EJA

Eur J Anaesthesiol 2024; **41:**234–244

OPEN

ORIGINAL ARTICLE

Associations between Alzheimer's disease biomarkers and postoperative delirium or cognitive dysfunction

A meta-analysis and trial sequential analysis of prospective clinical trials

Jun Geng*, Yaowen Zhang*, Hui Chen, Hui Shi, Zhen Wu, Jianqing Chen and Foquan Luo

BACKGROUND The relationship between Alzheimer's disease biomarkers and postoperative complications, such as postoperative delirium (POD) and postoperative cognitive dysfunction (POCD), remains a subject of ongoing debate.

OBJECTIVE This meta-analysis aimed to determine whether there is an association between perioperative Alzheimer's disease biomarkers and postoperative complications.

DESIGN We conducted a meta-analysis of observational clinical studies that explored the correlation between Alzheimer's disease biomarkers and POD or POCD in patients who have undergone surgery, following PRISMA guidelines. The protocol was previously published (INPLASY: INPLASY202350001).

DATA SOURCES A comprehensive search was conducted across PubMed, Embase, Web of Science, and Cochrane databases until March 2023.

ELIGIBILITY CRITERIA Surgical patients aged at least 18 years, studies focusing on POD or POCD, research involving Alzheimer's disease biomarkers, including Aβ or tau in blood or cerebrospinal fluid (CSF), and availability of the full text.

RESULTS Our meta-analysis included 15 studies: six focusing on POD and nine on POCD. The findings revealed a negative correlation between preoperative CSF β-amyloid 42 (Aβ42) levels and the onset of POD [mean difference −86.1, 95% confidence interval (CI), −114.15 to −58.05, I^2: 47%]; this association was strongly supported by trial sequential analysis (TSA). A similar negative correlation was discerned between preoperative CSF Aβ42 levels and the incidence of POCD (−165.01, 95% CI, −261.48 to −68.53, I^2: 95%). The TSA also provided robust evidence for this finding; however, the evidence remains insufficient to confirm a relationship between other Alzheimer's disease biomarkers [β-amyloid 40 (Aβ40), total tau (T-tau), phosphorylated tau (P-tau), and Aβ42/T-tau ratio] and POD or POCD.

CONCLUSION The study results indicate a negative correlation between preoperative CSF Aβ42 levels and the occurrence of both POD and POCD. Future investigations are warranted to identify the predictive cutoff value of preoperative CSF Aβ42 for POD and POCD.

KEY POINTS

- Lower preoperative CSF Aβ42 levels are associated with higher rates of POD and POCD.
- There is insufficient evidence to support a relationship between other Alzheimer's disease biomarkers and POD or POCD.
- Further research is required to determine the optimal cutoff value for preoperative CSF Aβ42 levels and to explore potential strategies to reduce the incidence of POD and POCD.

* JG and YZ contributed to the work equally and should be regarded as co-first authors.

From the Department of Anaesthesiology, Jiangyin Hospital Affiliated to Nantong University, Wuxi City, Jiangsu Province, China (JG, YZ, HC, HH, ZW, JC) and Center for Rehabilitation Medicine, Department of Anesthesiology, Zhejiang Provincial People's Hospital (Affiliated People's Hospital), Hangzhou Medical College, Gongshu District, Hangzhou City, Zhejiang Province, China (FL)

Correspondence to Foquan Luo, MD, Center for Rehabilitation Medicine, Department of Anesthesiology, Zhejiang Provincial People's Hospital (Affiliated People's Hospital), Hangzhou Medical College, 158 Shangtang Road, Gongshu District, Hangzhou City, Zhejiang Province, China.
E-mail: lfqxmc@ncu.edu.cn

DOI:10.1097/EJA.0000000000001933

Introduction

Emerging research underscores the potential long-term cognitive implications of anaesthesia and surgery.[1] In particular, postoperative delirium (POD) and postoperative cognitive dysfunction (POCD) have been recognized as two separate, albeit-related, cognitive impairment parameters discernible through neuropsychological testing at various points postsurgery.[2] Delirium is characterized by sudden shifts in mental status, including fluctuations in consciousness and difficulties with concentration.[2] POD, a specific form of delirium, is not related to the emergence from anaesthesia, whereas POCD refers to decline in cognitive function, principally in memory and executive functions, which may persist for months or even years postsurgery.[2,3]

The implications of these phenomena intimate a possible shared pathogenesis between Alzheimer's disease and postoperative cognitive decline.[4–6] Both in-vitro and in-vivo studies have suggested that anaesthesia and surgery contribute to key Alzheimer's disease pathological processes, such as the genesis of amyloid-β (Aβ) plaques[7,8] and tau phosphorylation.[9–11] Remarkably, previous studies have demonstrated that obstructing these processes can enhance postoperative memory in mouse models.[12,13]

Regarding neuropathogenesis of Alzheimer's disease, β-amyloid proteins – namely Aβ40 and Aβ42 – are crucial constituents of senile plaques found in Alzheimer's disease patients, whereas tau is the primary protein component of neurofibrillary tangles in neurons.[14] A reduction in Aβ42 concentration signifies an accumulation of Aβ in amyloid plaques,[15,16] whereas an increase in T-tau levels reflects the extent of axonal degeneration,[17,18] and an elevation in P-tau levels corresponds to the presence of neurofibrillary tangles in the brain.[19] Despite the potential of these Alzheimer's disease biomarkers to predict POD or cognitive changes, study outcomes have been inconsistent to date.[20–22]

In light of these considerations, we conducted a meta-analysis, the first of its kind in this field, to determine if perioperative Alzheimer's disease biomarkers in blood or cerebrospinal fluid (CSF) can serve as predictive markers for POD and POCD.

Methods

Search strategy and selection criteria

Our meta-analysis was performed in accordance with a protocol registered on INPLASY (ID: INPLASY 202350001, DOI: 10.37766/inplasy2023.5.0001). This manuscript conforms to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[23] Two independent reviewers performed a search for studies published before March 2023 that investigated Alzheimer's disease biomarkers in the blood or CSF of surgical patients experiencing POD or POCD. The search spanned databases such as PubMed, Embase, Web of Science and Cochrane, combining comprehensive text words and Medical Subject Heading (MeSH) terms such as 'delirium' or 'cognitive changes' and 'amyloid' or 'tau'. The detailed search strategy can be found in Supplementary Material S1, http://links.lww.com/EJA/A892. We limited the search to publications in English or Chinese.

The inclusion criteria for studies were as follows: studies involving surgical patients aged at least 18 years, studies focusing on POD or POCD, research involving Alzheimer's disease biomarkers, including Aβ or tau in blood or CSF and availability of full text (comprehensive information). The exclusion criteria were as follows: studies with lack of data suitable for pooling analysis, studies not involving humans and articles not in English or Chinese.

Data extraction and synthesis

The search results were reviewed independently by two reviewers who extracted data based on the inclusion criteria, and a third reviewer cross-checked their findings. Essential information from each article, including author and year of publication; title; sample size; anaesthesia type; type of surgery; time of blood or CSF sample; biomarkers; preoperative cognitive assessment and diagnostic methods for POD or POCD, were meticulously documented. In cases of multiple publications from the same trial, only the most recent publication with the most comprehensive data was included. Any disagreements were resolved by consensus.

Quantitative data, including mean and standard deviation (SD) of biomarker levels, sample sizes of POD and POCD cases and control groups, were extracted from the studies. In cases where studies reported only the median, minimum, maximum and/or quartile range, we used the formula proposed by Wan *et al.*[24] to estimate the mean and SD. If authors did not provide mean ± SD of biomarker levels but provided graphical data in the article, we used ImageJ software (version 1.53a, National Institutes of Health, Bethesda, Maryland, USA) to extract these values. This software is publicly available for download (http://rsbweb.nih.gov/ij/download.html).

Study quality assessment

Two authors independently assessed the quality of each study using the Newcastle–Ottawa Scale (NOS).[25] The NOS scores range from 0 to 9, calculated based on three main aspects: selection of the study group (0 to 4 stars), comparability of the study group (0 to 2 stars) and determination of exposure and outcome in case–control and cohort studies (0 to 3 stars). Studies receiving scores of 7 to 9 stars, 4 to 6 stars and 0 to 3 stars were deemed to be of high quality, medium quality and low quality, respectively. Any disagreements were resolved through discussion and consensus.

Statistical analysis

We calculated the mean difference (MD) and 95% confidence interval (CI) of each biomarker as a continuous outcome using both fixed-effects and random-effects models. These two effects models assign different weights to each study. In the fixed-effects model, the assignment of weights is closely related to the sample size, and studies with large samples contribute a greater value to the total combined effect size relative to studies with small samples, resulting in small-sample studies being more likely to be ignored. In contrast, the total effect size of the random-effects model is the mean value of the true effect size of each study, and the random-effects model assigns greater weight to small-sample studies compared with the fixed-effects model, but its CI is larger than that of the fixed-effects model, making it more difficult to detect differences. In the presence of significant heterogeneity, we preferred the classic DerSimonian and Laird random-effects meta-analysis method, which accounts for variations between studies. The meta-analysis findings are presented in the Results section. To quantify heterogeneity among the combined results, we used the Q statistic via the chi-square test, and calculated the I^2 index to assess the impact of heterogeneity.[26] The I^2 index describes the percentage of total between-study variation attributable to heterogeneity rather than chance and ranges from 0 to 100%. A value of 0% indicates that no heterogeneity was observed, whereas larger values indicate greater heterogeneity. We evaluated the presence of statistical heterogeneity among the study results using the I^2 statistic, considering heterogeneity to be significant when P less than 0.10 and I^2 greater than 50%. In the absence of heterogeneity (heterogeneity $P > 0.1$), a fixed-effects model was utilised to calculate the pooled effect. If heterogeneity was significant, a random-effects model was used. We examined publication bias using funnel plots and Egger's test. All statistical analyses were conducted using RevMan version 5.4.1 Mac, The Nordic Cochrane Center, Copenhagen, Denmark (http://tech.cochrane.org/revman/download). Two-sided hypothesis tests were used for P values, and a statistical significance threshold was set at P less than 0.05. The overall quality of the evidence was graded using the GRADE classification,[27] and the results are displayed in supplement S2, http://links.lww.com/EJA/A893.

In sensitivity analysis, we sought to ensure the reliability of our results using the trim-and-fill method or different effect models.

To address potential issues related to low sample sizes and the repeated testing of significance in included studies, which can increase the risk of random errors,[28] we conducted a trial sequential analysis (TSA) using version 0.9 beta software of TSA (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen, Denmark) (http://www.ctu.dk/tsa). This analysis was performed to further validate the reliability of the results obtained from the sensitivity analysis using RevMan software, where the heterogeneity was less than 75%.[29] TSA was employed to ascertain whether the CI and P values in our meta-analysis were adequate to demonstrate the expected effect.[30] The TSA model settings are as follows: effect measure is 'mean difference', model is 'fixed-effect', type I error (α) is 5%, power (1-β) is 80%, heterogeneity correction based on model variance and mean difference and variance based on empirical assumptions, all automatically generated by the software. We calculated the required sample size adjusted for our meta-analysis and established the trial sequential monitoring boundaries (TSMB).

Results

The detailed search process is presented in Supplement S3, http://links.lww.com/EJA/A894. Our meta-analysis included a total of 15 studies: six on POD and nine on POCD (Supplement S3, http://links.lww.com/EJA/A894).[21,22,31–43] The excluded studies and the reasons for their exclusion are shown in Supplement S4, http://links.lww.com/EJA/A895. All included studies were either government-funded or unfunded, and the funders were not involved in any part of the research. The technique used for biomarker measurements in the included studies was the commonly used ELISA. The patient and clinical characteristics of these studies are summarised in Table 1. However, it is worth noting that although the studies we included are all about POD and POCD, the definition of POCD in some of the studies does not adhere to the 'Recommendations for the Nomenclature of Cognitive Change Associated with Anaesthesia and Surgery-2018'.[44] In the current nomenclature, the accurate terminology should be 'delayed neurocognitive recovery' (DNCR) before day 30, and the exact terminology would be POCD after day 30. Due to the limited data available for this meta-analysis, we still combined the two components in our calculations. The high quality of the included articles is evidenced by their mean ± SD NOS scores of 7.25 ± 0.46 for POD and 7.56 ± 0.53 for POCD. No article was excluded because of the quality of the study. Funnel plots and Egger's test of all outcomes did not reveal significant publication bias.

Figure 1 illustrates the meta-analysis results regarding the correlations between Alzheimer's disease biomarkers and POD (Fig. 1, part a) or DNCR or POCD (Fig. 1, part b). These biomarkers include both CSF-based biomarkers (Aβ42, T-tau, P-tau, Aβ42/T-tau, Aβ42/P-tau) and blood-based biomarkers (Aβ40 and Aβ42).

Alzheimer's disease biomarkers and postoperative delirium

Figure 2 presents the associations between Alzheimer's disease biomarkers and POD. The meta-analysis, which included five studies comprising a total of 1139 participants,[21,31–34] revealed a negative correlation between preoperative CSF Aβ42 levels and POD (−86.1, 95% CI, −114.15 to −58.05, I^2: 47%) (Fig. 2, part a). This conclusion is corroborated by TSA results (Fig. 3, part a).

Table 1 Demographic and clinical characteristics of enrolled studies

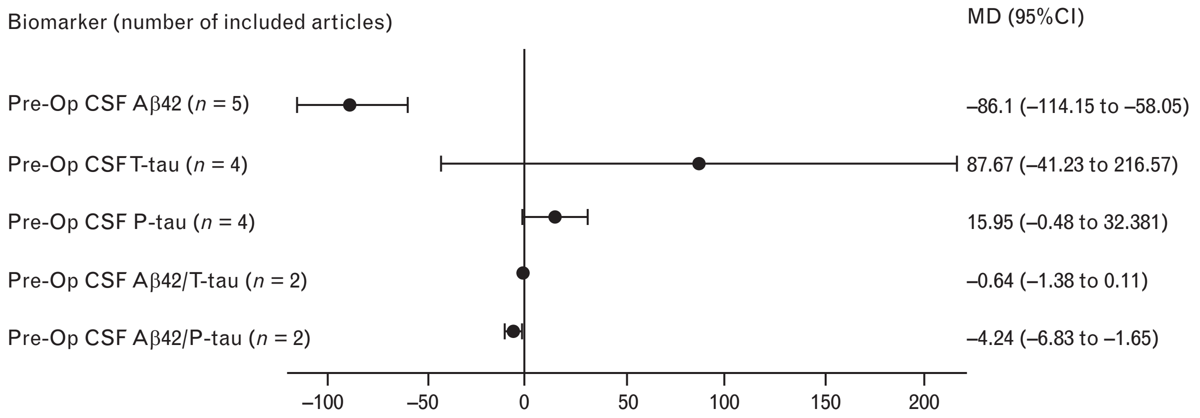
POD First author and publication year	Title	No. of case/ control	Anaesthesia type	Surgery type	Time of draw	Biomarkers	Preoperative cognitive assessment	Methods used to diagnose POD	Time of cognitive evaluation
Deng X 2022[30]	Cohort Analysis of the Association of Delirium Severity With Cerebrospinal Fluid Amyloid-Tau-Neurodegeneration Pathologies	123/534	Spinal-epidural anaesthesia (PNDABLE database)	laparoscopic colorectal cancer resection and knee or hip arthroplasty	Pre-Op	Aβ40, Aβ42, t-tau, p-tau (CSF)	Yes: MMSE	CAM	Twice a day on Postop days 1 to 7 (or before dis- charge)
Fong TG 2021[31]	Association of CSF Alzheimer's disease biomarkers with postoperative delirium in older adults	6/53	Spinal anaesthesia	knee and hip arthroplasty	Pre-Op	Aβ40, Aβ42, t-tau, p-tau (181) (CSF)	Yes: neuropsychological testing	CAM	Post-Op day 1 until discharge
Cunningham EL 2019[32]	CSF Beta-amyloid 1-42 Concentration Predicts Delirium Following Elective Arthroplasty Surgery in an Observational Cohort Study	40/242	Spinal anaesthesia (combined general anaesthesia in some patients)	elective hip or knee arthroplasty	Pre-Op	Aβ42, t-tau, p-tau (CSF)	Yes: MMSE	CAM	Post-Op day 1, post-Op day 2, post-Op day 3
Idland AV 2017[33]	Preclinical Amyloid-beta and Axonal Degeneration Pathology in Delirium	16/49	Spinal anaesthesia	hip arthroplasty	Pre-Op	Aβ42, T-tau, and P-tau (CSF)	Yes: IQCODE	CAM	Preoperative and postoperative until discharge
Xie Z 2014[23]	Preoperative cerebrospinal fluid beta-Amyloid/Tau ratio and postoperative delirium	31/122	Spinal anaesthesia	total hip/knee replacement	Pre-Op	Aβ40, Aβ42, tau (CSF)	No	CAM	Post-Op day 1, Post-Op day 2
Witlox 2011[22]	Cerebrospinal fluid beta-amyloid and tau are not associated with risk of delirium: a prospective cohort study in older adults with hip fracture	30/46	Spinal anaesthesia	hip arthroplasty	Pre-Op	Aβ42, t-tau, p-tau (CSF)	Yes: MMSE and IQCODE	CAM	Pre-Op post-Op day 1, Post-Op day 2, post-Op day 3, post-Op day 4, post-Op day 5

DNCR or POCD First author and publication year	title	No. of case/ control	Anaesthesia type	Surgery type	Time of draw	Biomarkers	Preoperative cognitive assessment	Methods used to diagnose POCC	Time of cognitive evaluation
Danielson M 2021[34]	Association between cerebrospinal fluid biomarkers of neuronal injury or amyloidosis and cognitive decline after major surgery.	6/21	Spinal anaesthesia	Knee or hip replacement	Pre-Op 4, 8, 24, 32, and 48 h after skin incision	T-tau, NFL, NSE, Aβ42 (CSF and blood)	Yes: MMSE, and a battery of seven neuropsychological tests	A battery of seven neuropsychological tests	Preop post-Op days 2 to 5, post-Op 3 months
Zhang X 2021[35]	Correlation of cerebrospinal fluid amyloid beta-protein 42 and neurofilament light protein levels with postoperative neurocognitive dysfunction in elderly patients	38/52	Combined spinal-epidural anaesthesia	Knee or hip replacement	Pre-Op	Aβ42, NFL (CSF)	Yes: a battery of six neuropsychological tests	A battery of six neuropsychological tests	Preop post-Op day 7
Wu Z 2018[36]	Ratio of beta-amyloid protein (Abeta) and Tau predicts the postoperative cognitive dysfunction on patients undergoing total hip/knee replacement surgery.	32/48	Combined spinal-epidural anaesthesia	Total hip arthroplasty or total knee replacement	Pre-Op	Aβ42, tau (CSF)	Yes: MMSE, and a battery of two neuropsychological tests	A battery of two neuropsychological tests	Preop post-Op day 7, post-Op 1 month, post-Op 3 months
Liang B 2016[37]	Correlations of plasma concentrations of β-amyloid peptide and S-100β with postoperative cognitive dysfunction in patients undergoing oral and maxillofacial cancer surgery	37/78	General anaesthesia	Oral and maxillofacial cancer surgeries	Pre-Op Post-Op day 1, day 7	Aβ40, S-100β (blood)	Yes: a battery of five neuropsychological tests	A battery of five neuropsychological tests	Preop post-Op day 7
Evered L 2016[38]	Cerebrospinal Fluid Biomarker for Alzheimer Disease Predicts Postoperative Cognitive Dysfunction.	11/46	Combined spinal and general anaesthesia	Elective total hip replacement	Pre-Op	Aβ42, T-tau, P-tau, NFL (CSF)	Yes: MMSE, CDR and a battery of eight neuropsychological tests	A battery of eight neuropsychological tests	Preop post-Op day 7, post-Op 3 months
Li XM 2014[39]	Relationship between postoperative cognitive dysfunction and regional cerebral oxygen saturation and beta-amyloid protein.	21/25	General anaesthesia	Elective laparoscopic pancreaticoduodenectomy	Pre-Op Post-Op day 1	Aβ (blood)	Yes: a battery of five neuropsychological tests	A battery of five neuropsychological tests	Preop post-Op day 7
Li X 2013[40]	Increase of beta-amyloid and C-reactive protein in liver transplant recipients with postoperative cognitive dysfunction.	11/14	General anaesthesia	Liver transplantation	Preop, 30 min after the start of the anhepatic phase 3 h after reperfusion of the new liver Postop 24 h	Aβ, CRP (blood)	Yes: a battery of six neuropsychological tests	A battery of six neuropsychological tests	Preop post-Op day 7
Ji MH 2013[41]	Changes in plasma and cerebrospinal fluid biomarkers in aged patients with early postoperative cognitive dysfunction following total hip-replacement surgery.	15/46	Spinal anaesthesia	Elective total hip-replacement	Pre-Op (CSF and blood) Post-Op day 7 (blood)	Aβ40, T-tau, P-tau, BDNF, IL-6, IL-1β (CSF) IL-1β, IL-6, BDNF, CRP, MDA (blood)	Yes: MMSE and a battery of three neuropsychological tests	A battery of three neuropsychological tests	Preop post-Op day 7
Evered LA 2009[42]	Plasma amyloid beta42 and amyloid beta40 levels are associated with early cognitive dysfunction after cardiac surgery	40/269	General anaesthesia	Elective CABG surgery	Pre-Op	Aβ40, Aβ42 (blood)	Yes: a battery of eight neuropsychological tests	A battery of eight neuropsychological tests	Preop post-Op 3 months. post-Op 12 months

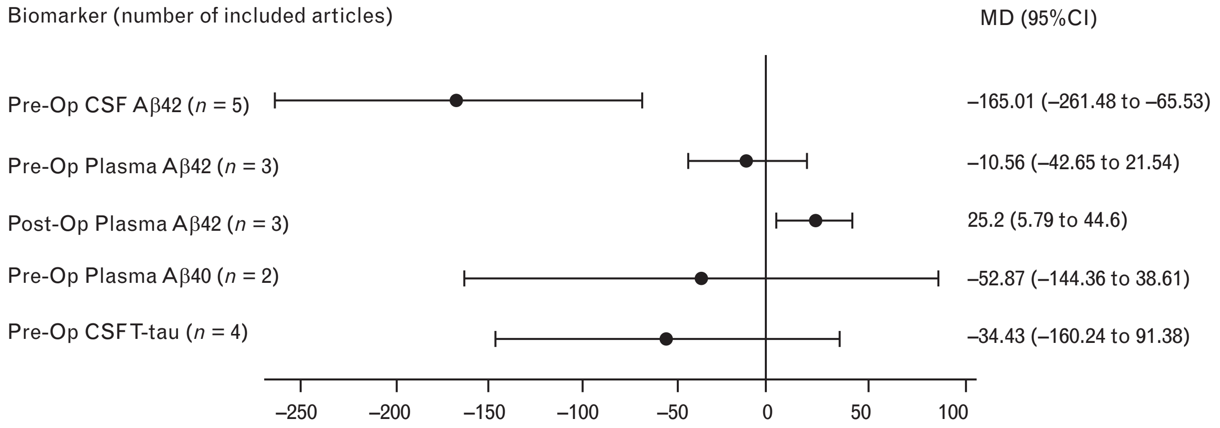
BDNF, brain-derived neurotrophic factor; CAM, confusion assessment method; CRP, C-reactive protein; CSF, cerebrospinal fluid; DNCR, delayed neurocognitive recovery; IQCODE, informant questionnaire on cognitive decline in the elderly; MDA, malonaldehyde; MMSE, mini-mental state examination; NFL, neurofilament light; NSE, neurone-specific enolase; POCD, postoperative cognitive dysfunction.

Fig. 1 Meta-analysis results: (a) correlations between AD biomarkers and POD, (b) correlations between AD biomarkers and POCD.

(a) POD



(b) POCD

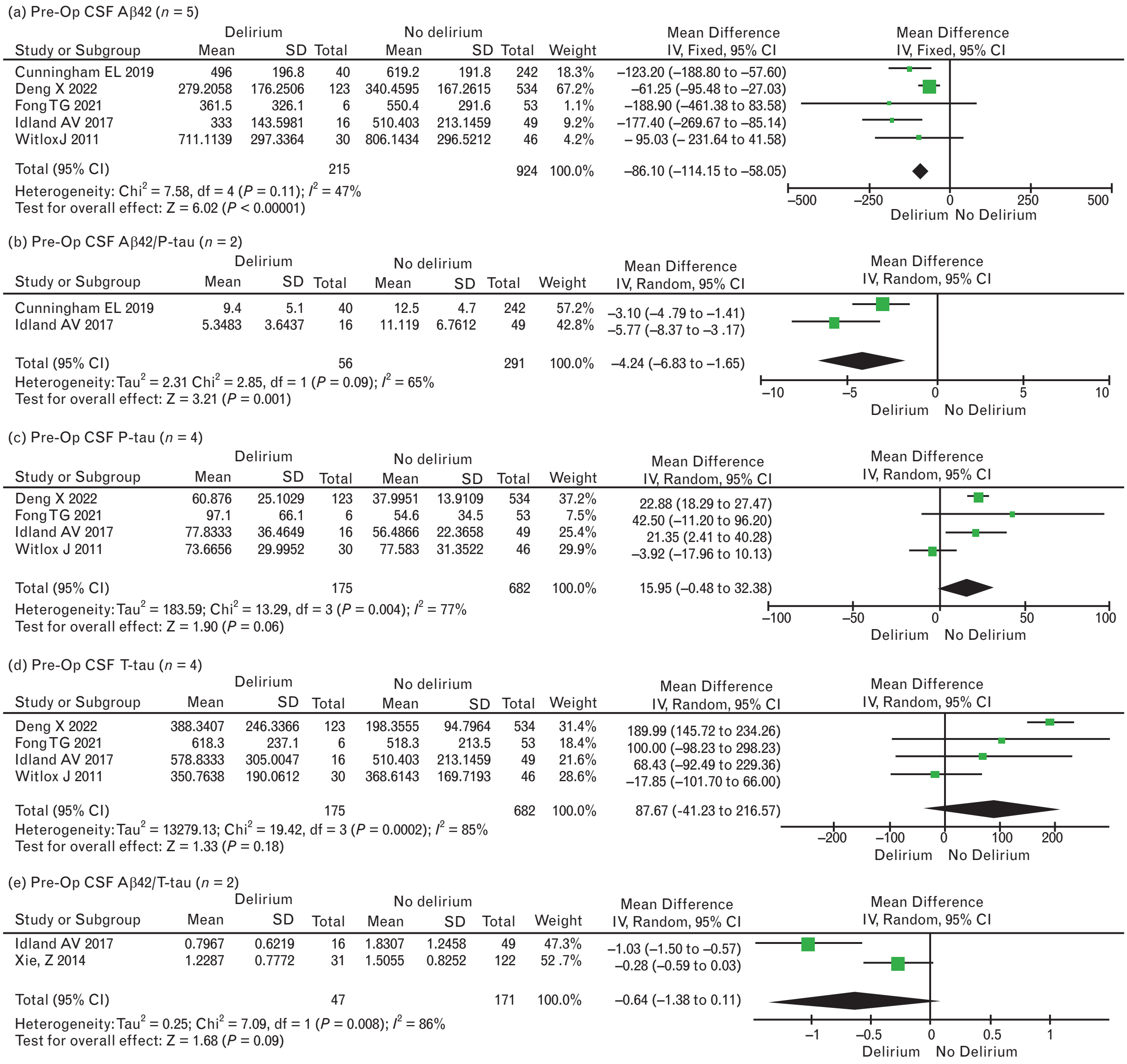


Importantly, Egger's test for this outcome did not reveal any significant publication bias ($P = 0.162$). Furthermore, pooled data from two studies with 347 participants indicated a negative correlation between preoperative CSF Aβ42/P-tau levels and POD (−4.24, 95% CI, −6.83 to −1.65, I^2: 65%) (Fig. 2, part b).[33,34] However, the TSA for this outcome did not provide sufficient evidence, as the *Z*-curve did not intersect the TSMB trial, suggesting uncertainty (Fig. 3, part b). In contrast, no significant associations were found between POD and other preoperative CSF Alzheimer's disease biomarkers, including preoperative CSF P-tau level ($n = 4$, 15.95, 95% CI, −0.48 to 32.381, I^2: 77%) (Fig. 2, part c),[21,31,32,34] T-tau level ($n = 4$, 87.67, 95% CI, −41.23 to 216.57, I^2: 85%) (Fig. 2, part d),[21,31,32,34] or Aβ42/T-tau level ($n = 2$, −0.64, 95% CI, −1.38 to 0.11, I^2: 86%) (Fig. 2, part e).[22,34]

Alzheimer's disease biomarkers and delayed neurocognitive recovery or postoperative cognitive dysfunction

The correlations between Alzheimer's disease biomarkers and DNCR or POCD are elucidated in Fig. 4. The pooled data from five studies including a total of 313 participants revealed a negative correlation between preoperative CSF Aβ42 levels and postoperative cognitive function changes (−165.01, 95% CI, −261.48 to −65.53, I^2: 95%) (Fig. 4, part a).[35–37,39,42] Egger's test for this outcome did not show the presence of publication bias ($P = 0.248$). We used the trim-and-fill method to validate the reliability of the results and obtained the same conclusion. The TSA further substantiated this conclusion based on these five studies (Fig. 5).[35–37,39,42] Additionally, data pooled from three studies, which involved 98 participants, showed a positive correlation between postoperative plasma Aβ42 levels and DNCR or POCD (25.20, 95% CI, 5.79 to 44.60, I^2: 96%) (Fig. 4, part b).[34,40,41] Conversely, no significant associations were identified between DNCR or POCD and preoperative plasma Aβ42 level ($n = 3$, −10.56, 95% CI, −42.65 to 21.54, I^2: 90%) (Fig. 4, part c),[35,41,43] preoperative plasma Aβ40 level ($n = 2$, −34.43, 95% CI, −160.24 to 91.38, I^2: 97%) (Fig. 4, part d),[38,43] or preoperative CSF T-tau level ($n = 4$, −52.87, 95% CI, −144.36 to 38.61, I^2: 91%) (Fig. 4, part e).[35,37,39,42]

Fig. 2 Forest plot showing the associations between AD biomarkers and POD: (a) pre-operative CSF Aβ42 levels and POD, (b) pre-operative CSF Aβ42/P-tau and POD, (c) pre-operative CSF P-tau levels and POD, (d) pre-operative T-tau levels and POD, (e) pre-operative CSF Aβ42/T-tau and POD.



(a) Pre-Op CSF Aβ42 (*n* = 5)

	Delirium			No delirium				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Cunningham EL 2019	496	196.8	40	619.2	191.8	242	18.3%	−123.20 (−188.80 to −57.60)
Deng X 2022	279.2058	176.2506	123	340.4595	167.2615	534	67.2%	−61.25 (−95.48 to −27.03)
Fong TG 2021	361.5	326.1	6	550.4	291.6	53	1.1%	−188.90 (−461.38 to 83.58)
Idland AV 2017	333	143.5981	16	510.403	213.1459	49	9.2%	−177.40 (−269.67 to −85.14)
WitloxJ 2011	711.1139	297.3364	30	806.1434	296.5212	46	4.2%	− 95.03 (− 231.64 to 41.58)
Total (95% CI)			215			924	100.0%	−86.10 (−114.15 to −58.05)

Heterogeneity: Chi^2 = 7.58, df = 4 (P = 0.11); I^2 = 47%
Test for overall effect: Z = 6.02 (P < 0.00001)

(b) Pre-Op CSF Aβ42/P-tau (*n* = 2)

	Delirium			No delirium				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Cunningham EL 2019	9.4	5.1	40	12.5	4.7	242	57.2%	−3.10 (−4 .79 to −1.41)
Idland AV 2017	5.3483	3.6437	16	11.119	6.7612	49	42.8%	−5.77 (−8.37 to −3 .17)
Total (95% CI)			56			291	100.0%	−4.24 (−6.83 to −1.65)

Heterogeneity: Tau^2 = 2.31 Chi^2 = 2.85, df = 1 (P = 0.09); I^2 = 65%
Test for overall effect: Z = 3.21 (P = 0.001)

(c) Pre-Op CSF P-tau (*n* = 4)

	Delirium			No delirium				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Deng X 2022	60.876	25.1029	123	37.9951	13.9109	534	37.2%	22.88 (18.29 to 27.47)
Fong TG 2021	97.1	66.1	6	54.6	34.5	53	7.5%	42.50 (−11.20 to 96.20)
Idland AV 2017	77.8333	36.4649	16	56.4866	22.3658	49	25.4%	21.35 (2.41 to 40.28)
Witlox J 2011	73.6656	29.9952	30	77.583	31.3522	46	29.9%	−3.92 (−17.96 to 10.13)
Total (95% CI)			175			682	100.0%	15.95 (−0.48 to 32.38)

Heterogeneity: Tau^2 = 183.59; Chi^2 = 13.29, df = 3 (P = 0.004); I^2 = 77%
Test for overall effect: Z = 1.90 (P = 0.06)

(d) Pre-Op CSF T-tau (*n* = 4)

	Delirium			No delirium				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Deng X 2022	388.3407	246.3366	123	198.3555	94.7964	534	31.4%	189.99 (145.72 to 234.26)
Fong TG 2021	618.3	237.1	6	518.3	213.5	53	18.4%	100.00 (−98.23 to 298.23)
Idland AV 2017	578.8333	305.0047	16	510.403	213.1459	49	21.6%	68.43 (−92.49 to 229.36)
Witlox J 2011	350.7638	190.0612	30	368.6143	169.7193	46	28.6%	−17.85 (−101.70 to 66.00)
Total (95% CI)			175			682	100.0%	87.67 (-41.23 to 216.57)

Heterogeneity: Tau^2 = 13279.13; Chi^2 = 19.42, df = 3 (P = 0.0002); I^2 = 85%
Test for overall effect: Z = 1.33 (P = 0.18)

(e) Pre-Op CSF Aβ42/T-tau (*n* = 2)

	Delirium			No delirium				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Idland AV 2017	0.7967	0.6219	16	1.8307	1.2458	49	47.3%	−1.03 (−1.50 to −0.57)
Xie, Z 2014	1.2287	0.7772	31	1.5055	0.8252	122	52 .7%	−0.28 (−0.59 to 0.03)
Total (95% CI)			47			171	100.0%	−0.64 (−1.38 to 0.11)

Heterogeneity: Tau^2 = 0.25; Chi^2 = 7.09, df = 1 (P = 0.008); I^2 = 86%
Test for overall effect: Z = 1.68 (P = 0.09)

Sensitivity analysis

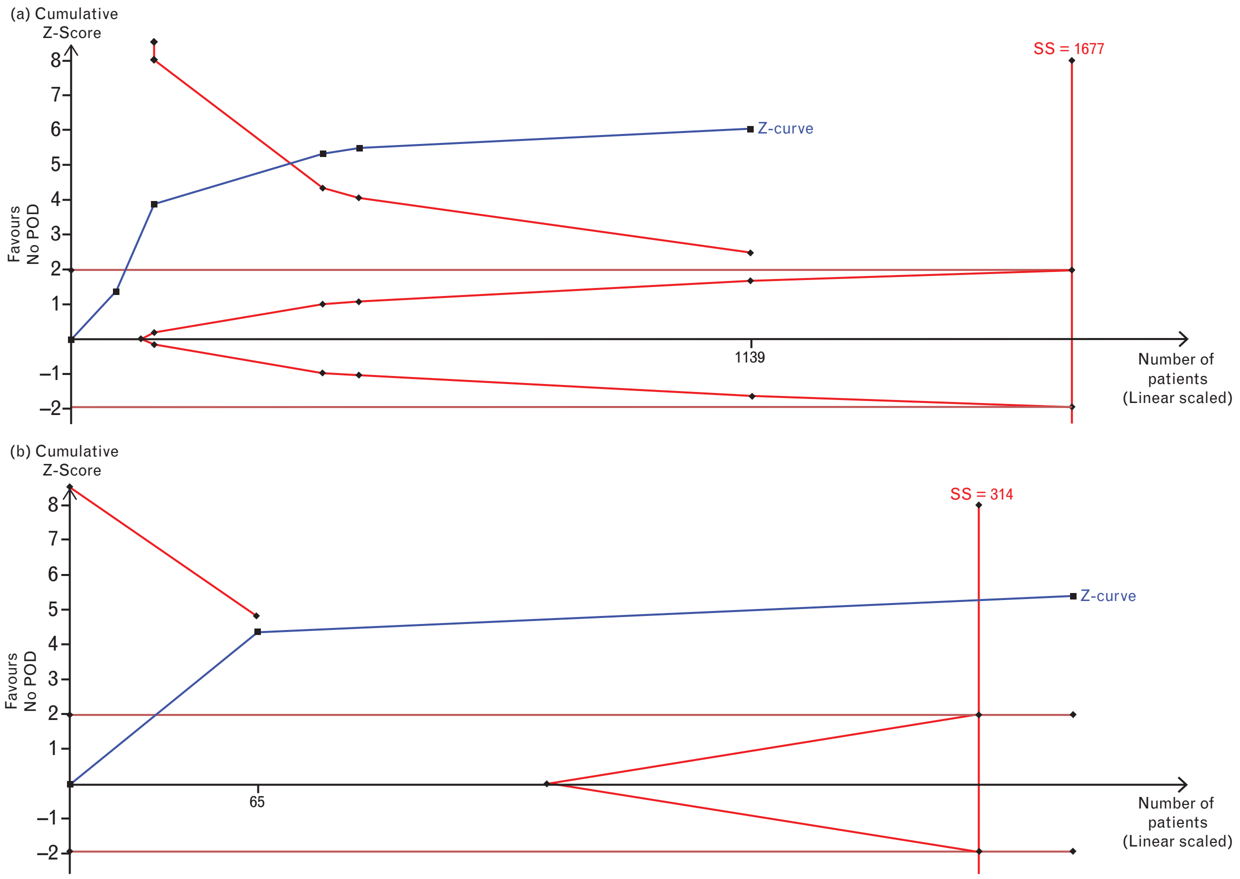
As shown in Figs. 2 and 4, significant study heterogeneity affected most of the analyses, particularly for studies of associations between preoperative CSF P-tau and POD ($I^2 = 77\%$, $P = 0.004$), preoperative CSF T-tau and POD ($I^2 = 85\%$, $P = 0.0002$), preoperative CSF Aβ42/T-tau and POD ($I^2 = 86\%$, $P = 0.008$), preoperative CSF Aβ42 and DNCR or POCD ($I^2 = 95\%$, $P < 0.00001$), postoperative plasma Aβ42 and DNCR or POCD ($I^2 = 96\%$, $P < 0.00001$), preoperative plasma Aβ42 and DNCR or POCD ($I^2 = 90\%$, $P < 0.00001$), preoperative plasma Aβ40 and DNCR or POCD ($I^2 = 97\%$, $P < 0.00001$) and preoperative CSF T-tau and DNCR or POCD ($I^2 = 91\%$, $P < 0.00001$). Based on this, we conducted a sensitivity analysis of all results using the RevMan software, applying various effect models to validate the reliability of the results. The results of this sensitivity analysis are summarised in Table 2.

Discussion

To our knowledge, this meta-analysis is the first study to examine the correlation between Alzheimer's disease biomarkers and the incidence of POD and DNCR or POCD. The robust evidence from TSA complemented our findings of a negative association between preoperative CSF Aβ42 levels and both POD and DNCR or POCD.

Previous research has established an association between POD with early POCD at 7 days and demonstrated that

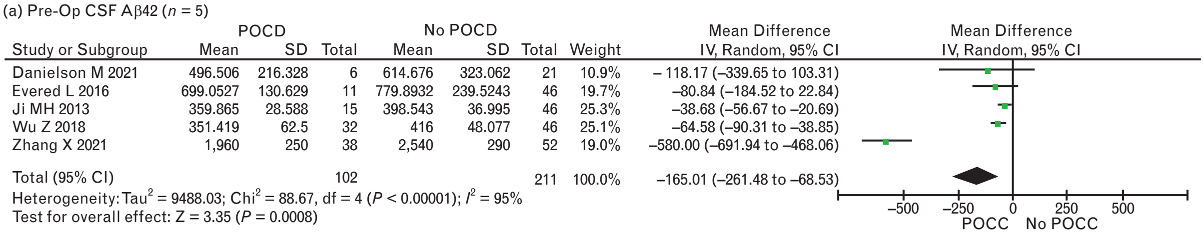
Fig. 3 Trial sequential analysis showing the associations between AD biomarkers and POD: (a) pre-operative CSF Aβ42 levels and POD, (b) pre-operative CSF Aβ42/P-tau and POD.



delirious patients have a 14-fold increased risk of developing POCD.[45,46] Nevertheless, there remains controversy regarding biomarkers for POD and POCD. These biomarkers include apolipoprotein E4 allele (APOE ε4 allele), IL-1β, IL-6, IL-8, IL-10, C-reactive protein (CRP), tumour necrosis factor (TNF)-α, S100β, neuron-specific enolase (NSE) and neurofilament light chain (NFL). APOE ε4 allele is thought to be involved in amyloid plaque deposition and play an important role in attention deficit disorder and other neurological disorders.[47] Hsiao *et al.*[48] found that the APOE ε4 allele is genetically associated with short-term and medium-term postoperative neurologic dysfunction. The relationship between POD and biomarkers for dementia (such as IL-1β, IL-6, IL-8, IL-10, CRP, TNF-α, S100β, NSE and NFL) has been discussed by Wang *et al.*[49] In their meta-analysis, they found that two inflammatory biomarkers (IL-6 and CRP) were significantly associated with POD, and two neuronal injury biomarkers (S100β and NFL) were positively associated with POD. In addition, no significant relationship was found between IL-1β, IL-8, IL-10, TNF-α, S100β and NSE. However, because of insufficient data, they did not analyse the correlation between amyloid and tau levels and POD. Therefore, our meta-analysis fills this research gap by investigating the relationships between Alzheimer's disease biomarkers (amyloid and tau), POD and DNCR or POCD.

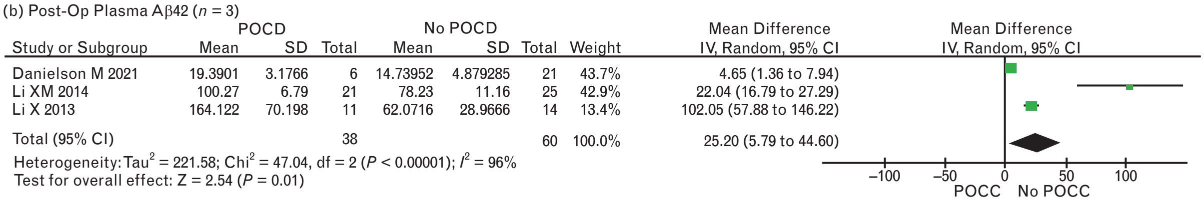
In a previous study, the pathogenic peptide Aβ42 level, which is more prevalent in the CSF of Alzheimer's disease patients, showed a decreasing trend.[43] Our meta-analysis confirmed this negative correlation between preoperative CSF Aβ42 levels and POD based on five studies.[21,31–34] Despite the TSA not reaching the required sample size, the *Z*-curve crossed the TSMB, indicating that this correlation has reached statistical significance. A similar negative relationship was observed between preoperative CSF Aβ42 levels and DNCR or POCD when pooling data from five studies.[35–37,39,42] However, this result was marked by considerable inter-study heterogeneity ($I^2 = 95\%$). In light of this, we conducted a sensitivity analysis using the trim-and-fill method, and the result remained unchanged. The TSA provided further evidence, cementing our belief in the negative correlation between preoperative CSF Aβ42 levels and DNCR or POCD. Aβ42, a central component

Fig. 4 Forest plot showing the associations between AD biomarkers and POCD: (a) pre-operative CSF Aβ42 levels and POCD, (b) post-operative plasma Aβ42 levels and POCD, (c) pre-operative plasma Aβ42 levels and POCD, (d) pre-operative Aβ40 levels and POCD, (e) pre-operative CSF T-tau levels and POCD.


(a) Pre-Op CSF Aβ42 (*n* = 5)

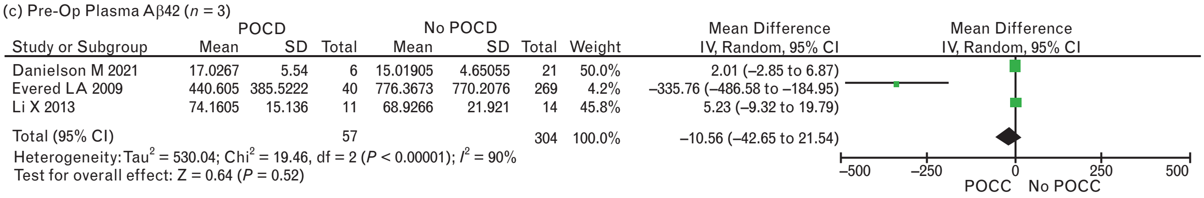
Study or Subgroup	POCD Mean	POCD SD	POCD Total	No POCD Mean	No POCD SD	No POCD Total	Weight	Mean Difference IV, Random, 95% CI
Danielson M 2021	496.506	216.328	6	614.676	323.062	21	10.9%	– 118.17 (–339.65 to 103.31)
Evered L 2016	699.0527	130.629	11	779.8932	239.5243	46	19.7%	–80.84 (–184.52 to 22.84)
Ji MH 2013	359.865	28.588	15	398.543	36.995	46	25.3%	–38.68 (–56.67 to –20.69)
Wu Z 2018	351.419	62.5	32	416	48.077	46	25.1%	–64.58 (–90.31 to –38.85)
Zhang X 2021	1,960	250	38	2,540	290	52	19.0%	–580.00 (–691.94 to –468.06)
Total (95% CI)			102			211	100.0%	–165.01 (–261.48 to –68.53)

Heterogeneity: $Tau^2 = 9488.03$; $Chi^2 = 88.67$, $df = 4$ ($P < 0.00001$); $I^2 = 95\%$
Test for overall effect: $Z = 3.35$ ($P = 0.0008$)


(b) Post-Op Plasma Aβ42 (*n* = 3)

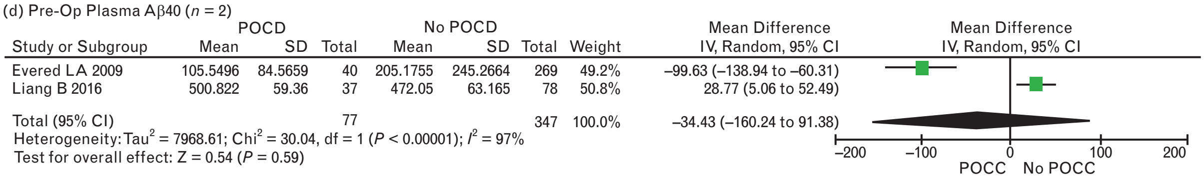
Study or Subgroup	POCD Mean	POCD SD	POCD Total	No POCD Mean	No POCD SD	No POCD Total	Weight	Mean Difference IV, Random, 95% CI
Danielson M 2021	19.3901	3.1766	6	14.73952	4.879285	21	43.7%	4.65 (1.36 to 7.94)
Li XM 2014	100.27	6.79	21	78.23	11.16	25	42.9%	22.04 (16.79 to 27.29)
Li X 2013	164.122	70.198	11	62.0716	28.9666	14	13.4%	102.05 (57.88 to 146.22)
Total (95% CI)			38			60	100.0%	25.20 (5.79 to 44.60)

Heterogeneity: $Tau^2 = 221.58$; $Chi^2 = 47.04$, $df = 2$ ($P < 0.00001$); $I^2 = 96\%$
Test for overall effect: $Z = 2.54$ ($P = 0.01$)


(c) Pre-Op Plasma Aβ42 (*n* = 3)

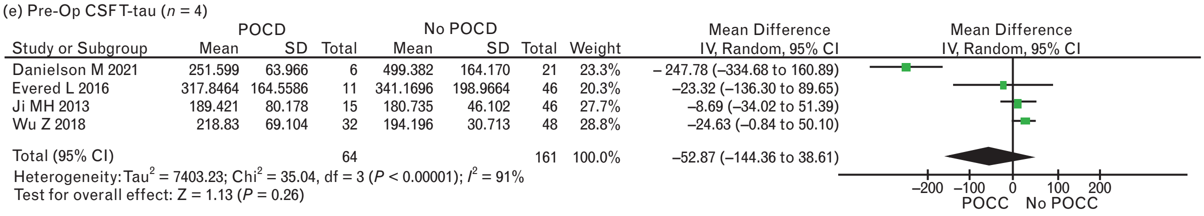
Study or Subgroup	POCD Mean	POCD SD	POCD Total	No POCD Mean	No POCD SD	No POCD Total	Weight	Mean Difference IV, Random, 95% CI
Danielson M 2021	17.0267	5.54	6	15.01905	4.65055	21	50.0%	2.01 (–2.85 to 6.87)
Evered LA 2009	440.605	385.5222	40	776.3673	770.2076	269	4.2%	–335.76 (–486.58 to –184.95)
Li X 2013	74.1605	15.136	11	68.9266	21.921	14	45.8%	5.23 (–9.32 to 19.79)
Total (95% CI)			57			304	100.0%	–10.56 (–42.65 to 21.54)

Heterogeneity: $Tau^2 = 530.04$; $Chi^2 = 19.46$, $df = 2$ ($P < 0.00001$); $I^2 = 90\%$
Test for overall effect: $Z = 0.64$ ($P = 0.52$)


(d) Pre-Op Plasma Aβ40 (*n* = 2)

Study or Subgroup	POCD Mean	POCD SD	POCD Total	No POCD Mean	No POCD SD	No POCD Total	Weight	Mean Difference IV, Random, 95% CI
Evered LA 2009	105.5496	84.5659	40	205.1755	245.2664	269	49.2%	–99.63 (–138.94 to –60.31)
Liang B 2016	500.822	59.36	37	472.05	63.165	78	50.8%	28.77 (5.06 to 52.49)
Total (95% CI)			77			347	100.0%	–34.43 (–160.24 to 91.38)

Heterogeneity: $Tau^2 = 7968.61$; $Chi^2 = 30.04$, $df = 1$ ($P < 0.00001$); $I^2 = 97\%$
Test for overall effect: $Z = 0.54$ ($P = 0.59$)


(e) Pre-Op CSF T-tau (*n* = 4)

Study or Subgroup	POCD Mean	POCD SD	POCD Total	No POCD Mean	No POCD SD	No POCD Total	Weight	Mean Difference IV, Random, 95% CI
Danielson M 2021	251.599	63.966	6	499.382	164.170	21	23.3%	– 247.78 (–334.68 to 160.89)
Evered L 2016	317.8464	164.5586	11	341.1696	198.9664	46	20.3%	–23.32 (–136.30 to 89.65)
Ji MH 2013	189.421	80.178	15	180.735	46.102	46	27.7%	–8.69 (–34.02 to 51.39)
Wu Z 2018	218.83	69.104	32	194.196	30.713	48	28.8%	–24.63 (–0.84 to 50.10)
Total (95% CI)			64			161	100.0%	–52.87 (–144.36 to 38.61)

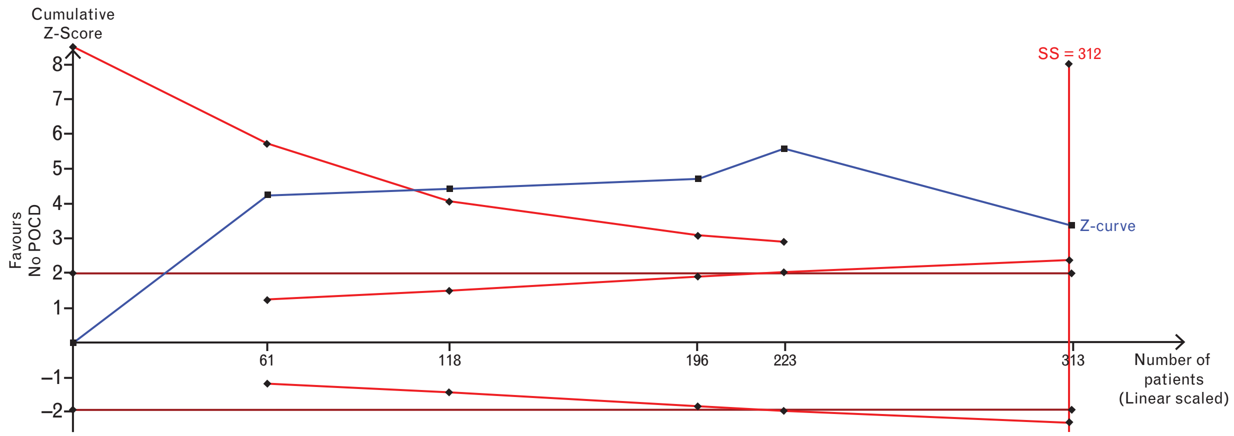
Heterogeneity: $Tau^2 = 7403.23$; $Chi^2 = 35.04$, $df = 3$ ($P < 0.00001$); $I^2 = 91\%$
Test for overall effect: $Z = 1.13$ ($P = 0.26$)

of extracellular neuroinflammatory plaques, is strongly associated with neuropathological processes and cognitive decline in Alzheimer's disease.[50] Therefore, it is reasonable to believe that preclinical Alzheimer's disease brain pathology may play a role in the pathophysiology of POD and POCD, implying that underlying Alzheimer's disease pathology, even without cognitive impairment (preclinical dementia), might contribute to the development of POD and POCD.

Considering the difficulty in obtaining CSF samples, which hampers the clinical application of CSF biomarkers, some studies have explored the relationship between plasma β-amyloid and POD or POCD.[51] Sun *et al.* found no significant correlation between preoperative plasma Aβ40 levels and POD, although postoperative plasma Aβ40 levels significantly increased in patients who developed POD. Our meta-analysis could not determine the relationship between preoperative plasma Aβ42 or Aβ40 level and DNCR or POCD, possibly because of the limited number of eligible studies and insufficient sample sizes. This suggests the need for further research. The pooled results of three studies suggest a positive correlation between postoperative plasma Aβ42 level and DNCR or POCD.[35,41,43] However, these studies exhibited significant inter-study heterogeneity, undermining the reliability of this result.

In this meta-analysis, we did not find strong evidence of a correlation between preoperative CSF T-tau or P-tau

Fig. 5 Trial sequential analysis showing the associations between pre-operative CSF Aβ42 levels and POCD.



levels and POD or DNCR or POCD. Although preoperative CSF T-tau and P-tau levels were positively correlated with POD in the fixed-effects model, the significant heterogeneity between studies raises concerns about these results. The findings of a previous study that was not included in this meta-analysis echoed our findings, reporting no significant correlation between preoperative CSF tau levels and POCD.[52] These findings should be validated through large-scale clinical studies.

Lower CSF Aβ42 levels have been associated with increased brain amyloid protein accumulation,[53] which in turn promotes Alzheimer's disease progression.[54] Higher CSF tau levels correlate with elevated brain tau levels and Alzheimer's disease progression.[55,56] Theoretically, a lower Aβ42/Tau ratio can differentiate Alzheimer's disease patients from healthy controls and predict Alzheimer's disease development. However, our meta-analysis failed to find a significant relationship between the Aβ42/T-tau ratio and POD from the pooling of data from two articles.[22,34] Similarly, the negative correlation between Aβ42/P-tau and POD was not conclusive, as the *Z*-curve from TSA did not cross the TSMB.[33,34] Some existing studies have found significant increases in CSF tau/Aβ42 and P-tau/Aβ42 ratios in POCD patients and lower Aβ-42/Tau ratios in the POCD group than in the non-POCD group.[37,42] Moreover, the preoperative CSF Aβ/tau ratio was reported to be associated with specific cognitive domain changes postsurgery.[57] Nevertheless, the limited number of studies on the correlation between Aβ42/tau and DNCR or POCD limits the available data for a meta-analysis to reach reliable conclusions; thus, further research is necessary.

This study has some limitations. First, the number of included studies is insufficient. While we have established negative correlations between preoperative CSF Aβ42 levels and POD and DNCR or POCD, the limited data available for other pooled results constrain our interpretation. Second, the heterogeneity in the included studies is apparent, particularly in those investigating the relationship between Alzheimer's disease biomarkers

Table 2 **Sensitivity analysis**

POD **Biomarker (number of included articles)**	**Fixed effect model** **MD (95% CI)**	***P* value**	**Random effects model** **MD (95% CI)**	***P* value**
Pre-Op CSF Aβ42 (*n* = 5)	−86.1 (−114.15 to −58.05)	<0.00001	138.99 (101.67 to 176.34)	<0.0001
Pre-Op CSF T-tau (*n* = 4)	138.99 (101.67 to 176.34)	<0.00001	87.67 (−41.23 to 216.57)	0.18
Pre-Op CSF P-tau (*n* = 4)	20.49 (16.25 to 24.72)	<0.00001	15.95 (−0.48 to 32.381)	0.06
Pre-Op CSF Aβ42/T-tau (*n* = 2)	0.51 (−0.77 to −0.25)	0.0001	−0.64 (−1.38 to 0.11)	0.09
Pre-Op CSF Aβ42/P-tau (*n* = 2)	−3.89 (−5.31 to −2.47)	<0.00001	−4.24 (−6.83 to −1.65)	0.001
DNCR and POCD **Biomarker (number of included articles)**	**Fixed effect model** **MD (95% CI)**	***P* value**	**Random effects model** **MD (95% CI)**	***P* value**
Pre-Op CSF Aβ42 (*n* = 5)	−57.01 (−71.45 to −42.56)	<0.00001	−165.01 (−261.48 to −68.53)	<0.00001
Pre-Op Plasma Aβ42 (*n* = 3)	2.02 (−2.59 to 6.62)	0.39	−10.56 (−42.65 to 21.54)	0.52
Post-Op Plasma Aβ42 (*n* = 3)	9.92 (7.14 to 12.7)	<0.00001	25.2 (5.79 to 44.6)	0.01
Pre-Op Plasma Aβ40 (*n* = 2)	−5.48 (−25.78 to 14.83)	0.6	−34.43 (−160.24 to 91.38)	0.59
Pre-Op CSF T-tau (*n* = 4)	3.52 (−17.33 to 24.37)	0.74	−52.87 (−144.36 to 38.61)	0.26

CI, confidence interval; DNCR, delayed neurocognitive recovery; MD, mean difference; POCD, postoperative cognitive dysfunction; POD, postoperative delirium.

and DNCR or POCD. Differences in surgical methods and diagnostic tools for POCD could contribute to this heterogeneity. Third, many included studies only evaluated POCD at postoperative day 7. Before day 30, patients may still be receiving acute pharmacologic interventions, experiencing postoperative complications, activity limitations, pain, and so forth. Therefore, according to the 2018 Nomenclature, the accurate terminology before day 30 should be DNCR rather than POCD.[44] POCD should be assessed after day 30, allowing for the expected recovery period encompassing physical, physiological and emotional aspects postsurgery. This meta-analysis did not differentiate between these two situations or perform subgroup analysis because of the limited data available, which is evidently a limitation and should be considered when interpreting our results.

Furthermore, the evaluation time points for POD and DNCR or POCD varied among different studies. We chose data corresponding to similar time points for this meta-analysis, which may have resulted in relatively limited findings. Finally, whether plasma biomarkers or CSF biomarkers, their correlation with POD and DNCR or POCD has some limitations. Although plasma biomarkers are more accessible during acute illness, plasma concentrations may be low. CSF biomarkers are thought to be more accurate, but collecting CSF can also be challenging, especially in clinical practice or large-scale studies. In addition, ultrasensitive assays to measure plasma biomarkers have now been developed, which will further facilitate research and understanding of the pathophysiology of delirium and DNCR or POCD.

Conclusion

Our selected TSA model strongly supports a negative correlation between preoperative CSF Aβ42 levels and both POD and DNCR or POCD, suggesting the involvement of preclinical Alzheimer's disease brain pathology in the pathophysiology of POD and DNCR or POCD. Despite these promising findings, further large-scale, high-quality, standardised research is warranted to determine the predictive cutoff value of preoperative CSF Aβ42 for POD and DNCR or POCD. Additionally, identifying the potential benefits of modulating preoperative CSF Aβ42 levels in reducing the incidence of POD and DNCR or POCD is crucial. Such studies would facilitate a deeper exploration of their relationship with POD and DNCR or POCD. This could considerably enhance early detection, diagnosis and treatment strategies for POD and DNCR or POCD in clinical settings.

Acknowledgements relating to this article

Assistance with the study: we would like to thank Editage for English language editing.

Financial support and sponsorship: none.

Conflicts of interest: none.

Presentation: none.

This manuscript was handled by Anne-Claire Lukaszewicz.

References

1 Bhushan S, Huang X, Duan Y, *et al.* The impact of regional versus general anesthesia on postoperative neurocognitive outcomes in elderly patients undergoing hip fracture surgery: a systematic review and meta-analysis. *Int J Surg* 2022; **105**:106854.
2 American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders. 5th ed., Washington, DC: American Psychiatric Association
3 Newman S, Stygall J, Hirani S, *et al.* Postoperative cognitive dysfunction after noncardiac surgery: a systematic review. *Anesthesiology* 2007; **106**:572–590.
4 Moller JT, Cluitmans P, Rasmussen LS, *et al.* Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. *Lancet* 1998; **351**:857–861.
5 Browndyke JN, Berger M, Harshbarger TB, *et al.* Resting- state functional connectivity and cognition after major cardiac surgery in older adults without preoperative cognitive impairment: preliminary findings. *J Am Geriatr Soc* 2017; **65**:e6–e12.
6 Browndyke JN, Berger M, Smith PJ, *et al.*, Duke Neurologic Outcomes Research Group (NORG). Task-related changes in degree centrality and local coherence of the posterior cingulate cortex after major cardiac surgery in older adults. *Hum Brain Mapp* 2018; **39**:985–1003.
7 Rombouts SA, Barkhof F, Goekoop R, *et al.* Altered resting state networks in mild cognitive impairment and mild Alzheimer's disease: an fMRI study. *Hum Brain Mapp* 2005; **26**:231–239.
8 Eckenhoff RG, Johansson JS, Wei H, *et al.* Inhaled anesthetic enhancement of amyloid-beta oligomerization and cytotoxicity. *Anesthesiology* 2004; **101**:703–709.
9 Xie Z, Culley DJ, Dong Y, *et al.* The common inhalation anesthetic isoflurane induces caspase activation and increases amyloid beta-protein level in vivo. *Ann Neurol* 2008; **64**:618–627.
10 Le Freche H, Brouillette J, Fernandez-Gomez FJ, *et al.* Tau phosphorylation and sevoflurane anesthesia: an association to postoperative cognitive impairment. *Anesthesiology* 2012; **116**:779–787.
11 Planel E, Bretteville A, Liu L, *et al.* Acceleration and persistence of neurofibrillary pathology in a mouse model of tauopathy following anesthesia. *FASEB J* 2009; **23**:2595–2604.
12 Whittington RA, Virág L, Gratuze M, *et al.* Dexmedetomidine increases tau phosphorylation under normothermic conditions in vivo and in vitro. *Neurobiol Aging* 2015; **36**:2414–2428.
13 Wan Y, Xu J, Meng F, *et al.* Cognitive decline following major surgery is associated with gliosis, beta-amyloid accumulation, and tau phosphorylation in old mice. *Crit Care Med* 2010; **38**:2190–2198.
14 Kamer AR, Galoyan SM, Haile M, *et al.* Meloxicam improves object recognition memory and modulates glial activation after splenectomy in mice. *Eur J Anaesthesiol* 2012; **29**:332–337.
15 Querfurth HW, LaFerla FM. Alzheimer's disease. *N Engl J Med* 2010; **362**:329–344.
16 Strozyk D, Blennow K, White LR, *et al.* CSF Abeta 42 levels correlate with amyloid-neuropathology in a population-based autopsy study. *Neurology* 2003; **60**:652–656.
17 Blennow K, Mattsson N, Scholl M, *et al.* Amyloid biomarkers in Alzheimer's disease. *Trends Pharmacol Sci* 2015; **36**:297–309.
18 Hesse C, Rosengren L, Andreasen N, *et al.* Transient increase in total tau but not phospho-tau in human cere- brospinal fluid after acute stroke. *Neurosci Lett* 2001; **297**:187–190.
19 Riemenschneider M, Wagenpfeil S, Vanderstichele H, *et al.* Phospho-tau/total tau ratio in cerebrospinal fluid discriminates Creutzfeldt-Jakob disease from other dementias. *Mol Psychiatry* 2003; **8**:343–347.
20 Tapiola T, Alafuzoff I, Herukka SK, *et al.* Cerebrospinal fluid beta-amyloid 42 and tau proteins as biomarkers of Alzheimer-type pathologic changes in the brain. *Arch Neurol* 2009; **66**:382–389.
21 Witlox J, Kalisvaart KJ, de Jonghe JF, *et al.* Cerebrospinal fluid beta-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**:1260–1267.
22 Xie Z, Swain CA, Ward SA, *et al.* Preoperative cerebrospinal fluid beta-Amyloid/Tau ratio and postoperative delirium. *Ann Clin Transl Neurol* 2014; **1**:319–328.
23 Liberati A, Altman DG, Tetzlaff J, *et al.* The PRISMA statement for reporting systematic reviews and meta- analyses of studies that evaluate healthcare in- terventions: explanation and elaboration. *PLoS Med* 2009; **6**:e1000100.

24 Wan X, Wang W, Liu J, *et al.* Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014; **14**:135.

25 Wells GA, Shea BJ, O'Connell D, *et al.* The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analysis. *Appl Eng Agric* 2014; **18**:727–734.

26 Higgins JP, Green S. *Cochrane handbook for systematic reviews of interventions*. vol. 35; 2014. p. 154.e5. Online Kensaku.

27 Higgins JPT, Li T, Deeks JJE. Chapter 6: Choosing effect measures and computing estimates of effect. In: Higgins JPT, Thomas J, Chandler J, *et al.* editors. *Cochrane handbook for systematic reviews of interventions*, version 6.0 (updated July 2019). Cochrane.

28 Brok J, Thorlund K, Wetterslev J, *et al.* Apparently conclusive meta-analyses may be inconclusive – trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. *Int J Epidemiol* 2009; **38**:e287–e298.

29 Thorlund K, Engstrøm J, Wetterslev J, *et al.* User manual for trial sequential analysis (TSA). vol. 1. Copenhagen, Denmark: Copenhagen Trial Unit, Centre for Clinical Intervention Research; 2011. p. 1.e115.

30 Jakobsen JC, Gluud C, Winkel P, *et al.* The thresholds for statistical and clinical significance – a five-step procedure for evaluation of intervention effects in randomised clinical trials. *BMC Med Res Methodol* 2014; **14**:34.

31 Deng X, Qin P, Lin Y, *et al.* The relationship between body mass index and postoperative delirium. *Brain Behav* 2022; **12**:e2534.

32 Fong TG, Vasunilashorn SM, Gou Y, *et al.* Association of CSF Alzheimer's disease biomarkers with postoperative delirium in older adults. *Alzheimers Dement (N Y)* 2021; **7**:e12125.

33 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**:1200–1205.

34 Idland AV, Wyller TB, Stoen R, *et al.* Preclinical amyloid-beta and axonal degeneration pathology in delirium. *J Alzheimers Dis* 2017; **55**:371–379.

35 Danielson M, Wiklund A, Granath F, *et al.* Association between cerebrospinal fluid biomarkers of neuronal injury or amyloidosis and cognitive decline after major surgery. *Br J Anaesth* 2021; **126**:467–476.

36 Zhang X, Fu Q. Correlation of cerebrospinal fluid amyloid β-protein 42 and neurofilament light protein levels with postoperative neurocognitive dysfunction in elderly patients. *Nan Fang Yi Ke Da Xue Xue Bao* 2021; **41**:574–578.

37 Wu Z, Zhang M, Zhang Z, *et al.* Ratio of beta-amyloid protein (Abeta) and Tau predicts the postoperative cognitive dysfunction on patients undergoing total hip/knee replacement surgery. *Exp Ther Med* 2018; **15**:878–884.

38 Liang B, Sun YQ, Jiang J, *et al.* Correlations of plasma concentrations of β-amyloid peptide and S-100β with postoperative cognitive dysfunction in patients undergoing oral and maxillofacial cancer surgery. *Shanghai Kou Qiang Yi Xue* 2016; **25**:707–710.

39 Evered L, Silbert B, Scott DA, *et al.* Cerebrospinal fluid biomarker for alzheimer disease predicts postoperative cognitive dysfunction. *Anesthesiology* 2016; **124**:353–361.

40 Li XM, Shao MT, Wang JJ, *et al.* Relationship between postoperative cognitive dysfunction and regional cerebral oxygen saturation and β-amyloid protein. *J Zhejiang Univ Sci B* 2014; **15**:870–878.

41 Li X, Wen DX, Zhao YH, *et al.* Increase of beta-amyloid and C-reactive protein in liver transplant recipients with postoperative cognitive dysfunction. *Hepatobiliary Pancreat Dis Int* 2013; **12**:370–376.

42 Ji MH, Yuan HM, Zhang GF, *et al.* Changes in plasma and cerebrospinal fluid biomarkers in aged patients with early postoperative cognitive dysfunction following total hip-replacement surgery. *J Anesth* 2013; **27**:236–242.

43 Evered LA, Silbert BS, Scott DA, *et al.* Plasma amyloid beta42 and amyloid beta40 levels are associated with early cognitive dysfunction after cardiac surgery. *Ann Thorac Surg* 2009; **88**:1426–1432.

44 Evered L, Silbert B, Knopman DS, *et al.*, Nomenclature Consensus Working Group. Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery-2018. *Br J Anaesth* 2018; **121**:1005–1012.

45 Rudolph JL, Marcantonio ER, Culley DJ, *et al.* Delirium is associated with early postoperative cognitive dysfunction. *Anaesthesia* 2008; **63**:941–947.

46 Hudetz JA, Patterson KM, Byrne AJ, *et al.* Postoperative delirium is associated with postoperative cognitive dysfunction at one week after cardiac surgery with cardiopulmonary bypass. *Psychol Rep* 2009; **105 (3 pt 1)**:921–932.

47 Yamazaki Y, Zhao N, Caulfield TR, *et al.* Apolipoprotein E and Alzheimer disease: pathobiology and targeting strategies. *Nat Rev Neurol* 2019; **15**:501–518.

48 Hsiao WJ, Chen CY, Kang YN, *et al.* Apolipoprotein E4 allele is genetically associated with risk of the short- and medium-term postoperative cognitive dysfunction: a meta-analysis and trial sequential analysis. *PLoS One* 2023; **18**:e0282214.

49 Wang S, Greene R, Song Y, *et al.* Postoperative delirium and its relationship with biomarkers for dementia: a meta-analysis. *Int Psychogeriatr* 2022; **17**:1–14.

50 Lopez Sanchez MIG, van Wijngaarden P, Trounce IA. Amyloid precursor protein-mediated mitochondrial regulation and Alzheimer's disease. *Br J Pharmacol* 2019; **176**:3464–3474.

51 Sun L, Jia P, Zhang J, *et al.* Production of inflammatory cytokines, cortisol, and Abeta1-40 in elderly oral cancer patients with postoperative delirium. *Neuropsychiatr Dis Treat* 2016; **12**:2789–2795.

52 Berger M, Browndyke JN, Cooter Wright M, *et al.*, MADCO-PC Investigators. Postoperative changes in cognition and cerebrospinal fluid neurodegenerative disease biomarkers. *Ann Clin Transl Neurol* 2022; **9**:155–170.

53 Grimmer T, Riemenschneider M, Forstl H, *et al.* Beta amyloid in Alzheimer's disease: increased deposition in brain is reflected in reduced concentration in cerebrospinal fluid. *Biol Psychiatry* 2009; **65**:927–934.

54 Blennow K. Cerebrospinal fluid protein biomarkers for Alzheimer's disease. *NeuroRx* 2004; **1**:213–225.

55 Tapiola T, Alafuzoff I, Herukka SK, *et al.* Cerebrospinal fluid {beta}-amyloid 42 and tau proteins as biomarkers of Alzheimer-type pathologic changes in the brain. *Arch Neurol* 2009; **66**:382–389.

56 Samgard K, Zetterberg H, Blennow K, *et al.* Cerebrospinal fluid total tau as a marker of Alzheimer's disease intensity. *Int J Geriatr Psychiatry* 2010; **25**:403–410.

57 Xie Z, McAuliffe S, Swain CA, *et al.* Cerebrospinal fluid abeta to tau ratio and postoperative cognitive change. *Ann Surg* 2013; **258**:364–369.