# The correlation of intraoperative hypotension and postoperative cognitive impairment: a meta-analysis of randomized controlled trials

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# Abstract

Background There is no consensus on whether intraoperative hypotension is associated with postoperative cognitive impairment. Hence, we performed a meta-analysis to evaluate the correlation of intraoperative hypotension and the incidence of postoperative delirium (POD) or postoperative cognitive dysfunction (POCD).

Methods We searched PubMed, Embase, and Cochrane library databases to find randomized controlled trials (RCTs) in which reported the relationship of intraoperative hypotension and POD or POCD. The retrieval time is up to January 2020, without language restrictions. Quality assessment of the eligible studies was conducted by two researchers independently using the Cochrane evaluation system.

Results Five RCTs were included. For the incidence of POD, there are two studies with 99 participants in the low-blood pressure (LP) group and 94 participants in the high-blood pressure (HP) group. For the incidence of POCD, there are four studies with 360 participants in the LP group and 341 participants in the HP group, with a study contains both POD and POCD. No significant difference between the LP and the HP group was observed in the incidence of POD (RR = 3.30, 95% CI 0.80 to 13.54, P = 0.10), or POCD (RR = 1.26, 95% CI 0.76 to 2.08, P = 0.37). Furthermore, it also demonstrated that intraoperative hypotension prolonged the length of ICU stay, but did not increased the mortality, the length of hospital stay, and mechanical ventilation (MV) time.

Conclusions There is no significant correlation between intraoperative hypotension and the incidence of POD or POCD.


# Background

Postoperative cognitive impairment, including postoperative delirium (POD) and postoperative cognitive dysfunction (POCD), is a common neuropsychological disorder after surgery among patients [1]. POD is an acute change of patient’s attention, consciousness, perception or cognition [2, 3] while POCD is characterized by short-term disturbances in memory, executive functioning, personality or sleep [4]. POD and POCD are related to adverse results, including prolonged length of hospital stay, increased mortality and unexpected complications, leading to increased medical costs and decreased the quality of patient’s life [2, 5–7].

The underlying pathophysiology of POD or POCD is multifactor and complicated. Immutable risk factors, such as surgery types, age and baseline cognitive function have been identified [4, 6]. Although the definitive preventive or therapeutic measure of POD or POCD is still unknown, there are increasing studies that hypoperfusion of the brain caused by hypotension during surgery may be one pathogenic mechanism [8–11].

Intraoperative hypotension is common during anesthesia and surgery with a lack of widely accepted definition, which often means the blood pressure below the level of the physiologic value [12, 13]. Hypotensive anesthesia provides many obvious conveniences for some surgeries, including visualized anatomy, dry surgical area, and reduced blood loss during surgery [14]. Thus, intraoperative hypotension induced by anesthesia is also frequently observed. Besides, it seems plausible that the temporary brain perfusion of a patient becomes impaired when experience severe and prolonged low blood pressure, leading to cognitive impairment [15]. However, the specific correlation between intraoperative hypotension and postoperative cognitive function remains unclear and controversial. Some evidence has shown a pivotal role for intraoperative hypotension in the development of cognitive impairment after surgery [8, 11, 16], whereas others have not [15, 17–22]. A single study cannot enough elucidate issues and different study designs may cause selection bias.

Therefore, the goal of the current meta-analysis is to evaluate the association between intraoperative hypotension and the incidence of POD or POCD undergoing surgery.

# Methods

### Search strategy

We performed the meta-analysis following the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [23]. A PRISMA checklist is available as a supplement (Table S1). Relevant studies searched by the following databases: PubMed, Embase, and Cochrane library databases. According to the predetermined strategy, for PubMed, following terms was conducted with both MeSH and free terms: ((“Postoperative Cognitive Complications” OR “Postoperative Cognitive Dysfunctions” OR “POCD”) OR (“Delirium” OR “Postoperative delirium” OR “POD”)) AND (“Hypotension” OR “Low Blood Pressure”) AND (randomized controlled trial) search Title/Abstract. We also manually searched or any additional relevant studies to ensure that all related articles were included. The retrieval time is up to January 2020, and no language restrictions were applied.

### Study selection

The eligible criteria were as follows: (1) Randomized controlled trials (RCTs); (2) Participants who underwent surgical operations; (3) According to the blood pressure in the process of surgery, the patients were divided into the low-blood pressure (LP) and high-blood pressure (HP) groups; (4) The outcome was the occurrence of postoperative cognitive impairment (POD or POCD). The exclusion criteria as follows: (1) Unavailable results for statistical analysis; (2) Reviews, meta-analysis, letters, et al.

### Data extraction and risk of bias

Two investigators (Feng and Hu) performed the processes of data extraction and the risk of bias independently, with controversy resolved by a third investigator (Xu). The following information was available after inclusion of eligible studies: first author, publication time, country, surgery type, age of the subjects, preoperative blood pressure, event numbers, methods and time of cognitive assessment, and outcomes. The following adverse events, including mortality, the length of hospital and ICU stay, and mechanical ventilation (MV) time were extracted as well. All data were collected using a standardized form. The risk of bias for the eligible study was conducted according to the Cochrane evaluation system [24]. This assessment includes seven parts: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each project was classified as low risk, high risk, or unclear risk of bias.

### Outcome measures

According to the author’s definition with objective assessment methods, the primary outcomes were the incidence of POD and POCD. The secondary outcomes were the mortality, the length of hospital and ICU stay, and MV time.

### Statistical analysis

The results of the meta-analysis were analyzed by Review Manager 5.2. For dichotomous variables (POD or POCD incidence, mortality), we computed the relative risk (RR) with 95% confidence intervals (CI) by the Mantel-Haenszel method. For continuous data (length of hospital and ICU stay, and MV time), we used Inverse variance method to calculate Mean differences (MD) with 95% CI. In addition, we converted some continuous data, described as median and interquartile range (IQR) [20, 21], to mean and standard deviation (SD) by the formulas of Luo and Wan [25, 26].

Heterogeneity was evaluated with inconsistency ($I^2$) statistic. Clinical heterogeneity relates to differences in design factors between studies (such as outcome definitions or blinding), while methodological heterogeneity originates from diversity in clinical factors (such as essential characteristics or surgical settings). Given a large amount of methodological and clinical heterogeneity, we selected a random-effect model in this study [27]. Subgroup analyses about the incidence of POCD were performed: (1) Cardiac surgery versus non-cardiac surgery; (2) General anesthesia versus epidural anesthesia. Significant statistical difference was defined as $P$ value < 0.05.

### Assessment of publication bias and sensitivity analysis

We estimated the publication bias by a funnel plot with Egger's tests when the number of included studies was more than ten [28]. Using the Peto odds ratio method to evaluate the stability of the results, and we conducted a sensitivity analysis of primary outcomes (the incidence of POD and POCD).

# Results

### Study characteristics

Initially, basing on the above mentioned search strategy, a total of 174 studies were identified (Pubmed = 24; Embase = 38; Cochrane library = 112; other = 0). Of these, 35 studies were removed due to duplication. According to the criteria mentioned above, the remaining 134 studies were excluded, and five studies were included in our final analysis [8, 19-22]. The flow diagram describing the study search is displayed in Figure 1.

The main characteristics of included studies are summarized in Table 1. Two and four studies assessed the incidence of POD [8, 20] and POCD [19-22] (a study contains both POD and POCD [20]), respectively. Three studies reported cardiac surgery [8, 20, 21], while the other two studies described non-cardiac surgery [19, 22]. Furthermore, the assessment methods of cognitive function were different, including neuropsychologic battery tests, Mini-mental state examination (MMSE) scores, International Study of Postoperative Cognitive Dysfunction (ISPOCD), and the Confusion Assessment Method adapted for the ICU (CAM-ICU) scale.

### Risk of bias

The methodological bias of the eligible studies is presented in Figure 2. Random sequence generation was considered as low risk of bias in all included studies, while allocation concealment was described in only two RCTs [8, 19, 20]. For performance bias, three RCTs reported an unclear risk [8, 19, 22], whereas the remaining two RCTs were assigned as low risk [20, 21]. All included studies were confirmed as a low risk of detection, reporting, and other biases. Three RCTs have a high risk of attrition bias [19-21]. Some participants of studies were possible to be lost due to the long-term follow-up period (up to 30 days).

### Primary outcome - incidence of POD

There are two studies that reported the incidence of POD, and the data were described as the number of patients [8, 20]. Langer et al. [20] performed the assessment of POD in the late afternoon with the CAM-ICU scale, while Siepe et al. [8] conducted it on 48 hours after surgery with MMSE scores. The study indicated a trend that patients in the LP group (89 participants) had a higher incidence of POD than those in the HP group (94 participants) (RR 3.30, 95% CI 0.80 to 13.54, P = 0.10, $I^2$ = 15%), but the difference did not have a clinical significance (Fig. 3).

### Primary outcome - incidence of POCD

For the incidence of POCD, there were four studies included [19-22]. Three studies assessed POCD at over three months postoperatively [19, 20, 22], while one study reported the values of both seven days and three months after surgery [21]. To avoid repeated counting and ensure the accuracy of the results, we only obtained the data reported three months postoperatively. In this meta-analysis, the incidence of POCD in the LP group and the HP group was 9.5% and 7.5%, respectively, showed no significant difference (RR 1.26, 95% CI 0.76 to 2.08, P = 0.37, $I^2$ = 0%) (Fig. 4).

### Secondary outcomes

Four studies reported postoperative mortality in 638 patients [8, 19-21], which no significant difference was observed between the LP group and the HP group (RR 0.86, 95% CI 0.14 to 5.37, P = 0.88, $I^2$ = 44%). The length of hospital stay (described as days) data were available for 638 patients across four studies [8, 19-21]. It was noted that the value of the LP group was lower than the HP group, but the difference was so small that it did not have a statistical significance (MD 0.37, 95% CI -0.17 to 0.91, P = 0.18, $I^2$ = 0%). Data on the length of ICU stay (described as hours) was extracted from three studies evaluated 537 patients [8, 19, 21], indicating that the time of the LP group was longer compared to the HP group (MD 1.82, 95% CI 0.83 to 2.82, P = 0.0003, $I^2$ = 0%). Two studies reported MV time of the two groups [8, 21], and showed no significant difference (MD 0.40, 95% CI -1.26 to 2.06, P = 0.64, $I^2$ = 58%). The secondary outcomes of this study are shown in Table 2. Besides, we converted data described as median and IQR to mean and SD (Table S2).

### Subgroup analysis

For POCD, there were two studies described cardiac surgery [19, 21] and non-cardiac surgery [20, 22], respectively. We further conducted a subgroup analysis of cardiac surgery versus non-cardiac surgery. When we excluded the results of non-cardiac surgery, no significance was found between the LP and the HP groups (RR 1.16, 95% CI 0.63 to 2.12, P = 0.64, $I^2$ = 0%; 389 participants, Fig. 5). Also, there was no obvious difference between the subgroups (P = 0.80, Fig. 5). For POD, one RCT focuses on cardiac surgery [8] and another addresses non-cardiac surgery [20]; thus, we did not compare the incidence.

For POCD, three studies described general anesthesia [19-21], whereas one study described epidural anesthesia [22]. The further subgroup analysis on the POCD incidence of general and epidural anesthesia indicated no obvious significance between the LP and the HP group when epidural anesthesia was excluded (RR 1.06, 95% CI 0.61 to 1.86, P = 0.84, $I^2$ = 0%; 466 participants, Fig 6). No significant difference was observed in the subgroups (P = 0.18, Fig. 6). For POD, all patients of the included studies underwent general anesthesia [8, 20], so we did not perform a subgroup analysis.

### Assessment of publication bias and sensitivity analysis

Given that the number of the eligible studies was small, we did not assess publication bias [29]. Sensitivity analysis of the primary outcomes (the incidence of POD and POCD) by the Peto odds ratio method was yielded stable (POD: OR 3.67, 95% CI 0.86 to 15.62, P = 0.08 $I^2$ = 12%; POCD: OR 1.30, 95% CI 0.75 to 2.25, P = 0.35, $I^2$ = 0%).

## Discussion

In this study, we assessed the correlation of intraoperative hypotension and postoperative cognitive impairment following surgery and anesthesia. For the incidence of POD or POCD, the combined results illustrated no significant difference between the LP and the HP participants. Furthermore, it demonstrated that intraoperative hypotension prolonged the length of ICU stay. Nevertheless, we did not notice obvious differences in the mortality, the length of hospital stay, and MV time between groups.

Postoperative cognitive impairment (POD and POCD) is associated with high mortality and increased societal costs, receiving increasing attention [1, 5–7]. Till now, both POD and POCD have no formal definition, but the following characteristics might contribute to distinguishing POD from POCD [30]. Above all, in the initial postoperative stage, the mental status change in POD is acute or undulating. At the same time, POCD is not associated with a difference in the level of consciousness or fluctuations over the day. What's more, POD occurs in several hours or days after the operation, while POCD usually appears in weeks or months after surgery. Lastly, POD duration is usually short (a few days), while POCD can last for months or longer.

The present concepts on the etiology of POD or POCD contains anesthesia-, surgery-, and patient-related factors [2, 4, 30]. Previous studies have reported that inflammation, neurotransmitter imbalance as well as sleep deprivation play essential roles in the pathogenesis of cognitive impairment [3, 5, 6, 31]. Moreover, some studies indicated that intraoperative hypotension was linked to the development of POD or POCD [8, 11, 16].

In this meta-analysis, we found that the mean age of patients was more than 50 years old in most of the included researches. The possible explanation is that as population aging, more elderly patients are undergoing the operation, leading to a higher risk of cognitive impairment than younger patients. Furthermore, in this study, two studies utilized the CAM-ICU scale [20] and MMSE scores [8] to assess the incidence of POD. The CAM-ICU scale had almost 100% sensitivity, specificity and interrater reliability [32], and MMSE scores had 96% sensitivity and 38% specificity [33]. For POCD, the incidence of three studies was elevated by neuropsychological tests [20–22], a sensitive method of evaluating the change and in detecting beneficial results [34], while the remaining one used MMSE scores [8]. According to our study, the incidence of POD and POCD in the HP group is only 3% and 7%, which were marginally lower than the reported rate in a systematic review (11–43% and 15–25%) [35]. Possible interpretations for this discrepancy include the considerable differences in test methods, the definition of POD or POCD, the baseline evaluation, and the control groups used. Additionally, not only the occurrence of POD and POCD varied widely depending on the surgical variables, demographic as well as the clinical environment, but also increased with advancing age. [2, 3].

Our meta-analysis suggested that intraoperative hypotension has no identified relationship on the incidence of POD, in line with previous studies on cardiac or non-cardiac surgery [8, 20]. However, two studies about colorectal [11] and surgical surgery [10] (a logistic regression and a retrospective cohort analysis) shown that intraoperative hypotension can significantly increase the incidence of POD. We speculate the possible reasons for the finding were that the definition of hypotension used was different, and mentioned above two studies were not RCTs. Therefore, close monitoring and appropriate intervention of blood pressure during surgery seem to be crucial for preventing POD, which needed to further clarify by RCTs with a larger sample size.

There is no significant correlation between the POCD incidence and intraoperative hypotension in our study. This finding was consistent with most studies [18–22, 36, 37] expect for a clinical, randomized study [8], which found that maintaining mean perfusion during cardiopulmonary bypass surgery at physiological values (80–90 mmHg) is associated with less early POCD. This discrepancy may be attributable to methodological issues concerning POCD: this study assessed at 48 hours after surgery, while others assessed it on over three months postoperatively; hence, Siepe et al. defined this cognitive impairment as early POCD.

The result of our secondary outcomes indicated that intraoperative hypotension significantly prolonged the length of ICU stay, while not being followed by increased mortality, the length of hospital stay, and MV time. Furthermore, we also performed subgroup analysis for the effect of type of surgery (cardiac versus non-cardiac surgery) and anesthesia (general versus epidural anesthesia) on the incidence of POCD, which is consistent with a study revealed that the incidence is not associated with the type of anesthesia and surgery [38].

Several limitations of this study should be noted. First, the number of eligible studies was relatively small, resulting in a high risk of overestimation effects and lacking assessment of publication bias. Second, surgery types, intraoperative hypotension levels, different definitions, and evaluation tools of POD or POCD varied among included studies. Thus, clinical heterogeneity was relatively high, which may weaken the reliability and precision of our conclusion. Third, given the fact that the incidence of POD and POCD were our primary outcomes, studies that did not contain POD or POCD data were excluded; thus, the application of our secondary outcomes may be limited. Therefore, these results of this meta-analysis should be further confirmed by the depth and high-quality studies.

## Conclusions

To our knowledge, this meta-analysis is the first systematic review to confirm the correlation of intraoperative hypotension and postoperative cognitive impairment, which provides a comprehensive summary of all currently available data on this crucial issue. Our study found that no significant relationship was seen between intraoperative hypotension and POD or POCD. Furthermore, it also demonstrated that intraoperative hypotension prolonged the length of ICU stay, but not increased the mortality, the length of hospital stay, and MV time. The current study has potential clinical implications for intraoperative blood pressure management, but other large, well-designed RCTs will be needed to validate our conclusions.

## Abbreviations

CAM-ICU: Confusion Assessment Method adapted for the ICU; CI: Confidence intervals; HP: High-blood pressure; ISPOCD: International Study of Postoperative Cognitive Dysfunction; IQR: Interquartile range; LP: Low-blood pressure; MD: Mean difference; MMSE: Mini-mental state examination; MV: Mechanical ventilation; OR: Odds ratio; POD: Postoperative delirium; POCD: Postoperative cognitive dysfunction; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCTs: Randomized controlled trails; RR: Relative ratios; SD: Standard deviation.

# Declarations


### Acknowledgement

Not applicable.


### Authors' contributions

X.F. designed this study and drafted the manuscript. X.F. and J.H. searched literature and extracted data. F.H., J.Z. and L.Z. provided substantial contributions to statistical analysis and English expression. G.X. revised the article. All the authors read and approved the final version of the work.


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### Availability of data and materials

All data generated or analyzed during this study are included in this published article.

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests. As the BMC Assistant Editor, Jing Zhang will not review this manuscript to ensure transparency.

# References


1. Winterer G, Androsova G, Bender O, Boraschi D, Borchers F, Dschietzig TB, et al. Personalized risk prediction of postoperative cognitive impairment - rationale for the EU-funded BioCog project. Eur Psychiatry. 2018;50:34–9.
2. Aldecoa C, Bettelli G, Bilotta F, Sanders RD, Audisio R, Borozdina A, et al. European Society of Anaesthesiology evidence-based and consensus-based guideline on postoperative delirium. Eur J Anaesthesiol. 2017;34(4):192–214.
3. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet. 2014;383(9920):911–22.
4. Kotekar N, Shenkar A, Nagaraj R. Postoperative cognitive dysfunction - current preventive strategies. Clin Interv Aging. 2018;13:2267–73.
5. Kapoor I, Prabhakar H, Mahajan C. Postoperative Cognitive Dysfunction. Indian J Crit Care Med. 2019;23(Suppl 2):162-4.
6. Oh ST. Park. JY. Postoperative delirium. Korean J Anesthesiol. 2019;72(1):4–12.
7. Crocker E, Beggs T, Hassan A, Denault A, Lamarche Y, Bagshaw S, et al. Long-Term Effects of Postoperative Delirium in Patients Undergoing Cardiac Operation: A Systematic Review. Ann Thorac Surg. 2016;102(4):1391–9.

8. Siepe M, Pfeiffer T, Gieringer A, Zemann S, Benk C, Schlensak C, et al. Increased systemic perfusion pressure during cardiopulmonary bypass is associated with less early postoperative cognitive dysfunction and delirium. Eur J Cardiothorac Surg. 2011;40(1):200–7.
9. Brady K, Hogue CW. Intraoperative hypotension and patient outcome: does "one size fit all?". Anesthesiology. 2013;119(3):495–7.
10. Maheshwari K, Ahuja S, Khanna AK, Mao G, Perez-Protto S, Farag E, et al. Association Between Perioperative Hypotension and Delirium in Postoperative Critically Ill Patients: A Retrospective Cohort Analysis. Anesth Analg. 2020;130(3):636–43.
11. Patti R, Saitta M, Cusumano G, Termine G, Vita GD. Risk factors for postoperative delirium after colorectal surgery for carcinoma. Eur J Oncol Nurs. 2011;15(5):519–23.
12. Bijker JB, van Klei WA, Kappen TH, van Wolfswinkel L, Moons KG, Kalkman CJ. Incidence of intraoperative hypotension as a function of the chosen definition: literature definitions applied to a retrospective cohort using automated data collection. Anesthesiology. 2007;107(2):213–20.
13. Hartmann B, Junger A, Klasen J, Benson M, Jost A, Banzhaf A, et al. The incidence and risk factors for hypotension after spinal anesthesia induction: an analysis with automated data collection. Anesth Analg. 2002;94(6):1521–9.
14. Lin S, McKenna SJ, Yao CF, Chen YR, Chen C. Effects of Hypotensive Anesthesia on Reducing Intraoperative Blood Loss, Duration of Operation, and Quality of Surgical Field During Orthognathic Surgery: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Oral Maxillofac Surg. 2017;75(1):73–86.
15. Wesselink EM, Kappen TH, van Klei WA, Dieleman JM, van Dijk D, Slooter AJ. Intraoperative hypotension and delirium after on-pump cardiac surgery. Br J Anaesth. 2015;115(3):427–33.
16. Tognoni P, Simonato A, Robutti N, Pisani M, Cataldi A, Monacelli F, et al. Preoperative risk factors for postoperative delirium (POD) after urological surgery in the elderly. Arch Gerontol Geriatr. 2011;52(3):e166-9.
17. Hirsch J, DePalma G, Tsai TT, Sands LP, Leung JM. Impact of intraoperative hypotension and blood pressure fluctuations on early postoperative delirium after non-cardiac surgery. Br J Anaesth. 2015;115(3):418–26.
18. Vedel AG, Holmgaard F, Siersma V, Langkilde A, Paulson OB, Ravn HB, et al. Domain-specific cognitive dysfunction after cardiac surgery. A secondary analysis of a randomized trial. Acta Anaesthesiol Scand. 2019;63:730–8.
19. Gold JP, Charlson ME, Williams-Russo P, Szatrowski TP, Peterson JC, Pirraglia PA, et al. Improvement of outcomes after coronary artery bypass. A randomized trial comparing intraoperative high versus low mean arterial pressure. J Thorac Cardiovasc Surg. 1995;110(5):1302–11. discussion 1311-4.
20. Langer T, Santini A, Zadek F, Chiodi M, Pugni P, Cordolcini V, et al. Intraoperative hypotension is not associated with postoperative cognitive dysfunction in elderly patients undergoing general anesthesia for surgery: results of a randomized controlled pilot trial. J Clin Anesth. 2019;52:111–8.
21. Vedel AG, Holmgaard F, Rasmussen LS, Langkilde A, Paulson OB, Lange T, et al. High-Target Versus Low-Target Blood Pressure Management During Cardiopulmonary Bypass to Prevent Cerebral Injury in Cardiac Surgery Patients: a Randomized Controlled Trial. Circulation. 2018;137(17):1770–80.
22. Williams-Russo P, Sharrock NE, Mattis S, Liguori GA, Mancuso C, Peterson MG, et al. Randomized trial of hypotensive epidural anesthesia in older adults. Anesthesiology. 1999;91(4):926–35.
23. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
24. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj. 2011;343:d5928.
25. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res. 2018;27(6):1785–805.
26. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14:135.

27. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189–98.
28. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. J Clin Epidemiol. 2008;61(10):991–6.
29. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Bmj. 1997;315(7109):629–34.
30. Nadelson MR, Sanders RD, Avidan MS. Perioperative cognitive trajectory in adults. Br J Anaesth. 2014;112(3):440–51.
31. Capri M, Yani SL, Chattat R, Fortuna D, Bucci L, Lanzarini C, et al. Pre-Operative, High-IL-6 Blood Level is a Risk Factor of Post-Operative Delirium Onset in Old Patients. Front Endocrinol (Lausanne). 2014;5:173.
32. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). Jama. 2001;286(21):2703–10.
33. Wong CL, Holroyd-Leduc J, Simel DL, Straus SE. Does this patient have delirium?: value of bedside instruments. Jama. 2010;304(7):779–86.
34. Newman SP. Analysis and interpretation of neuropsychologic tests in cardiac surgery. Ann Thorac Surg. 1995;59(5):1351–5.
35. Newman MF, Mathew JP, Grocott HP, Mackensen GB, Monk T, Welsh-Bohmer KA, et al. Central nervous system injury associated with cardiac surgery. Lancet. 2006;368(9536):694–703.
36. Sartcaoglu F, Celiker V, Basgul E, Yapakci O, Aypar U. The effect of hypotensive anaesthesia on cognitive functions and recovery at endoscopic sinus surgery. Eur J Anaesthesiol. 2005;22(2):157–9.
37. Charlson ME, Peterson JC, Krieger KH, Hartman GS, Hollenberg JP, Briggs WM, et al. Improvement of outcomes after coronary artery bypass II: a randomized trial comparing intraoperative high versus customized mean arterial pressure. J Card Surg. 2007;22(6):465–72.
38. Evered L, Scott DA, Silbert B, Maruff P. Postoperative Cognitive Dysfunction Is Independent of Type of Surgery and Anesthetic. Anesth Analg. 2011;112(5):1179–85.

# Tables

**Table 1** Characteristics of the included studies.

| Author/ year | Country | Surgery type | Anesthesia type | Age | Preoperative blood pressure (mm Hg) | | LP | | HP | | Cognitive assessment | | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | LP | HP | Events | Total | Events | Total | Method | Time (after surgery) | |
| Gold 1995 | USA | CPB | General anesthesia | No reported | 50–60 | 80–100 | 13 | 113 | 12 | 112 | Neuropsychologic battery | 6 months | POCD |
| Langer 2019 | Italy | Non-cardiac surgery | General anesthesia | ≥75 | No-Target | ≥90% of baseline | 3 | 41 | 4 | 36 | MMSE scores | 3 months | POCD |
| | | | | | | | 7 | 51 | 3 | 50 | CAM-ICU scale | Once daily | POD |
| Siepe 2011 | Germany | CPB | General anesthesia | ≥55 | 60-70 | 80-90 | 6 | 48 | 0 | 44 | MMSE scores | 48 hours | POD |
| Vedel 2018 | Denmark | CPB | General anesthesia | ≥18 | 40-50 | 70-80 | 8 | 89 | 5 | 75 | ISPOCD battery | 3 months | POCD |
| Williams 1999 | USA | Total hip replacement | Epidural anesthesia | ≥50 | 45–55 | 55–70 | 10 | 117 | 4 | 118 | Neuropsychologic battery | 4 months | POCD |

LP: Low-blood pressure; HP: High-blood pressure; CPB: Cardiopulmonary bypass; MMSE: Mini-mental state examination; CAM-ICU: Confusion Assessment Method Intensive Care Unit; ISPOCD: International Study of Postoperative Cognitive Dysfunction; POD: Postoperative delirium; POCD: Postoperative cognitive dysfunction.

**Table 2** Secondary outcomes of this meta-analysis.

| Outcome | Number of studies | Number of participants | | RR or MD | 95% CI | Hterogeneity/$I^2$ | P value |
|---|---|---|---|---|---|---|---|
| | | LP | HP | | | | |
| Mortality | 4 | 322 | 316 | 0.86 | 0.14 to 5.37 | 44% | 0.88 |
| Length of hospital stay | 4 | 322 | 316 | 0.37 | -0.17 to 0.91 | 0% | 0.18 |
| Length of ICU stay | 3 | 271 | 266 | 1.82 | 0.83 to 2.82 | 0% | 0.0003 |
| MV time | 2 | 147 | 142 | 0.40 | -1.26 to 2.06 | 58% | 0.64 |

LP: Low-blood pressure; HP: High-blood pressure; RR: Risk ratio; MD: Mean difference; CI: Confidence interval; MV: Mechanical ventilation.

# Figures

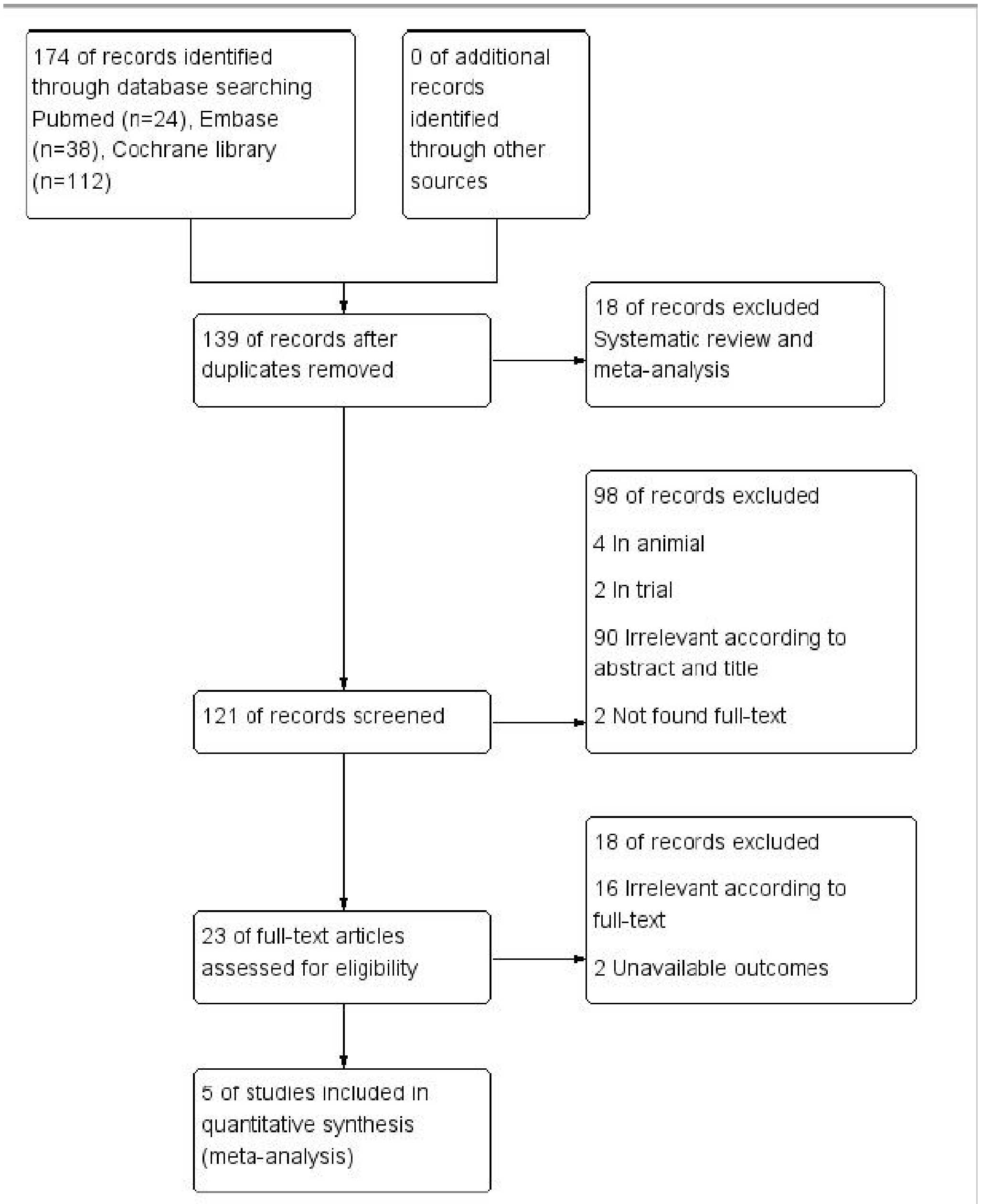


**Figure 1**

PRISMA diagram of study selection in this meta-analysis.

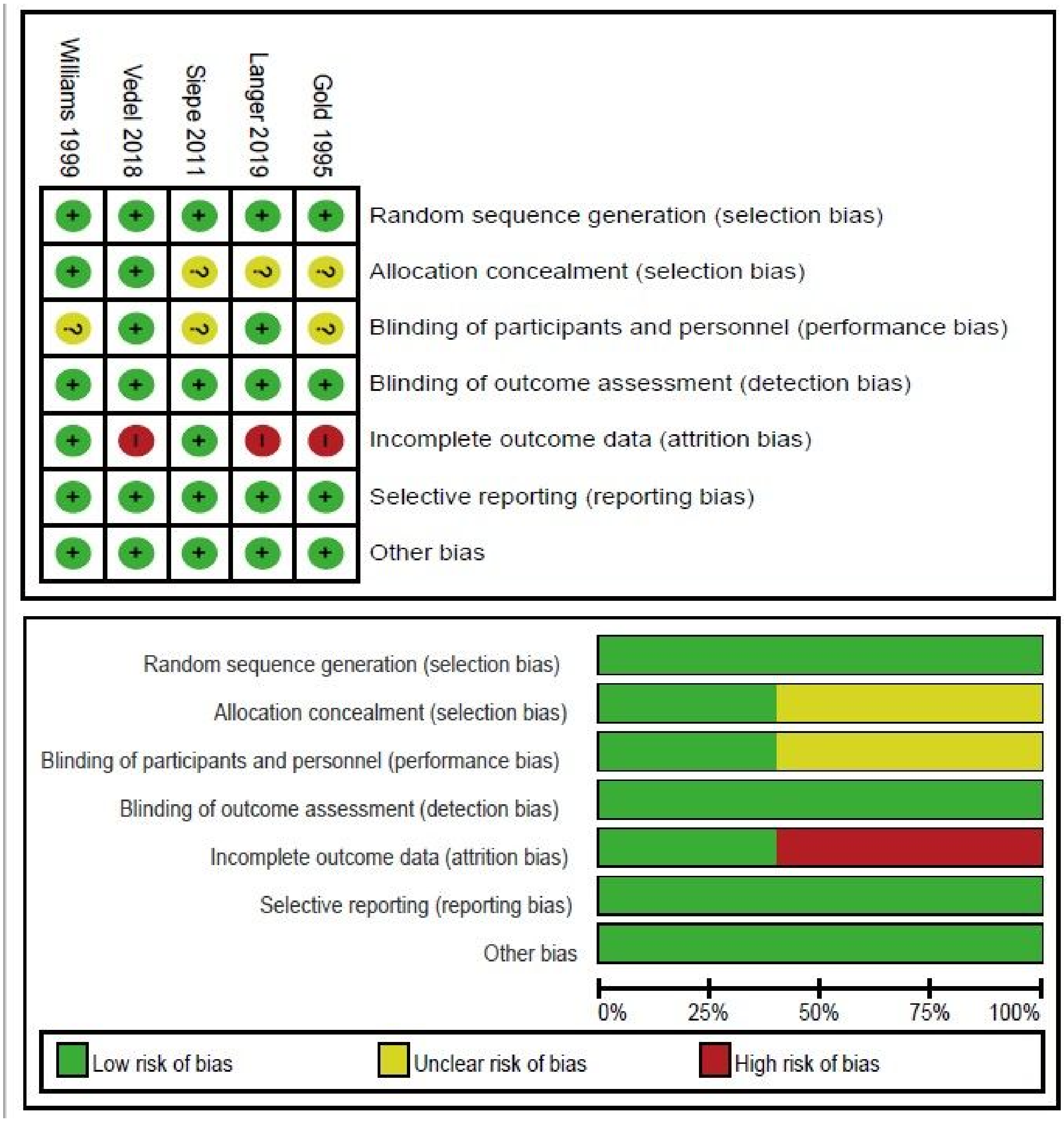


**Figure 2**

Risk of bias assessment for each included study.


**Figure 3**

Forest plot of primary outcome - incidence of POD.

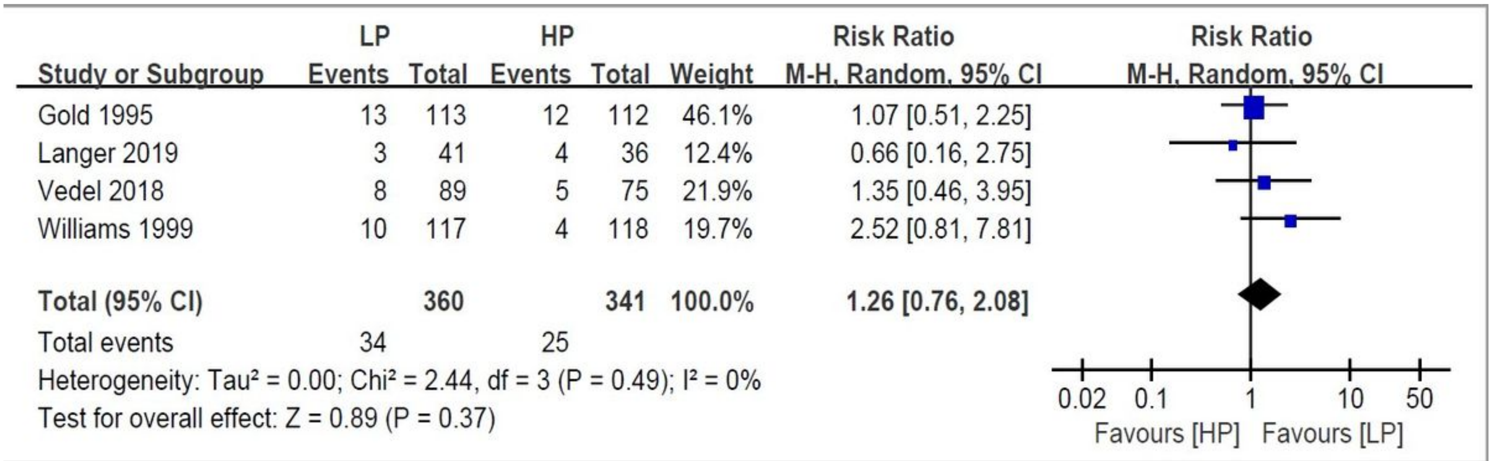


**Figure 4**

Forest plot of primary outcome - incidence of POCD.

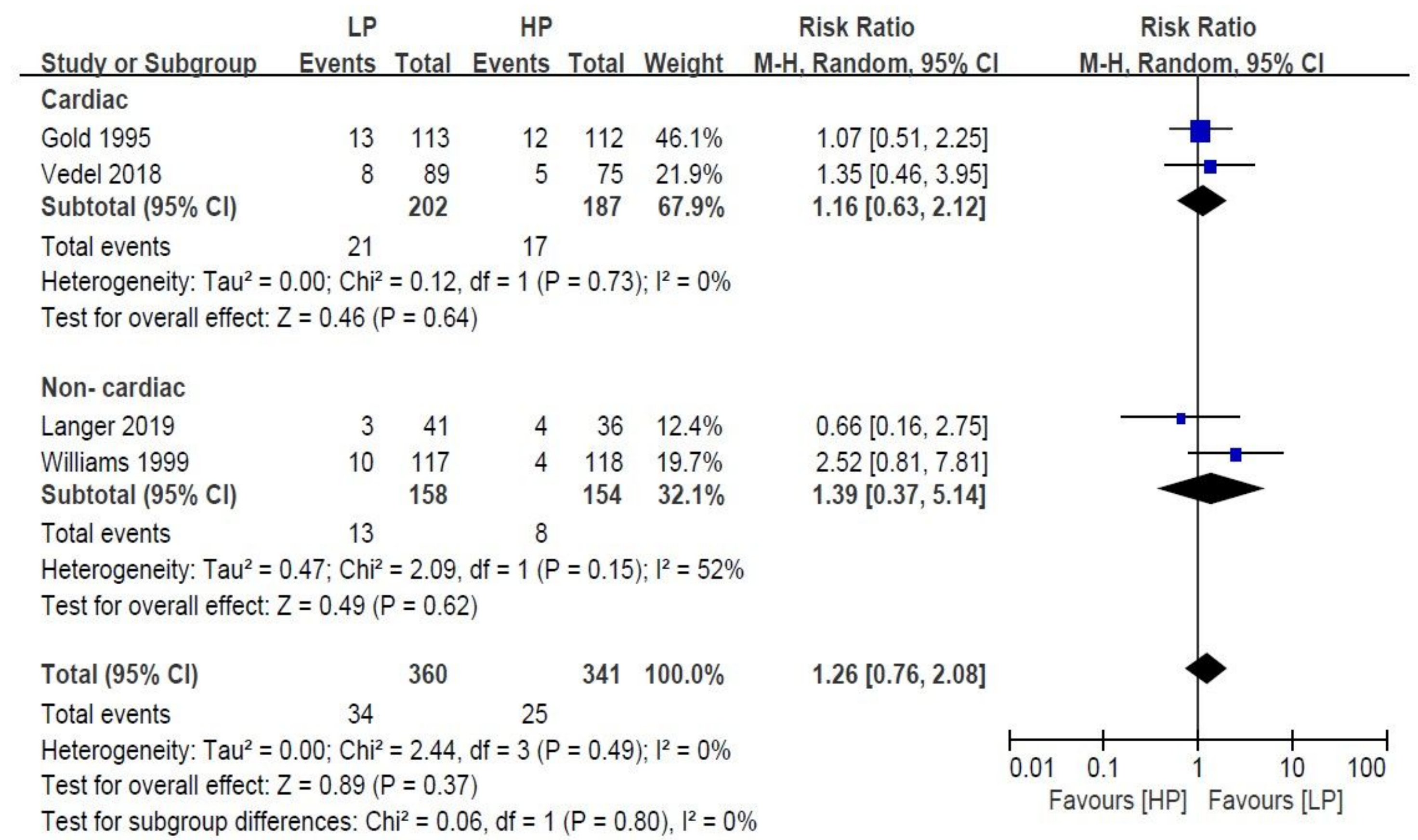


**Figure 5**

Subgroup analysis of cardiac surgery versus non-cardiac surgery.

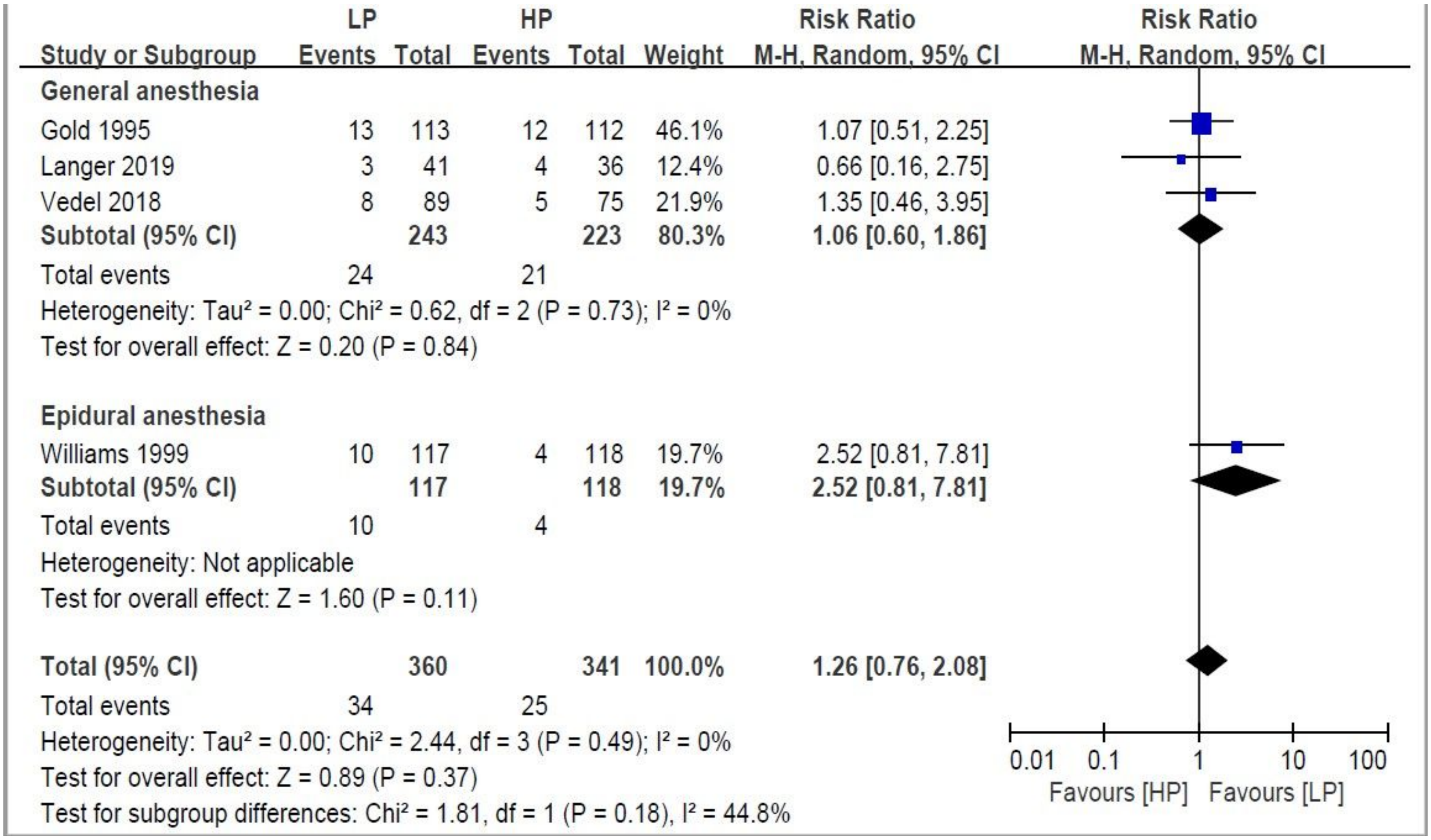


**Figure 6**

Subgroup analysis of general anesthesia versus epidural anesthesia.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTableS12.docx