16.44%)	3 (12.00%)	8 (20.00%)	2 (33.33%)	0.996
A- | T+	1 (1.37%)	0 (0.00%)	6 (15.00%)	0 (0.00%)	0.999
A- | T-	59 (80.82%)	21 (84.00%)	24 (60.00%)	3 (50.00%)	-
Baseline Quality of Life, Mental Health and Physical Function Measures					

	Surgical Patients		Nonsurgical Controls		
	Not LTFU (N=80)	LTFU (N=57)	Not LTFU (N=40)	LTFU (N=8)	P-Value
CESD (-)[d]	8 [4, 15]	9 [2, 16]	7 [4, 11.5]	10.5 [5.5, 17.5]	0.257
STAI (-)[e]	28 [23.5, 37.5]	29 [22, 37]	27 [22.5, 32.5]	27 [23, 38.06]	0.440
DASI (+)[e]	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
SF-36 General Health Perception (-)[d]	2.5 [2, 3]	3 [2, 4]	2 [1, 3]	2 [1.5, 3]	0.668
SF-36 Work Activities (-)[a]	7 [5, 9]	6 [4, 11]	6 [5, 8]	5 [4, 6.5]	0.107
IADL (-)[a]	6 [6, 6]	6 [6, 7]	6 [6, 6]	6 [6, 7.7]	0.366
Cognitive Difficulties (-)[e]	79 [64, 95]	74 [61.58, 88]	76.65 (15.55)	81.26 (8.88)	0.277
Social Activities (-)[d]	16 [13, 19]	16 [12, 20]	13.5 [11, 18.5]	13 [11.5, 15]	0.507
Social Support (+)[e]	86.56 [73.00, 94.00]	86 [74, 92]	82 [63.5, 93]	87.5 [57.25, 92.39]	0.976
Symptom Limitations (-)[e]	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

[1]Wilcoxon, [2]Chi-Square, [3]T-test, [4]Fisher's Exact test. [a]Missing for 4 surgical patients. [b]Missing for 1 surgical patient. [c]Missing for 39 surgical patients, 2 nonsurgical controls. [d]Missing for 2 surgical patients. [e]Missing for 3 surgical patients. A minus sign (-) indicates that a lower score is better; a positive sign (+) indicates that a higher score is better. A minus sign in parentheses (-) indicates a measure for which lower scores are better (ie more healthy, a plus sign in parentheses (+) indicates a measure for which higher scores are better (ie more healthy). MMSE – Mini-Mental State Examination; CCI – continuous cognitive index; CESD – Center for Epidemiologic Studies Depression Scale; STAI – State-Trait Anxiety Inventory; DASI – Duke Activity Status Index; SF-36 – Medical Outcomes Study 36-Item Short Form Health Survey; IADL – Instrumental Activities of Daily Living.

Figure 1

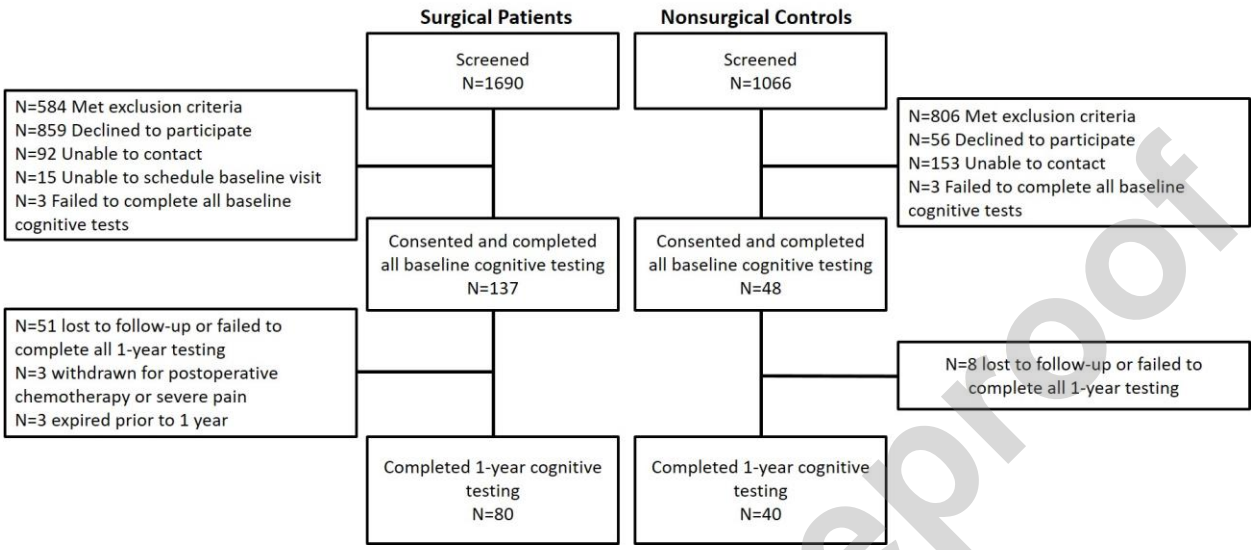

Figure 2

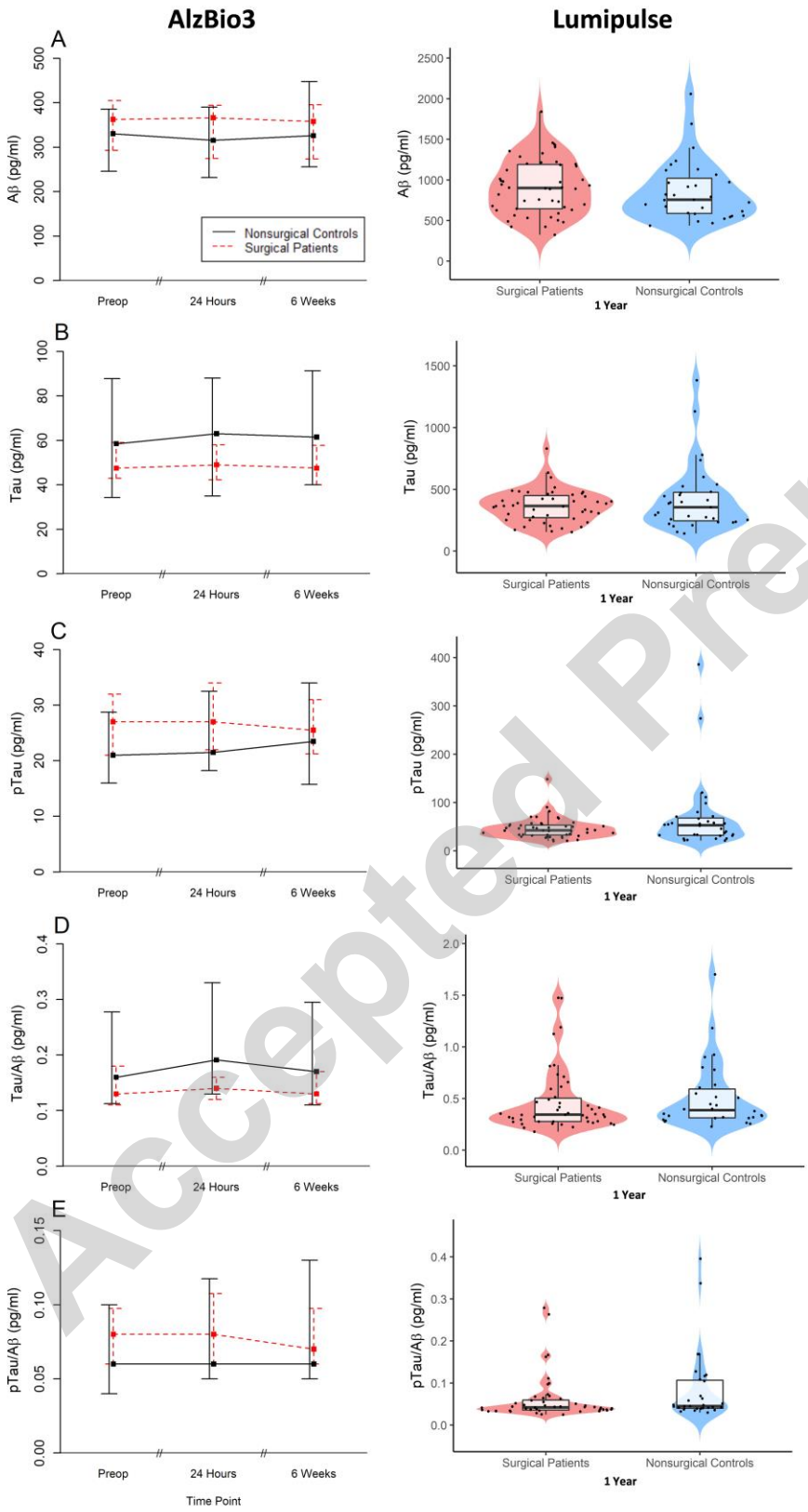

Figure 3