Inflammatory markers in postoperative delirium (POD) and cognitive dysfunction (POCD): A meta-analysis of observational studies

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Abstract

Background

The aim of this study was to summarize and discuss the similarities and differences in inflammatory biomarkers in postoperative delirium (POD) and cognitive dysfunction (POCD).

Methods

A systematic retrieval of literature up to June 2017 in PubMed, Embase, the Cochrane Library, the China National Knowledge Infrastructure database, and the Wanfang database was conducted. Extracted data were analyzed with STATA (version 14). The standardized mean difference (SMD) and the 95% confidence interval (95% CI) of each indicator were calculated using a random effect model. We also performed tests of heterogeneity, sensitivity analysis, assessments of bias, and meta-regression in this meta-analysis.

Results

A total of 54 observational studies were included. By meta-analysis we found significantly increased C-reactive protein (CRP) (9 studies, SMD 0.883, 95% CI 0.130 to 1.637, $P = 0.022$ in POD; 10 studies, SMD -0.133, 95% CI -0.512 to 0.246, $P = 0.429$ in POCD) and interleukin (IL)-6 (7 studies, SMD 0.386, 95% CI 0.054 to 0.717, $P = 0.022$ in POD; 16 studies, SMD 0.089, 95% CI -0.133 to 0.311, $P = 0.433$ in POCD) concentrations in both POD and POCD patients. We also found that the SMDs of CRP and IL-6 from POCD patients were positively correlated with surgery type in the meta-regression (CRP: Coefficient = 1.555365, $P = 0.001$, 10 studies; IL-6: Coefficient = -0.6455521, $P = 0.086$, 16 studies).

Conclusion

Available evidence from medium-to-high quality observational studies suggests that POD and POCD are indeed correlated with the concentration of peripheral and cerebrospinal

fluid (CSF) inflammatory markers. Some of these markers, such as CRP and IL-6, play roles in both POD and POCD, while others are specific to either one of them.

Introduction

An emerging body of evidence suggests that both anesthesia and surgery have long-term effects on cognition. These cognitive impairments have been detected by various neuropsychological tests at different time points after operation. This has given rise to the terms "postoperative cognitive dysfunction" (POCD) and "postoperative delirium" (POD). We refer to both simultaneously as "postoperative cerebral dysfunction".

Delirium is a neuropsychiatric behavioral syndrome, manifested as an altered level of consciousness, inattention, and sleep-wake cycle disturbance. The two main features of delirium are acute onset and fluctuating course [1–3]. POD is age-related, affecting 15%-53% of elderly patients after surgery [4–6].

POCD is a common complication of the central nervous system after surgery, which occurs in patients over 65 years old [7], and mainly manifests as damage to memory, mental capacity, language ability, or other aspects of cerebral function [8]. The World Health Organization has not yet classified this clinical phenomenon as an independent disease, making it difficult to accurately define it [9]. POCD can last from several days to several years.

POD and POCD have been associated with various adverse outcomes, including prolonged hospitalization, increased complications and mortality, and decreased quality of life [10–12]. There is already a great deal of knowledge about the epidemiology of POD and POCD, but they are only clinically diagnosed, without any precise biomarkers to guide diagnosis. However, there is growing evidence that an inflammatory response may play a role in the presence of POD/POCD. Therefore, this meta-analysis aimed to identify the current published literature examining blood or CSF in POD/POCD to summarize the existing knowledge and to determine the relationship between POD/POCD and specific inflammatory markers.

Materials and methods

Literature search

Two reviewers searched studies published before 15 June 2017 that examined inflammatory markers in the serum or CSF of patients with POD/POCD. Searches were performed using a comprehensive text-word and Medical Subject Headings-based electronic search of PubMed, Embase, Web of Science, Cochrane, the China National Knowledge Infrastructure database, and the Wanfang database. We used terms including "delirium" or "cognitive dysfunction," and "inflammation mediators" or "cytokine" (S1 Appendix). Studies were restricted to English and Chinese language publications.

Study selection

The inclusion criteria were as follows:

1. Study design: case-control or cohort study with non-POD/POCD subjects as controls;

2. POD assessment tool: Diagnostic and Statistical Manual of Mental Disorders (DSM Third Edition; or DSM Fourth Edition) [13], Confusion Assessment Method (CAM) [14], Confusion Assessment Method for the ICU (CAM-ICU), Delirium Rating Scale (DRS) [15], or

International Classification of Diseases, Tenth Revision (ICD-10) criteria [16]; POCD assessment tool: Mini-mental State Examination (MMSE) [17] or a series of neuropsychological tests (see "Definitions of POD and POCD" below);

3. Subjects: human;

4. Full text available (detailed information);

5. Data on inflammatory biomarker findings in serum or CSF in POD/POCD patients could be extracted.

The exclusion criteria were:

1. Case reports and reviews;

2. Randomized controlled trials (RCTs) measuring the effects of drugs;

3. No identifiable POD/POCD subgroups;

4. Unavailable data format.

Data extraction and synthesis

Two reviewers independently screened the search results according to the inclusion criteria and extracted relevant data, which was checked by another reviewer. The following information was tabulated from each paper: (1) author and year of publication; (2) country; (3) study design; (4) sample size and participant characteristics; (5) type of anesthesia; (6) type of surgery; (7) biomarker(s) studied; and (8) method used to diagnose POD/POCD. In cases in which more than one publication of the same trial existed, only the latest publication with the most complete data was included. Disagreements were settled by consensus.

For studies expressing effect sizes as the median with the range or interquartile range, we applied appropriate formulas to converted them to mean and standard deviation (SD). The median can be used to estimate mean when the sample size is larger than 25. When the sample size was moderate ($15 < n \leq 70$, it was most appropriate to use the formula range/4 [18] to estimate SD. For a larger sample size ($n > 70$), the formula range/6 gives the optimal estimator for the SD. The formula interquartile range/1.35 [19] was used to calculate SD from interquartile ranges.

Assessment of study quality

Study quality was assessed independently by two of the authors using the Newcastle-Ottawa scale (NOS) [20]. The NOS score ranges from 0–9 stars. A quality score was calculated based on three major components: (1) the selection of study groups (0–4 stars), (2) the comparability of study groups (0–2 stars), and (3) ascertainment of the exposure and outcome of interest in the case-control and cohort studies (0 to 3 stars). Studies with scores of 7–9, 4–6, and 0–3 stars were respectively considered to be of high, medium, and low quality. Disagreement was resolved by discussion and consensus.

Statistical analyses

Where factors of interest were reported by two or more studies, the standardized mean difference (SMD) and 95% confidence interval (95% CI) were calculated under random effects models (REM) or fixed-effect models (FEM). A Q statistic was calculated using a chi-squared test to quantify the heterogeneity among combined trials, with $P \leq 0.10$ used for statistical existent

heterogeneity. Inconsistency was calculated using an I^2 index to determine the impact of heterogeneity. In case of the presence of statistical heterogeneity, the REM was used for the analysis. In the absence of statistically significant heterogeneity, the FEM was used.

Subgroup analyses were carried out in order to explore possible sources of heterogeneity. These included the type of surgery and ethnicity. For each variable, subgroup analyses were pre-specified and then meta-analyzed. The overall effect sizes of each member of a subgroup pair were subjected to two-tailed z tests to examine the significance of the difference. Sensitivity analyses were performed to investigate the influence of each individual study on the overall meta-analysis summary estimate and the validity of the effect size. The risk of publication bias was assessed using Egger's tests. Meta-regression analysis, with $P \leq 0.10$ indicating statistical significance, was used to test whether effect sizes were influenced by specific study design features.

All data was sorted through Excel 2016, and meta-analyses were undertaken in STATA 14.1 (Stata Corporation, College Station, Texas, USA)

Results

Results of literature search

Details of the flow of study identification are shown in Fig 1. Multiple database literature searches led to the identification of 1304 article abstracts. After checking for duplicates, 1115 publications remained, of which 867 were excluded at the screening stage. Of these, 111 publications were excluded at the study eligibility determination stage. The main reasons for the exclusions included: unavailable data format (n = 22); no diagnosis of POD/POCD made (n = 10); no identifiable POD/POCD subgroup (n = 65); other inflammation (11); relevant hypotheses (n = 2); study protocol (n = 1). Thus, 54 studies were included in the meta-analysis, of which 30 were about POD [21–50], 23 about POCD [51–73], and one included both POD and POCD [74]. The major characteristics of the included studies are presented in S1 Table.

The quality of the included studies, in general, ranged from medium to high, when weighed with the NOS (S2 Table). Among the included studies, 10 were case-control studies, and 44 were cohort studies.

Definitions of POD and POCD

Definition of POD. The Confusion Assessment Method (CAM: sensitivity of 94%, specificity of 89% with high inter-rater reliability [75]) is a widely used, standardized method for the identification of delirium. Twenty-five studies applied CAM to define POD [22–27, 29–31, 33–36, 38–40, 42–50] of which three were assessed with CAM and confirmed with the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision; DSM-IV-TR) [25–27], and one was evaluated through CAM and the Delirium Rating Scale [24] (DRS: sensitivity of 82% and specificity of 94%, cut-off score of 10 [15]). Two studies used DRS to define delirium [21, 28]. In one study, delirium was diagnosed using DSM-IV and DRS [32].

Definition of POCD. Unlike for POD, clear diagnostic criteria are lacking for POCD [76]. Changes in cognitive function were measured before and after surgery using standardized neuropsychological assessment tools. Twelve studies assessed the neuropsychological state of patients using a battery of neuropsychological tests [51, 52, 54–57, 60, 62, 65, 68, 69, 73] (see S1 Table for details). In these studies, "the 1 SD-criterion" (a decline of more than 1 SD from baseline) and "a combined Z-score" (at least two Z-scores for single test parameters >2 or the combined Z-score >2) were used as diagnostic criteria for POCD [76]. The other twelve
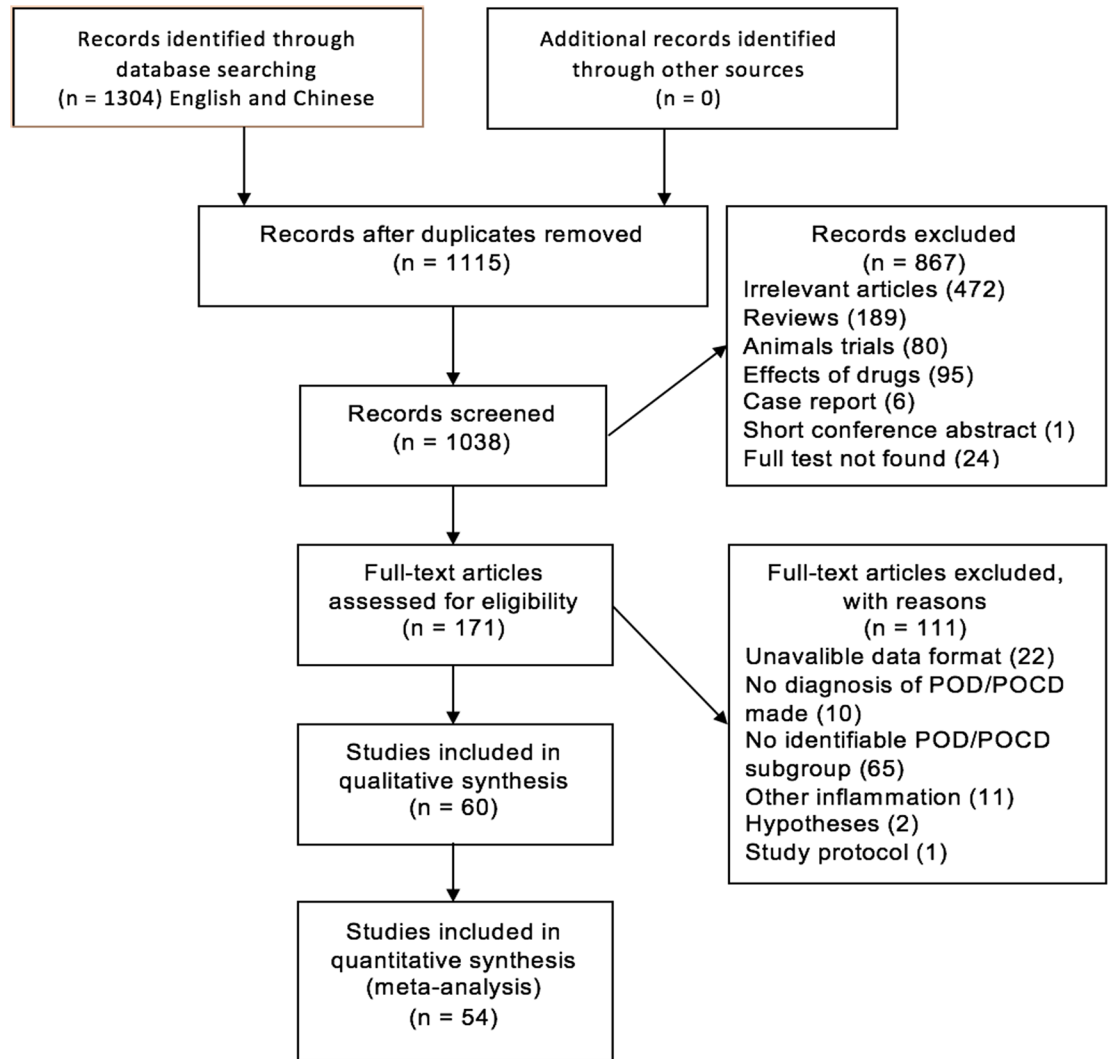
Fig 1. Flow diagram of article selection.

studies used the raw change on the MMSE [53, 58, 59, 61, 63, 64, 66, 67, 69, 71, 72, 74], a fast cognitive screening instrument [17], to determine the incidence of POCD.

Cytokine concentrations

Major findings of the meta-analyses are presented in Figs 2 and 3.

CRP (peripheral) levels before surgery: In POD. There was a significant increase in peripheral CRP levels in POD patients (9 studies, n[POD/non-POD] = 241/531, SMD 0.883, 95% CI 0.130 to 1.637, P = 0.022; REM) with significant heterogeneity between the studies ($P_{heterogeneity}$ = 0.000; I^2 = 94.8%) (Fig 4A).

CRP (peripheral) levels before surgery: In POCD. There was no significant difference in peripheral CRP levels between POCD and non-POCD patients (10 studies, n[POCD/non-POCD] = 211/383, SMD -0.133, 95% CI -0.512 to 0.246, P = 0.429; REM) with significant heterogeneity between the studies ($P_{heterogeneity}$ = 0.000; I^2 = 77.9%) (Fig 4B).

Peripheral inflammatory markers
CRP pre-op (N=9) (SMD 0.883, 95% CI 0.130 to 1.637); *P*=0.022
CRP post-op (N=10) (SMD 1.167, 95% CI 0.513 to 1.822); *P*=0.000

IL-6 pre-op (N=7) (SMD 0.386, 95% CI 0.054 to 0.717); *P*=0.022
IL-6 post-op (N=6) (SMD 1.343, 95% CI 0.390 to 2.296); *P*=0.006

S-100β pre-op (N=4) (SMD 0.048, 95% CI -0.335 to 0.431); *P*=0.806
S-100β post-op (N=5) (SMD 0.952, 95% CI 0.041 to 1.863); *P*=0.041

NSE pre-op (N=4) (SMD 0.139, 95% CI -0.133 to 0.411); *P*=0.316
NSE post-op (N=4) (SMD 0.377, 95% CI -0.204 to 0.957); *P*=0.204

IL-8 pre-op (N=3) (SMD 0.059, 95% CI -0.227 to 0.346); *P*=0.684
IL-8 post-op (N=3) (SMD 0.243, 95% CI 0.020 to 0.466); *P*=0.033

IL-1β pre-op (N=3) (SMD 0.303, 95% CI -0.713 to 1.319); *P*=0.559

TNF-α pre-op (N=3) (SMD 0.060, 95% CI -0.258 to 0.378); *P*=0.711
TNF-α post-op (N=4) (SMD 0.474, 95% CI -0.061 to 1.010); *P*=0.083

cortisol pre-op (N=3) (SMD 1.019, 95% CI -0.347 to 2.386); *P*=0.144
cortisol post-op (N=5) (SMD 2.876, 95% CI 1.386 to 4.367); *P*=0.000

IGF-1 pre-op (N=6) (SMD -0.267, 95% CI -0.591 to 0.056); *P*=0.105
IGF-1 post-op (N=2) (SMD 0.098, 95% CI -0.539 to 0.736); *P*=0.763

IL-10 pre-op (N=2) (SMD -0.144, 95% CI -0.459 to 0.170); *P*=0.369

IL-1ra pre-op (N=2) (SMD 0.505, 95% CI -0.732 to 1.739); *P*=0.425

CSF inflammatory markers
IL-1ra pre-op (N=2) (SMD -0.898, 95% CI -1.915 to 0.118); *P*=0.083
IL-6 pre-op (N=2) (SMD -0.355, 95% CI -0.899 to 0.189); *P*=0.201
CRP pre-op (N=2) (SMD 0.246, 95% CI -0.559 to 1.051); *P*=0.549

-4   -2   0   2   4
Favours [non-POD]   Favours [POD]

Fig 2. Results of the random-effects meta-analysis for the association between inflammatory markers and POD. Positive values indicate higher levels in POD patients; negative values indicate higher levels in control patients. CRP, C-reactive protein; IL-6, interleukin-6; S-100β, S-100 calcium binding protein beta subunit; NSE, neuron-specific enolase; IL-8, interleukin-8; IL-1β, interleukin-1 beta; TNF-α, tumor necrosis factor alpha; IGF-1, insulin-like growth factor-1; IL-10, interleukin-10; IL-1ra, interleukin-1 receptor antagonist; pre-op, pre-operation; post-op, post-operation; N, number of studies; SMD, standardized mean difference; CI, confidence interval.

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Peripheral inflammatory markers

CRP pre-op (N=10) (SMD -0.133, 95% CI -0.512 to 0.246); P=0.429
CRP post-op (N=11) (SMD 1.351, 95% CI 0.728 to 1.974); P=0.000

IL-6 pre-op (N=16) (SMD 0.089, 95% CI -0.133 to 0.311); P=0.433
IL-6 post-op (N=17) (SMD 1.013, 95% CI 0.627 to 1.399); P=0.000

S-100β pre-op (N=4) (SMD -0.302, 95% CI -0.878 to 0.274); P=0.304
S-100β post-op (N=5) (SMD 0.357, 95% CI -0.368 to 1.083); P=0.334

NSE pre-op (N=3) (SMD 0.549, 95% CI 0.020 to 1.078); P=0.042
NSE post-op (N=3) (SMD 2.283, 95% CI -0.133 to 4.700); P=0.064

IL-8 pre-op (N=2) (SMD 0.273, 95% CI -0.188 to 0.735); P=0.246
IL-8 post-op (N=2) (SMD 0.660, 95% CI -0.853 to 2.173); P=0.393

IL-1β pre-op (N=9) (SMD 0.171, 95% CI -0.285 to 0.627); P=0.462
IL-1β post-op (N=10) (SMD 0.685, 95% CI 0.290 to 1.080); P=0.001

TNF-α pre-op (N=9) (SMD 0.627, 95% CI -0.033 to 1.287); P=0.063
TNF-α post-op (N=9) (SMD 0.027, 95% CI -0.523 to 0.576); P=0.925

IL-10 pre-op (N=3) (SMD -0.323, 95% CI -1.539 to 0.892); P=0.602
IL-10 post-op (N=3) (SMD 1.942, 95% CI -0.071 to 3.954); P=0.059

IL-1ra pre-op (N=2) (SMD 0.466, 95% CI -0.980 to 1.913); P=0.528

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-4      -2       0       2       4
Favours [non-POCD]  Favours [POCD]
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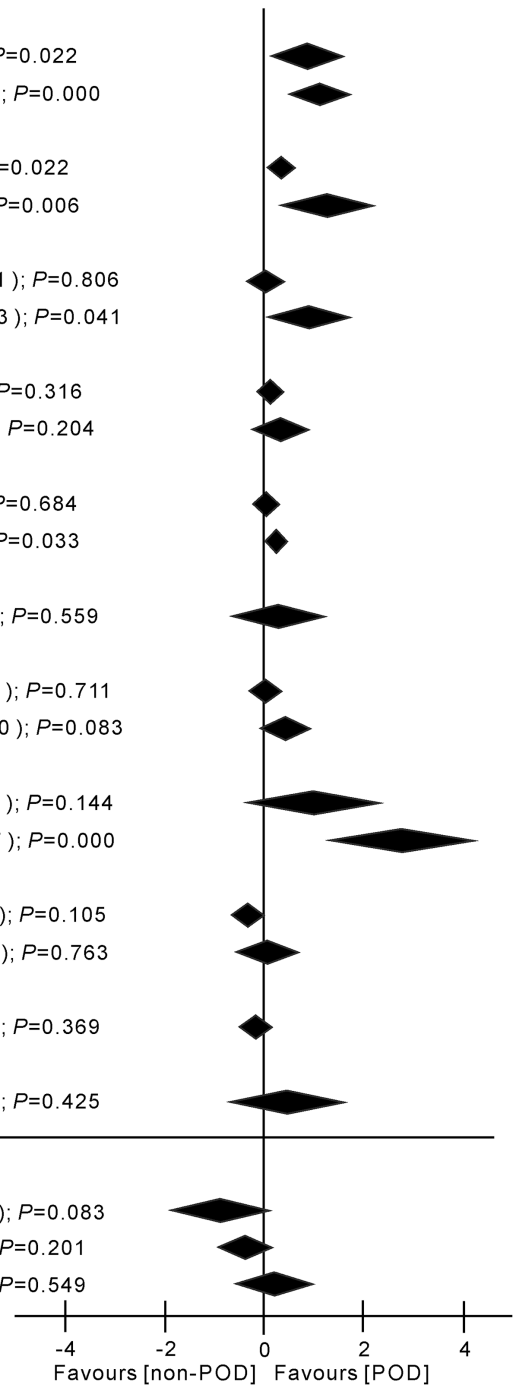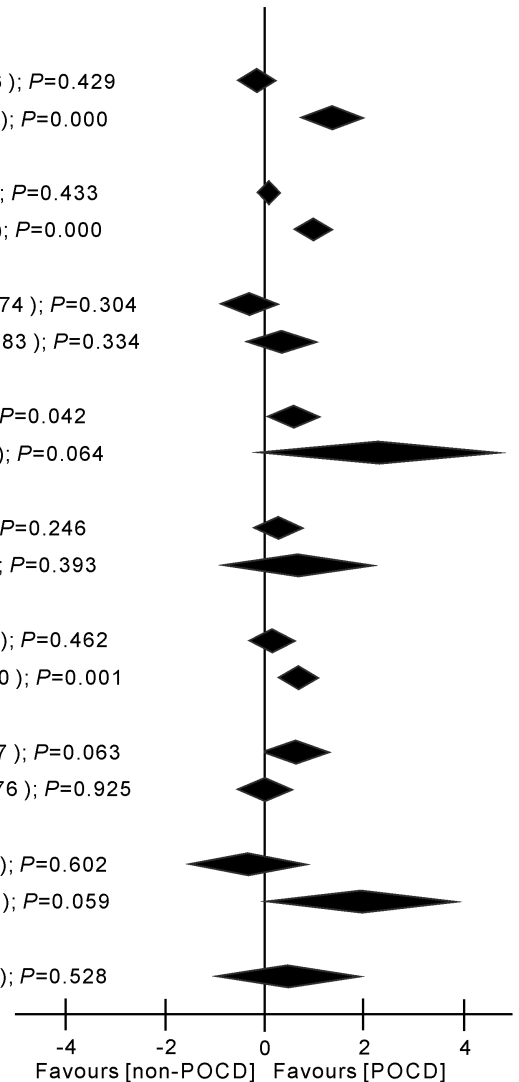
Fig 3. Results of the random-effects meta-analysis for the association between inflammatory markers and POCD. Positive values indicate higher levels in POCD patients; negative values indicate higher levels in control patients. CRP, C-reactive protein; IL-6, interleukin-6; S-100β, S-100 calcium binding protein beta subunit; NSE, neuron-specific enolase; IL-8, interleukin-8; IL-1β, interleukin-1 beta; TNF-α, tumor necrosis factor alpha; IL-10, interleukin-10; IL-1ra, interleukin-1 receptor antagonist; pre-op, pre-operation; post-op, post-operation; N, number of studies; SMD, standardized mean difference; CI, confidence interval.

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IL-6 (peripheral) levels before surgery: In POD. There was a significant increase in peripheral IL-6 levels in POD patients (7 studies, n[POD/non-POD] = 241/531, SMD 0.386, 95% CI 0.054 to 0.717, P = 0.022; REM) with significant heterogeneity between the studies ($P_{heterogeneity}$ = 0.001; I^2 = 73.2%) (Fig 5A).

IL-6 (peripheral) levels before surgery: In POCD. There was no significant difference in peripheral IL-6 levels between POCD and non-POCD patients (16 studies, n[POCD/non-POCD] = 333/638, SMD 0.089, 95% CI -0.133 to 0.311, P = 0.433; REM) with significant heterogeneity between the studies ($P_{heterogeneity}$ = 0.001; I^2 = 60.7%) (Fig 5B)

S-100β (peripheral) levels post-surgery: In POD. There was a significant increase in peripheral S-100β levels in POD patients (5 studies, n[POD/non-POD] = 151/220, SMD 0.952,
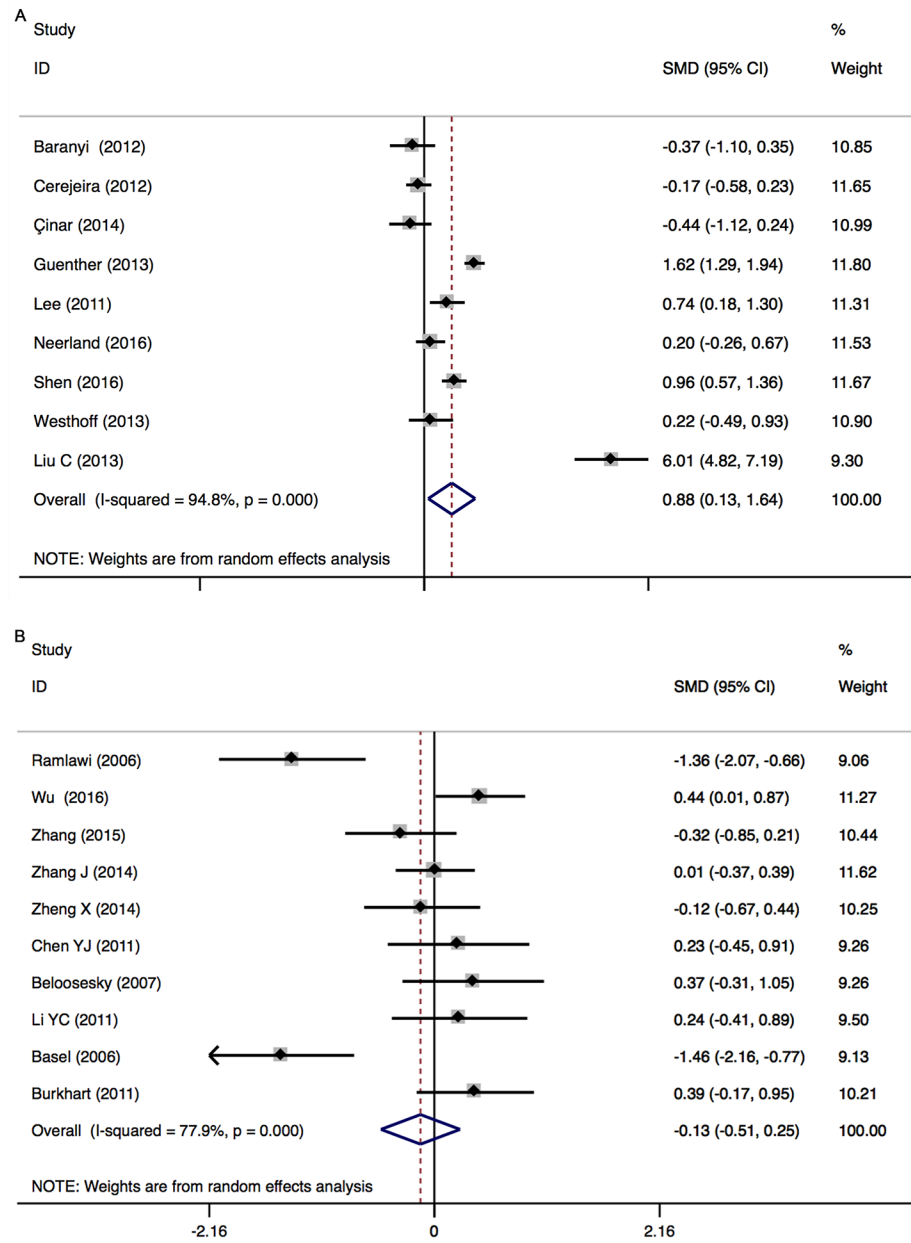
Fig 4. CRP (Peripheral) levels before surgery in patients with POD (A) and POCD (B).

95% CI 0.041 to 1.863, $P = 0.041$; REM) with significant heterogeneity between the studies ($P_{heterogeneity} = 0.000$; $I^2 = 92.6\%$) (Fig 6A).

S-100β (peripheral) levels post-surgery: In POCD. There was no significant difference in peripheral S-100β levels between POCD and non-POCD patients (5 studies, n[POCD/non-POCD] = 101/120, SMD 0.357, 95% CI -0.368 to 1.083, $P = 0.334$; REM) with significant heterogeneity between the studies ($P_{heterogeneity} = 0.000$; $I^2 = 85.2\%$) (Fig 6B).

NSE (peripheral) levels before surgery: In POD. There was no significant difference in peripheral NSE levels between POD and non-POD patients (4 studies, n[POCD/non-
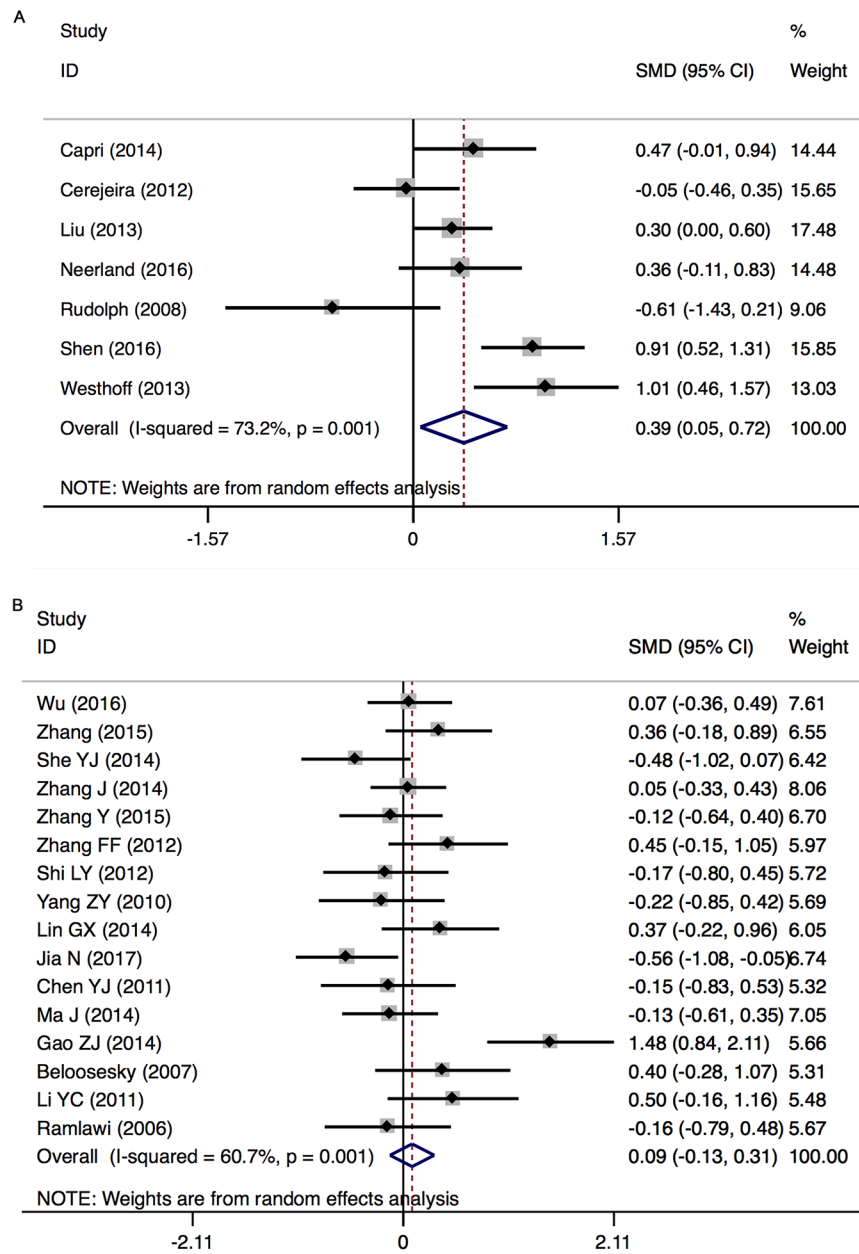
Fig 5. IL-6 (Peripheral) levels before surgery in patients with POD (A) and POCD (B).

POCD] = 89/162, SMD 0.139, 95% CI -0.133 to 0.411, P = 0.316; FEM) with no heterogeneity between the studies ($P_{heterogeneity}$ = 0.569; I^2 = 0.0%) (Fig 2).

NSE (peripheral) levels before surgery: In POCD. There was a significant increase in peripheral NSE levels in POCD patients (3 studies, n[POD/non-POD] = 65/74, SMD 0.549, 95% CI 0.020 to 1.078, P = 0.042; REM) with mild heterogeneity between the studies ($P_{heterogeneity}$ = 0.096; I^2 = 57.3%) (Fig 3).

IL-8 (peripheral) levels after surgery: In POD. Peripheral IL-8 levels significantly increased in the samples taken from POD patients after surgery (3 studies, n[POD/non-POD] = 149/170, SMD 0.243, 95% CI 0.020 to 0.466, P = 0.033; FEM) with no heterogeneity between the studies ($P_{heterogeneity}$ = 0.765; I^2 = 0.0%) (Fig 2).
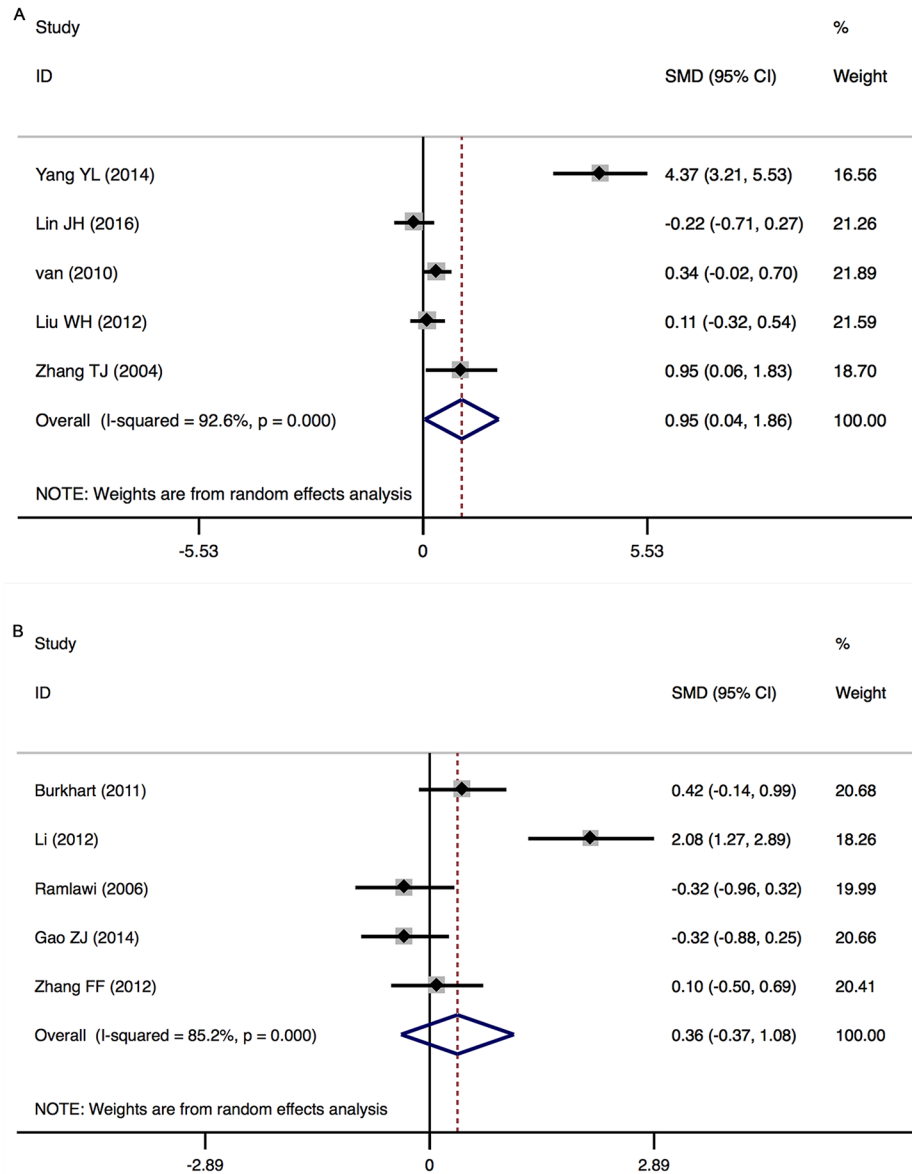
Fig 6. S-100β (Peripheral) Levels Post-Surgery in Patients with POD (A) and POCD (B).

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IL-8 (peripheral) levels after surgery: In POCD. No significant differences were found in peripheral IL-8 levels between POCD and control patients (2 studies, n[POD/non-POD] = 29/52, SMD 0.660, 95% CI -0.853 to 2.173, P = 0.393; REM; $P_{heterogeneity}$ = 0.002; I^2 = 89.6%) (Fig 3).

Subgroup analyses

Above we described the biomarkers that we found to have different effects in POD and POCD perioperatively. CRP and IL-6 levels increased significantly after surgery in patients with POD as well as those with POCD. In addition, we found that preoperative IL-1β, S-100β, IL-8, IL-10, and IL-1ra levels and postoperative TNF-α, and NSE levels did not differ between patients

with POD/POCD and normal patients. There are few studies on the relationship between POD/POCD and inflammatory cytokines in CSF [23, 34, 40, 49], and no significant differences were found in the CSF, IL-1ra, IL-6, and CRP levels of patients with and without POD. For the evaluation of other inflammatory cytokines, data were either not available or insufficient for meta-analyses.

In the subgroup analyses, preoperative CRP levels were significantly higher in patients with POD who underwent non-cardiac vs cardiac surgery; general anesthesia vs regional anesthesia; and in Chinese vs Caucasians. Preoperative CRP levels were significantly higher in patients with POCD who underwent cardiac vs non-cardiac surgery; but there were no significant differences between Chinese and Caucasians. Only one study measured IL-6 levels preoperatively in samples from patients with POD who underwent cardiac surgery and there were no differences found between Chinese and Caucasians; but increased significantly in POD patients underwent regional vs general anesthesia. IL-6 levels in patients with POCD did not differ with surgery type or ethnicity (Fig 7 and S3 Table).

Meta-regression

We conducted meta-regression only if at least ten observations (i.e. ten studies per meta-analysis) were available for each characteristic modelled. In this paper, meta-regression analyses were used to assess the relationships of surgery type and ethnicity with peripheral levels of the studied inflammatory markers. A significant positive association between the SMD of CRP and IL-6 levels from patients with POCD and the surgery type was found (CRP: Coef. = 1.555365, P = 0.001, 10 studies; IL-6: Coef. = -0.6455521, P = 0.086, 16 studies) (Table 1). No associations were found between the SMD and ethnicity (CRP: Coef. = 0.5673341, P = 0.222, 10 studies; IL-6: Coef. = -0.0243988, P = 0.951, 16 studies) (Table 1).

Sensitivity analysis

Sensitivity analyses were performed to investigate the influence of each individual study on the overall meta-analysis summary estimate and the validity of the effect size. By excluding the included studies one by one, we found that no single study had a significant impact on the outcome of the combined analysis. This suggests that the results of this meta-analysis are stable.

Publication biases

Significant risk of publication bias was not detected, as demonstrated by funnel plots. Tests for funnel plot asymmetry were only recommended for use when at least 10 studies were included in the meta-analysis. Therefore, Egger's test was implemented to evaluate asymmetry and publication bias. The results showed no evidence of publication bias (Table 2).

Discussion

Postoperative cognitive impairment is receiving increasing attention, particularly as it primarily affects the elderly population. The fact that POD/POCD is associated with adverse long-term outcomes provides a compelling reason to further investigate the pathogenesis and consequences of POD/POCD. The incidence of POD/POCD varies depending on the study and the type of operation or medical procedure.

There is no formalized medical definition for POD, rather POD falls under the category of postoperative cognitive disorder that is characterized by heightened confusion, a lack of awareness, and a decline in memory and executive function in the brain [77, 78]. According to the ICD-10 Classification of Mental and Behavioural Disorders [79], POD has the following
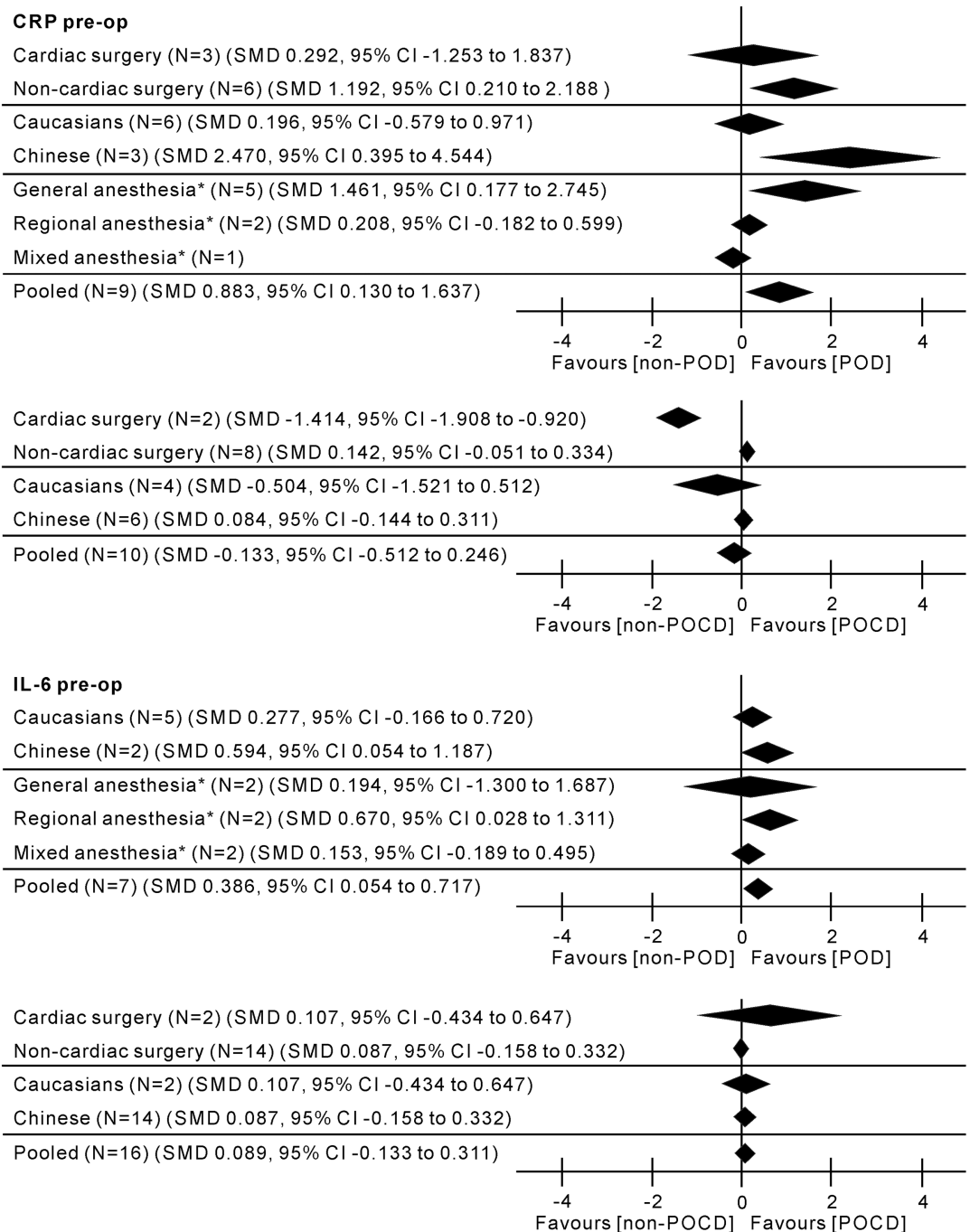
CRP pre-op

Cardiac surgery (N=3) (SMD 0.292, 95% CI -1.253 to 1.837)
Non-cardiac surgery (N=6) (SMD 1.192, 95% CI 0.210 to 2.188)
Caucasians (N=6) (SMD 0.196, 95% CI -0.579 to 0.971)
Chinese (N=3) (SMD 2.470, 95% CI 0.395 to 4.544)
General anesthesia* (N=5) (SMD 1.461, 95% CI 0.177 to 2.745)
Regional anesthesia* (N=2) (SMD 0.208, 95% CI -0.182 to 0.599)
Mixed anesthesia* (N=1)
Pooled (N=9) (SMD 0.883, 95% CI 0.130 to 1.637)

-4   -2   0   2   4
Favours [non-POD]   Favours [POD]

Cardiac surgery (N=2) (SMD -1.414, 95% CI -1.908 to -0.920)
Non-cardiac surgery (N=8) (SMD 0.142, 95% CI -0.051 to 0.334)
Caucasians (N=4) (SMD -0.504, 95% CI -1.521 to 0.512)
Chinese (N=6) (SMD 0.084, 95% CI -0.144 to 0.311)
Pooled (N=10) (SMD -0.133, 95% CI -0.512 to 0.246)

-4   -2   0   2   4
Favours [non-POCD]   Favours [POCD]

IL-6 pre-op

Caucasians (N=5) (SMD 0.277, 95% CI -0.166 to 0.720)
Chinese (N=2) (SMD 0.594, 95% CI 0.054 to 1.187)
General anesthesia* (N=2) (SMD 0.194, 95% CI -1.300 to 1.687)
Regional anesthesia* (N=2) (SMD 0.670, 95% CI 0.028 to 1.311)
Mixed anesthesia* (N=2) (SMD 0.153, 95% CI -0.189 to 0.495)
Pooled (N=7) (SMD 0.386, 95% CI 0.054 to 0.717)

-4   -2   0   2   4
Favours [non-POD]   Favours [POD]

Cardiac surgery (N=2) (SMD 0.107, 95% CI -0.434 to 0.647)
Non-cardiac surgery (N=14) (SMD 0.087, 95% CI -0.158 to 0.332)
Caucasians (N=2) (SMD 0.107, 95% CI -0.434 to 0.647)
Chinese (N=14) (SMD 0.087, 95% CI -0.158 to 0.332)
Pooled (N=16) (SMD 0.089, 95% CI -0.133 to 0.311)

-4   -2   0   2   4
Favours [non-POCD]   Favours [POCD]

Fig 7. Subgroup analyses for the assessment of impact of surgery type, anesthesia, and ethnicity on peripheral CRP and IL-6 levels perioperatively. Positive values indicate higher levels in POD/POCD patients; negative values indicate higher levels in control patients. All results are from random-effects models. pre-op, pre-operation; post-op, post-operation; N, number of studies; SMD, standardized mean difference; CI, confidence interval; *Data missing for N = 1 study.

clinical features: The onset of mental status change must be either acute or fluctuating; Delirium is marked by inattention, which is considered the cardinal symptom of delirium [80]; Finally, patients with delirium must have either sleep-wake cycle disturbances, hallucinations, an altered level of consciousness, or disorganized thinking [81].

Table 1. Meta-regression between the SMDs of peripheral CRP and IL-6 Levels before surgery and the potential sources of heterogeneity.

Potential sources of heterogeneity	Coef.	Std. Err.	t	P	95% CI	
CRP levels before surgery in POCD/non-POCD						
Surgery	1.555365	0.2772488	5.61	0.001	0.9160284	2.194702
Ethnicity	0.5673341	0.4286524	1.32	0.222	-0.4211402	1.555808
IL-6 levels before surgery in POCD/non-POCD						
Surgery	-0.6455521	0.3490707	-1.85	0.086	-1.394234	0.1031301
Ethnicity	-0.0243988	0.3926422	-0.06	0.951	-0.8665325	0.8177349

Without unified diagnostic criteria, POCD is often detected by abnormalities in neuropsychological testing [82, 83]. It may manifest clinically as memory loss, psychomotor derangement, dementia, delirium or depression, difficulties with fine-motor coordination, and impaired higher-level cognitive functions [84, 85]. Several aspects of POCD help to distinguish it from POD [86]. Unlike the early onset of POD (during the initial post-operative period, after an interval of only a few hours or days), POCD usually occurs weeks or sometimes months after the operation. The duration of POD is generally short (1–3 days) whereas POCD can last for several months, sometimes even longer.

The current theories on the etiology of POD/POCD now include surgery-, anesthesia-, and patient-related factors. One factor that is likely to be common to all patients with POD or POCD is an inflammatory state. This meta-analysis aimed to examine and discuss the current published literature concerning delirium and cognitive dysfunction postoperatively, with an emphasis on the evidence for a role of inflammation as a common etiological factor. The current knowledge about the contributing inflammatory biomarkers to POD and POCD his summarized in Figs 2 and 3. POD and POCD have a wide range of contributing mechanisms and some biomarkers overlap.

CRP is a marker of a nonspecific acute-phase response in inflammation, infection, and tissue damage [87], correlated with cognitive decline [88]. An association between high CRP levels and delirium was shown in several studies [89–91]. Patients with POCD have elevated CRP levels after coronary artery bypass grafting [92], liver transplantation [53] and lumbar discectomy [93]. van Munster et al. found elevated levels of IL-6 in patients with delirium [94]. However, in another study the association between delirium and higher IL-6 plasma levels was not confirmed [95]. In this meta-analysis, elevated peripheral CRP and IL-6 levels were detected in both POD and POCD patients postoperatively. We have found that elevated levels of preoperative CRP and IL-6 were associated with POD, but not with POCD.

Likewise, POCD but not POD patients have increased serum levels of NSE preoperatively, which is an indicator of neuronal injury. NSE is a specific enzyme that is mainly present in neurons and neuroendocrine cells and participates in glycolysis [96]. When neurons are

Table 2. Egger's test results for publication and selective reporting bias.

	Egger's test
Cytokines	P
CRP (peripheral) levels before surgery in POD	0.865
CRP (peripheral) levels before surgery in POCD	0.227
IL-6 (peripheral) levels before surgery in POD	0.752
IL-6 (peripheral) levels before surgery in POCD	0.354
S-100β (peripheral) levels post-surgery in POD	0.125
S-100β (peripheral) levels post-surgery in POCD	0.112

damaged or necrotic, NSE enters the CSF and blood. As brain glial cells and other brain tissues do not contain NSE, it is a specific indicator of neuronal damage [97].

As for the other inflammatory markers measured preoperatively, including IL-1β, TNF-α, S-100β, IL-8, IL-10, and IL-1ra, no associations were found between them and POD or POCD. Similarly, there were no effects of postoperative TNF-α or NSE in either POD or POCD. We found that postoperative S-100β and IL-8 levels were associated with POD, while there were few studies concerning their roles in POCD. A few studies in this meta-analysis showed that CRP, IL-6, and IL-1ra levels in the CSF are not connected to POD. However, we cannot draw any exact conclusions as to their role in POCD because of the limited number of studies.

This systematic literature review aimed to identify the current published literature examining inflammatory markers in POD/POCD in order to summarize existing knowledge and to provide a rational basis for future studies. Moreover, the identification of the differences between the inflammatory factors that play a role in POD and POCD advances our understanding of the pathophysiology of POD/POCD and could ultimately lead to new interventions that could improve patient outcomes.

It has been suggested that surgical wounds in combination with anesthetic lesions lead to a primary inflammatory response in the body, which leads to neuroinflammation and the increased risk of developing post-operative cognitive decline [98]. Keeping the importance of neuroinflammation in POCD in mind, targeting these inflammatory processes has been an area of interest for the prevention and treatment of POCD. Statins have been found to exert powerful anti-inflammatory effects and reduce neuroinflammation [99, 100]. Marcela et al. noted an improvement of hippocampal-dependent contextual memory and spatial learning in post-surgical mice which had received atorvastatin, in contrast to post-surgical controls without any treatment [101]. Their findings suggest that the anti-inflammatory and neuroprotective properties of atorvastatin provide a rationale for its use as a therapeutic strategy for postoperative cognitive decline. As for POD, Su et al. demonstrated that the use of a low-dose dexmedetomidine infusion in patients after noncardiac surgery reduced the risk of delirium in the postoperative period [102]. It is the first study to report on the efficacy of a sub-sedative dose of dexmedetomidine to reduce the development of delirium and included patients that were not intubated and those requiring sedation with γ-aminobutyric acid (GABA) receptor agonists. The study adds to the growing body of evidence that dexmedetomidine can reduce the development of delirium [103–105]. Neuroinflammation mediated by microglia has been implicated in delirium. As biomarkers of inflammation were not measured in the abovementioned research, it is not possible to assess whether low-dose dexmedetomidine infusion suppresses the inflammation associated with the aseptic trauma of surgery. Notably, one group found that dexmedetomidine had direct anti-inflammatory effects on microglia, but these were seen only at concentrations an order of magnitude higher than those used clinically [106].

The neuroprotective effects of the drugs mentioned above in animal models and patients are closely related to their anti-inflammatory properties. This confirms that neuroinflammation is closely associated with postoperative cognitive decline, and also suggests that inflammation is an important target for the prevention and treatment of POD/POCD. However, the development of POD/POCD is the result of a comprehensive interaction of various factors. Therefore, it is still necessary to conduct further study on the etiology, molecular mechanisms, and pharmacological interventions of POD/POCD.

There remains the question of the impact of anesthetic technique on POD and POCD. Several clinical trials have attempted to distinguish the effects of regional anesthesia and general anesthesia on POCD. A clinical multi-center evaluation of the impact of anesthesia on POCD was published by Rasmussen and his colleagues [107], which showed a higher incidence of

POCD in the general group than the regional one (19.7% vs. 12.5%) one week postoperatively, but no differences were found at 3 months (14.3% vs. 13.9%). Mason et al. concluded that there were no significant differences between general anesthesia and regional or combined anesthesia on the development of POD, but general anesthesia was found to have a slight association with an increased rate of POCD [OR (Odds Ratio) = 1.34, 95% CI 0.93–1.95] [108]. Davis et al. came to a similar conclusion through a meta-analysis of 16 studies, in which three studies showed some difference in cognitive function between regional and general anesthesia, whereas the remaining 13 showed no differences [109]. Fodale et. al believed that the use of certain general anesthetics (e.g. inhalational anesthetics) for elderly patients may worsen amyloid β peptide oligomerization and deposition, thereby increasing the risk of developing POCD [110]. Several studies have shown that the inhalation of small molecular-sized anesthetics do play a leading role in Aβ oligomerization compared to intravenous anesthetics such as propofol or diazepam [111–113]. The specific method of anesthesia was not one of our exclusion or inclusion criteria. As the main concern of this manuscript is to summarize and discuss inflammatory biomarkers in POD/POCD, any study measuring inflammatory marker concentrations in patients with POD/POCD qualified for inclusion. In one case, a study included both patients who received general anesthesia and those who received regional anesthesia. In some other cases, patients who were administered general anesthesia received a combination of both inhalational and intravenous anesthetics. Therefore, we could not address the specific correlation between POD/POCD and the type of anesthesia (e.g. inhalational vs. intravenous, or general vs. regional) in this meta-analysis. Instead, we performed sensitivity analyses to investigate the influence of each individual study on the overall meta-analysis summary estimate and the validity of the effect size.

The main limitation of this study was the small number of papers that could be included in some of the meta-analytical comparisons. As a result, the evidence regarding the roles of IL-1β, TNF-α, IL-8, and NSE in POD/POCD remain inconclusive. The heterogeneity methodology may also have some impact on the overall outcomes; It is possible that our findings cannot be interpreted as truly negative due to the small sample sizes and significant heterogeneity between studies.

Patients with POCD display biomarkers distinct from those with POD, which might be related not only to pathology but also to postoperative time. Most inflammatory markers immediately reached the peak postoperative value [114], but the peak serum concentration was not always the most valuable measure in the prediction of outcome. Therefore, the strength of evidence from this study was undermined by the choice of sampling times that may have missed potential early postoperative differences.

Conclusion

It is clear that POD and POCD are multifactorial conditions. Among the identified pathomechanisms, some inflammatory biomarkers were common, such as the elevation of CRP and IL-6 postoperatively. S-100β and IL-8 were elevated in only POD postoperatively and during the preoperative period, CRP and IL-6 increased in POD, while NSE levels increased in POCD. No changes in IL-1β, TNF-α, S-100β, IL-8, and IL-10 were found in POD preoperatively, or in TNFα and NSE in POCD postoperatively.

Supporting information

S1 Checklist. Reporting items for the meta-analyses.
(DOC)

S1 Appendix. Search strategies.
(DOCX)

S1 Table. Characteristics of the association studies that were included in the meta-analysis and that examined the peripheral and/or the CSF inflammatory markers.
(DOCX)

S2 Table. Quality score evaluation.
(DOCX)

S3 Table. Subgroup analyses for the assessment of impact of surgery type, anesthesia, and ethnicity on peripheral CRP and IL-6 levels perioperatively.
(DOCX)

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