**Prospective analysis of plasma amyloid beta and postoperative delirium in the Interventions for Postoperative Delirium: Biomarker-3 study**

Thomas Payne 1, Jennifer Taylor 1, Cameron Casey 2, David Kunkel 2, Maggie Parker 2, Kaj Blennow 3, Henrik Zetterberg 4, Robert A Pearce 2, Richard C Lennertz 2, Robert D Sanders 5

1Central Clinical School, Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia; Department of Anaesthetics, Royal Prince Alfred Hospital, Sydney Local Health District, Sydney, NSW, Australia.
2Department of Anesthesiology, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI, USA.
3Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden; Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden.
4Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden; Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden; Department of Neurodegenerative Disease, UCL Institute of Neurology, London, UK; UK Dementia Research Institute at UCL, London, UK; Hong Kong Center for Neurodegenerative Diseases, Clear Water Bay, Hong Kong, China.
5Central Clinical School, Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia; Department of Anaesthetics, Royal Prince Alfred Hospital, Sydney Local Health District, Sydney, NSW, Australia; Institute of Academic Surgery, Royal Prince Alfred Hospital, Sydney Local Health District, Sydney, NSW, Australia; NHMRC Clinical Trials Centre, University of Sydney, Sydney, NSW, Australia. Electronic address: robert.sanders@sydney.edu.au.

PMID: 36842841 DOI: 10.1016/j.bja.2023.01.020

## Abstract

Background: The effect of postoperative delirium on the amyloid cascade of Alzheimer's dementia is poorly understood. Using early postoperative plasma biomarkers, we explored whether surgery and delirium are associated with changes in amyloid pathways.

Methods: We analysed data from 100 participants in the Interventions for Postoperative Delirium: Biomarker-3 (IPOD-B3) cohort study in the USA (NCT03124303 and NCT01980511), which recruited participants aged >65 yr undergoing non-intracranial surgery. We assessed the relationship between the change in plasma amyloid beta ratio (AβR; Aβ42:Aβ40) and delirium incidence (defined by the 3-Minute Diagnostic Confusion Assessment Method) and severity (quantified by the Delirium Rating Scale-Revised-98, the study's primary outcome). We also tested the relationship between plasma amyloid beta and intraoperative variables.

Results: Across all participants, the plasma AβR increased from the preoperative period to postoperative Day 1 (Wilcoxon P<0.001). However, this increase was not associated with delirium incidence (Wilcoxon P=0.22) or peak severity after adjusting for confounders (log[incidence rate ratio]=0.43; P=0.14). Postoperative Day 1 change in plasma AβR was not associated with postoperative Day 1 change in plasma tau, neurofilament light, or inflammatory markers (interleukin [IL]-1β, IL-1Ra, IL-2, IL-4, IL-6, IL-8, IL-10, and IL-12), or with operative time or low intraoperative arterial pressure.

Conclusions: Perioperative changes in plasma amyloid do not appear to be associated with postoperative delirium. Our findings do not support associations of dynamic changes in amyloid with postoperative delirium.

# Introduction

Surgery has been associated with short-term (acute delirium)[1] and long-term (postoperative cognitive dysfunction (POCD))[2,3] cognitive decline. It has been postulated that postoperative delirium may play a causal role in accelerating long-term cognitive decline;[4,5] however, confounding factors in this relationship mean inferences of causation are tenuous. Moreover, not all studies have observed poorer overall long-term cognition in patients with postoperative delirium.[6] Investigation of this topic is hampered by uncertainty regarding the neuropathological mechanisms that could underlie this relationship.

The Amyloid–Tau–Neurodegeneration (ATN) model has been recently introduced as a pathogenic framework of Alzheimer's disease (AD).[7] From analysis of our cohort, we have shown associations of delirium with markers of neurodegeneration (neurofilament light (NfL)[8,9] and tau[9,10]), which has been replicated in other studies.[11,12] Recent commentary by Walker and colleagues[13] highlighted the need for a greater understanding of the biological link between postoperative delirium and long-term cognitive changes, particularly with respect to the amyloid hypothesis as a possible explanation. Herein we extend our biomarker analyses focussing on the amyloid hypothesis.

The amyloid hypothesis remains a leading theory for the pathogenesis of AD,[14-16] despite the ubiquitous failure of therapeutic trials that address this hypothesis[17,18] and recent allegations that part of the evidence base was falsified.[19] The amyloid hypothesis posits that a cascade triggered by pathogenic amyloid beta (AB) peptide aggregation is central to the pathogenesis of AD.[20] Preclinical studies have shown that anaesthetic exposure is associated with increased AB production and aggregation,[21] possibly implicating anaesthetics (especially volatile agents[22]) in amyloid-mediated postoperative cognitive decline.

The role that delirium could play in the interaction between any possible aberration in the amyloid pathway induced by surgery and long-term cognitive decline is unclear. Of two small human PET imaging studies, one observed no correlation between cerebral amyloid burden and postoperative delirium,[23] while our pilot study reported a positive association with delirium severity.[24] The pitfall of these neuroimaging studies is that the static "snapshot" of imaging may fail to track important short-term changes, which may influence the pathological trajectory longer term. Short-term perioperative increases in plasma NfL and

tau, which are known biomarkers of AD,[25,26] have been associated with postoperative delirium.[8,27] However, perioperative changes in AB peptides are less well-understood. While low preoperative cerebrospinal fluid (CSF) AB42 has been associated with postoperative delirium in one study,[28] another study found no such relationship.[29] A recent, small study by our group reported that cerebrospinal fluid and plasma amyloid beta ratio (ABR; AB42:AB40) increased across the pre- to postoperative period, but peak postoperative change in cerebrospinal fluid and plasma ABR were not associated with peak delirium severity or delirium incidence.[9]

Due to the limited sample size in our prior report from matched CSF and plasma samples, we analysed data from a much larger study with corresponding tau and NfL data. The overarching goal of this observational study is to provide evidence for or against a causal relationship between delirium and AD. We contend that a strong correlation between perioperative changes in plasma amyloid and delirium that is not explained by known confounders would provide evidence in favour of a causal relationship, supporting an amyloid hypothesis linking delirium and dementia. Our specific aims were: (1) investigate the relationship between plasma ABR and delirium incidence and severity; (2) confirm the postoperative increase in plasma ABR in a larger cohort than our previous study; (3) establish covariates that could explain such an increase in plasma ABR.

# Methods

We report outcomes from participants in the Interventions for Postoperative Delirium Biomarker-3 (IPOD-B3) study (NCT03124303 and NCT01980511), which is an ongoing prospective observational cohort study in the United States enrolling patients undergoing non-intracranial surgery aged ≥65 years old. The University of Wisconsin-Madison (UWM) Institutional Review Board provided ethical approval for the study (2015-374). Further details on this cohort are described elsewhere.[10,30] The 14 participants in our previous study[9] with data for POD change in plasma ABR were also included in this study. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were used to report our findings.[31]

## Outcomes

The primary outcome of this study was POD1 change in ABR relative to peak delirium severity, as defined by Delirium Severity Score-Revised-98 (DRS-R-98).[32] Consistent with our previous work,[8] POD1 change was preferred over peak postoperative change as the latter is biased towards sicker patients with longer postoperative stays. Secondary outcomes included POD1 change in ABR based on delirium incidence, which was assessed using the 3-minute Diagnostic Confusion Assessment Method (3D-CAM)[33] or CAM for the intensive care unit (CAM-ICU)[34] (if intubated). Assessments were performed twice daily from postoperative days 1 to 4, between 06:00–10:00 and 16:00–20:00. Preoperative baseline cognitive testing was performed using the Montreal Cognitive Assessment (MoCA),[35] Trail Making Test B (TMTB),[36] and Controlled Oral Word Association Test (COWAT). Intraoperative data, including operation time, blood pressure, and blood loss, were obtained from the medical record. Secondary analyses were performed for all outcomes using AB40 and AB42, and using the peak postoperative change in AB40, AB42, and ABR. We also analysed the correlation between the postoperative change in amyloid and operative time, intraoperative blood pressure, and anaesthetic dose to assess the relationship to intraoperative variables. Age-adjusted median sevoflurane (AMS) concentration was calculated by dividing the median sevoflurane concentration (in minimum alveolar concentration (MAC) units) by $1.8*10^{(-0.00269*(age-40)}$.[37]

## Biomarker collection & analysis

Blood was collected in ethylenediaminetetraacetic acid (EDTA) tubes prior to surgery and each morning (06:00–10:00) from POD1 to 9. Blood samples were taken as close as possible to the time of delirium assessment and stored at –80 ºC. Samples were also taken at long-term follow-up, at POD90 and 365. We sent samples to the University of Gothenburg for analysis using an ultrasensitive Single molecule array (Simoa)[38] immunoassay for quantification of plasma AB40 and AB42 according to instructions from the manufacturer (Quanterix, Billerica, MA, USA). Blood samples were analysed by laboratory technicians who were blinded to the patient's clinical details.

## Power analysis

Our primary outcome of POD1 change in ABR and peak delirium severity was adjusted for known confounders: age, sex, and cognitive baseline. Based on a four-factor general linear model, 61 participants would be required to show a moderate effect size (Cohen $F_2 = 0.25$)

with 90% power at the 0.05 significance level. In order to ensure this sample size was reached and allow correspondence to the prior analyses of tau and NfL, we sent 105 subject samples for analysis.

### Statistical analysis

All analyses were performed in R (R Studio 2022.02.1 build 461, base R 4.1.3). The ABR was calculated by dividing the plasma concentration of AB42 by that of AB40. Changes in each biomarker were calculated by subtracting the baseline value from the value at the postoperative time of interest. We used $\log_{10}$-transformed biomarker data due to significantly skewed distributions. For all analyses, outliers were identified using Cook's distance with a threshold of >4μ to justify exclusion. The Shapiro–Wilk test, skewness, and visual inspection of the histogram plot were used to assess for normality. Where data were normally distributed, Pearson methods for regression and independent samples t-test for continuous variables were used. In cases of non-normal distribution, Spearman methods were used for linear regression and Mann–Whitney/Wilcoxon Rank Sum tests with continuity correction were used to compare continuous outcomes. Chi squared tests of association or Fisher's exact test (when a cell count was <5) were used to compare proportions between groups. Pre- to postoperative change in amyloid was assessed using a paired sample Wilcoxon test or paired sample t-test, depending on distribution. Poisson family multivariable regression was used for models in which peak DRS was the dependent variable, as this is a count variable with significant rightward skew. Predictors for multivariable models were selected based on previous evidence of their influence on delirium severity or plasma AB level. Predictors were added using forced entry methods. Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) were used to assess model fit. A p-value of <0.05 was used as the threshold for statistical significance. No adjustments were made for multiple comparisons.

## Results

A total of 101 participants in the IPOD-B3 study had documented delirium assessments and baseline plasma amyloid data. One patient experienced acute alcohol withdrawal and was excluded from our analysis, leaving 100 patients (Supplementary Figure 1). The baseline characteristics of participants in this study are provided in Table 1. Thirty-five of the 100 patients (35%) were diagnosed with postoperative delirium. Greater intraoperative blood loss (Wilcoxon p<0.001) and longer operation times (Wilcoxon p<0.001) were observed in

patients with delirium. Higher National Survey Quality Improvement Program risk of death (NSQIP-D) (Wilcoxon $p<0.001$) and serious complications (NSQIP-SC) (Wilcoxon $p<0.001$) scores were also noted in the delirium group. In the delirium group, mean baseline COWAT scores were lower (Wilcoxon $p=0.001$) and mean baseline TMTB scores were higher than in the no-delirium group, although the latter did not reach our threshold for statistical significance in this dataset (Wilcoxon $p=0.058$).

## Time course of AB

Time course plots of plasma AB40, AB42, and ABR concentrations (normalised to baseline) over the first 4 postoperative days are shown in Figure 1. Smooth conditional mean curves are presented separately for patients with and without delirium. While there was no statistically significant change in plasma AB40 (Wilcoxon $p=0.15$, Figure 1B) or AB42 (Wilcoxon $p=0.45$, Figure 1D) from baseline to POD1, there was a statistically significant increase in plasma ABR across this time period (Wilcoxon $p<0.001$, Figure 1F). This finding remained significant when excluding the 14 participants who overlapped from our previous study (Supplementary Figure 2). A Gaussian family generalised linear model suggested that age, gender, NSQIP-D, and area under the curve (AUC) of sevoflurane did not explain this POD1 rise in ABR (Table 2). Analyses using peak postoperative change in AB showed statistically significant increases in AB40, AB42, and ABR from baseline (Supplementary Figure 3).

## Primary outcome: Association of amyloid with postoperative peak delirium severity

Based on Spearman methods for simple linear regression, there was no statistically significant correlation between peak DRS and POD1 change in AB40 (Spearman $\rho=-0.067$, $p=0.54$, Figure 2A), AB42 (Spearman $\rho=0.0085$, $p=0.94$, Figure 2C), or ABR (Spearman $\rho=0.13$, $p=0.23$, Figure 2E). Similarly, there was no statistically significant difference in patients with and without delirium in terms of POD1 change in AB40 (Wilcoxon $p=0.54$, Figure 2B), AB42 (Wilcoxon $p=0.78$, Figure 2D), or ABR (Wilcoxon $p=0.22$, Figure 2F).

Our Poisson family generalised linear regression compared peak DRS with POD1 plasma AB change after adjusting for age, sex, and baseline TMTB (Table 3). A decrease in plasma AB40 on POD1 was associated with more severe delirium in unadjusted ($\log(IRR)=-0.31$,

p<0.001) and adjusted (log(IRR)=-0.23, p=0.023) models. Conversely, POD1 change in plasma AB42 was not associated with peak delirium severity in unadjusted (log(IRR)=-0.19, p=0.288) or adjusted (log(IRR)=-0.13, p=0.492) models. An increase in POD1 plasma ABR was associated with higher delirium severity in unadjusted (log(IRR)=0.57, p<0.001) but not adjusted (log(IRR)=0.43, p=0.140) models.

## Secondary analysis: Peak change in amyloid and delirium severity

Analyses based on Spearman correlation methods using peak change in plasma AB showed a statistically significant association of change in plasma AB40 with peak DRS (Spearman ρ=0.26, p=0.013), and the change in AB40 was higher in delirious patients (Wilcoxon p=0.0024); there were no associations between peak plasma AB42 or ABR and delirium incidence or severity (Supplementary Figure 4). Peak DRS was not correlated with preoperative plasma AB40, AB42, or ABR, and preoperative levels of these biomarkers were not different in patients with postoperative delirium compared to those without delirium (Supplementary Figure 5).

Using Poisson family multivariable regression, an increase in peak plasma AB40 and AB42 was associated with peak delirium severity in adjusted and unadjusted models. ABR was significant in the unadjusted but not the adjusted model (Supplementary Table 1).

## Secondary outcome: Association of perioperative variables with amyloid

There was no relationship between AUC low blood pressure (<10% of baseline) and plasma AB40, AB42, and ABR on either POD1 or peak change analyses (Supplementary Figure 6). Similarly, there was no correlation between operation time and peak or POD1 change in plasma AB40, AB42, and ABR, with the exception of peak change in AB40, which was positively correlated with operation time (Spearman ρ=0.26, p=0.012, Supplementary Figure 7). There was no statistically significant correlation between POD1 change in plasma ABR and POD1 changes in plasma inflammatory markers (IL-1B, IL-1Ra, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12) (Supplementary Figure 8).

A total of 70 participants received sevoflurane for maintenance for anaesthesia, while the remaining 30 did not receive a volatile agent. There was no difference in POD1 change in

plasma AB40, AB42, and ABR in those with an AMS concentration of 0.2–1.0 MAC compared to those with AMS >1.0 MAC (Supplementary Figure 9).
POD1 change in both plasma AB40 and AB42 was positively correlated with the POD1 change in plasma tau, whereas there was no correlation between ABR and tau. POD1 change in plasma NfL was not correlated with POD1 change in any plasma amyloid biomarker (Supplementary Figure 10).

## Discussion

Our findings explore the short-term relationship between surgery, postoperative delirium, and plasma AB. We confirmed the finding from our previous study[9] that plasma ABR increases from baseline to POD1. However, after adjusting for covariates, this increase did not appear to be associated with delirium incidence or peak severity. Based on our findings, evidence for a pathophysiological chain linking postoperative delirium with long-term postoperative cognitive decline via the amyloid hypothesis of AD appears weak.

Our observation that the plasma ABR increases after surgery adds to the limited body of evidence describing short-term perioperative changes in amyloid levels. It is unclear for how long the short-term increase in plasma ABR that we observed would persist and if there is any impact on long-term trends in plasma ABR, brain amyloid deposition or cognitive function. Long-term longitudinal studies have shown that plasma ABR decreases proportionally with age and increasing cerebral amyloid deposition,[39,40] and this decrease is associated with greater cognitive decline in many[41,42] but not all[43] studies. It is possible that the increase in plasma ABR somehow relates to worsening AD pathology that is independent of any effect on postoperative delirium, although the links drawn here would be speculative. Moreover, if general anaesthesia was increasing the accumulation of the more pathogenic AB42 species in the brain, we may expect a decrease, not increase, in the plasma ABR following surgery.

Our findings stand in contrast to that of Tang and colleagues, who reported no changes in CSF AB42 in 11 patients in the 48 hours following surgery.[44] Conversely, one study in 10 cardiac surgery patients has suggested CSF AB42 increases postoperatively,[45] a finding which aligns with our previous CSF study in 13 patients.[9] The increase in CSF and plasma ABR observed by these studies could represent increased amyloid clearance from the central

nervous system (CNS) by microglia—expression of IL-1B is increased in surgery, and stimulation by IL-1B has been shown to promote microglial clearance of AB.[46] While this hypothesis and other provocative neuropathological explanations are attractive, they are difficult to defend. Firstly, we observed no correlation between plasma inflammatory markers and POD1 change in plasma ABR. Secondly, plasma AB is a less reliable indicator of AD compared to CSF AB.[47,48] AB in the brain readily diffuses into the CSF, whereas its movement across the blood–brain barrier (BBB) is restricted. Moreover, AB is produced by other organs (e.g., liver, kidney)[49] in which homeostasis is often perturbed by surgery. Changes in plasma AB have also been associated with white matter hyperintensities, lacunar infarcts and hypoxic brain injury following cardiac arrest,[50,51] meaning perioperative plasma AB is likely influenced by ischaemia. Together, these observations suggest plasma AB could fluctuate in the perioperative period independent of any change in cerebral amyloid burden that is of pathophysiological significance to delirium and AD. Finally, we are not aware of a rationale for the relative *increase* in plasma AB42 over AB40 in the perioperative period. While differential cleavage of the amyloid precursor protein (APP) in central or peripheral tissues could be induced by anaesthesia, or AB42 could be preferentially cleared from plaques in the brain, preclinical studies have shown no obvious signal for this.[21,22,52]

Our results point away from AB as an explanatory link for any possible causative relationship between short- and long-term postoperative cognitive decline. These findings are supported by a recent cross-sectional study that observed an association between past surgery and cortical thinning on PET imaging in areas typically implicated in AD, but no association between past surgery and cerebral amyloid deposition.[53] Considering the reported association between surgery and accelerated cognitive decline in many[53,54] but not all[55] high-quality studies, current evidence suggests a harmful effect of surgery on neurodegeneration via a mechanism that is independent of cerebral AB deposition. This is consistent with the association of postoperative day 1 changes in the neurodegeneration biomarker, neurofilament light, with delirium[8] and longer term cognition.[56] For example, support for the role of tau in the clinical progression of AD appears to outpacing that for AB,[57] and plasma tau has recently been associated with postoperative delirium incidence and severity.[10,58] We observed a positive correlation of change in plasma tau with AB40 and AB42, and no correlation with ABR. Given the postoperative day 1 change in plasma AB40 and AB42 was not related to delirium incidence, and there was no correlation between amyloid and NfL, the relationship between tau and amyloid likely arose from processes separate to those occurring

in delirium. Neuroinflammation driven by the surgery-induced peripheral inflammatory response has also emerged as a potentially critical mediator of delirium and postoperative cognitive decline,[59] and inflammation was unrelated to amyloid in our data.

This study had some limitations. We did not control for apolipoprotein E (*APOE*) ε4 status, which is known to affect plasma AB levels.[60] However, *APOE* status has been found to not be associated with delirium.[61] Our findings may be difficult to compare to those of other groups due to the known effects on plasma AB arising from differences in assays, age, disease severity, and subjective clinical assessment of cognitive function.[43] Our attrition rate for biomarker collection from POD1 onwards was an expected consequence of patient discharge from hospital.

## Conclusion

We observed an increase in the plasma ABR from the pre- to post-operative period; however, after adjusting for confounders, this increase was not associated with the incidence or severity of postoperative delirium. Perioperative fluctuations in the plasma ABR therefore appear to be of little short-term clinical consequence. Our data do not support the amyloid hypothesis of AD as a mechanistic link between previously reported associations between postoperative delirium and long-term postoperative cognitive decline. Current evidence points more towards a neuroinflammatory cascade and aberrations in the tau pathway as possible explanations, and future research should consider focusing on these avenues of investigation.

## Details of author contributions

RS, RL and RP designed the study in consultation with MP, CC, DK, and CR recruited participants, and collected and processed data. HZ and KB supplied the assays and managed biofluids analysis. TP analysed data and drafted the manuscript with input from JT. All authors provided critical feedback on the manuscript.

## Data availability

Study data available on request to qualified investigators upon reasonable request.

## Declarations of interests

All authors have completed the International Committee of Medical Journal Editors (ICJME) disclosure of interest form (available on request from the corresponding author). HZ has served at scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Passage Bio, Pinteon Therapeutics, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. The other authors declare no competing interests that may be relevant to the submitted work.

## Funding

This work is supported by US National Institutes of Health (NIH) grant R01 AG063849-01 (RDS, RL, and RAP). RDS is also supported by NIH K23 AG055700. HZ is a Wallenberg Scholar supported by grants from the Swedish Research Council (#2018-02532), the European Union's Horizon Europe research and innovation programme under grant agreement No 101053962, Swedish State Support for Clinical Research (#ALFGBG-71320), the Alzheimer Drug Discovery Foundation (ADDF), USA (#201809-2016862), the AD Strategic Fund and the Alzheimer's Association (#ADSF-21-831376-C, #ADSF-21-831381-C, and #ADSF-21-831377-C), the Bluefield Project, the Olav Thon Foundation, the Erling-Persson Family Foundation, Stiftelsen för Gamla Tjänarinnor, Hjärnfonden, Sweden (#FO2022-0270), the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 860197 (MIRIADE), the European Union Joint Programme – Neurodegenerative Disease Research (JPND2021-00694), and the UK Dementia Research Institute at UCL (UKDRI-1003).

## Supplementary material

Supplementary material is available online.

# References


1. Rudolph JL, Marcantonio ER. Review articles: postoperative delirium: acute change with long-term implications. Anesth Analg 2011;112:1202-11.
2. Krause BM, Sabia S, Manning HJ, Singh-Manoux A, Sanders RD. Association between major surgical admissions and the cognitive trajectory: 19 year follow-up of Whitehall II cohort study. BMJ 2019;366:l4466.
3. Schulte PJ, Roberts RO, Knopman DS, et al. Association between exposure to anaesthesia and surgery and long-term cognitive trajectories in older adults: report from the Mayo Clinic Study of Aging. Br J Anaesth 2018;121:398-405.
4. Saczynski JS, Marcantonio ER, Quach L, et al. Cognitive Trajectories after Postoperative Delirium. New England Journal of Medicine 2012;367:30-9.
5. Inouye SK, Marcantonio ER, Kosar CM, et al. The short-term and long-term relationship between delirium and cognitive trajectory in older surgical patients. Alzheimers Dement 2016;12:766-75.
6. Brown CHIV, Probert J, Healy R, et al. Cognitive Decline after Delirium in Patients Undergoing Cardiac Surgery. Anesthesiology 2018;129:406-16.
7. Jack CR, Jr., Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement 2018;14:535-62.
8. Casey CP, Lindroth H, Mohanty R, et al. Postoperative delirium is associated with increased plasma neurofilament light. Brain 2019;143:47-54.
9. Parker M, White M, Casey C, et al. Cohort Analysis of the Association of Delirium Severity With Cerebrospinal Fluid Amyloid-Tau-Neurodegeneration Pathologies. J Gerontol A Biol Sci Med Sci 2022;77:494-501.
10. Ballweg T, White M, Parker M, et al. The association of plasma tau and postoperative delirium. Br J Anaesth 2020.
11. Fong TG, Vasunilashorn SM, Ngo L, et al. Association of Plasma Neurofilament Light with Postoperative Delirium. Annals of Neurology 2020;88:984-94.
12. Page VJ, Watne LO, Heslegrave A, et al. Plasma neurofilament light chain protein as a predictor of days in delirium and deep sedation, mortality and length of stay in critically ill patients. eBioMedicine 2022;80:104043.
13. Walker KA, Eckenhoff RG, Brown CH. Untangling anaesthesia and amyloid. British Journal of Anaesthesia 2020;125:232-5.
14. Karran E, De Strooper B. The amyloid hypothesis in Alzheimer disease: new insights from new therapeutics. Nature Reviews Drug Discovery 2022;21:306-18.
15. Bateman RJ, Xiong C, Benzinger TLS, et al. Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease. New England Journal of Medicine 2012;367:795-804.
16. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 2002;297:353-6.
17. Doody RS, Thomas RG, Farlow M, et al. Phase 3 Trials of Solanezumab for Mild-to-Moderate Alzheimer's Disease. New England Journal of Medicine 2014;370:311-21.
18. Salloway S, Sperling R, Fox NC, et al. Two Phase 3 Trials of Bapineuzumab in Mild-to-Moderate Alzheimer's Disease. New England Journal of Medicine 2014;370:322-33.
19. Lesné S, Koh MT, Kotilinek L, et al. A specific amyloid-β protein assembly in the brain impairs memory. Nature 2006;440:352-7.

20. Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol Med 2016;8:595-608.
21. Wan Y, Xu J, Meng F, et al. Cognitive decline following major surgery is associated with gliosis, β-amyloid accumulation, and τ phosphorylation in old mice. Critical Care Medicine 2010;38.
22. Eckenhoff Roderic G, Johansson Jonas S, Wei H, et al. Inhaled Anesthetic Enhancement of Amyloid-β Oligomerization and Cytotoxicity. Anesthesiology 2004;101:703-9.
23. Rolandi E, Cavedo E, Pievani M, et al. Association of postoperative delirium with markers of neurodegeneration and brain amyloidosis: a pilot study. Neurobiol Aging 2018;61:93-101.
24. Torres-Velázquez M, Parker M, Bo A, et al. Amyloid deposition on positron emission tomography correlates with severity of perioperative delirium: a case-control pilot study. British Journal of Anaesthesia 2022;128:e226-e8.
25. Jin M, Cao L, Dai Y-p. Role of Neurofilament Light Chain as a Potential Biomarker for Alzheimer's Disease: A Correlative Meta-Analysis. Frontiers in Aging Neuroscience 2019;11.
26. Mattsson N, Zetterberg H, Janelidze S, et al. Plasma tau in Alzheimer disease. Neurology 2016;87:1827-35.
27. Ballweg T, White M, Parker M, et al. Association between plasma tau and postoperative delirium incidence and severity: a prospective observational study. Br J Anaesth 2021;126:458-66.
28. Cunningham EL, McGuinness B, McAuley DF, et al. CSF Beta-amyloid 1-42 Concentration Predicts Delirium Following Elective Arthroplasty Surgery in an Observational Cohort Study. Ann Surg 2019;269:1200-5.
29. Witlox J, Kalisvaart KJ, de Jonghe JF, et al. Cerebrospinal fluid β-amyloid and tau are not associated with risk of delirium: a prospective cohort study in older adults with hip fracture. J Am Geriatr Soc 2011;59:1260-7.
30. Tanabe S, Mohanty R, Lindroth H, et al. Cohort study into the neural correlates of postoperative delirium: the role of connectivity and slow-wave activity. Br J Anaesth 2020;125:55-66.
31. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. The Lancet 2007;370:1453-7.
32. Trzepacz PT, Mittal D, Torres R, Kanary K, Norton J, Jimerson N. Validation of the Delirium Rating Scale-revised-98: comparison with the delirium rating scale and the cognitive test for delirium. J Neuropsychiatry Clin Neurosci 2001;13:229-42.
33. Marcantonio ER, Ngo LH, O'Connor M, et al. 3D-CAM: derivation and validation of a 3-minute diagnostic interview for CAM-defined delirium: a cross-sectional diagnostic test study. Ann Intern Med 2014;161:554-61.
34. Ely EW, Margolin R, Francis J, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med 2001;29:1370-9.
35. Freitas S, Simões MR, Alves L, Santana I. Montreal cognitive assessment: validation study for mild cognitive impairment and Alzheimer disease. Alzheimer Dis Assoc Disord 2013;27:37-43.

36. Giovagnoli AR, Del Pesce M, Mascheroni S, Simoncelli M, Laiacona M, Capitani E. Trail making test: normative values from 287 normal adult controls. The Italian Journal of Neurological Sciences 1996;17:305-9.
37. Mapleson WW. Effect of age on MAC in humans: a meta-analysis. Br J Anaesth 1996;76:179-85.
38. Rissin DM, Kan CW, Campbell TG, et al. Single-molecule enzyme-linked immunosorbent assay detects serum proteins at subfemtomolar concentrations. Nature Biotechnology 2010;28:595-9.
39. Burnham SC, Fandos N, Fowler C, et al. Longitudinal evaluation of the natural history of amyloid-β in plasma and brain. Brain Communications 2020;2:fcaa041.
40. Fandos N, Pérez-Grijalba V, Pesini P, et al. Plasma amyloid β 42/40 ratios as biomarkers for amyloid β cerebral deposition in cognitively normal individuals. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 2017;8:179-87.
41. Seppälä TT, Herukka SK, Hänninen T, et al. Plasma Aβ42 and Aβ40 as markers of cognitive change in follow-up: a prospective, longitudinal, population-based cohort study. Journal of Neurology, Neurosurgery & Psychiatry 2010;81:1123.
42. Schupf N, Tang MX, Fukuyama H, et al. Peripheral Abeta subspecies as risk biomarkers of Alzheimer's disease. Proc Natl Acad Sci U S A 2008;105:14052-7.
43. Toledo JB, Vanderstichele H, Figurski M, et al. Factors affecting Aβ plasma levels and their utility as biomarkers in ADNI. Acta Neuropathol 2011;122:401-13.
44. Tang Junxia X, Baranov D, Hammond M, Shaw Leslie M, Eckenhoff Maryellen F, Eckenhoff Roderic G. Human Alzheimer and Inflammation Biomarkers after Anesthesia and Surgery. Anesthesiology 2011;115:727-32.
45. Reinsfelt B, Westerlind A, Blennow K, Zetterberg H, Ricksten SE. Open-heart surgery increases cerebrospinal fluid levels of Alzheimer-associated amyloid β. Acta Anaesthesiologica Scandinavica 2013;57:82-8.
46. Rivera-Escalera F, Pinney JJ, Owlett L, et al. IL-1β-driven amyloid plaque clearance is associated with an expansion of transcriptionally reprogrammed microglia. Journal of Neuroinflammation 2019;16:261.
47. Rissman RA, Trojanowski JQ, Shaw LM, Aisen PS. Longitudinal plasma amyloid beta as a biomarker of Alzheimer's disease. J Neural Transm (Vienna) 2012;119:843-50.
48. Toledo JB, Shaw LM, Trojanowski JQ. Plasma amyloid beta measurements - a desired but elusive Alzheimer's disease biomarker. Alzheimer's Research & Therapy 2013;5:8.
49. Selkoe DJ, Podlisny MB, Joachim CL, et al. Beta-amyloid precursor protein of Alzheimer disease occurs as 110- to 135-kilodalton membrane-associated proteins in neural and nonneural tissues. Proc Natl Acad Sci U S A 1988;85:7341-5.
50. van Dijk EJ, Prins ND, Vermeer SE, et al. Plasma amyloid beta, apolipoprotein E, lacunar infarcts, and white matter lesions. Ann Neurol 2004;55:570-5.
51. Gurol ME, Irizarry MC, Smith EE, et al. Plasma beta-amyloid and white matter lesions in AD, MCI, and cerebral amyloid angiopathy. Neurology 2006;66:23-9.
52. Xie Z, Xu Z. General anesthetics and β-amyloid protein. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2013;47:140-6.
53. Sprung J, Warner DO, Knopman DS, et al. Exposure to surgery with general anaesthesia during adult life is not associated with increased brain amyloid deposition in older adults. British Journal of Anaesthesia 2020;124:594-602.
54. Eriksson LI, Lundholm C, Narasimhalu K, et al. Hospitalization, surgery, and incident dementia. Alzheimer's & Dementia 2019;15:534-42.

55. Sprung J, Jankowski CJ, Roberts RO, et al. Anesthesia and incident dementia: a population-based, nested, case-control study. Mayo Clin Proc 2013;88:552-61.
56. Brown CH, Lewis A, Probert J, et al. Perioperative Neurofilament Light Plasma Concentrations and Cognition before and after Cardiac Surgery: A Prospective Nested Cohort Study. Anesthesiology 2022;137:303-14.
57. Brier MR, Gordon B, Friedrichsen K, et al. Tau and Aβ imaging, CSF measures, and cognition in Alzheimer's disease. Sci Transl Med 2016;8:338ra66.
58. McKay TB, Qu J, Liang F, et al. Tau as a serum biomarker of delirium after major cardiac surgery: a single centre case-control study. British Journal of Anaesthesia 2022;129:e13-e6.
59. Cortese GP, Burger C. Neuroinflammatory challenges compromise neuronal function in the aging brain: Postoperative cognitive delirium and Alzheimer's disease. Behavioural Brain Research 2017;322:269-79.
60. Swaminathan S, Risacher SL, Yoder KK, et al. Association of plasma and cortical amyloid beta is modulated by APOE ε4 status. Alzheimer's & Dementia 2014;10:e9-e18.
61. Vasunilashorn S, Ngo L, Kosar CM, et al. Does Apolipoprotein E Genotype Increase Risk of Postoperative Delirium? Am J Geriatr Psychiatry 2015;23:1029-37.