Journal of the American Heart Association

SYSTEMATIC REVIEW AND META-ANALYSIS

Risk Factors for Delirium and Cognitive Decline Following Coronary Artery Bypass Grafting Surgery: A Systematic Review and Meta-Analysis

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BACKGROUND: Coronary artery bypass grafting (CABG) is known to improve heart function and quality of life, while rates of surgery-related mortality are low. However, delirium and cognitive decline are common complications. We sought to identify preoperative, intraoperative, and postoperative risk or protective factors associated with delirium and cognitive decline (across time) in patients undergoing CABG.

METHODS AND RESULTS: We conducted a systematic search of Medline, PsycINFO, EMBASE, and Cochrane (March 26, 2019) for peer-reviewed, English publications reporting post-CABG delirium or cognitive decline data, for at least one risk factor. Random-effects meta-analyses estimated pooled odds ratio for categorical data and mean difference or standardized mean difference for continuous data. Ninety-seven studies, comprising data from 60 479 patients who underwent CABG, were included. Moderate to large and statistically significant risk factors for delirium were as follows: (1) preoperative cognitive impairment, depression, stroke history, and higher European System for Cardiac Operative Risk Evaluation (EuroSCORE) score, (2) intraoperative increase in intubation time, and (3) postoperative presence of arrythmia and increased days in the intensive care unit; higher preoperative cognitive performance was protective for delirium. Moderate to large and statistically significant risk factors for acute cognitive decline were as follows: (1) preoperative depression and older age, (2) intraoperative increase in intubation time, and (3) postoperative presence of delirium and increased days in the intensive care unit. Presence of depression preoperatively was a moderate risk factor for midterm (1–6 months) post-CABG cognitive decline.

CONCLUSIONS: This meta-analysis identified several key risk factors for delirium and cognitive decline following CABG, most of which are nonmodifiable. Future research should target preoperative risk factors, such as depression or cognitive impairment, which are potentially modifiable.

REGISTRATION: URL: https://www.crd.york.ac.uk/prospero/; Unique identifier: CRD42020149276.

Key Words: cognitive decline ■ coronary artery bypass grafting ■ delirium ■ meta-analysis

Coronary artery bypass grafting (CABG) surgery is the main treatment for multivessel coronary disease and remains one of the most common cardiac procedures worldwide.[1,2] CABG has low mortality rates, and improves coronary vascularization and cardiac function.[3] However, CABG is associated with high rates of postoperative cognitive impairments, including delirium.[4–6]

A recent meta-analysis investigating post-CABG cognitive outcomes (cross-sectional approach by percentage at specific time points)[4] revealed postoperative cognitive impairment or decline was prevalent in

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CLINICAL PERSPECTIVE

What Is New?

- This meta-analysis is the first to comprehensively identify risk and protective factors for postoperative delirium and cognitive decline in patients who underwent coronary artery bypass grafting (CABG).
- Findings demonstrate that there are many risk and protective factors for delirium and cognitive decline post-CABG, some of which are modifiable, such as depression, diabetes mellitus, hypertension, and cognitive impairment.
- The presence of preoperative depression was a common risk factor across outcomes, which at least doubled the risk of post-CABG delirium in hospital and cognitive decline acutely and up to 6 months following surgery.

What Are the Clinical Implications?

- Risk and protective factors identified in this meta-analysis could be used to improve delirium and cognitive decline risk prediction tools, leading to more accurate identification of at-risk patients undergoing CABG, improving care and prognosis.
- Findings can inform the design of future intervention trials aimed at reducing the incidence of delirium and cognitive decline post-CABG, by targeting identified modifiable risk factors.

Nonstandard Abbreviations and Acronyms

ACC	aortic cross-clamp
CPB	cardiopulmonary bypass
SMD	standardized mean difference

43% of patients up to 4 days, and remains high (39%) up to 1 month post-CABG. This reduces in the midterm (6–12 months) following CABG to ≈25% and increases up to nearly 40% in the long-term (1–5 years). The presence of delirium (an acute and fluctuating syndrome of deficits in attention and arousal) was apparent in 24% of patients, up to 1 week post-CABG, when a standardized tool was used alongside clinical criteria.[4]

The presence of cognitive decline following CABG is associated with increased depression risk and decreased quality of life, functional capacity, and the ability to perform activities of daily living.[7] Delirium presence in older adults is associated with increased mortality, length of stay (LOS), hospital readmissions, as well as cognitive decline and dementia, along with reduced quality of life.[8–11] Research attempting to prevent these post-CABG cognitive outcomes has been largely unsuccessful, including pharmacological, anesthetic intervention, and surgical techniques.[12–16] There has been some evidence of therapeutic effect for advanced surgical methods, such as hypothermia and increasing systemic perfusion intraoperatively.[17] However, the expertise and technology needed are not routinely available.

Understanding risk and protective factors for delirium and cognitive decline post-CABG has critical clinical implications, including more precise targeting of preoperative and perioperative interventions and the development of a sensitive risk screening tool for these outcomes. The use of a prediction tool for delirium and cognitive decline in a post-CABG setting could lead to earlier intervention opportunities, greater prognosis, and, in turn, better patient management.

Previous meta-analyses of all surgical type cardiac patients have provided greater depth of knowledge surrounding the effects of surgery method on cognitive decline (on versus off pump)[15,16] and the effect of pharmacological and anesthetic interventions on postoperative delirium.[18,19] Specific risk or protective factors for cognitive outcomes (delirium and cognitive decline) have not been comprehensively investigated through meta-analysis in patients undergoing CABG. In addition, no meta-analysis has investigated the time course of effects for risk factors in relation to cognitive decline following CABG, especially in the long-term (>12 months). This systematic review and meta-analysis aims to investigate risk and protective factors for the following: (1) post-CABG delirium (1–7 days) and (2) post-CABG cognitive decline across multiple time points: short-term (immediately postoperatively up to 1 month), midterm (1–6 months postoperatively), and long-term (12–15 months postoperatively).

METHODS

The protocol for this systematic review and meta-analysis was registered and published with the international prospective register of systematic reviews (PROSPERO) (registration number: CRD42020149276). This article is reported in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.[20] The data that support the findings of this study are available from the corresponding author on reasonable request.

Search Strategy

We updated a search from a published meta-analysis.[4] We searched Medline, PsycINFO, EMBASE, and the

Cochrane databases using the Ovid platform when possible. Searches of all databases were last performed on March 26, 2019. Search terms and medical subject headings used were as follows: (Coronary Artery Bypass/ OR "coronary artery bypass" OR CABG) AND (Cognition/ OR Delirium/ OR Dementia/ OR Alzheimer Disease/ OR Neuropsychological Tests/ OR Cognit* OR Deliri* OR Dementia* OR Alzheimer* MCI or "mild cognitive impairment*" OR "mild-cognitive impairment*" OR neuropsycholo* OR POCD OR "postoperative cognitive" OR "post-operative cognitive" OR MMSE OR "mini-mental state examination" OR "cerebral function" OR neurocognit* OR encephalopath*). Article selection and data extraction, of the updated search, were undertaken by at least 2 reviewers (between D.G., E.S.G., and T.J.R.), with disagreements resolved by consensus.

Study Eligibility

Inclusion criteria were as follows: peer-reviewed, full-text, English-language studies that reported usable risk or protective factor data of those who had undergone CABG surgery (including CABG plus concomitant surgeries). Studies needed to report a cognitive outcome (using a standardized test result, neuropsychological battery, or a clinical diagnosis) for presence of delirium versus no delirium or cognitive decline versus no cognitive decline, and include usable data for at least one risk factor.

Exclusion criteria included the following: case series (n<5), dissertations, book chapters, protocol articles, reviews, news articles, conference abstracts, letters to the editor, editorials, and comment publications; and studies with no description of their operationalization (or definition used for categorizing participants with cognitive decline/delirium) or incomplete reporting in respect to risk factor data.

All possible risk/protective factors were tallied for presence across eligible studies (eg, data reported within text or within a table split by cognitive outcome or results of measures of association, such as odds ratios [ORs]). Unique risk factors that were reported in >10 studies (across delirium and cognitive decline) were included in this review. A list of these factors was circulated to academic clinicians (coauthors P.J.P. and D.H.J.D.) to ensure that no clinically relevant factors had been missed. This led to the additional extraction of delirium as a risk factor for cognitive decline (although only present in 3 studies). Following this, factors were categorized as follows: preoperative, intraoperative, or postoperative. Studies that did not report information pertaining to the target risk factors analyzed within the study (eg, studies reporting data related to hematocrit, height, or sepsis) were subsequently excluded (categorized as inappropriate data). In addition, if multiple studies investigated the same cohort, duplicate samples were excluded.

Quality Assessment

Study design and reporting quality were assessed by at least 2 reviewers (between D.G., E.S.G., and T.J.R.), with disagreements resolved by consensus. An adapted tool was used, on the basis of 2 existing assessment checklists,[21,22] where higher scores indicated greater overall quality (0–12) (Data S1).

Data Extraction

Data extracted from each included study consisted of: country, sample size, age, sex, cognitive decline/delirium assessment criteria, and risk factor data relative to time periods and cognitive outcome (delirium versus no delirium): 1 to 7 days postoperatively; postoperative cognitive decline versus no decline: short-term (immediately postoperatively up to 1 month), midterm (1–6 months postoperatively), and long-term (12–15 months postoperatively). There may be a small degree of overlap between the outcomes of delirium and acute cognitive decline, yet this overlap is representative of the population at this time point. Many of the studies included in this meta-analysis did not explicitly aim to assess risk factors for these cognitive outcomes through inferential statistical analyses. Yet, these studies still reported extractable descriptive data related to the cognitive outcome (eg, table presenting counts or mean and SD for preoperative, intraoperative, and postoperative variables, split by cognitive outcome). As fewer articles reported data as a result of an inferential statistical analysis, the extraction of descriptive data was prioritized. For each risk factor, descriptive data (eg, mean and SD/event rates) were extracted when available. In the absence of descriptive data, the results of inferential statistical analyses (eg, ORs) were extracted. To increase the consistency within our analyses, only univariate (or unadjusted) data were extracted, as the number and type of covariates used within risk factor analyses varied greatly across studies. When data were reported and extracted as median and interquartile range values, they were converted to mean and SD values.[23,24] Only data pertaining to risk/protective factors could be extracted for each cognitive outcome for the time periods reported in identified studies. There were substantially fewer articles within the literature that investigate midterm and long-term cognitive decline, compared with delirium and acute cognitive decline. Therefore, fewer risk factors could be investigated for midterm and long-term cognitive decline. It may be the case that there are important risk factors for these time points that we were unable to identify herein with our approach.

Statistical Analysis

Demographic data were calculated from the reported preoperative samples. The I^2 statistic was used to

express the proportion of between-study heterogeneity out of total variance and was classified as low (I^2=25%–50%), moderate (I^2=50%–75%), or high (I^2≥75%), using classification criteria suggested by Higgins et al.[25] Total between-study variance was quantified using τ^2. All analyses were based on random-effects model. Before data analyses, checks were conducted to detect extreme outliers. Effect size estimates that fell an abnormally large distance from other estimates (mainly because of separation or quasi-separation for a given outcome) were excluded. This process did not exclude the remaining study data from remaining risk factor analyses.

All analyses were performed in Comprehensive Meta-Analysis software (version 3). A result was considered statistically significant when P<0.05. Each risk or protective factor was analyzed separately and, therefore, independence from other factors cannot be assumed. Separate random effect meta-analyses were used to estimate pooled OR for categorical risk factor data and mean difference or standardized mean difference (SMD) for continuous risk factor data, comparing cognitive outcomes (delirium versus no delirium or cognitive decline versus no cognitive decline) post-CABG. A risk or protective factor was meta-analyzed when data from ≥2 studies were available for the analysis. All meta-analyses were conducted on univariate data (no multivariate data were extracted) and therefore should be interpreted as unadjusted pooled estimates. The SMD was also calculated to provide a supplementary common effect size across pooled estimates (Tables S1 through S4). SMD values can be interpreted using the same cutoff as Cohen *d,* where ≥0.20, ≥0.50, and ≥0.80 are considered as small, moderate, and large, respectively.[26] For cognitive decline post-CABG, analyses were conducted for each time point: short-term (immediately postoperatively up to 1 month), midterm (1–6 months postoperatively), and long-term (12–15 months postoperatively). Some of the extracted predictor variables were presented as both categorical and continuous data across articles (eg, education >12 years [categorical] or total years of education [continuous]). Others provided data that could be sorted into multiple categories (eg, preoperative cognitive test scores): (1) different cognitive tests used between studies (SMD used) or (2) the same test used between studies, such as Mini-Mental State Examination (mean difference used). In these cases, subanalyses were performed for each data format or category, for each risk factor. For statistically significant results, small study effect was examined by visually inspecting funnel plots of effect size versus SE.[27] When at least 10 studies were available for analyses, small study effect was formally assessed using the Egger test of the intercept.[28] When there was evidence for small study effect (1-tailed P<0.1), we used the Duvall and Tweedie[29] trim and fill method to quantify the extent of potential bias. When there were <10 studies, we performed sensitivity analyses by removing outliers.

Random-effects meta-regressions (using mean age as a covariate within the analysis) were performed to investigate whether age was related to the pooled effect estimates. Only analyses containing both risk factor and age data of ≥10 studies, as stated in recent Cochrane guidelines,[30] were interpreted. We also performed stratified random-effects subgroup analyses to investigate any possible effects of diagnostic approach for delirium (inclusion of a standardized instrument versus none) for each risk factor. For this, stratified random-effects meta-analyses were performed for each risk or protective factor variable relative to (1) studies using a standardized instrument (eg, Confusion Assessment Method or the Delirium Rating Scale) to inform the reference standard and (2) studies not using a specific instrument. Therefore, 2 subgroup meta-analyses were conducted for each risk factor variable (1 of studies using a diagnostic tool and 1 of studies using no tool), allowing comparison of the pooled estimates. Subgroup analyses investigating differing methods of classifying cognitive decline were not conducted because of the limited numbers of articles across most time points.

RESULTS

The search identified 4260 articles, of which 2647 records were screened by title and abstract, following duplicate removal. Full-text screening was conducted on 963 articles; of these, 97 were included in this review (Figure 1, see Table S5 for articles excluded and rationale for exclusion, at full-text review stage).

The 97 included studies were published across 4 decades, with 3, 7, 38, and 49 studies published in the 1980s, 1990s, 2000s, and 2010s, respectively. Of the included studies, 17 were conducted in the United States, 13 in Japan, 9 in Canada, 8 in Australia, and 6 each in China and the Netherlands. The remaining 38 studies were conducted across 22 individual countries. The included articles comprised data from 60 479 patients, with individual study sample sizes ranging from 8 to 14 262. The mean age of patients across included studies was 64.54 years, and 68.55% of patients were men (calculated only from studies with available data). The included studies were of good quality on the basis of the critical appraisals, ranging from 4 to 12, with a median study score of 10 (of 12) and interquartile range of 8 to 11.5. No studies were excluded from the analysis on the basis of their quality (see Table S6 for individual study information).

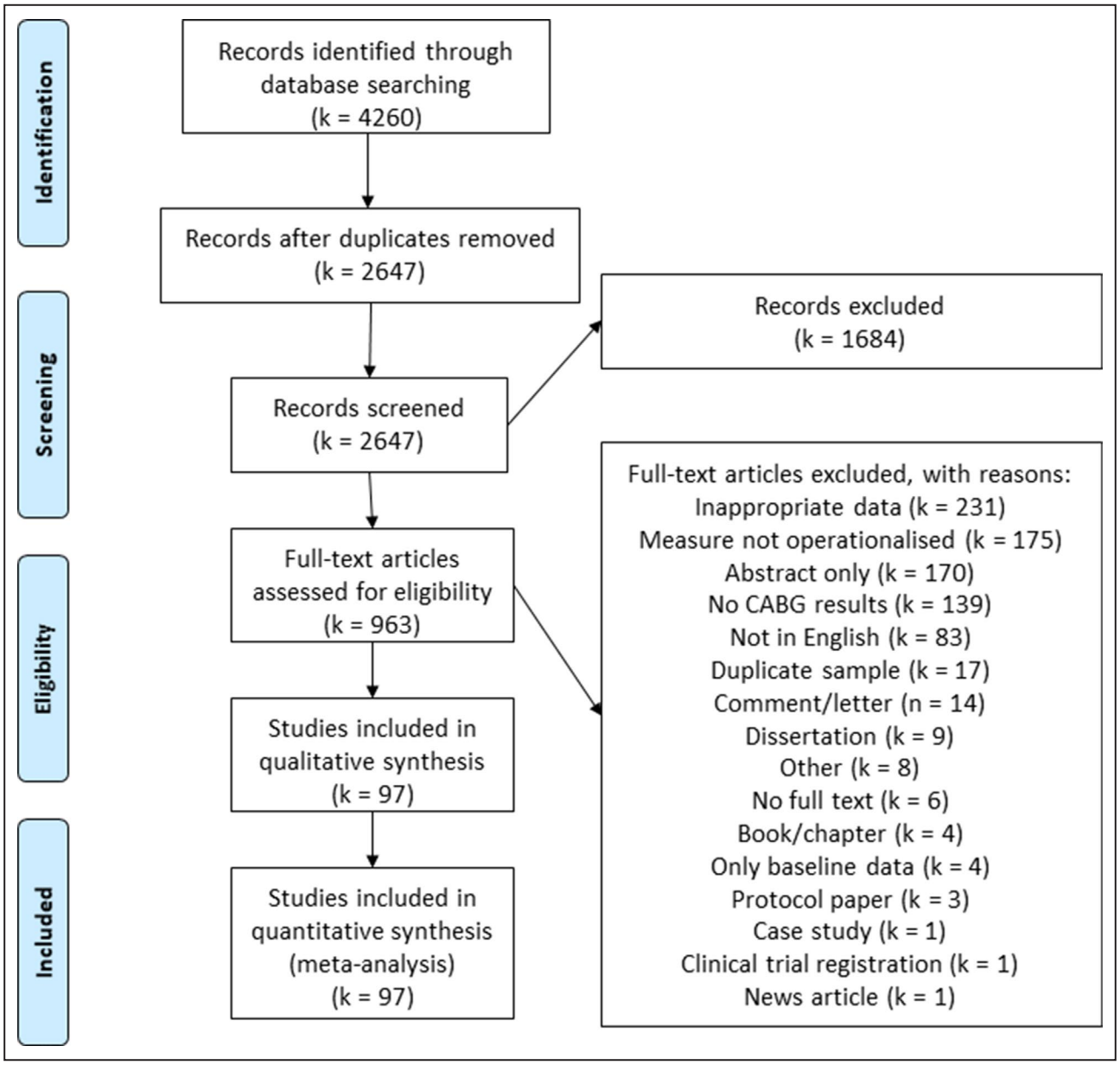

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram.
CABG indicates coronary artery bypass grafting.

Preanalysis checks for extreme outliers resulted in data from 3 studies being excluded from separate analyses (delirium analyses of: presence of depression, kidney injury, and LOS in intensive care unit [ICU]); however, these studies remained within other analyses and therefore were not excluded from this article.

Delirium

Data from 48 individual studies were used within 33 analyses (including subcategory analyses), investigating 27 separate risk or protective factors for delirium presence post-CABG. Across the analyses, heterogeneity of statistically significant results spanned from low to high (I^2 range, 0–98.40; τ^2 range, 0–325.89) (see Table S1 for results of each meta-analysis and Figure S1 for forest plots). Potential small-study effect was found in 2 analyses (preoperative age and European System for Cardiac Operative Risk Evaluation (EuroSCORE)), where trim and fill estimation led to decreases in effect size (see Figure S2 for funnel plots and small study effect investigation).

Statistically significant preoperative risk factors of developing delirium post-CABG, from largest to smallest effect size, were: the presence of cognitive impairment, stroke history, depression, arrhythmia, including atrial fibrillation (AF), peripheral vascular

disease, kidney injury/disease, body mass index >30 kg/m^2, diabetes mellitus, and hypertension, along with continuous risk factors of higher EuroSCORE and older age. Statistically significant intraoperative risk factors, from largest to smallest effect size, were increased intubation time (hours), duration of surgery (minutes), aortic cross-clamp (ACC) time (minutes), and cardiopulmonary bypass (CPB) time (minutes). Statistically significant postoperative risk factors, from largest to smallest effect size, were: increased LOS in the ICU (days) and the presence of arrhythmia, including AF. Statistically significant protective factors for developing delirium post-CABG were higher preoperative cognition test scores and years of education (Table S1 and Figure 2).

Preoperative factors that did not reach statistical significance were: the presence of alcoholism, body mass index >28 kg/m^2, dyslipidemia/hyperlipidemia,

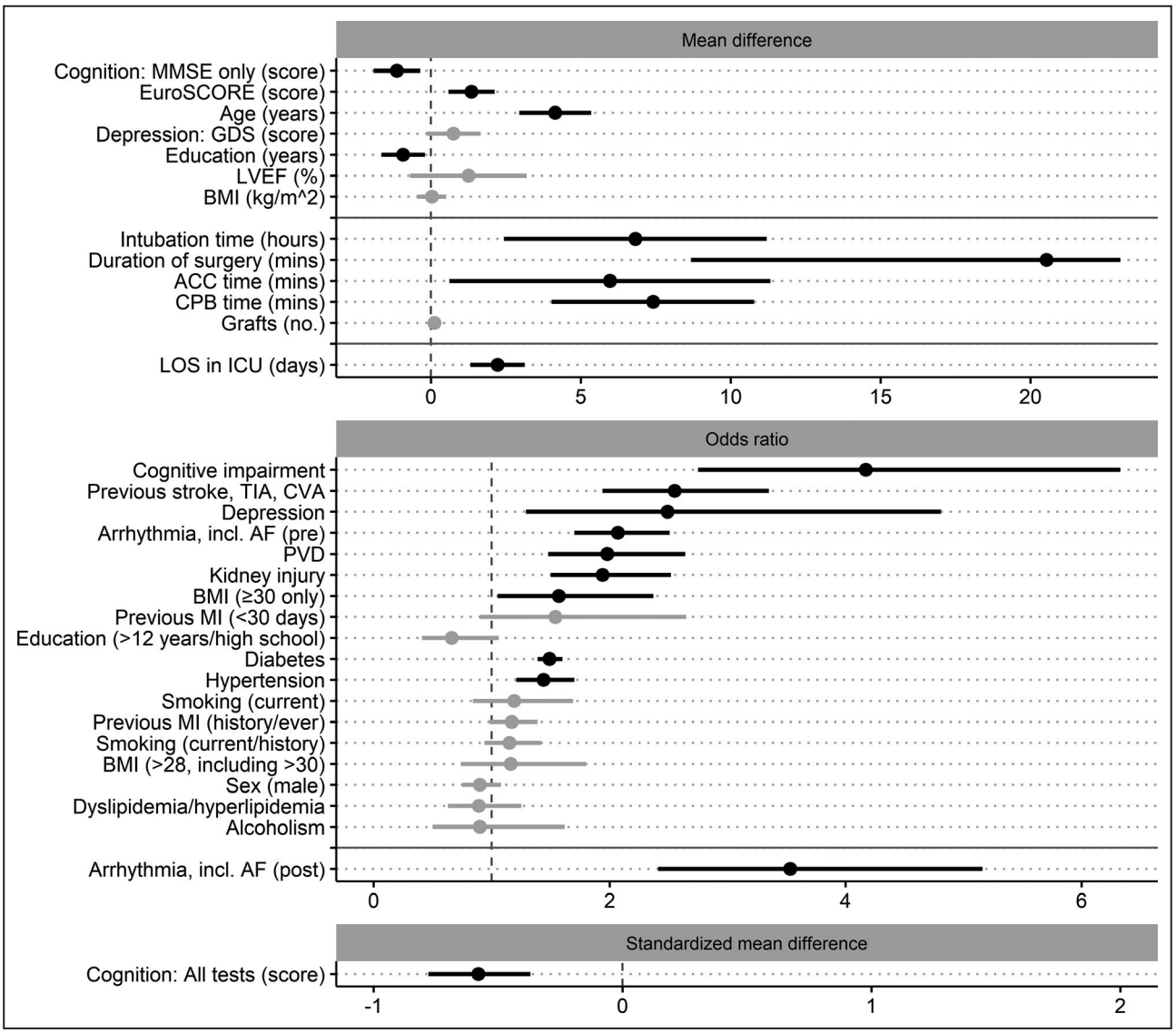

Figure 2. Forest plots of pooled estimates for risk or protective factors of post–coronary artery bypass grafting delirium. Factors grouped according to the primary pooled estimate of the analysis (mean difference [MD], odds ratio, or standardized MD [SMD]), where solid gray horizontal lines indicate separation of preoperative, intraoperative, and postoperative factors and dashed gray vertical lines divide protective (left side) and risk (right side) factor estimates. The pooled estimates are ordered by the common calculated effect size (SMD) from largest to smallest (largest at the top). Estimates that are black represent statistically significant factors; those that are gray did not reach statistical significance. The scale for all continuous variables (MD and SMD plots) is listed within each factor name. The CIs for duration of surgery extend further than the visible portion of the figure. This was not shown to allow appropriate visibility of all pooled estimates. ACC indicates aortic cross-clamp; AF, atrial fibrillation; BMI, body mass index; CPB, cardiopulmonary bypass; CVA, cerebrovascular attack; GDS, Geriatric Depression Scale; ICU, intensive care unit; LOS, length of stay; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MMSE, Mini-Mental State Examination; PVD, peripheral vascular disease; and TIA, transient ischemic attack.

>12 years of education, male sex, previous myocardial infarction, and previous/current smoking; and continuous factors of higher body mass index, depression score, and left ventricular ejection fraction. With respect to intraoperative factors, number of grafts did not reach statistical significance (Table S1 and Figure 2).

Subgroup analyses investigating the effect of diagnostic criteria for delirium (studies using standardized measurement tool along with diagnostic criteria versus studies using no tool) revealed no meaningful differences for any risk factors, with CIs overlapping for all analyses (Table S7). Meta-regressions with mean age as a model factor (covariate) revealed statistically significant results for risk factors of ACC time (age: β=−1.33, Z=−2.49, P=0.013, R^2=0.50) and LOS in ICU (age: β=−0.22, Z=−1.99, P=0.046, R^2=0.10). These results suggest that as the mean age of the study sample increases, the delirium risk associated with ACC time and LOS in ICU decreases. The results also suggest that 50% (for ACC time) and 10% (for LOS in ICU) of the variance in delirium presence relating to these risk factors can be attributed to age.

Acute Cognitive Decline (Immediately to 1-Month Post-CABG)

Data from 35 individual studies were used within 30 analyses (including subcategory analyses), investigating 25 separate risk or protective factors for the presence of cognitive decline acutely (immediately up to 1 month) post-CABG. Across the analyses, heterogeneity of statistically significant results spanned from low to high (I^2 range, 0–92.85; τ^2 range, 0–32.28) (see Table S2 for results of each meta-analysis and Figure S3 for forest plots). Potential small study effect was found in 2 analyses. Trim and fill estimation for preoperative age led to a decrease in effect size (see Figure S4 for funnel plots and small study effect investigation). A sensitivity analysis was performed for postoperative delirium (removal of outlier), which resulted in a decrease in effect size (Table S2 and Figure 3).

Statistically significant preoperative risk factors for acute post-CABG cognitive decline, from largest to smallest effect size, were: the presence of depression, stroke history, hypertension, and diabetes mellitus, along with continuous risk factors of older age and higher EuroSCORE. Statistically significant intraoperative continuous risk factors, from largest to smallest effect size, were increased intubation time (hours) and duration of surgery (minutes). Statistically significant postoperative risk factors, from largest to smallest effect size, were: the presence of delirium and arrhythmia, including AF, and the continuous risk factor of increased LOS in the ICU (days). Higher body mass index was a statistically significant protective factor for acute post-CABG cognitive decline (Table S2 and Figure 3).

Preoperative factors that did not reach statistical significance were the presence of arrhythmia, including AF, cognitive impairment, dyslipidemia/hyperlipidemia, male sex, kidney injury/disease, previous myocardial infarction, peripheral vascular disease, and previous/current smoking; and continuous factors of higher cognitive test score, depression score, years of education, and lower left ventricular ejection fraction. Intraoperative factors that did not reach statistical significance were increase in ACC time (minutes), CPB time (minutes), number of grafts, and total microemboli count (Table S2 and Figure 3).

Meta-regressions revealed that 49% of the variance in acute cognitive decline for the risk factor of increased CPB time (age: β=−0.88, Z=−2.24, P=0.025, R^2=0.49) can be attributed to age. These results suggest that as the mean age of the study sample increases, the risk of cognitive decline associated with CPB time decreases.

Midterm Cognitive Decline (1–6 Months Post-CABG)

Data from 24 individual studies were used within 19 analyses (including subcategory analyses), investigating 17 separate risk or protective factors for the presence of cognitive decline in the midterm (1–6 months) post-CABG. Across the analyses, heterogeneity of statistically significant results spanned from low to moderate (I^2 range, 0–68.84; τ^2 range, 0–0.04) (see Table S3 for results of each meta-analysis and Figure S5 for forest plots). Two analyses revealed statistically significant results, with no indication of small study effect (Figure S6). Preoperative depression and higher cognitive test scores (across all tests) were risk factors for midterm post-CABG cognitive decline (Table S3 and Figure 4).

Preoperative factors that did not reach statistical significance were the presence of diabetes mellitus, male sex, hypertension, previous myocardial infarction, stroke history, peripheral vascular disease, and current smoking; and continuous factors of higher age, cognitive test score (when using cognitive index), depression score, years of education, and left ventricular ejection fraction. No intraoperative or postoperative factors reached statistical significance, including increase in ACC time (minutes), CPB time (minutes), number of grafts, total microemboli count, and LOS in ICU (days) (Table S3 and Figure 4). No meta-regressions investigating the influence of age were significant for this time point.

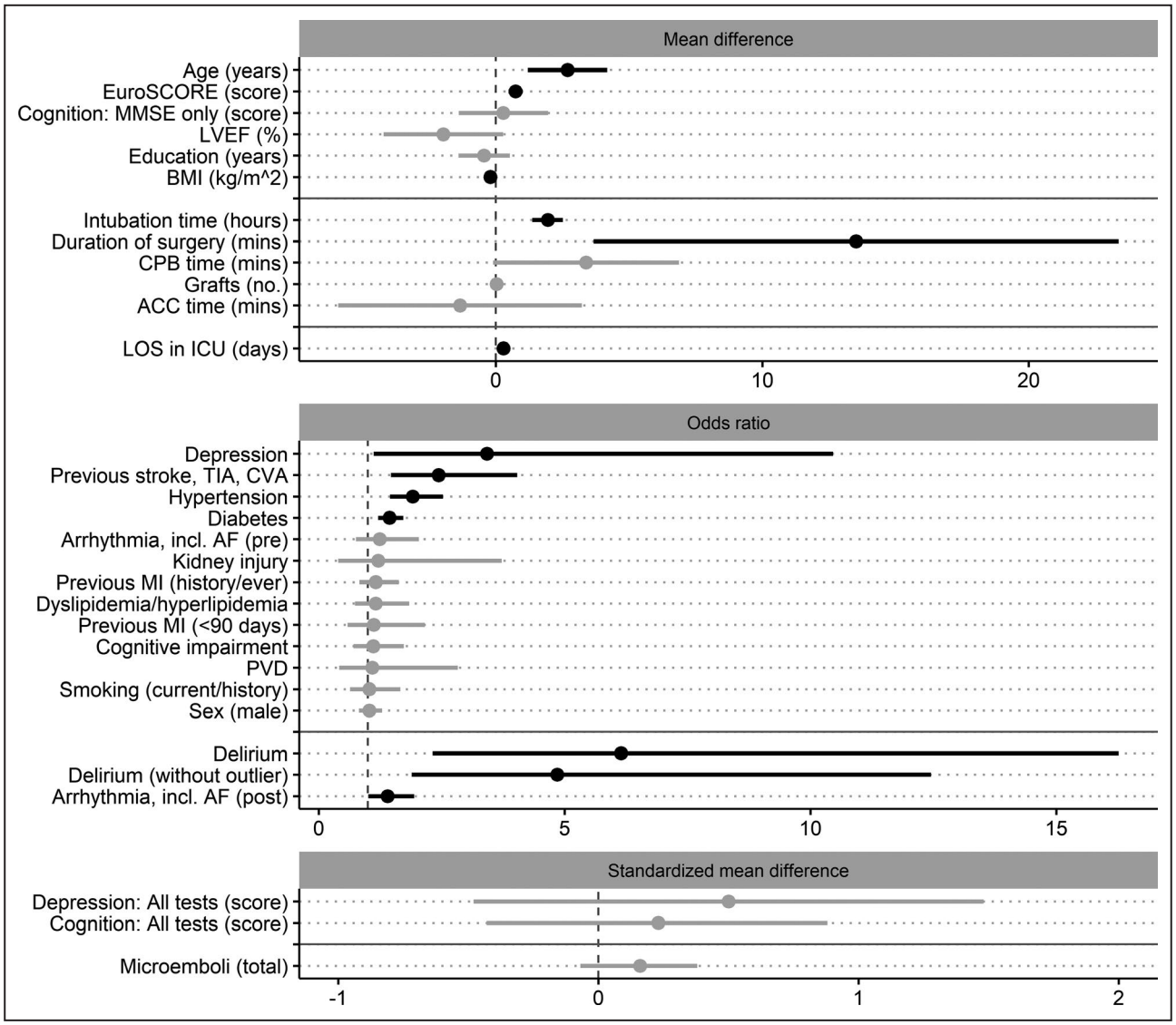

Figure 3. Forest plots of pooled estimates for risk or protective factors of post–coronary artery bypass grafting acute cognitive decline.

Factors grouped according to the primary pooled estimate of the analysis (mean difference [MD], odds ratio, or standardized MD [SMD]), where solid gray horizontal lines indicate separation of preoperative, intraoperative, and postoperative factors and dashed gray vertical lines divide protective (left side) and risk (right side) factor estimates. The pooled estimates are ordered by the common calculated effect size (SMD) from largest to smallest (largest at the top). Estimates that are black represent statistically significant factors; those that are gray did not reach statistical significance. The scale for all continuous variables (MD and SMD plots) is listed within each factor name. ACC indicates aortic cross-clamp; AF, atrial fibrillation; BMI, body mass index; CPB, cardiopulmonary bypass; CVA, cerebrovascular attack; ICU, intensive care unit; LOS, length of stay; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MMSE, Mini-Mental State Examination; PVD, peripheral vascular disease; and TIA, transient ischemic attack.

Long-Term Cognitive Decline (12–15 Months Post-CABG)

Data from 5 individual studies were used within 6 separate risk factor analyses for cognitive decline in the long-term (12–15 months) post-CABG. No analyses revealed statistically significant results, including presence of preoperative cognitive impairment, diabetes mellitus, male sex, and hypertension, nor older age or higher number of intraoperative grafts (see Table S4 for results of each meta-analysis, Figure S7 for forest plots, and Figure 5). No meta-regressions were performed for this time point.

DISCUSSION

This meta-analysis quantifies data from >60 000 patients to identify risk and protective factors for the development of cognitive decline, including delirium,

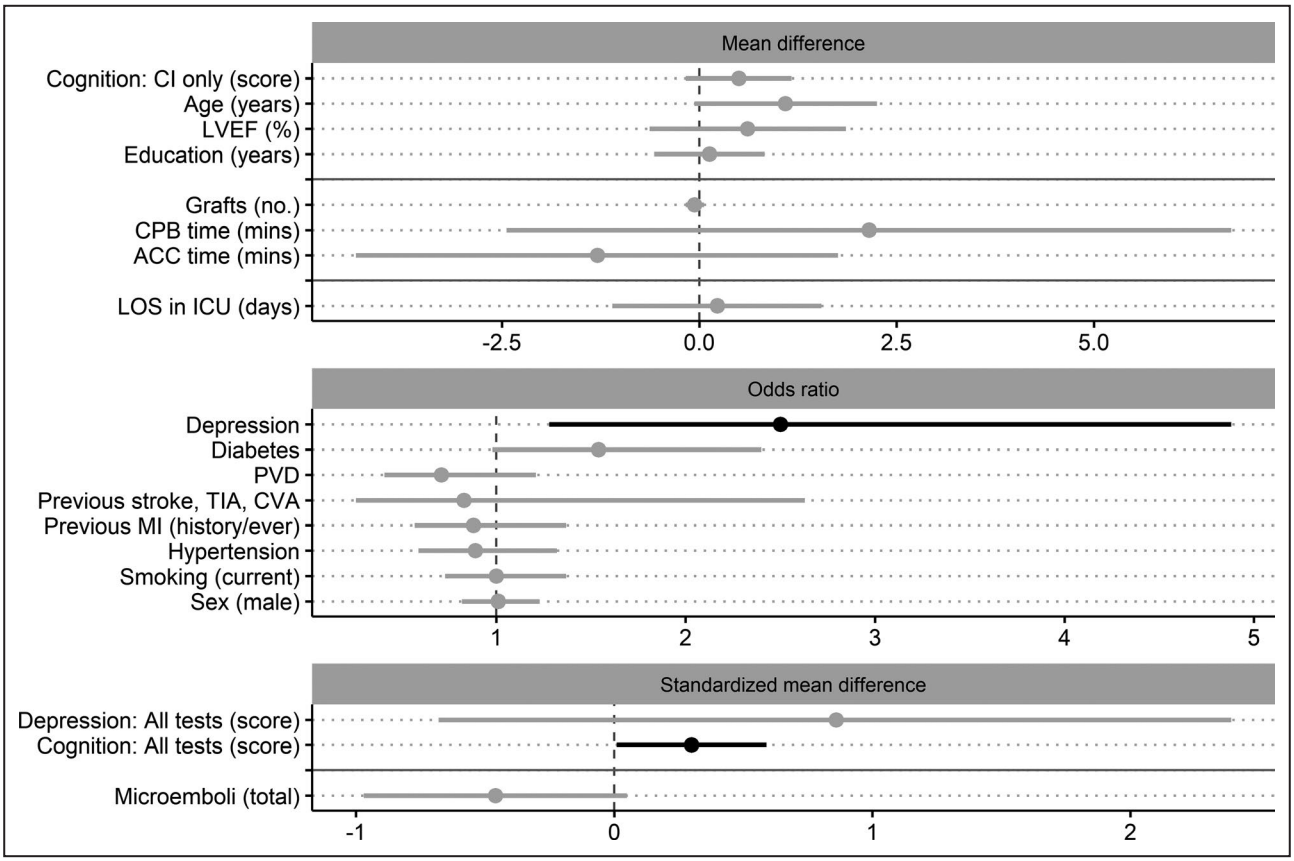

Figure 4. Forest plots of pooled estimates for risk or protective factors of post–coronary artery bypass grafting midterm cognitive decline.

Factors grouped according to the primary pooled estimate of the analysis (mean difference [MD], odds ratio, or standardized MD [SMD]), where solid gray horizontal lines indicate separation of preoperative, intraoperative, and postoperative factors and dashed gray vertical lines divide protective (left side) and risk (right side) factor estimates. The pooled estimates are ordered by the common calculated effect size (SMD) from largest to smallest (largest at the top). Estimates that are black represent statistically significant factors; those that are gray did not reach statistical significance. The scale for all continuous variables (MD and SMD plots) is listed within each factor name. ACC indicates aortic cross-clamp; CI, cognitive index score; CPB, cardiopulmonary bypass; CVA, cerebrovascular attack; ICU, intensive care unit; LOS, length of stay; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PVD, peripheral vascular disease; and TIA, transient ischemic attack.

immediately following CABG and in the midterm and long-term. Findings highlight that there are many risk factors for both delirium and cognitive decline following CABG. These factors could be integrated into existing delirium tools or shortlisted in the development of prediction tools for postoperative cognitive decline.[31,32] Further development of these clinical risk screening tools for both delirium and cognitive decline post-CABG could lead to more accurate identification of at-risk patients, improved prognosis, targeting of interventions, and patient management.

Risk prediction for delirium has been discussed at length for nonsurgical patients, with current models generally thought to have inadequate accuracy.[32] Most published delirium prediction tools are based on individual clinical studies with low statistical power, decreasing their generalizability.[33–36] To our knowledge, no tools have been developed for predicting postoperative cognitive decline, nor have they been developed for delirium specifically following CABG. The results of this meta-analysis can provide a shortlist of risk and protective factors that should be considered in future research for the modeling of prediction tools. Specifically, results should be considered when modifying or developing tools related to post-CABG cognitive outcomes, as the operative process differs from other surgeries (eg, the use of CPB). Similar risk and protective factors may be applicable to other surgery types (cardiac and noncardiac); however, these factors cannot be ascertained from the current meta-analysis. The development of CABG-specific tools (delirium and cognitive decline) may lead to better prognosis, because of earlier identification and risk reduction strategies.

Delirium has been said to be preventable in up to 40% of cases.[9] Recent editorials[37,38] have highlighted

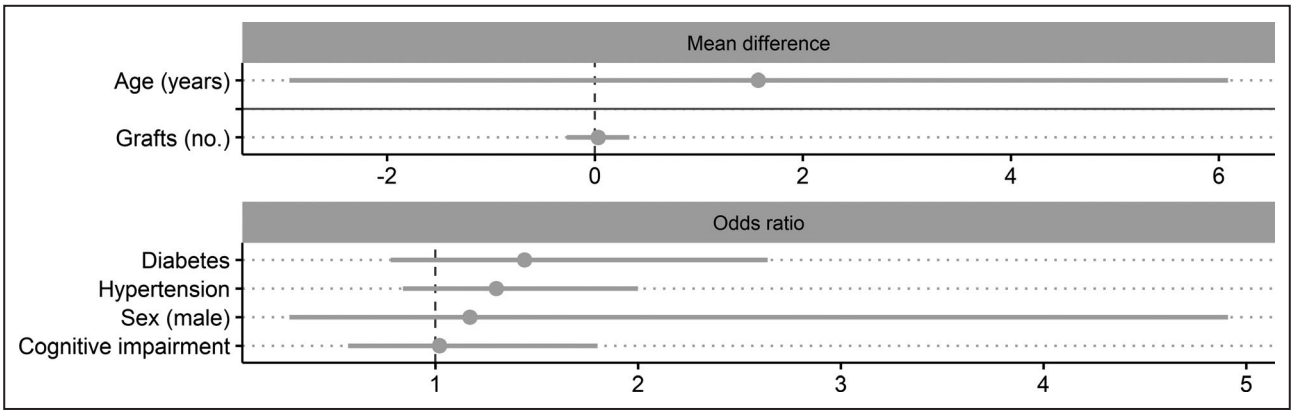

Figure 5. Forest plots of pooled estimates for risk or protective factors of post–coronary artery bypass grafting long-term cognitive decline.
Factors grouped according to the primary pooled estimate of the analysis (mean difference [MD], odds ratio, or standardized MD [SMD]), where solid gray horizontal lines indicate separation of preoperative, intraoperative, and postoperative factors and dashed gray vertical lines divide protective (left side) and risk (right side) factor estimates. The pooled estimates are ordered by the common calculated effect size (SMD) from largest to smallest (largest at the top). Estimates that are black represent statistically significant factors; those that are gray did not reach statistical significance. The scale for all continuous variables (MD and SMD plots) is listed within each factor name.

the importance of decreasing the incidence of delirium and cognitive decline to decrease patient and economic burden. In this meta-analysis, modifiable risk factors, such as the presence of preoperative depression, diabetes mellitus, and hypertension, were found to increase the risk (ORs, 1.44—3.42) for both delirium and cognitive decline acutely post-CABG. Future research should investigate the effectiveness of implementing preoperative management strategies of these factors on cognitive outcomes (delirium and cognitive decline) post-CABG. The presence of cognitive impairment resulted in over a 4-fold increase in risk of developing post-CABG delirium. Cognition is known to be modifiable through cognitive training in older populations, including those presenting with heart failure,[39–41] and therefore may be a viable preoperative target of intervention.[42]

In this meta-analysis, preoperative depression moderately (moderate effect sizes) increased the risk of delirium (OR, 2.49), acute cognitive decline (OR, 3.42), and midterm cognitive decline (OR, 2.50) post-CABG. In addition, a higher preoperative depression score revealed moderate to large (SMD, 0.50–0.86) increases in the risk of developing acute and midterm cognitive decline post-CABG, yet these analyses were not statistically significant, possibly because of high heterogeneity (I^2, 93.32–96.08; τ^2, 0.92–1.75). Depression in late life is known to occur concurrently with cognitive impairment and can hasten the onset of dementia.[43] The presence of vascular disease (indicative of undergoing CABG) is considered to have a strong link to the development of depression and dementia.[44] Therefore, the effects seen across the meta-analyses in relation to depression may not be independent from other factors. We endeavored to investigate the influence of these factors through meta-regression, yet it was not possible because of limited studies concurrently reporting data relating to depression, cognitive impairment, and vascular disease (eg, peripheral vascular disease, hypertension, and dyslipidemia).

The presence of delirium following CABG resulted in a near 5-fold increase (OR, 4.85, following sensitivity analysis) in risk of acute post-CABG cognitive decline (up to 1 month). This pooled effect size was not adjusted for any preoperative or intraoperative risk factors and, therefore, its independence cannot be assumed and should be interpreted with this in mind. It may be argued that in a short-term setting, this risk can be inflated because of the cognitive deficits of the delirium episode itself. However, the presence of delirium at this time (acute cognitive decline) is unlikely, as the assessment period for the 3 included studies was between days 7 and 9, whereas we know delirium typically resolves by day 5.[45–47] No studies reported data related to associations between post-CABG delirium and cognitive decline in the midterm and long-term. Delirium in late life (not specifically surgery related) is associated with doubling the rate of cognitive decline[37] and greatly increases the risk of incident dementia.[48] It should therefore be a priority for surgery-related research to investigate if post-CABG delirium has similar impact on long-term cognitive decline and even dementia incidence.

Only 5 studies assessed cognitive decline in the long-term (>12 months post-CABG), restricting risk or protective factors that could be extracted. These analyses revealed no significant results, likely because of smaller sample sizes and study variability. Cognitive

decline is seen in nearly 40% of patients 1 to 5 years post-CABG.[4] The presence of cognitive decline is associated with decreased quality of life, functional capacity, and increased rates of depression.[7] In addition, longer-term cognitive decline can lead to a loss of support networks, such as friends and neighbors, and can strain familial relationships.[49] Yet, from this meta-analysis, because of the lack of data at this time point, no possible risk reduction strategies can be suggested.

Meta-regressions generally found that age was not related to the pooled effect estimates. The 3 significant meta-regressions (delirium: ACC time and LOS in ICU; acute cognitive decline: CPB time) revealed a negative relationship with age, meaning as mean age of the study sample increased, the effect of the risk factor decreased. For example, as age increased, there was a smaller difference in ACC time between those who developed delirium and those who did not. These results could be influenced by older age increasing the risk of post-CABG complications (eg, AF, dialysis, reintubation, and stroke).[50] These complications are likely to increase LOS in the ICU, regardless of the presence of delirium or cognitive decline. In addition, because of increased complications, greater surgical precautions may be taken with older adults (eg, prioritizing dangerously stenosed arteries over complete revascularization of coronary arteries), which may decrease overall ACC and CPB time, minimizing group differences. Although these meta-regressions reached significance, most of the variance (≥50%) was not explained by age. Therefore, these risk factors should still be considered clinically meaningful.

This meta-analysis revealed multiple risk factors for post-CABG delirium and cognitive decline based on group-level data from included studies. Future research could identify clusters of risk factors by accessing patient-level data. This investigation could be guided by common risk factors identified in this meta-analysis, specifically depression, cognitive impairment, stroke history, diabetes mellitus, and vascular factors (hypertension and AF).

This is the only meta-analysis to investigate risk and protective factors for multiple outcomes (delirium and cognitive decline) across multiple time points in patients undergoing CABG. Although this study is not without limitations, the pooled sample size is >60 000 patients, allowing for greater generalizability of the results. The pooled results of this meta-analysis cannot be directly compared across time (for cognitive decline), as the same individuals are not represented at all time points. As only studies published in English were included, there may be a geographical bias. All extracted data within this meta-analysis were unadjusted for covariates, which does not permit investigation of independence. In addition, no temporal adjustments were conducted (eg, adjusting for preoperative depression within the intraoperative and postoperative factor meta-analyses). Therefore, caution should be used in interpreting study results, especially on the utility of identified intraoperative and postoperative risk factors in risk prediction tools. Within the literature, substantially fewer articles investigated midterm and long-term cognitive decline (than acute cognitive decline), which means that there may be important risk factors for these time periods that our approach could not identify. Many analyses conducted herein resulted in medium to high heterogeneity. Investigation into small study effect (publication bias) generally did not change the conclusions of this study (Figures S2, S4, and S6). The heterogeneity may be partially driven by the wide range of tests, screening tools, and methods of classifying delirium and cognitive decline within the included studies (Tables S8 and S9), although, notably, our subgroup analyses for delirium diagnosis (when using a diagnostic tool versus no tool) revealed no meaningful differences (Table S7).

CONCLUSIONS

There are many risk factors for delirium and cognitive decline (acutely and in the midterm) following CABG, which could be used in clinical practice, including the development or modification of a clinical prediction tool. Use of a CABG-specific risk tool could improve prognosis and, in turn, lead to better patient management. This is especially critical for delirium, as it is severely underrecognized and has serious outcomes.[9] To improve prediction ability of these risk tools, future development could also integrate the results of functional neuroimaging (eg, electroencephalography) and biomarker research, related to CABG.

The most clinically meaningful finding from this meta-analysis was the identification of modifiable preoperative risk factors for delirium and cognitive decline, of depression, diabetes mellitus, hypertension, and cognitive impairment. Improving the management of depression, diabetes mellitus, and hypertension in a preoperative setting may result in reductions in incident delirium and cognitive decline post-CABG. Targeting cognitive impairment through cognitive training interventions also has potential. Even if these are small reductions in incidence rates, they will have great impact at scale. Future work should investigate if we can target modifiable risk factors to reduce the incidence of delirium and cognitive decline post-CABG.

ARTICLE INFORMATION

Received June 25, 2020; accepted October 6, 2020.

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Acknowledgments

The authors would like to acknowledge and thank Monique Boord, who was involved in the screening of articles from the original search, before being updated for this meta-analysis.

Sources of Funding

D. Greaves is supported by the Australian Government Research Training Program Scholarship. Dr Keage is supported by a National Health and Medical Research Council Boosting Dementia Research Leadership Fellowship (GNT1135676) and the National Heart Foundation of Australia Vanguard Grant (101758–VG 2017). Dr Psaltis is supported by a National Heart Foundation of Australia Future Leader Fellowship (FLF100412) and a National Health and Medical Research Council Career Development Fellowship (CDF1161506). Dr Davis is supported by a Wellcome Trust Intermediate Clinical Fellowship (WT107467). Dr Lampit is supported by a National Health and Medical Research Council–Australian Research Council Dementia Research Development Fellowship (GNT1108520). Dr Smith is supported by a National Health and Medical Research Council–Australian Research Council Dementia Research Development Fellowship (GNT1097397). This project was supported by a National Heart Foundation of Australia Vanguard Grant (101758–VG 2017).

Disclosures

None.

Supplementary Material

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SUPPLEMENTAL MATERIAL

Data S1.

Quality Assessment Tool

Critical Appraisal Checklist for Cohort Studies & Studies Reporting Prevalence Data

This checklist and scoring instructions, was developed for the purpose of our meta-analysis using checklists created by the Joanna Briggs Institute [21, 22].

2 points: Sufficiently fulfilled

1 point: Partially fulfilled or unclear

0 points: Unfulfilled or not reported

	2	1	0
1. Were the study participants and the setting described in detail (i.e., sample size, sex proportion, age, recruitment hospital)?			
2. Were valid and reliable methods used for the identification of the condition (i.e., cognitive decline or delirium)?*			
3. Was the condition measured in a standard, reliable way for all participants (i.e., were the assessors who administered the measures adequately trained)? If there was more than one assessor, were they similar in ability/experience?*			
4. Were appropriate procedures in place to minimise attrition?			
5. Was the follow-up time reported?			
6. Was follow up complete, and if not, were the reasons to loss to follow-up described (i.e., was there a clear and justifiable description of why participants dropped out or were excluded from the analysis)?			
Notes:			

*For studies that reported data for more than one outcome (i.e., cognitive impairment and delirium) the point scheme was relative to all outcomes. That is, a study would only score 2 on these items if all outcomes/conditions were identified using valid and reliable tests (item 2), in a valid and reliable manner (item 3).

Overall Appraisal Grade: /12

Scoring Instructions

1. **Were the study participants and the setting described in detail (i.e., sample size, sex proportion, age, recruitment hospital)?**

The study sample should be described in sufficient detail so that other researchers can determine if it is comparable to the population of interest to them. That is, did the researchers provide details on sample size, sex proportion, age and hospital recruited from for either the total sample at baseline, or the sample of participants included in the analyses?

- 2 = All details reported
- 1 = Some details reported
- 0 = No details reported

2. Were valid and reliable methods used for the identification of the condition (i.e., cognitive impairment or delirium)?

Here we are looking for measurement or classification bias. Many health problems are not easily diagnosed or defined and some measures may not be capable of including or excluding appropriate levels or stages of the health problem. If the outcomes were assessed based on existing definitions or diagnostic criteria, then the answer to this question is likely to be yes. If the outcomes were assessed using observer reported, or self-reported scales, the risk of over- or under-reporting is increased, and objectivity is compromised. Importantly, determine if the measurement tools used were validated instruments as this has a significant impact on outcome assessment validity.

Studies that reported only delirium data were assigned 2 points for this item if they used a standardized cognition or delirium assessment, and 1 point if they used a recognized criteria or guidelines (e.g., the Society of Thoracic Surgeons (STS) definition or The Diagnostic and Statistical Manual of Mental Disorders criteria.

- 2 = All measures were standardized and validated
- 1 = Some measures were standardized and validated
- 0 = No measures were standardized and validated

3. Was the condition measured in a standard, reliable way for all participants (i.e., were the assessors who administered the measures adequately trained)? If there was more than one assessor, were they similar in ability/experience?

Were those involved in collecting data trained or educated in the use of the instrument/s? If there was more than one data collector, were they similar in terms of level of education, and clinical or research experience. Overall, was the condition measured in the same way for all participants?

- 2 = The paper states that the assessor or assessors were trained. If the assessors were stated to be psychologists, neuropsychologists or psychometrists it was assumed they were adequately trained.
- 1 = Researchers mention that the tests were administered by assessors/investigators but do not mention their experience or training
- 0 = No clear statement of who conducted the assessments

4. Were appropriate procedures in place to minimize attrition?

Appropriate measures for minimizing attrition are systematic contact strategies (e.g., contacting participants three times; by letter, phone and email). A procedure would be considered inappropriate if it was not systematic (e.g., letting participants contact them, and therefore relying on their motivation).

If there was only one follow-up time that was <10 days and a strategy for minimizing attrition was not mentioned, the study was still assigned 2 points as the strategy was assumed not to be necessary (i.e., the patients were still in hospital). Also, studies that reported only delirium data were assigned 2 points using this same rationale, as the patients are assumed to still be in hospital during the delirium assessments.

- 2 = Studies that utilized a systematic contact strategy that was explicit and would be thought to lead to greater retention at follow-up, or N/A.
- 1 = Procedure mentioned (e.g., called participants) but not clear if the contact process was thorough
- 0 = No strategy mentioned

5. Was the follow up time reported?

The time points for follow-up assessments should be clearly stated. Studies with multiple follow-up assessments were assigned 2 points for this item if all follow-up time points were clearly and precisely stated, 1 point if some of the time-points were clearly and precisely stated, or all time-points were stated, but inexactly (e.g., “6 weeks”).

- 2 = When the participant were likely to be out of hospital at time of assessment, studies that reported a mean and SD of the number of days/months for all follow-ups were assigned 2 points. If the follow-up time was likely to be when the patient was in hospital (e.g., 3 days) it was assumed that this was a precise value and the study was awarded 2 points.
- 1 = Studies that report a vague/inexact follow-up time (e.g., 6 months), which is likely to have varied between participants, for some or all follow-ups
- 0 = Follow-up time not reported

6. Was follow up complete, and if not, were the reasons to loss to follow up described?

Reporting of efforts to follow up participants that dropped out may be regarded as an indicator of a well conducted study. Therefore, this item is scored depending on whether a clear and justifiable description of why people were left out, excluded, dropped out, etc. was provided.

- 2 = Follow-up was complete, or if not, there was a statement of how many participants dropped out and for what reasons
- 1 = There is an unclear statement outlining reasons for drop-out and how many participants for each reason (i.e., reasons for drop-out are given but not how many participants for each reason)
- 0 = There was drop out but no mention of reasons why

Table S1. Pooled estimates and corresponding effect size (OR, MD, SMD) for pre, intra, and post-operative variables for delirium (1-7 days) post-CABG.

Variable	Pooled Estimate				Heterogeneity		Common effect size
	k (n)	OR/MD†/ SMD‡	95%CI	p value	I^2	Tau^2	SMD
Pre-Operative (Categorical)							
Alcoholism	6 (994)	0.90	0.50—1.62	.721	13.45	0.08	0.06
Arrhythmia, incl. AF	15 (31746)	2.07	1.70—2.51	<.001	25.35	0.03	0.40
BMI >28 (including >30)	7 (16297)	1.16	0.74—1.80	.516	56.28	0.17	0.08
BMI ≥30 only	5 (1786)	1.57	1.05—2.37	.030	0	0	0.25
Cognitive impairment	7 (1039)	4.17	2.75—6.33	<.001	0	0	0.79
Depression	4 (580)	2.49	1.29—4.81	.006	29.16	0.13	0.50
Diabetes	30 (48465)	1.49	1.39—1.60	<.001	0	0	0.22
Dyslipidemia/Hyperlipidemia	13 (6449)	0.89	0.63—1.25	.502	51.79	0.18	0.06
Education>12years/high school	4 (567)	0.66	0.41—1.06	.088	0	0	0.23
Hypertension	27 (38362)	1.44	1.21—1.70	<.001	52.54	0.07	0.20
Sex (male)	35 (37851)	0.90	0.75—1.08	.263	53.35	0.10	0.06
Kidney injury	14 (25264)	1.94	1.50—2.52	<.001	27.49	0.05	0.37
Previous MI <30 days	5 (926)	1.54	0.90—2.65	.116	37.82	0.14	0.24
Previous MI history/ever	11 (10662)	1.17	0.98—1.39	.075	0	0	0.09
Previous stroke, TIA, CVA	15 (27127)	2.55	1.94—3.35	<.001	44.42	0.10	0.52
PVD	14 (16340)	1.98	1.48—2.64	<.001	38.76	0.09	0.38
Smoking current	14 (17825)	1.19	0.84—1.69	.321	72.37	0.24	0.10
Smoking current/history	21 (25813)	1.15	0.94—1.42	.174	56.81	0.09	0.08
Pre-Operative (Continuous)							
Age (years) *	28 (9303)	4.14†	2.95—5.34	<.001	78.61	7.14	0.49

BMI	5 (2143)	0.03†	-0.46—0.51	.915	0	0	0.01
Cognition: All tests	9 (887)	-0.58‡	-0.78— -0.37	<.001	34.11	0.03	0.58
Cognition: MMSE only	7 (621)	-1.14†	-1.91— -0.36	.004	77.72	0.68	0.52
Depression GDS	2 (233)	0.75†	-0.15—1.65	.101	0	0	0.30
Education (years)	6 (665)	-0.93†	-1.65— -0.20	.012	19.31	0.16	0.25
EuroSCORE *	10 (11199)	1.35†	0.58—2.12	.001	96.10	1.38	0.51
LVEF (%)	11 (3308)	1.25†	-0.69—3.19	.208	79.34	7.97	0.13
Intra-Operative (Continuous)							
ACC time (mins)	16 (7488)	5.97†	0.62— 11.32	.029	90.65	101.19	0.29
CPB time (mins)	21 (12412)	7.41†	4.03—10.78	<.001	51.93	25.72	0.25
Duration of surgery (mins)	13 (3218)	20.53†	8.67—32.38	.001	75.96	325.89	0.35
Intubation time (hours)	11 (6693)	6.82†	2.44—11.20	.002	98.40	52.26	0.75
Number of grafts	8 (2731)	0.11†	-0.02—0.24	.084	34.30	0.01	0.13
Post-Operative (Categorical)							
Arrhythmia, incl. AF	16 (8809)	3.53	2.41—5.16	<.001	71.51	0.37	0.70
Post-Operative (Continuous)							
LOS in ICU (days)	14 (7177)	2.22†	1.32—3.13	<.001	97.84	2.69	1.20

Note: * indicates potential small-study effect or publication bias, see (**Figure S2)** and for forest plots **(Figure S1)**. Symbols following pooled estimates denote different effect sizes: indicating OR (no symbol), MD† and SMD‡. ACC= aortic cross-clamp, AF= atrial fibrillation, BMI= body mass index, CPB= cardiopulmonary bypass, CVA= cerebrovascular attack, GDS= geriatric depression scale, ICU= intensive care unit, k= number of estimates (number of studies), LOS= length of stay, LVEF= left ventricular ejection fraction, , MD= mean difference, MI= myocardial infarction, MMSE= mini mental state examination, n= pooled sample size, OR= odds ratio, PVD= peripheral vascular disease, SMD= standardized mean difference and TIA= transient ischemic attack..

Table S2. Pooled estimates and corresponding effect size (OR, MD, SMD) for pre, intra, and post-operative variables for acute cognitive decline (immediately up to 1-month) post-CABG.

Variable	Pooled Estimate				Heterogeneity		Effect size
	k (n)	OR/MD†/ SMD‡	95%CI	p value	I^2	Tau^2	SMD
Pre-Operative (Categorical)							
Arrhythmia, incl. AF	7 (945)	1.24	0.76—2.04	.389	0	0	0.12
Cognitive impairment	4 (714)	1.11	0.71—1.73	.653	0	0	0.06
Depression	2 (330)	3.42	1.12—10.46	.031	61.53	0.40	0.68
Diabetes	17 (3008)	1.44	1.21—1.72	<.001	4.18	0.01	0.20
Dyslipidemia/Hyperlipidemia	6 (836)	1.16	0.74—1.84	.512	35.86	0.11	0.08
Hypertension	15 (2012)	1.91	1.45—2.53	<.001	34.10	0.09	0.36
Sex (male)	18 (2299)	1.03	0.82—1.29	.824	0	0	0.01
Kidney injury	4 (749)	1.21	0.40—3.72	.735	54.22	0.67	0.11
Previous MI <90 days	3 (418)	1.12	0.59—2.16	.724	0	0	0.07
Previous MI history/ever	7 (1011)	1.16	0.83—1.63	.394	25.17	0.05	0.08
Previous stroke, TIA, CVA	5 (745)	2.44	1.47—4.04	.001	0	0	0.49
PVD	4 (856)	1.09	0.42—2.83	.865	57.17	0.50	0.05
Smoking current/history	9 (1400)	1.03	0.64—1.66	.892	68.09	0.31	0.02
Pre-Operative (Continuous)							
Age (years) *	22 (2761)	2.69†	1.20—4.18	<.001	92.85	9.17	0.53
BMI	5 (906)	-0.20†	-0.25— -0.14	<.001	0	0	0.10
Cognition: All tests	3 (151)	0.23‡	-0.43—0.88	.492	69.56	0.23	0.23
Cognition: MMSE only	2 (116)	0.28†	-1.39—1.96	.740	82.66	1.21	0.24
Depression: All tests	4 (448)	0.50‡	-0.48—1.48	.316	93.32	0.92	0.50

Education (years)	6 (534)	-0.44†	-1.40—0.53	.377	49.52	0.65	0.11
EuroSCORE	4 (582)	0.74†	0.48—1.01	<.001	0	0	0.46
LVEF %	9 (1126)	-1.97†	-4.21—0.28	.086	72.49	8.28	0.21
Intra-Operative (Continuous)							
ACC time (mins)	7 (867)	-1.34†	-5.91—3.23	.566	61.81	20.52	0.07
CPB time (mins)	13 (1699)	3.39†	-0.10—6.88	.057	59.34	16.87	0.15
Duration of surgery (mins)	6 (723)	13.52†	3.67—23.38	.007	21.27	32.28	0.26
Intubation time (hours)	6 (1193)	1.95†	1.37—2.52	<.001	28.29	0.15	0.82
Number of grafts	7 (1113)	0.03†	-0.03—0.09	.400	7.50	0	0.10
Total microemboli	4 (771)	0.16‡	-0.07—0.38	.167	45.77	0.02	0.16
Post-Operative (Categorical)							
Arrhythmia, incl. AF	6 (1045)	1.40	1.01—1.94	.042	0	0	0.19
Delirium	3 (355)	6.15	2.32—16.27	<.001	6.32	0.07	1.00
Without outlier	2 (308)	4.85	1.89—12.45	.001	0	0	0.87
Post-Operative (Continuous)							
LOS in ICU (days)	7 (1055)	0.29†	0.04—0.55	.025	77.82	0.08	0.77

Note: * indicates potential small-study effect or publication bias, see (**Figure S4)** and for forest plots **(Figure S3)**. Symbols following pooled estimates denote different effect sizes: indicating OR (no symbol), MD† and SMD‡. ACC= aortic cross-clamp, AF= atrial fibrillation, BMI= body mass index, CPB= cardiopulmonary bypass, CVA= cerebrovascular attack, ICU= intensive care unit, k= number of estimates (number of studies), LOS= length of stay, LVEF= left ventricular ejection fraction, , MD= mean difference, MI= myocardial infarction, n= pooled sample size, OR= odds ratio, PVD= peripheral vascular disease, SMD= standardized mean difference and TIA= transient ischemic attack

Table S3. Pooled estimates and corresponding effect size (OR, MD, SMD) for pre, intra, and post-operative variables for cognitive decline in the mid-term (1 to 6-months) post-CABG.

Variable	Pooled Estimate				Heterogeneity		Effect size
	k (n)	OR/MD†/ SMD‡	95%CI	p value	I^2	Tau^2	SMD
Pre-Operative (Categorical)							
Depression	2 (471)	2.50	1.28—4.88	.007	0	0	0.51
Diabetes	10 (2046)	1.54	0.98—2.40	.059	61.33	0.28	0.24
Sex (male)	12 (2599)	1.01	0.82—1.23	.965	0	0	0.00
Hypertension	12 (2350)	0.89	0.59—1.32	.558	69.32	0.31	0.07
Previous MI history/ever	3 (975)	0.88	0.57—1.37	.580	41.32	0.06	0.07
Previous stroke, TIA, CVA	2 (761)	0.83	0.26—2.63	.748	0	0	0.11
PVD	2 (761)	0.71	0.41—1.21	.209	0	0	0.19
Smoking (current)	5 (1006)	1.00	0.73—1.37	.983	0	0	0.00
Pre-Operative (Continuous)							
Age (years)	12 (2093)	1.09†	-0.06—2.25	.063	29.21	1.12	0.13
Cognition: All tests	3 (855)	0.30‡	0.01—0.59	.041	68.84	0.04	0.30
Cognition: CI only	2 (795)	0.50†	-0.17—1.17	.146	89.28	0.21	0.43
Depression: All tests	3 (429)	0.86‡	-0.68—2.39	.273	96.08	1.75	0.86
Education (years)	5 (950)	0.13†	-0.57—0.83	.715	44.26	0.24	0.05
LVEF %	7 (1266)	0.61†	-0.63—1.86	.336	0	0	0.06
Intra-Operative (Continuous)							
ACC time (mins)	4 (890)	-1.29†	-4.35—1.76	.407	0	0	0.06
CPB time (mins)	7 (1266)	2.15†	-2.44—6.74	.359	28.63	10.41	0.06
Number of grafts	4 (1124)	-0.06†	-0.17—0.06	.358	0	0	0.06

Total microemboli	4 (542)	-0.46‡	-0.97—0.05	.076	51.03	0.12	0.46
Post-Operative (Continuous)							
LOS in ICU (days)	2 (100)	0.23†	-1.10—1.55	.736	88.27	0.80	0.33

Note: * indicates potential small-study effect or publication bias, see (**Figure S6)** and for forest plots **(Figure S5)**. Symbols following pooled estimates denote different effect sizes: indicating OR (no symbol), MD† and SMD‡. ACC= aortic cross-clamp, CI= cognitive index score, CPB= cardiopulmonary bypass, CVA= cerebrovascular attack, ICU= intensive care unit, k= number of estimates (number of studies), LOS= length of stay, LVEF= left ventricular ejection fraction, , MD= mean difference, MI= myocardial infarction, n= pooled sample size, OR= odds ratio, PVD= peripheral vascular disease, SMD= standardized mean difference and TIA= transient ischemic attack.

Table S4. **Pooled estimates and corresponding effect size (OR, MD, SMD) for pre, intra, and post-operative variables for cognitive decline in the long-term (12 to 15-months) post-CABG.**

Variable	Pooled Estimate				Heterogeneity		Effect size
	k (n)	OR/MD†/ SMD‡	95%CI	p value	I^2	Tau^2	SMD
Pre-Operative (Categorical)							
Cognitive impairment	2 (343)	1.02	0.57—1.80	.952	0	0	0.01
Diabetes	2 (504)	1.44	0.78—2.64	.245	0	0	0.20
Sex (male)	2 (301)	1.17	0.28—4.91	.830	28.63	0.49	0.09
Hypertension	2 (504)	1.30	0.84—2.00	.241	0	0	0.14
Pre-Operative (Continuous)							
Age (years)	2 (301)	1.57†	-2.94—6.09	.495	46.03	5.30	0.17
Intra-Operative (Continuous)							
Number of grafts	2 (301)	0.03†	-0.27—0.33	.832	0	0	0.04

Note: * indicates potential small-study effect or publication bias. See **(Figure S7)** for forest plots. Symbols following pooled estimates denote different effect sizes: indicating OR (no symbol), MD† and SMD‡. k= number of estimates (number of studies), MD= mean difference, n= pooled sample size, OR= odds ratio, SMD= standardized mean difference.

Table S5. Excluded references from full-text screening with associated reason.

Reference	Exclusion Reason
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Wu M, Liang Y, Dai Z, Wang S. Perioperative dexmedetomidine reduces delirium after cardiac surgery: A meta-analysis of randomized controlled trials. Journal of Clinical Anesthesia. 2018;50:33-42	other
Yuan SM, Lin H. Postoperative cognitive dysfunction after coronary artery bypass grafting. Brazilian Journal of Cardiovascular Surgery. 2019;34:76-84	other
Maggio M, Nicolini F, Cattabiani C, Beghi C, Gherli T, Schwartz RS, Valenti G, Ceda GP. Effects of testosterone supplementation on clinical and rehabilitative outcomes in older men undergoing on-pump cabg. Contemporary Clinical Trials. 2012;33:730-738	protocol paper
Uva MS, Matias F, Cavaco S, Magalhaes MP. Rationale, design and methodology for a prospective randomized study of graft patency in off-pump and on-pump multi-vessel coronary artery bypass surgery (promiss) using multidetector computed tomography. Trials. 2008;9:44	protocol paper
Whitlock R, Teoh K, Vincent J, Devereaux PJ, Lamy A, Paparella D, Zuo Y, Sessler DI, Shah P, Villar JC, et al. Rationale and design of the steroids in cardiac surgery trial. American Heart Journal. 2014;167:660-665	protocol paper

Table S6. **Demographic data, presence in statistical analyses and quality assessment scores for included studies within risk and protective factor meta-analyses for delirium and cognitive-decline post CABG.**

Ref. No.	Lead Author, Year	Total No. of Patients	Total No. of Males	Mean/Median Age	SD/Range/IQR of Age	Cognitive Decline				QA (/12)
						C1	C2	C3	Del	
[51]	Al Tmimi, 2016	92	78	67	R: 46-86	-	-	-	x	12
[52]	Baba, 2007	218	152	71.25	5.5	x	-	-	-	10
[53]	Boodhwani, 2006*	448	390	68.3	0.4	x	-	-	-	12
[54]	Braekken, 1998	14	14	N/A	N/A	-	x	-	-	7
[55]	Bucerius, 2005	9682	7500	N/A	N/A	-	-	-	x	6
[56]	Caldas 2019	67	51	64.3	9.5	-	-	-	x	12
[57]	Chen, 2017	136	104	60.85	7.76	-	-	-	x	10
[58]	Christiansen, 2016	8	7	63.38	10.69	x	-	-	-	7
[59]	Coffey, 1983	1669	1384	52.15	SEM: 8	-	-	-	x	7
[60]	Colak, 2015	190	148	62.66	7.96	x	-	-	-	7
[61]	Cumurcu, 2008	50	37	59.62	10.66	-	-	-	x	9

Ref. No.	Lead Author, Year	Total No. of Patients	Total No. of Males	Mean/Median Age	SD/Range/IQR of Age	Cognitive Decline				QA (/12)
						C1	C2	C3	Del	
[62]	deTournay-Jette, 2011	61	51	70.39	4.69	x	x	-	-	10
[63]	Dieleman, 2009	281	192	61.3	9	-	x	x	-	10
[64]	Djaiani, 2003	417	293	60.34	10	-	x	-	-	9
[65]	Dong, 2014	108	83	63	7.9	x	-	-	x	10
[66]	Eriksson, 2002	52	40	70.27	5.53	-	-	-	x	12
[67]	Goto, 2000	177	117	70.26	4.99	x	-	-	-	11
[68]	Gottesman, 2010	5052	3682	63.92	N/A	-	-	-	x	7
[69]	Hall, 1999	35	27	65.9	9.1	x	-	-	-	12
[70]	Harmon, 2004†	35	28	61.7	7.51	x	x	-	-	9
[71]	Harmon, 2005†	36	30	64.07	N/A	x	-	-	-	12
[72]	Humphreys, 2016	173	148	63.47	10.1	-	-	-	x	7
[73]	Kadoi, 2001‡	185	138	N/A	N/A	x	x	-	-	6
[74]	Kadoi, 2002§	60	53	62.75	8.5	-	x	-	-	9

Ref. No.	Lead Author, Year	Total No. of Patients	Total No. of Males	Mean/Median Age	SD/Range/IQR of Age	Cognitive Decline				QA (/12)
						C1	C2	C3	Del	
[75]	Kadoi, 2003‡	180	136	65	9	-	x	-	-	9
[76]	Kadoi, 2005§	280	210	65.07	9.93	x	x	-	-	9
[77]	Kadoi, 2007§	106	53	62.55	10.45	-	x	-	-	9
[78]	Kadoi, 2011 (a)§	124	89	61.29	5.39	x	-	-	-	12
[79]	Kadoi, 2011 (b)§	90	68	65	9	x	x	-	-	9
[80]	Kazmierski, 2014 (a)‖¶	113	90	64	R: 59-71	-	-	-	x	12
[81]	Kazmierski, 2014 (b)¶	102	N/A	N/A	N/A	-	-	-	x	12
[82]	Kazmierski, 2014 (c) ‖¶	113	90	Med: 64	R: 59-71	-	-	-	x	12
[83]	Khan, 2014	735	577	55.64	9.65	-	-	-	x	10
[84]	Khatri, 1999	170	127	61	10	-	x	-	-	7
[85]	Kok, 2017	57	N/A	N/A	N/A	-	-	x	-	5
[86]	Kumpaitiene, 2019	59	34	66.49	8.04	x	-	-	-	11
[87]	Lachmann, 2018	252	180	61.0	9.1	-	-	x	-	8

Ref. No.	Lead Author, Year	Total No. of Patients	Total No. of Males	Mean/Median Age	SD/Range/IQR of Age	Cognitive Decline				QA (/12)
						C1	C2	C3	Del	
[88]	Leenders, 2018	357	304	66.20	8.84	-	-	-	x	9
[89]	Li, 2015	38	34	62.4	11.8	-	-	-	x	10
[90]	Liu, 2009	227	209	60	8	x	x	-	-	9
[91]	Loponen, 2008	300	237	66.17	8.89	-	-	-	x	8
[92]	Mardani, 2012	196	183	61.84	11.83	-	-	-	x	9
[93]	Mariscalco, 2012	4079	3220	67.8	9.2	-	-	-	x	12
[94]	Martin, 2010[#]	14262	10912	N/A	N/A	-	-	-	x	5
[95]	Martin, 2012[#]	8474	6391	N/A	N/A	-	-	-	x	7
[96]	Mathew, 2006[**]	121	N/A	N/A	N/A	-	x	-	-	8
[97]	Mathew, 2007[**]	677	471	61.7	10.5	-	x	-	-	9
[98]	Miyazaki, 2011	768	N/A	N/A	N/A	-	-	-	x	6
[99]	Mu, 2010	243	200	61	8.3	-	-	-	x	12
[100]	Mu, 2013	166	141	60	8.9	x	-	-	-	12

Ref. No.	Lead Author, Year	Total No. of Patients	Total No. of Males	Mean/Median Age	SD/Range/IQR of Age	Cognitive Decline				QA (/12)
						C1	C2	C3	Del	
[101]	Newman, 1987	67	62	55.0	7.8	x	-	-	-	10
[102]	Nikolic, 2012	370	271	N/A	N/A	-	-	-	x	7
[103]	Norkiene, 2007	1367	1035	64.98	9.14	-	-	-	x	10
[104]	Norkiene, 2011	127	103	60.91	7.24	x	-	-	-	11
[105]	Oh, 2008	46	36	63	5.5	x	-	-	-	11
[106]	Oh, 2017	292	211	N/A	N/A	-	-	-	x	10
[107]	Oldham, 2015	102	76	65.1	9	-	-	-	x	11
[108]	Oldham, 2019	131	96	65.8	9.2	-	-	-	x	12
[109]	Omiya, 2015	88	N/A	69	7	-	-	-	x	10
[110]	Otomo, 2013	153	109	72	7	-	-	-	x	12
[111]	Palmbergen, 2012	642	452	68.5	9.79	-	-	-	x	11
[112]	Plaschke, 2010	114	89	68.98	8.39	-	-	-	x	12
[113]	Reents, 2002	47	41	60.4	8	x	-	-	-	10

Ref. No.	Lead Author, Year	Total No. of Patients	Total No. of Males	Mean/Median Age	SD/Range/IQR of Age	Cognitive Decline				QA (/12)
						C1	C2	C3	Del	
[114]	Restrepo, 2002	13	10	65	9	x	-	-	-	10
[115]	Ringaitiene, 2015	99	70	67.6	7.78	-	-	-	x	10
[116]	Robson, 2000	124	N/A	59.44	9.25	-	x	-	-	7
[117]	Rodriguez, 2010	356	325	63	9	x	x	-	-	5
[118]	Rolfson, 1999 (a)††	75	59	N/A	N/A	-	-	-	x	12
[119]	Rolfson, 1999 (b)††	71	57	71	N/A	-	-	-	x	11
[120]	Royse, 2000	47	37	64.22	1.78	x	x	-	-	8
[121]	Royse, 2011	180	153	62.79	10.5	-	-	-	x	10
[122]	Rudolph, 2005	36	36	68.8	9.2	-	-	-	x	12
[123]	Rudolph, 2006‡‡	80	62	74.9	6.2	-	-	-	x	11
[124]	Rudolph, 2009‡‡	68	67	70.7	8.2	-	-	-	x	12
[125]	Sahan, 2018	40	34	65.85	6.02	x	x	-	-	9
[6]	Santos, 2004	220	142	70.71	5.48	-	-	-	x	11

Ref. No.	Lead Author, Year	Total No. of Patients	Total No. of Males	Mean/Median Age	SD/Range/IQR of Age	Cognitive Decline				QA (/12)
						C1	C2	C3	Del	
[126]	Scott, 2002	103	84	64.77	1.3	x	-	-	-	12
[127]	Sevuk, 2015	200	128	70.65	3.95	-	-	-	x	12
[128]	Siepe, 2011	92	74	66.87	8.98	-	-	-	x	12
[129]	Silbert, 2006[§§]	326	252	67.9	7.6	x	x	-	-	9
[130]	Silbert, 2008[§§]	264	203	67.8	7.7	x	-	x	-	7
[131]	Slater, 2009	240	201	64.74	9.96	x	x	-	-	7
[132]	Smith, 1986	55	51	54.7	R: 37-74	x	-	-	-	9
[133]	Smith, 2000	381	308	N/A	N/A	-	x	-	-	8
[134]	Stump, 1996	167	138	61	10	x	-	-	-	8
[135]	Subramaniam, 2019	120	101	Med: 69	IQR: 63-76	-	-	-	x	12
[136]	Suksompong, 2002	110	110	61.95	7.58	x	-	-	-	10
[137]	Swaminathan, 2002	282	201	61	10.44	-	x	-	-	8
[138]	Sylivris, 1998	41	31	69.8	6.9	x	-	-	-	10

Ref. No.	Lead Author, Year	Total No. of Patients	Total No. of Males	Mean/Median Age	SD/Range/IQR of Age	Cognitive Decline				QA (/12)
						C1	C2	C3	Del	
[139]	Tagarakis, 2007	137	99	69.55	7.63	-	-	-	x	7
[140]	Tamura, 2019	88	76	69.3	2.5	-	-	-	x	10
[141]	Toeg, 2013[*]	652	576	64.37	9	x	-	-	-	10
[142]	Trubnikova, 2014	101	101	56.6	5.85	x	-	x	-	4
[143]	Tully, 2010	158	125	64.68	10.56	-	-	-	x	10
[144]	van Dijk, 2004	281	191	61.2	9.0	-	x	-	-	7
[145]	Yilmaz, 2016	137	105	61.02	7.83	-	-	-	x	10
[146]	Zhang, 2015	249	197	62.9	9.34	-	-	-	x	12

†, ‡, §, ¶, ‡‡ Suspected overlap of samples; *, |, #, **, ††, §§ Known overlap of sample

Ref No. = supplementary reference list number; C1= acute cognitive decline (immediately post-operatively up to 1-month); C2= mid-term cognitive decline (1 to 6-months post-operatively); C3= long-term cognitive decline (12 to 15-months post-operatively). Del = delirium; Med = median; IQR= inter quartile range; QA = quality assessment; SD = standard deviation.

Table S7. Subgroup meta-analyses of diagnostic tool, for pre, intra and post-operative variables for the development of delirium following CABG.

Variable	Delirium Diagnosis	Pooled Estimate k (n)	OR/MD*/ SMD†	95%CI	p value	Heterogeneity I^2	Heterogeneity Tau^2
Pre-Operative (Categorical)							
Alcoholism	No Tool	Insufficient Data					
	Tool	5 (694)	0.77	0.46—1.29	.317	0	0
Arrhythmia, incl. AF	No Tool	7 (31550)	2.05	1.77—2.37	<.001	0	0
	Tool	8 (1252)	1.91	1.15—3.16	<.001	45.09	0.21
BMI >28 (including >30)	No Tool	2 (15629)	0.86	0.51—1.47	.587	62.68	0.10
	Tool	5 (668)	1.46	0.89—2.41	.133	11.02	0.04
BMI ≥30 only	No Tool	Insufficient Data					
	Tool	4 (419)	1.85	1.09—3.14	.023	0.00	0
Cognitive Impairment	No Tool	Insufficient Data					
	Tool	6 (790)	4.11	2.59—6.53	<.001	0	0
Depression	No Tool	2 (378)	2.06	0.75—5.67	.162	66.06	0.35
	Tool	2 (202)	4.14	1.37—12.51	.012	0	0
Diabetes	No Tool	12 (42736)	1.46	1.33—1.60	<.001	13.34	0
	Tool	18 (5419)	1.57	1.32—1.87	<.001	0	0
Dyslipidaemia/Hyperlipidaemia	No Tool	4 (2283)	0.70	.033—1.49	.355	66.26	0.39
	Tool	9 (4166)	0.99	0.67—1.45	.943	46.78	0.14
Education>12years/high school	No Tool	Insufficient Data					
	Tool	3 (347)	0.78	0.45—1.35	.374	0	0
Hypertension	No Tool	11 (33054)	1.65	1.38—1.98	<.001	50.98	0.04
	Tool	16 (5308)	1.18	0.88—1.57	.267	38.51	0.12
Sex (male)	No Tool	10 (30814)	1.10	0.87—1.40	.415	62.44	0.06
	Tool	25 (6639)	0.78	0.60—1.01	.056	41.95	0.16
Kidney injury	No Tool	6 (23602)	1.91	1.40—2.60	<.001	36.40	0.05

Variable	Delirium Diagnosis	Pooled Estimate k (n)	OR/MD*/ SMD†	95%CI	p value	Heterogeneity I^2	Heterogeneity Tau^2
	Tool	8 (1662)	1.96	1.18—3.25	.009	29.13	0.14
Previous MI <30 days	No Tool	3 (101)	1.98	0.88—4.49	.100	52.09	0.27
	Tool	2 (200)	1.04	0.56—1.93	.909	0	0
Previous MI history/ever	No Tool	3 (6877)	1.04	0.72—1.51	.822	45.06	0.05
	Tool	8 (3785)	1.24	0.92—1.67	.160	0	0
Previous stroke, TIA, CVA	No Tool	6 (22297)	2.73	1.92—3.88	<.001	56.18	0.09
	Tool	9 (4830)	2.37	1.50—3.70	<.001	35.96	0.16
PVD	No Tool	4 (11604)	2.11	1.73—2.58	<.001	0.90	0
	Tool	10 (4736)	2.01	1.28—3.15	.003	49.82	0.24
Smoking current	No Tool	5 (16780)	1.19	1.07—3.53	.030	85.56	0.33
	Tool	9 (1045)	0.83	0.60—1.15	.265	17.36	0.04
Smoking current/history	No Tool	8 (24122)	1.41	1.04—1.92	.029	76.07	0.12
	Tool	13 (1691)	0.92	0.73—1.15	.458	0	0
Pre-Operative (Continuous)							
Age (years)	No Tool	8 (3118)	3.11*	1.50—4.72	<.001	51.30	2.31
	Tool	20 (6185)	4.52*	2.95—6.09	<.001	82.93	9.67
BMI	No Tool		Insufficient Data				
	Tool	4 (776)	0.023*	-0.6—0.65	.653	15.02	0.07
Cognition: All tests	No Tool		Insufficient Data				
	Tool	9 (887)	-0.58†	-0.78— -0.37	<.001	34.11	0.03
Cognition: MMSE only	No Tool		Insufficient Data				
	Tool	7 (621)	1.14*	-1.91— -0.36	.004	77.72	0.68
Depression GDS	No Tool		Insufficient Data				
	Tool	2 (233)	0.75*	-0.15—1.65	.101	0	0
Education (years)	No Tool		Insufficient Data				
	Tool	6 (665)	-0.93*	-1.65— -0.20	.012	19.31	0.16
EuroSCORE	No Tool	3 (1058)	3.06*	0.28— 5.83	0.31	95.87	5.71

Variable	Delirium Diagnosis	Pooled Estimate k (n)	OR/MD*/ SMD†	95%CI	p value	Heterogeneity I^2	Tau^2
	Tool	7 (10141)	0.65*	0.14—1.16	.012	89.23	0.37
LVEF (%)	No Tool	4 (2518)	1.91*	-1.94—5.77	.330	91.24	13.83
	Tool	7 (790)	0.82*	-1.24—2.89	.435	57.05	4.24
Intra-Operative (Continuous)							
ACC time (mins)	No Tool	7 (3026)	9.88*	-0.52— 20.29	.063	94.19	176.11
	Tool	9 (4462)	3.61*	-0.97—8.18	.123	75.77	34.07
CPB time (mins)	No Tool	8 (7693)	4.98*	2.33—7.63	<.001	0	0
	Tool	13 (4719)	7.91*	2.37—13.45	.005	60.91	52.60
Duration of surgery (mins)	No Tool	Insufficient Data					
	Tool	12 (1851)	19.66*	7.18—32.14	.002	77.61	342.16
Intubation time (hours)	No Tool	3 (2194)	7.391*	1.78—13.00	.010	94.02	22.48
	Tool	8 (4499)	6.62*	1.25—12.00	.016	98.50	57.31
Number of grafts	No Tool	3 (1863)	0.06*	-0.27—0.38	.738	58.79	0.05
	Tool	5 (868)	0.15*	0.04—0.27	.009	0	0
Post-Operative (Categorical)							
Arrhythmia, incl. AF	No Tool	7 (4423)	4.26	2.16—8.40	<.001	82.46	0.65
	Tool	9 (4386)	2.98	1.93—4.61	<.001	52.46	0.20
Post-Operative (Continuous)							
LOS in ICU (days)	No Tool	4 (2390)	3.39*	-0.16—6.94	.061	99.04	12.59
	Tool	10 (4787)	1.69*	1.06—2.31	<.001	94.03	0.86

Note: "Delirium Diagnosis" indicates analyses conducted by categorization of diagnostic method, where "No Tool" represents studies that did not utilize a specific instrument and "Tool" represents studies utilizing a standardized instrument e.g. Confusion Assessment Method (CAM) or the Delirium Rating Scale (DRS) to inform the reference standard. ACC= aortic cross-clamp, AF= atrial fibrillation, BMI= body mass index, CI= cognitive index score, CPB= cardiopulmonary bypass, CVA= cerebrovascular attack, GDS= geriatric depression scale, k= number of estimates (number of studies), LOS= length of stay, LVEF= left ventricular ejection fraction, MD= mean difference, MI= myocardial infarction, MMSE= mini mental state examination, n= pooled sample size, OR= odds ratio, PVD= peripheral vascular disease, SMD= standardised mean difference and TIA= transient ischemic attack. Symbols following pooled estimates denote different effect sizes: indicating OR (no symbol), MD* and SMD†.

Table S8. **Study specific information regarding instruments utilized and method of classification/diagnosis utilized.**

Reference No.	Lead Author, Year	Instruments	Definitions of Cognitive Decline and Delirium (Standardized Delirium Measurement Tool: Y/N)
[51]	Al Tmimi, 2016	Delirium: CAM or CAM-ICU	Delirium: Positive CAM/CAM-ICU score (Y)
[52]	Baba, 2007	Cognition: HDS, Kana pick-out test, digit symbol, digit span (forward & backward)	Cognition: 20% method
[53]	Boodhwani, 2006	Cognition: Total learning free recall, consistent long-term retrieval, long-term retrieval, long-term storage, delayed recall, digit span (forward & backward), trails A & B, grooved pegboard, symbol digit modalities, RAVLT, Buschke selective reminding, WMS-III/mental control	Cognition: 0.5 SD method
[54]	Braekken, 1998	Cognition: WAIS vocabulary, WAIS picture completion, RCPM, CVLT-L, CVLT-S, CVLT-L, serial digit learning, WMS drawing, trails A & B, letter cancellation task, WAIS	Cognition: 1 SD method

Reference No.	Lead Author, Year	Instruments	Definitions of Cognitive Decline and Delirium (Standardized Delirium Measurement Tool: Y/N)
		digit symbol, computerized RT, COWAT, grooved pegboard	
55	Bucerius, 2005	Delirium: APA guidelines	Delirium: According to APA guidelines (N)
56	Caldas, 2019	Delirium: CAM-ICU	Delirium: Positive CAM-ICU score (Y)
57	Chen, 2017	Delirium: CAM-ICU	Delirium: Positive CAM-ICU score (Y)
58	Christiansen, 2016	Cognition: VVLT, CST, stroop test, LDCT	Cognition: Decline of >20% in ≥2 tests
59	Coffey, 1983	Delirium: DSM-III criteria	Delirium: DSM-III diagnostic criteria (N)
60	Colak, 2015	Cognition: MMSE, color trail test, grooved pegboard	Cognition: Miscellaneous
		Delirium: DSS	Delirium: Patient met criteria specific to study (N)
61	Cumurcu, 2008	Delirium: DRS (for severity), DSM-IV-TR criteria, MMSE	Delirium: DSM-IV-TR diagnostic criteria (N)

Reference No.	Lead Author, Year	Instruments	Definitions of Cognitive Decline and Delirium (Standardized Delirium Measurement Tool: Y/N)
[62]	de Tournay-Jette, 2011	Cognition: MMSE (pre-screen, excluded if <24 pre-surgery), logical memory subtest (of the Rivermead battery), RAVLT, digit symbol, trails A & B, stroop test, verbal fluency test	Cognition: 1 SD method
[63]	Dieleman, 2009	Cognition: RAVLT-L, RAVLT-R, grooved pegboard, trails A & B, Sternberg memory comparison, line orientation test, stroop test, continuous performance task, self-ordering tasks, visuospatial working memory, symbol digit modalities	Cognition: RCI method
[64]	Djaiani, 2003	Cognition: Randt short story, WAIS digit span, WMS figural memory, WAIS digit symbol, Trails B, RAVLT	Cognition: 1 SD method
[65]	Dong, 2014	Cognition: 12 neuropsychological tests used to assess cognitive functions including attention, memory and executive function	Cognition: RCI method

Reference No.	Lead Author, Year	Instruments	Definitions of Cognitive Decline and Delirium (Standardized Delirium Measurement Tool: Y/N)
		Delirium: CAM-ICU	Delirium: Positive CAM-ICU score (Features 1 and 2 are present and either Feature 3 or 4 is present) (Y)
		Delirium: DSM-III-R	Delirium: DSM-III-R diagnostic criteria (N)
66	Eriksson, 2002	Delirium: CAM and OBS scale	Delirium: Positive CAM score and fulfilled DSM-IV criteria (Y)
67	Goto, 2000	Cognition: HDS	Cognition: Cutoff method
68	Gottesman, 2010	Delirium: DSS	Delirium: Charts reviewed for delirium in those with neurologic injury (N)
69	Hall, 1999	Cognition: Trails A & B, digit span (forward & backward), COWAT	Cognition: Z-score method
70	Harmon, 2004	Cognition: RAVLT, trails A & B, grooved pegboard, COWAT, digit symbol	Cognition: RCI method

Reference No.	Lead Author, Year	Instruments	Definitions of Cognitive Decline and Delirium (Standardized Delirium Measurement Tool: Y/N)
		Delirium: DSM-III-R, MMSE	Delirium: Diagnosis based on the DSM-III-R criteria and the MMSE (N)
[71]	Harmon, 2005	Cognition: RAVLT, trails A & B, grooved pegboard, COWAT, digit symbol	Cognition: RCI method
		Delirium: DSM-III-R, MMSE	Delirium: Diagnosis based on the DSM-III-R criteria and the MMSE (N)
		Delirium: ICDSC	Delirium: ICDSC score ≥ 4 (Y)
[72]	Humphreys, 2016	Delirium: DSI, SPMSQ	Delirium: Positive DSI score (had any one of the critical symptoms of delirium: disorientation, disturbance of consciousness, or perceptual disturbance) (Y)
[73]	Kadoi, 2001	Cognition: MMSE, RAVLT, trails A & B, digit span (forward), grooved pegboard	Cognition: 1 SD method

Reference No.	Lead Author, Year	Instruments	Definitions of Cognitive Decline and Delirium (Standardized Delirium Measurement Tool: Y/N)
74	Kadoi, 2002	Cognition: MMSE, RAVLT, trails A & B, digit span (forward), grooved pegboard	Cognition: 1 SD method
75	Kadoi, 2003	Cognition: MMSE, RAVLT, trails A & B, digit span (forward), grooved pegboard	Cognition: 1 SD method
76	Kadoi, 2005	Cognition: MMSE, RAVLT, trails A & B, digit span (forward), grooved pegboard	Cognition: 1 SD method
77	Kadoi, 2007	Cognition: MMSE, RAVLT, trails A & B, digit span (forward), grooved pegboard	Cognition: 1 SD method
79	Kadoi, 2011 (a)	Cognition: MMSE, RAVLT, trails A & B, digit span (forward), grooved pegboard	Cognition: 1 SD method
78	Kadoi, 2011 (b)	Cognition: MMSE, RAVLT, trails A & B, digit span (forward), grooved pegboard	Cognition: 1 SD method
80	Kazmierski, 2014 (a)	Cognition: MoCA, trails B	Cognition: Cutoff method

Reference No.	Lead Author, Year	Instruments	Definitions of Cognitive Decline and Delirium (Standardized Delirium Measurement Tool: Y/N)
		Delirium: CAM or CAM-ICU, RASS	Delirium: If RASS was above –4 (–3 through +4), assessment with the CAM-ICU was administered (Y)
[81]	Kazmierski, 2014 (b)	Delirium: CAM-ICU, MDAS (for severity)	Delirium: Positive CAM-ICU score (Feature 1 and Feature 2 and either Feature 3 or 4 are present) (Y)
[82]	Kazmierski, 2014 (c)	Delirium: CAM-ICU	Delirium: If RASS was above –4 (–3 through +4), assessment with the CAM-ICU was administered (Y)
[83]	Khan, 2014	Delirium: DSM-IV	Delirium: Diagnosed using DSM-IV criteria (N)
[84]	Khatri, 1999	Cognition: Randt short story, WAIS-R digit span, WAIS-R digit symbol, trails B, figural memory	Cognition: 20% method
[85]	Kok, 2017	Cognition: CogState brief computerized test battery (detection task, identification task, one card learning task and one back task)	Cognition: RCI method

Reference No.	Lead Author, Year	Instruments	Definitions of Cognitive Decline and Delirium (Standardized Delirium Measurement Tool: Y/N)
[86]	Kumpaitiene, 2019	Cognition: MMSE, RAVLT, WAIS digit span, WAIS digit symbol, Shulte table	Cognition: Pre-post change of >2 points in combined studentized score, or >2 points in ≥2 individual studentized test scores.
[87]	Lachmann, 2018	Motor choice RT, grooved pegboard, Trails A & B, symbol digit modalities, stroop test, continuous performance task, RAVLT, self-ordering tasks, visual/spatial working memory, Sternberg memory comparison, line orientation	Cognition: Decrease of ≥20% on ≥3 tests
[88]	Leenders, 2018	Delirium: CAM, CAM-ICU, multidisciplinary consultation	Delirium: Administration of haloperidol in addition to positive CAM or CAM-ICU score and multidisciplinary consultation (Y)
[89]	Li, 2015	Delirium: CAM	Delirium: Positive CAM score (Features 1 and 2 are present and either Feature 3 or 4 is present) (Y)
[90]	Liu, 2009	Cognition: WMS mental control, WMS visual retention, WMS paired-associate verbal learning, digit span (forward and backward),	Cognition: RCI method

Reference No.	Lead Author, Year	Instruments	Definitions of Cognitive Decline and Delirium (Standardized Delirium Measurement Tool: Y/N)
		WAIS-R digit symbol, trails A, grooved pegboard (dom & non-dom)	
91	Loponen, 2008	Delirium: DSS (clinically diagnosed)	Delirium: Clinically diagnosed with requirement that temporary medication, i.e. diazepam or haloperidol, was needed to sedate the delirious patient (N)
92	Mardani, 2012	Delirium: DSM-IV, MMSE	Delirium: DSM-IV criteria interviews conducted on patients with a MMSE score ≤ 23 (N)
93	Mariscalco, 2012	Delirium: CAM-ICU	Delirium: At least 2 positive assessments on CAM-ICU (Features 1 and 2 are present and either Feature 3 or 4 is present) (Y)
94	Martin, 2010	Delirium: STS	Delirium: Defined according to STS definition (N)
95	Martin, 2012	Delirium: STS	Delirium: Defined according to STS definition (N)

Reference No.	Lead Author, Year	Instruments	Definitions of Cognitive Decline and Delirium (Standardized Delirium Measurement Tool: Y/N)
96	Mathew, 2006	Cognition: Randt short story, WMS modified visual reproduction test, WAIS-R digit span, WAIS-R digit symbol, trails B	Cognition: 1 SD method (domain)
97	Mathew, 2007	Cognition: Randt short story, WMS modified visual reproduction test, WAIS-R digit span, WAIS-R digit symbol, trails B	Cognition: 1 SD method (domain)
98	Miyazaki, 2011	Delirium: DSM-IV	Delirium: Diagnosed according to DSM-IV criteria or administering antipsychotic agents by reviewing medical records during the ICU stay (N)
99	Mu, 2010	Delirium: CAM-ICU, RASS	Delirium: If RASS was above –4 (–3 through +4), assessment with the CAM-ICU was administered (4-step algorithm) (Y)
100	Mu, 2013	Cognition: Trails A, grooved pegboard (dom & non-dom), the WMS-Chinese edn. of the mental control subtest, digit span subtest (forward & backward), visual retention subtest,	Cognition: 1 SD method (preop) / RCI method

Reference No.	Lead Author, Year	Instruments	Definitions of Cognitive Decline and Delirium (Standardized Delirium Measurement Tool: Y/N)
		paired associate verbal learning subtest, digit symbol subtest	
101	Newman, 1987	Cognition: RAVLT, non-verbal recognition memory test (computer-administered), Trails A & B, WAIS block design, Purdue Pegboard (left, right, and both hands), letter cancellation test, symbol digit replacement (computer-based), choice RT (computer-based)	Cognition: Decrease of ≥1SD in >3 tests
102	Nikolic, 2012	Delirium: CAM	Delirium: Positive CAM score (Features 1 and 2 are present and either Feature 3 or 4 is present) (Y)
103	Norkiene, 2007	Delirium: DSM-IV	Delirium: Clinician diagnosis according to DSM-IV criteria (N)
104	Norkiene, 2011	Cognition: MMSE, RAVLT, trails A & B, digit span, digit symbol, cube drawing	Cognition: 1 SD method
		Delirium: DSM-IV	Delirium: Defined according to DSM-IV criteria (N)

Reference No.	Lead Author, Year	Instruments	Definitions of Cognitive Decline and Delirium (Standardized Delirium Measurement Tool: Y/N)
[105]	Oh, 2008	Cognition: MMSE, trails A, grooved pegboard	Cognition: 20% method
[106]	Oh, 2017	Delirium: DSS (psychiatric consultation & DSM-IV)	Delirium: Diagnosed by psychiatric consultation according to DSM-IV criteria (N)
[107]	Oldham, 2015	Cognition: CDR, MMSE, digit span, HVLT, WMS-IV, progressive digit sequencing, three word fluency tasks, NAB mazes subtest, trails A & B, digit symbol	Cognition: Cutoff method, 1 SD method
		Delirium: aDST, CAM, DI, MMSE	Delirium: Determined based on CAM (Y)
[108]	Oldham, 2019	Delirium: CAM, MMSE, abbreviated digit span test, DI	Delirium: Psychiatrist diagnosis based on CAM, MMSE, digit span test and delirium index (Y)
[109]	Omiya, 2015	Delirium: DRS-R-98	Delirium: DRS-R-98 score $\geq$ 8 (Y)
[110]	Otomo, 2013	Delirium: DSM-IV, DRS	Delirium: Diagnosed according to DSM-IV criteria & DRS score (Y)

Reference No.	Lead Author, Year	Instruments	Definitions of Cognitive Decline and Delirium (Standardized Delirium Measurement Tool: Y/N)
[111]	Palmbergen, 2012	Delirium: DOS scale, confirmed by geriatrician or internist	Delirium: DOS scale for screening. If suspected, confirmed by geriatrician or internist (Y)
[112]	Plaschke, 2010	Delirium: CAM-ICU (German), RASS	Delirium: Positive CAM-ICU score (Y)
[113]	Reents, 2002	Cognition: d2-letter cancellation test, trails B, Benton‘s visual retention test, WAIS block design, WAIS digit span	Cognition: 1 SD method
		Delirium: DSM-IV	Delirium: Defined according to DSM-IV criteria (N)
[114]	Restrepo, 2002	Cognition: Trails B, oral and written naming test, oral reading tests, line cancellation, Bells tests	Cognition: Z-score method
[115]	Ringaitiene, 2015	Delirium: CAM-ICU	Delirium: Positive CAM-ICU score (Y)
[116]	Robson, 2000	Cognition: RAVLT, trails A & B, PASAT, grooved pegboard, COWAT, NART, block design, object assembly test, digit symbol, picture completion test	Cognition: 1 SD method (<20% tests), 0.5 SD method (<20% tests)

Reference No.	Lead Author, Year	Instruments	Definitions of Cognitive Decline and Delirium (Standardized Delirium Measurement Tool: Y/N)
[117]	Rodriguez, 2010	Cognition: Group 1: RAVLT, trails A & B, grooved pegboard, symbol digit modalities, WAIS-R digit span, WMS mental control, letter (FAS test), category fluency (animal naming), finger tapping; Group 2: RAVLT, trails A & B, grooved pegboard, symbol digit modalities, WAIS-R digit span, verbal fluency (FAS test), categories (animal naming)	Cognition: Z-score method
[118]	Rolfson, 1999 (a)	Delirium: CAM, MMSE, DSM-III-R	Delirium: Diagnosed according to DSM-III-R criteria, based on results from standardized measures (e.g. CAM) and consultation with nurses, family members and hospital records (Y)
[119]	Rolfson, 1999 (b)	Delirium: DSM-III-R on clinical grounds (CAM, CAM-MD, CAM-RN, MMSE, clock drawing test, MD chart review, RN chart review - used to determine clinical diagnosis)	Delirium: Clinically diagnosed according to DSM-III-R criteria, based on results from standardized measures (Y)

Reference No.	Lead Author, Year	Instruments	Definitions of Cognitive Decline and Delirium (Standardized Delirium Measurement Tool: Y/N)
[120]	Royse, 2000	Cognition: Recall (short-term & delayed), COWAT, trails A & B, grooved pegboard (dom & non-dom), digit symbol, digit span (forward & backward)	Cognition: 20% method
[121]	Royse, 2011	Cognition: Trails A & B, COWAT, stroop test, letter cancellation, grooved pegboard (dom & non-dom), RAVLT, digit span (forward & backward), symbol digit modalities	Cognition: 1 SD method (<20% tests)
		Delirium: CAM	Delirium: Positive CAM score (Y)
[122]	Rudolph, 2005	Delirium: CAM, digit span, DSI, MDAS, MMSE	Delirium: Positive CAM score (Features 1 and 2 are present and either Feature 3 or 4 is present) (Y)
[123]	Rudolph, 2006	Delirium: CAM (CAM-ICU for postoperatively intubated patients), digit span, DSI, MDAS, MMSE	Delirium: Positive CAM score (Features 1 and 2 are present and either Feature 3 or 4 is present) (Y)

Reference No.	Lead Author, Year	Instruments	Definitions of Cognitive Decline and Delirium (Standardized Delirium Measurement Tool: Y/N)
[124]	Rudolph, 2009	Delirium: CAM, digit span, DSI, MDAS, MMSE	Delirium: Positive CAM score (Features 1 and 2 are present and either Feature 3 or 4 is present) (Y)
[125]	Sahan, 2018	Cognition: WMS logical memory, clock drawing test, word list generation test, digit span, visuomotor spatial skills test	Cognition: 1 SD method (≥2 tests)
[6]	Santos, 2004	Delirium: DSM-IV	Delirium: Diagnosed by geriatrician based on DSM-IV criteria, in addition to notes from nurses and physicians (N)
[126]	Scott, 2002	Cognition: WMS-R logical memory (I & II), altered form of WMS-R digit span, trails A & B, COWAT	Cognition: 1 SD method (<20% tests), 1 SD method
[127]	Sevuk, 2015	Delirium: DRS-R-98 (for severity), ICDSC	Delirium: ICDSC score ≥ 4 (Y)
[128]	Siepe, 2011	Delirium: MMSE, psychologist assessment	Delirium: 10 point drop or more on MMSE from pre-op and a positive assessment by a psychologist (N)

Reference No.	Lead Author, Year	Instruments	Definitions of Cognitive Decline and Delirium (Standardized Delirium Measurement Tool: Y/N)
[129]	Silbert, 2006	Cognition: CERAD AVLT, digit symbol, Trails A & B, COWAT, semantic fluency test, grooved pegboard test (dom & non-dom)	Cognition: 1 SD method and 20% method (≥2 tests)
[130]	Silbert, 2008	Cognition: CERAD AVLT, Digit symbol, Trails A & B, COWAT, semantic fluency test, grooved pegboard test (dom & non-dom)	Cognition: 1 SD method (≥2 tests)
[131]	Slater, 2009	Cognition: MMSE, Trails A & B, HVLT (trials 1, 2, 3, B & C), grooved pegboard (dom & non-dom), stroop test (part C & CW)	Cognition: 1 SD method (<20% tests)
		Delirium: DRS	Delirium: Based on DRS (Y)
[132]	Smith, 1986	Cognition: WAIS vocab and picture completion subtests, RAVLT, block design, grooved pegboard, trails A & B, letter cancellation, digit symbol replacement, two-choice RT	Cognition: 1 SD method

Reference No.	Lead Author, Year	Instruments	Definitions of Cognitive Decline and Delirium (Standardized Delirium Measurement Tool: Y/N)
[133]	Smith, 2000	Cognition: RAVLT, Rey auditory nonverbal memory, Trails A & B, letter cancellation, symbol-digit replacement, visual RT, grooved pegboard (dom & non-dom), finger tapping (dom & non-dom)	Cognition: 20% method (≥2 tests)
[134]	Stump, 1996	Cognition: Trails A & B, grooved pegboard (dom & non-dom), finger tapping (dom & non-dom), symbol digit, letter cancellation, visual RT, verbal and nonverbal memory	Cognition: 20% method (≥2 tests)
[135]	Subramaniam, 2019	Delirium: CAM, CAM-ICU	Delirium: Positive CAM or CAM-ICU score (Y)
[136]	Suksompong, 2002	Cognition: Thai Mental State Exam	Cognition: Miscellaneous
[137]	Swaminathan, 2002	Cognition: Randt short story (immediate & delay), digit symbol, trails B, digit span (forward & backward), figural memory (immediate & delayed)	Cognition: 1 SD method (domain)

Reference No.	Lead Author, Year	Instruments	Definitions of Cognitive Decline and Delirium (Standardized Delirium Measurement Tool: Y/N)
138	Sylivris, 1998	Cognition: WAIS-R general information questionnaire, digit span, digit symbol, RAVLT, COWAT	Cognition: Miscellaneous
139	Tagarakis, 2007	Delirium: DRS	Delirium: Based on DRS, which was performed on patients suspected to develop delirium (Y)
140	Tamura, 2019	Delirium: ICDSC	Delirium: ICDSC >3
141	Toeg, 2013	Cognition: Buschke selective reminding or RAVLT, WAIS-R digit span, finger tapping task, letter and category fluency, trails A & B, grooved pegboard, symbol digit modalities	Cognition: 1 SD method (domain)
142	Trubnikova, 2014	Cognition: Complex visuomotor reaction (reaction time, number of errors), functional mobility of nervous processes and performance of brain responses to feedback (reaction time, number of errors, missed signals), Bourdons test, visual short-term memory tests	Cognition: 20% method

Reference No.	Lead Author, Year	Instruments	Definitions of Cognitive Decline and Delirium (Standardized Delirium Measurement Tool: Y/N)
		(memorisation of 10 numbers, 10 words, 10 nonsense syllables)	
[143]	Tully, 2010	Delirium: DSI, DSM-IV-TR, SPMSQ	Delirium: Classification based on DSM-IV-TR criteria. Evidence of perceptual disturbance and/or language disturbance was requisite for a delirium diagnosis. Neurology assessments, SPMSQ results and medical notes also evaluated. (N)
[144]	van Dijk, 2004	Cognition: RAVLT-L, RAVLT-R, grooved pegboard, trails A & B, Sternberg memory comparison, line orientation test, stroop test	Cognition: 20% method
[145]	Yilmaz, 2016	Delirium: CAM-ICU	Delirium: Positive CAM-ICU score (Features 1 and 2 are present and either Feature 3 or 4 is present) (Y)
[146]	Zhang, 2015	Delirium: CAM-ICU, RASS	Delirium: Positive CAM-ICU score (Features 1 and 2 are present and either Feature 3 or 4 is present) (Y)

Reference No.	Lead Author, Year	Instruments	Definitions of Cognitive Decline and Delirium (Standardized Delirium Measurement Tool: Y/N)

Note. *see Supplementary Table 9 for glossary of instrument acronyms*

Table S9. **Glossary of abbreviations.**

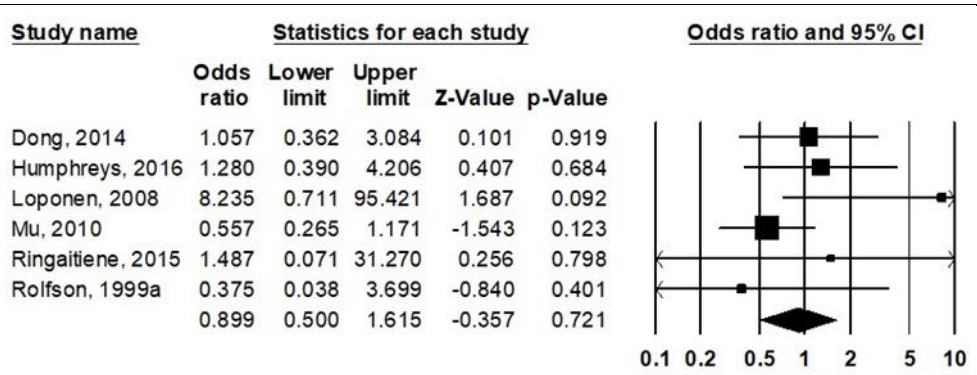
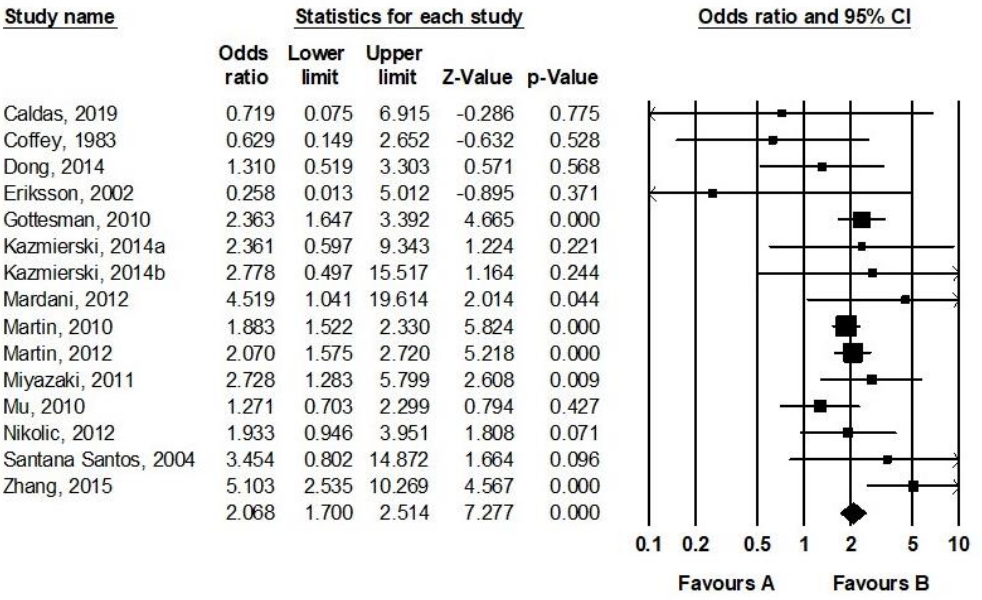
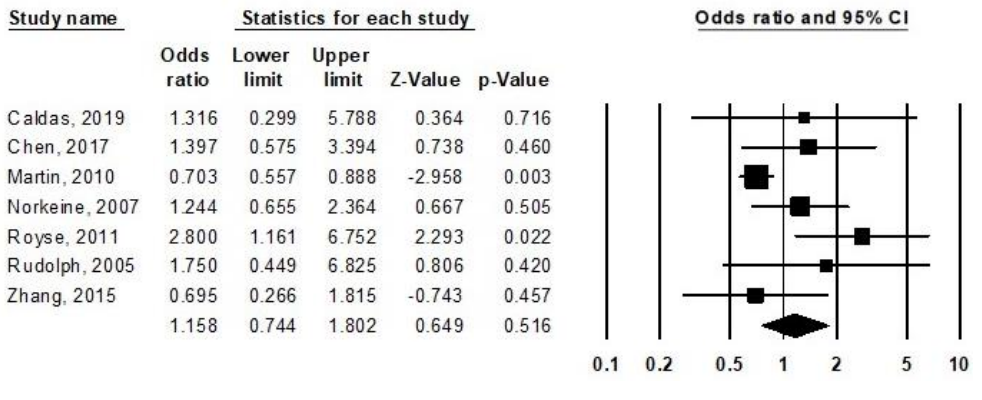
Cognitive Impairment	
AVLT	Auditory Verbal Learning Test
CDR	Clinical Dementia Rating scale
CERAD	The Consortium to Establish a Registry for Alzheimer's Disease
COWAT	Controlled Oral Word Association Test
CST	Concept Shifting Test
CVLT	California Verbal Learning Test
Digit symbol	Digit Symbol Substitution Task
HDS	Hasegawa Dementia Scale
HVLT	Hopkins Verbal Learning Test
LDCT	Letter-Digit Coding Test
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
NAB	Neuropsychological Assessment Battery
NART	National Adult Reading Test
PASAT	Paced Auditory Serial Addition Task
Randt short story	Randt Memory Test Short-Story Module
RAVLT	Rey Auditory Verbal Learning Test
RAVLT-L	Rey Auditory-Verbal Learning – Learning Trial
RAVLT-R	Rey Auditory-Verbal Learning – Recognition Trial
RCPM	Raven Coloured Progressive Matrices
RT	Reaction Time
Stroop test	Stroop Colour Word Interference Test
Trails A & B	Halstead-Reitan Trail-making tests A & B

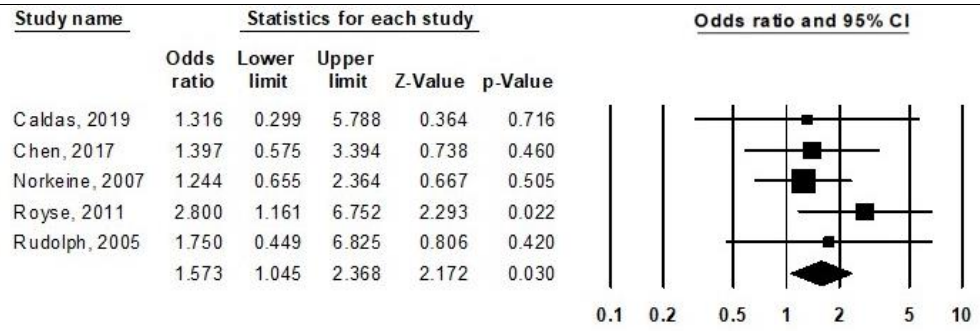
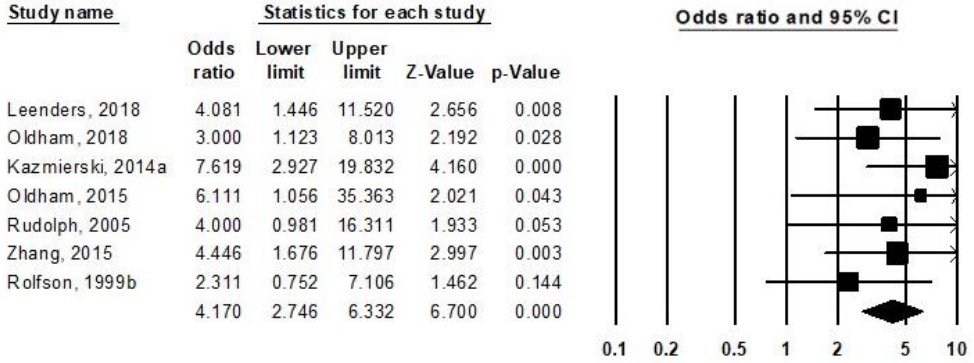
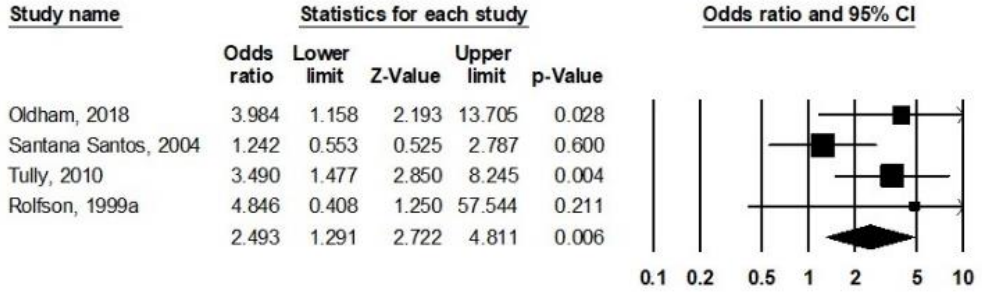
VVLT	Visual Verbal Learning Test
WAIS	Wechsler Adult Intelligence Scale
WMS	Wechsler Memory Scale

Delirium

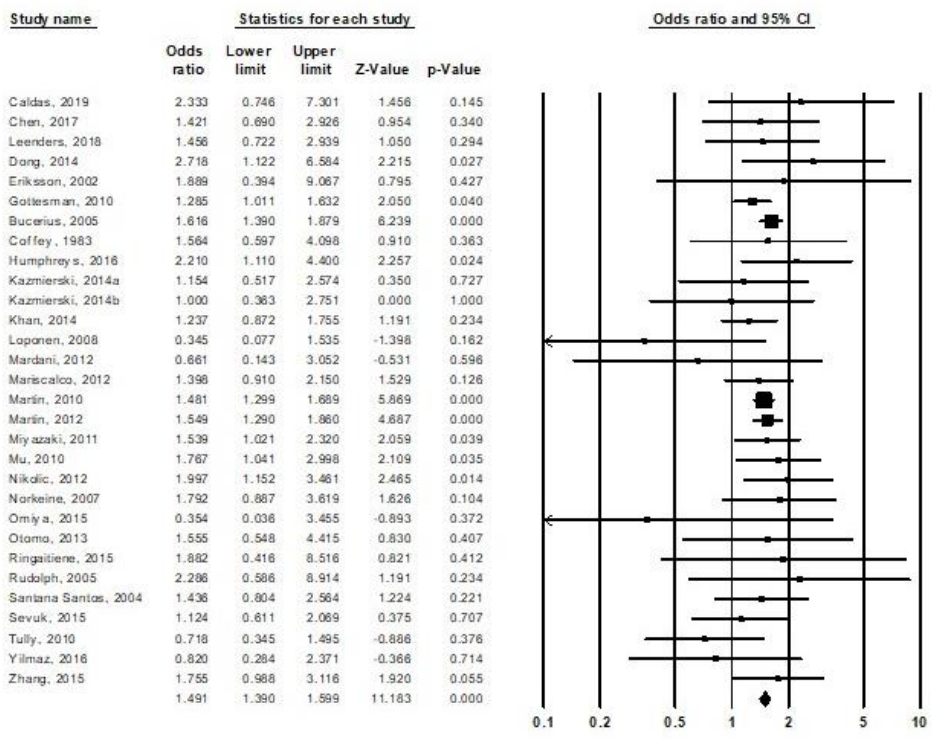
aDST	abbreviated Digit Span Test
APA	American Psychiatric Association
CAM	Confusion Assessment Method
CAM-ICU	Confusion Assessment Method for the ICU
DI	Delirium Index
DOS	Delirium Observation Screening scale
DRS	Delirium Rating Scale
DRS-R-98	Delirium Rating Scale Revised-98
DSI	Delirium Symptom Interview
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders 3rd ed., Revised.
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders 4th ed.
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders 4th ed., Text Revision
DSS	Definition that is specific to the study
ICDSC	The Intensive Care Delirium Screening Checklist
MDAS	Memorial Delirium Assessment Scale
MMSE	Mini Mental State Examination
OBS	Organic Brain Syndrome scale
RASS	The Richmond Agitation Sedation Scale
SPMSQ	Short Portable Mental Status Questionnaire
STS	Accordance with Society of Thoracic Surgeons

Figure S1. Forest plots for delirium post-CABG analyses.

Variable	Forest Plot
Pre-Operative (Categorical)	
Alcoholism	
Arrhythmia, incl. AF	
BMI >28 (including >30)	

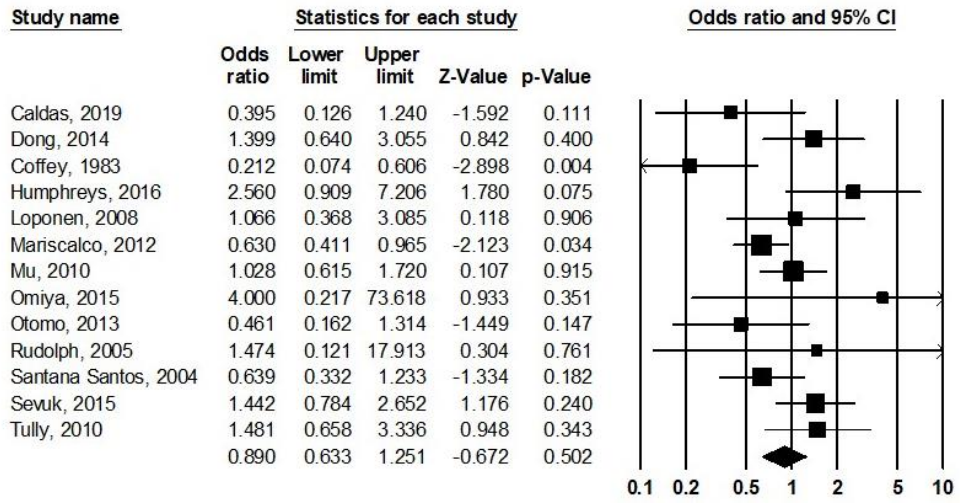
BMI ≥30 only	
Cognitive Impairment	
Depression	

Diabetes



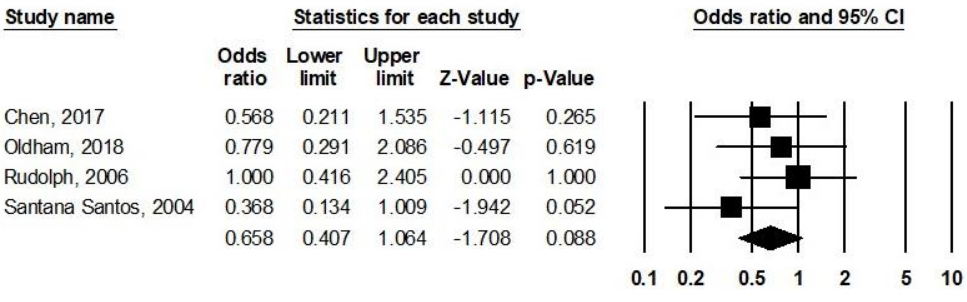
Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Caldas, 2019	2.333	0.746	7.301	1.456	0.145
Chen, 2017	1.421	0.690	2.926	0.954	0.340
Leenders, 2018	1.456	0.722	2.939	1.050	0.294
Dong, 2014	2.718	1.122	6.584	2.215	0.027
Eriksson, 2002	1.889	0.394	9.067	0.795	0.427
Gottesman, 2010	1.285	1.011	1.632	2.050	0.040
Bucerius, 2005	1.616	1.390	1.879	6.239	0.000
Coffey, 1983	1.564	0.597	4.098	0.910	0.363
Humphreys, 2016	2.210	1.110	4.400	2.257	0.024
Kazmierski, 2014a	1.154	0.517	2.574	0.350	0.727
Kazmierski, 2014b	1.000	0.363	2.751	0.000	1.000
Khan, 2014	1.237	0.872	1.755	1.191	0.234
Loponen, 2008	0.345	0.077	1.535	-1.398	0.162
Mardani, 2012	0.661	0.143	3.052	-0.531	0.596
Mariscalco, 2012	1.398	0.910	2.150	1.529	0.126
Martin, 2010	1.481	1.299	1.689	5.869	0.000
Martin, 2012	1.549	1.290	1.860	4.687	0.000
Miyazaki, 2011	1.539	1.021	2.320	2.059	0.039
Mu, 2010	1.767	1.041	2.998	2.109	0.035
Nikolic, 2012	1.997	1.152	3.461	2.465	0.014
Norkeine, 2007	1.792	0.887	3.619	1.626	0.104
Omiya, 2015	0.354	0.036	3.455	-0.893	0.372
Otomo, 2013	1.555	0.548	4.415	0.830	0.407
Ringaitiene, 2015	1.882	0.416	8.516	0.821	0.412
Rudolph, 2005	2.286	0.586	8.914	1.191	0.234
Santana Santos, 2004	1.436	0.804	2.564	1.224	0.221
Sevuk, 2015	1.124	0.611	2.069	0.375	0.707
Tully, 2010	0.718	0.345	1.495	-0.886	0.376
Yilmaz, 2016	0.820	0.284	2.371	-0.366	0.714
Zhang, 2015	1.755	0.988	3.116	1.920	0.055
	1.491	1.390	1.599	11.183	0.000

Dyslipidemia/Hyperlipidemia



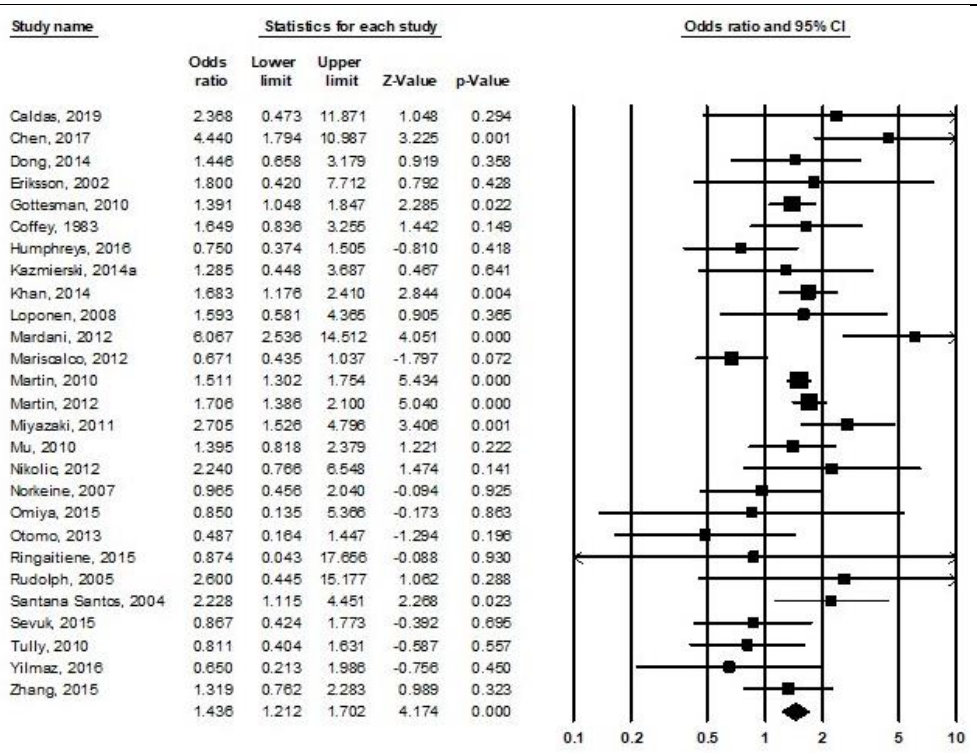
Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Caldas, 2019	0.395	0.126	1.240	-1.592	0.111
Dong, 2014	1.399	0.640	3.055	0.842	0.400
Coffey, 1983	0.212	0.074	0.606	-2.898	0.004
Humphreys, 2016	2.560	0.909	7.206	1.780	0.075
Loponen, 2008	1.066	0.368	3.085	0.118	0.906
Mariscalco, 2012	0.630	0.411	0.965	-2.123	0.034
Mu, 2010	1.028	0.615	1.720	0.107	0.915
Omiya, 2015	4.000	0.217	73.618	0.933	0.351
Otomo, 2013	0.461	0.162	1.314	-1.449	0.147
Rudolph, 2005	1.474	0.121	17.913	0.304	0.761
Santana Santos, 2004	0.639	0.332	1.233	-1.334	0.182
Sevuk, 2015	1.442	0.784	2.652	1.176	0.240
Tully, 2010	1.481	0.658	3.336	0.948	0.343
	0.890	0.633	1.251	-0.672	0.502

Education>12years/high school

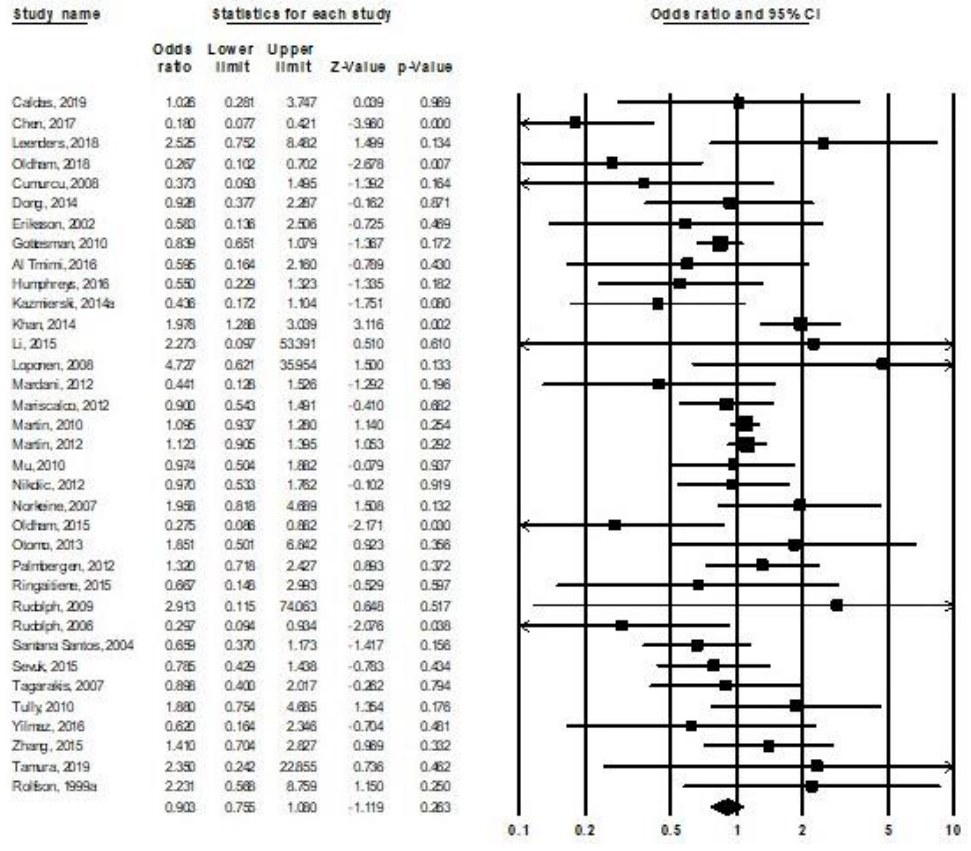


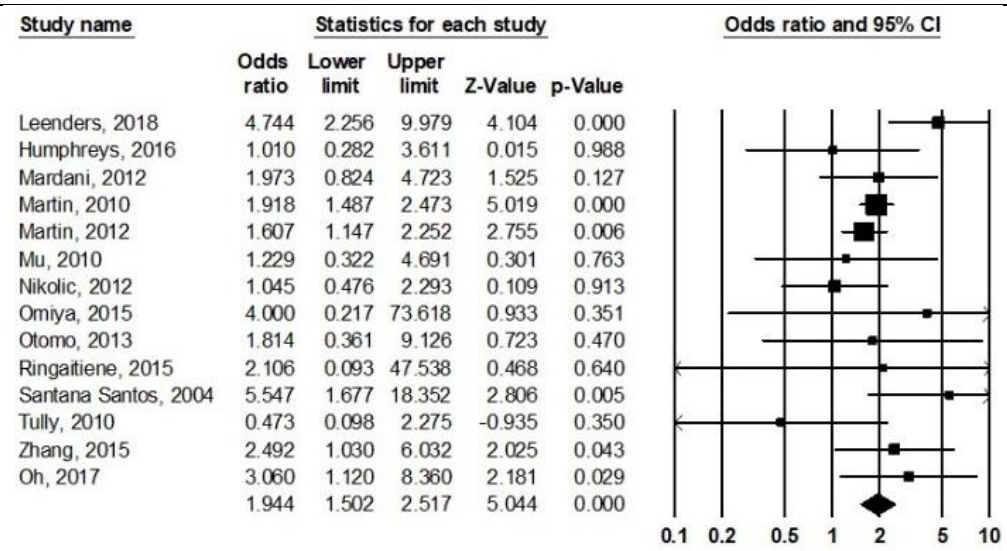
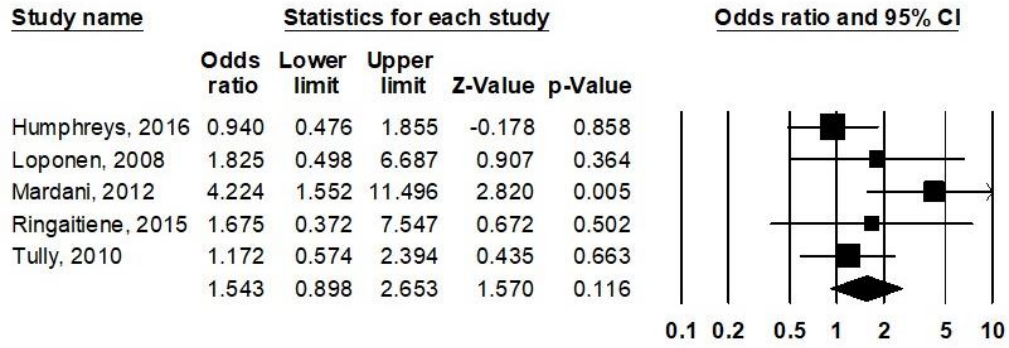
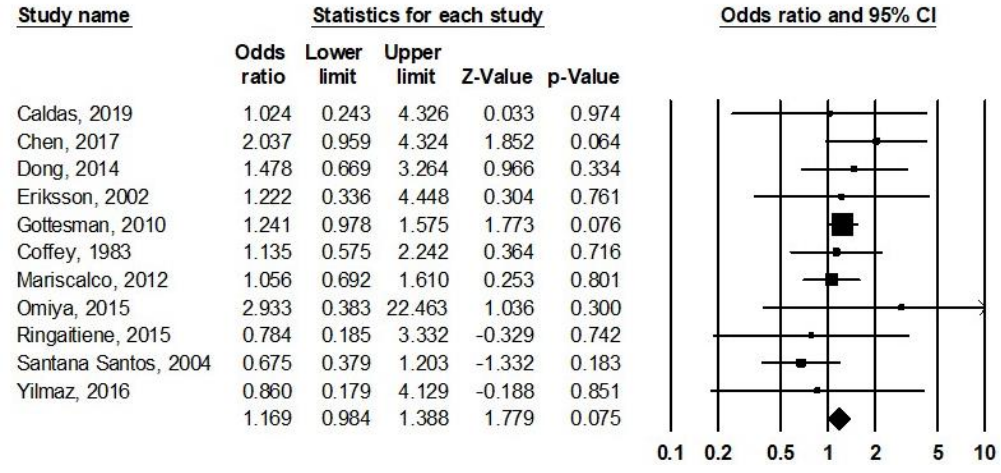
Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Chen, 2017	0.568	0.211	1.535	-1.115	0.265
Oldham, 2018	0.779	0.291	2.086	-0.497	0.619
Rudolph, 2006	1.000	0.416	2.405	0.000	1.000
Santana Santos, 2004	0.368	0.134	1.009	-1.942	0.052
	0.658	0.407	1.064	-1.708	0.088

Hypertension



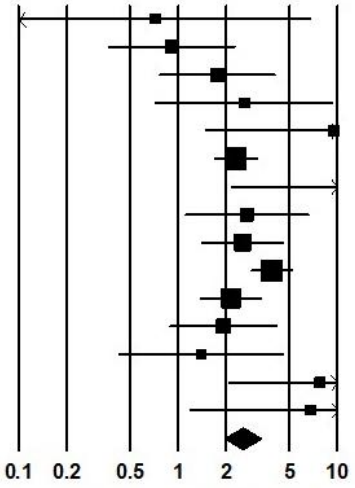
Sex (male)



Kidney injury	
Previous MI <30 days	
Previous MI history/ever	

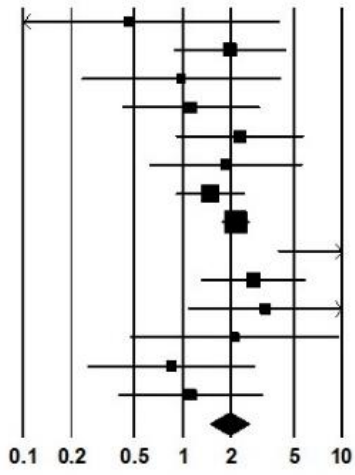
Previous stroke, TIA, CVA

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Caldas, 2019	0.719	0.075	6.915	-0.286	0.775
Chen, 2017	0.914	0.363	2.300	-0.192	0.848
Leenders, 2018	1.765	0.760	4.100	1.321	0.186
Dong, 2014	2.603	0.714	9.490	1.449	0.147
Eriksson, 2002	9.486	1.475	60.991	2.370	0.018
Gottesman, 2010	2.309	1.683	3.168	5.190	0.000
Khan, 2014	18.365	2.130	158.346	2.648	0.008
Mardani, 2012	2.709	1.102	6.662	2.171	0.030
Mariscalco, 2012	2.545	1.389	4.666	3.022	0.003
Martin, 2010	3.895	2.869	5.290	8.709	0.000
Miyazaki, 2011	2.150	1.365	3.386	3.304	0.001
Mu, 2010	1.924	0.879	4.212	1.637	0.102
Norkeine, 2007	1.400	0.422	4.644	0.550	0.582
Palmbergen, 2012	7.781	2.063	29.354	3.029	0.002
Rolfson, 1999a	6.769	1.178	38.898	2.144	0.032
	2.546	1.936	3.350	6.680	0.000



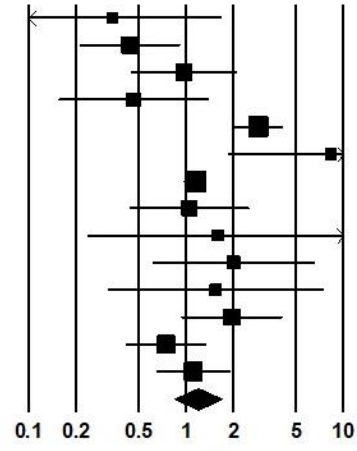
PVD

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Caldas, 2019	0.458	0.051	4.107	-0.697	0.486
Leenders, 2018	1.982	0.881	4.459	1.653	0.098
Coffey, 1983	0.982	0.232	4.160	-0.025	0.980
Humphreys, 2016	1.130	0.417	3.065	0.240	0.810
Kazmierski, 2014a	2.295	0.905	5.816	1.751	0.080
Kazmierski, 2014b	1.871	0.616	5.683	1.105	0.269
Mariscalco, 2012	1.498	0.910	2.465	1.589	0.112
Martin, 2012	2.159	1.765	2.642	7.478	0.000
Nikolic, 2012	10.733	3.963	29.068	4.669	0.000
Norkeine, 2007	2.790	1.303	5.970	2.643	0.008
Otomo, 2013	3.314	1.088	10.094	2.109	0.035
Ringaitiene, 2015	2.130	0.468	9.689	0.978	0.328
Sevuk, 2015	0.854	0.253	2.881	-0.254	0.799
Tully, 2010	1.128	0.397	3.203	0.226	0.821
	1.977	1.482	2.637	4.636	0.000

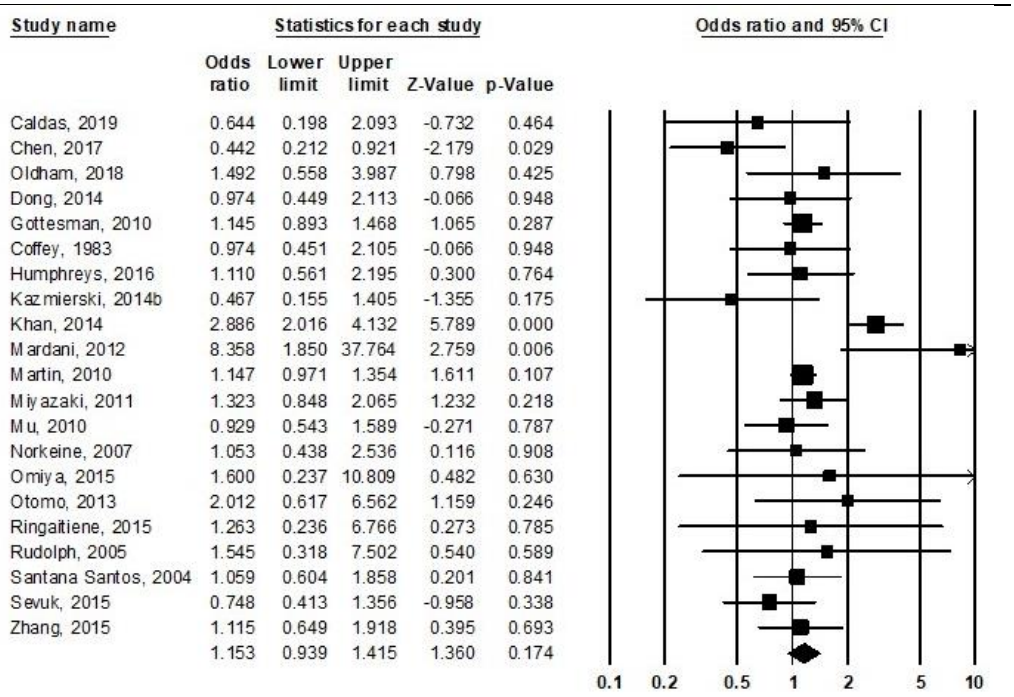


Smoking current

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Caldas, 2019	0.343	0.069	1.697	-1.312	0.190
Chen, 2017	0.442	0.212	0.921	-2.179	0.029
Dong, 2014	0.974	0.449	2.113	-0.066	0.948
Kazmierski, 2014b	0.467	0.155	1.405	-1.355	0.175
Khan, 2014	2.886	2.016	4.132	5.789	0.000
Mardani, 2012	8.358	1.850	37.764	2.759	0.006
Martin, 2010	1.147	0.971	1.354	1.611	0.107
Norkeine, 2007	1.053	0.438	2.536	0.116	0.908
Omiya, 2015	1.600	0.237	10.809	0.482	0.630
Otomo, 2013	2.012	0.617	6.562	1.159	0.246
Rudolph, 2005	1.545	0.318	7.502	0.540	0.589
Santana Santos, 2004	1.962	0.935	4.118	1.781	0.075
Sevuk, 2015	0.748	0.413	1.356	-0.958	0.338
Zhang, 2015	1.115	0.649	1.918	0.395	0.693
	1.194	0.841	1.694	0.992	0.321



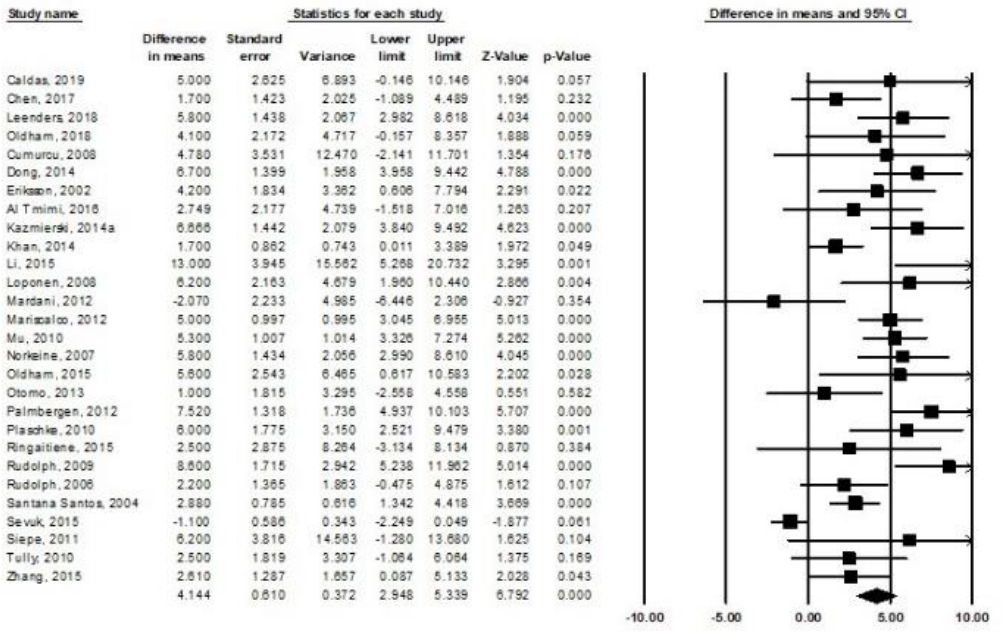
Smoking current/history



Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Caldas, 2019	0.644	0.198	2.093	-0.732	0.464
Chen, 2017	0.442	0.212	0.921	-2.179	0.029
Oldham, 2018	1.492	0.558	3.987	0.798	0.425
Dong, 2014	0.974	0.449	2.113	-0.066	0.948
Gottesman, 2010	1.145	0.893	1.468	1.065	0.287
Coffey, 1983	0.974	0.451	2.105	-0.066	0.948
Humphreys, 2016	1.110	0.561	2.195	0.300	0.764
Kazmierski, 2014b	0.467	0.155	1.405	-1.355	0.175
Khan, 2014	2.886	2.016	4.132	5.789	0.000
Mardani, 2012	8.358	1.850	37.764	2.759	0.006
Martin, 2010	1.147	0.971	1.354	1.611	0.107
Miyazaki, 2011	1.323	0.848	2.065	1.232	0.218
Mu, 2010	0.929	0.543	1.589	-0.271	0.787
Norkeine, 2007	1.053	0.438	2.536	0.116	0.908
Omiya, 2015	1.600	0.237	10.809	0.482	0.630
Otomo, 2013	2.012	0.617	6.562	1.159	0.246
Ringaitiene, 2015	1.263	0.236	6.766	0.273	0.785
Rudolph, 2005	1.545	0.318	7.502	0.540	0.589
Santana Santos, 2004	1.059	0.604	1.858	0.201	0.841
Sevuk, 2015	0.748	0.413	1.356	-0.958	0.338
Zhang, 2015	1.115	0.649	1.918	0.395	0.693
	1.153	0.939	1.415	1.360	0.174

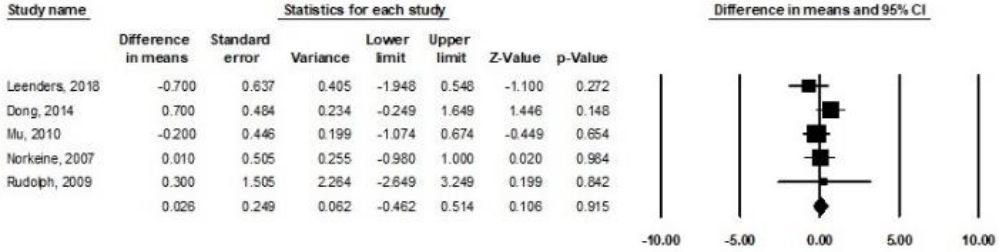
Pre-Operative (Continuous)

Age (years) *



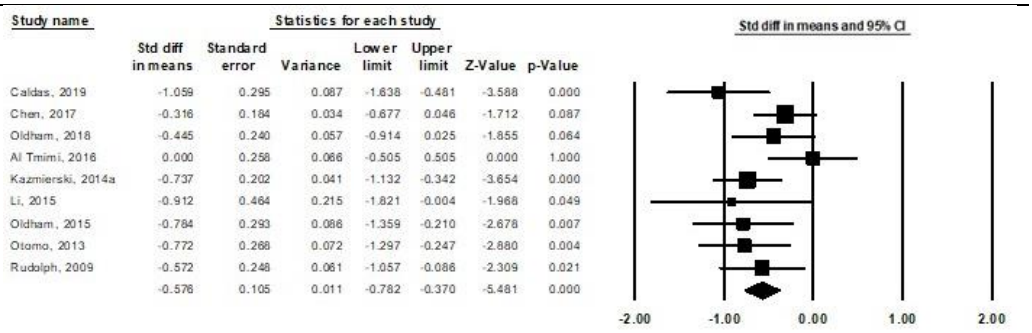
Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Caldas, 2019	5.000	2.625	6.893	-0.146	10.146	1.904	0.057
Chen, 2017	1.700	1.423	2.025	-1.089	4.489	1.195	0.232
Leenders, 2018	5.800	1.438	2.067	2.982	8.618	4.034	0.000
Oldham, 2018	4.100	2.172	4.717	-0.157	8.357	1.888	0.059
Cumurcu, 2008	4.780	3.531	12.470	-2.141	11.701	1.354	0.176
Dong, 2014	6.700	1.399	1.958	3.958	9.442	4.788	0.000
Eriksson, 2002	4.200	1.834	3.362	0.606	7.794	2.291	0.022
Al Tmimi, 2016	2.749	2.177	4.739	-1.518	7.016	1.263	0.207
Kazmierski, 2014a	6.666	1.442	2.079	3.840	9.492	4.623	0.000
Khan, 2014	1.700	0.862	0.743	0.011	3.389	1.972	0.049
Li, 2015	13.000	3.945	15.562	5.268	20.732	3.295	0.001
Loponen, 2008	6.200	2.163	4.679	1.960	10.440	2.866	0.004
Mardani, 2012	-2.070	2.233	4.985	-6.446	2.306	-0.927	0.354
Mariscalco, 2012	5.000	0.997	0.995	3.045	6.955	5.013	0.000
Mu, 2010	5.300	1.007	1.014	3.326	7.274	5.262	0.000
Norkeine, 2007	5.800	1.434	2.056	2.990	8.610	4.045	0.000
Oldham, 2015	5.600	2.543	6.465	0.617	10.583	2.202	0.028
Otomo, 2013	1.000	1.815	3.295	-2.558	4.558	0.551	0.582
Palmbergen, 2012	7.520	1.318	1.736	4.937	10.103	5.707	0.000
Plaschke, 2010	6.000	1.775	3.150	2.521	9.479	3.380	0.001
Ringaitiene, 2015	2.500	2.875	8.264	-3.134	8.134	0.870	0.384
Rudolph, 2009	8.600	1.715	2.942	5.238	11.962	5.014	0.000
Rudolph, 2006	2.200	1.365	1.863	-0.475	4.875	1.612	0.107
Santana Santos, 2004	2.880	0.785	0.616	1.342	4.418	3.669	0.000
Sevuk, 2015	-1.100	0.586	0.343	-2.249	0.049	-1.877	0.061
Siepe, 2011	6.200	3.816	14.563	-1.280	13.680	1.625	0.104
Tully, 2010	2.500	1.819	3.307	-1.064	6.064	1.375	0.169
Zhang, 2015	2.610	1.287	1.657	0.087	5.133	2.028	0.043
	4.144	0.610	0.372	2.948	5.339	6.792	0.000

BMI



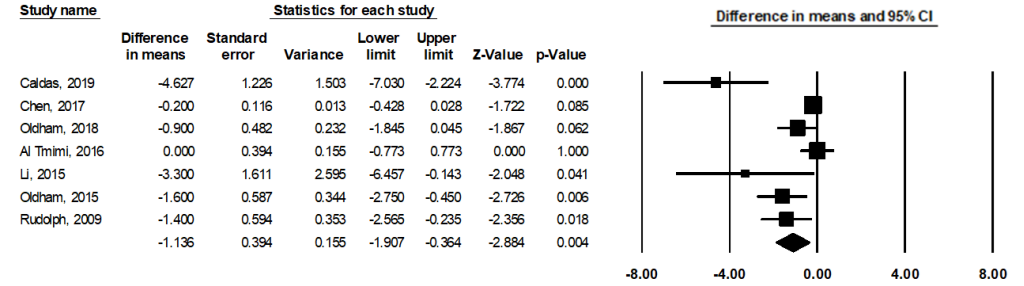
Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Leenders, 2018	-0.700	0.637	0.405	-1.948	0.548	-1.100	0.272
Dong, 2014	0.700	0.484	0.234	-0.249	1.649	1.446	0.148
Mu, 2010	-0.200	0.446	0.199	-1.074	0.674	-0.449	0.654
Norkeine, 2007	0.010	0.505	0.255	-0.980	1.000	0.020	0.984
Rudolph, 2009	0.300	1.505	2.264	-2.649	3.249	0.199	0.842
	0.026	0.249	0.062	-0.462	0.514	0.106	0.915

Cognition: All tests



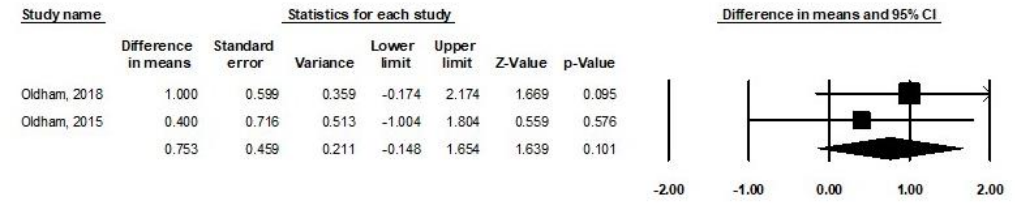
Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Caldas, 2019	-1.059	0.295	0.087	-1.638	-0.481	-3.588	0.000
Chen, 2017	-0.316	0.184	0.034	-0.677	0.046	-1.712	0.087
Oldham, 2018	-0.445	0.240	0.057	-0.914	0.025	-1.855	0.064
Al Tmimi, 2016	0.000	0.258	0.066	-0.505	0.505	0.000	1.000
Kazmierski, 2014a	-0.737	0.202	0.041	-1.132	-0.342	-3.654	0.000
Li, 2015	-0.912	0.464	0.215	-1.821	-0.004	-1.968	0.049
Oldham, 2015	-0.784	0.293	0.086	-1.359	-0.210	-2.678	0.007
Otomo, 2013	-0.772	0.268	0.072	-1.297	-0.247	-2.880	0.004
Rudolph, 2009	-0.572	0.248	0.061	-1.057	-0.086	-2.309	0.021
	-0.576	0.105	0.011	-0.782	-0.370	-5.481	0.000

Cognition: MMSE only



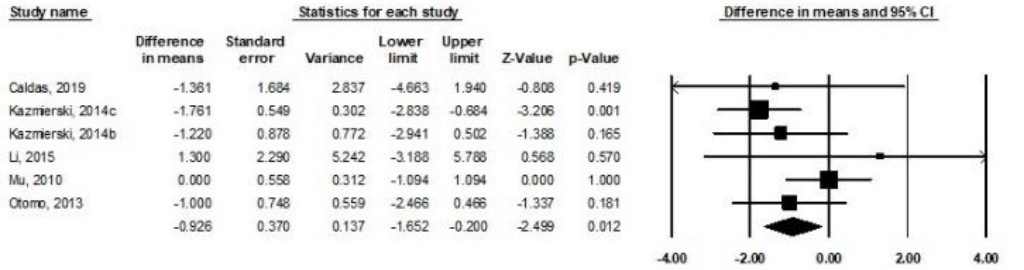
Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Caldas, 2019	-4.627	1.226	1.503	-7.030	-2.224	-3.774	0.000
Chen, 2017	-0.200	0.116	0.013	-0.428	0.028	-1.722	0.085
Oldham, 2018	-0.900	0.482	0.232	-1.845	0.045	-1.867	0.062
Al Tmimi, 2016	0.000	0.394	0.155	-0.773	0.773	0.000	1.000
Li, 2015	-3.300	1.611	2.595	-6.457	-0.143	-2.048	0.041
Oldham, 2015	-1.600	0.587	0.344	-2.750	-0.450	-2.726	0.006
Rudolph, 2009	-1.400	0.594	0.353	-2.565	-0.235	-2.356	0.018
	-1.136	0.394	0.155	-1.907	-0.364	-2.884	0.004

Depression GDS



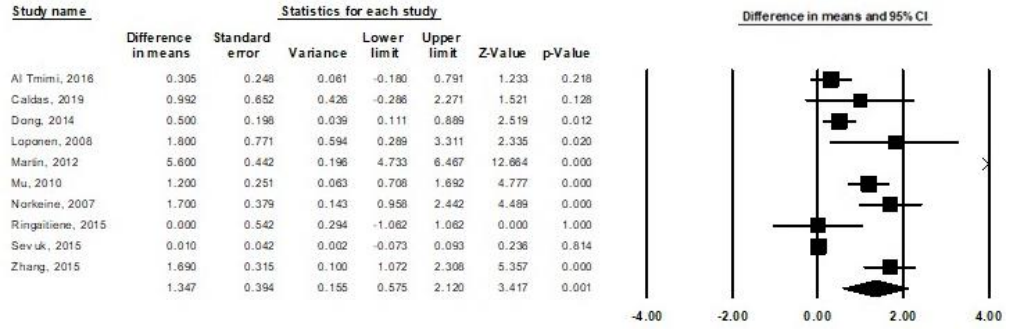
Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Oldham, 2018	1.000	0.599	0.359	-0.174	2.174	1.669	0.095
Oldham, 2015	0.400	0.716	0.513	-1.004	1.804	0.559	0.576
	0.753	0.459	0.211	-0.148	1.654	1.639	0.101

Education (years)



Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Caldas, 2019	-1.361	1.684	2.837	-4.663	1.940	-0.808	0.419
Kazmierski, 2014c	-1.761	0.549	0.302	-2.838	-0.684	-3.206	0.001
Kazmierski, 2014b	-1.220	0.878	0.772	-2.941	0.502	-1.388	0.165
Li, 2015	1.300	2.290	5.242	-3.188	5.788	0.568	0.570
Mu, 2010	0.000	0.558	0.312	-1.094	1.094	0.000	1.000
Otomo, 2013	-1.000	0.748	0.559	-2.466	0.466	-1.337	0.181
	-0.926	0.370	0.137	-1.652	-0.200	-2.499	0.012

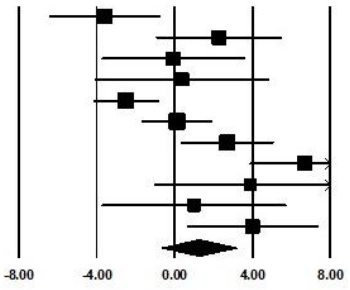
EuroSCORE



Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Al Tmimi, 2016	0.305	0.248	0.061	-0.180	0.791	1.233	0.218
Caldas, 2019	0.992	0.652	0.426	-0.286	2.271	1.521	0.128
Dong, 2014	0.500	0.198	0.039	0.111	0.889	2.519	0.012
Loponen, 2008	1.800	0.771	0.594	0.289	3.311	2.335	0.020
Martín, 2012	5.600	0.442	0.196	4.733	6.467	12.664	0.000
Mu, 2010	1.200	0.251	0.063	0.708	1.692	4.777	0.000
Norkeine, 2007	1.700	0.379	0.143	0.958	2.442	4.489	0.000
Ringaitiene, 2015	0.000	0.542	0.294	-1.062	1.062	0.000	1.000
Sevuk, 2015	0.010	0.042	0.002	-0.073	0.093	0.236	0.814
Zhang, 2015	1.690	0.315	0.100	1.072	2.308	5.357	0.000
	1.347	0.394	0.155	0.575	2.120	3.417	0.001

LVEF (%)

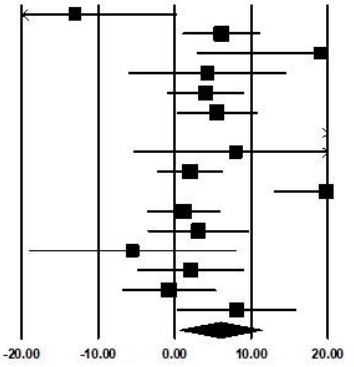
Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Caldas, 2019	-3.577	1.461	2.133	-6.440	-0.714	-2.449	0.014
Chen, 2017	2.300	1.657	2.745	-0.948	5.548	1.388	0.165
Kazmierski, 2014c	-0.054	1.882	3.540	-3.742	3.634	-0.029	0.977
Kazmierski, 2014b	0.398	2.292	5.255	-4.096	4.891	0.173	0.862
Khan, 2014	-2.490	0.870	0.756	-4.194	-0.786	-2.863	0.004
Mardani, 2012	0.120	0.922	0.849	-1.686	1.926	0.130	0.896
Mu, 2010	2.700	1.222	1.492	0.306	5.094	2.210	0.027
Norkeine, 2007	6.700	1.455	2.118	3.848	9.552	4.604	0.000
Ringaitiene, 2015	3.900	2.524	6.372	-1.047	8.847	1.545	0.122
Rudolph, 2009	1.000	2.426	5.887	-3.756	5.756	0.412	0.680
Santana Santos, 2004	4.000	1.725	2.975	0.619	7.381	2.319	0.020
	1.247	0.990	0.979	-0.692	3.187	1.260	0.208



Intra-Operative (Continuous)

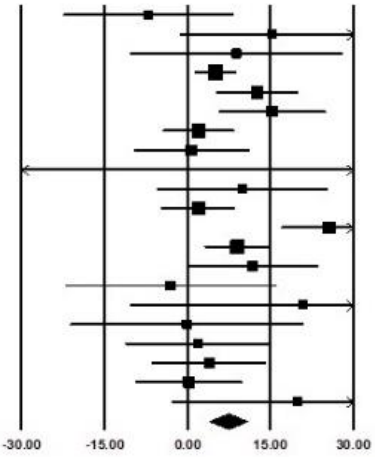
ACC time (mins)

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Caldas, 2019	-13.000	6.766	45.776	-26.261	0.261	-1.921	0.055
Leenders, 2018	6.100	2.598	6.749	1.008	11.192	2.348	0.019
Cumurcu, 2008	18.940	8.191	67.093	2.886	34.994	2.312	0.021
Eriksson, 2002	4.300	5.280	27.879	-6.049	14.649	0.814	0.415
Kazmierski, 2014a	4.012	2.586	6.687	-1.056	9.081	1.552	0.121
Kazmierski, 2014b	5.534	2.703	7.307	0.236	10.832	2.047	0.041
Khan, 2014	28.220	2.004	4.017	24.292	32.148	14.081	0.000
Loponen, 2008	8.000	6.821	46.528	-5.369	21.369	1.173	0.241
Mardani, 2012	2.000	2.182	4.760	-2.276	6.276	0.917	0.359
Mariscalco, 2012	19.800	3.501	12.260	12.937	26.663	5.655	0.000
Nikolic, 2012	1.177	2.456	6.032	-3.637	5.991	0.479	0.632
Norkeine, 2007	3.100	3.378	11.414	-3.522	9.722	0.918	0.359
Ringaitiene, 2015	-5.500	6.913	47.789	-19.049	8.049	-0.796	0.426
Santana Santos, 2004	2.040	3.579	12.810	-4.975	9.055	0.570	0.569
Sevuk, 2015	-0.733	3.151	9.930	-6.910	5.443	-0.233	0.816
Tully, 2010	8.100	3.994	15.956	0.271	15.929	2.028	0.043
	5.970	2.732	7.462	0.616	11.324	2.185	0.029

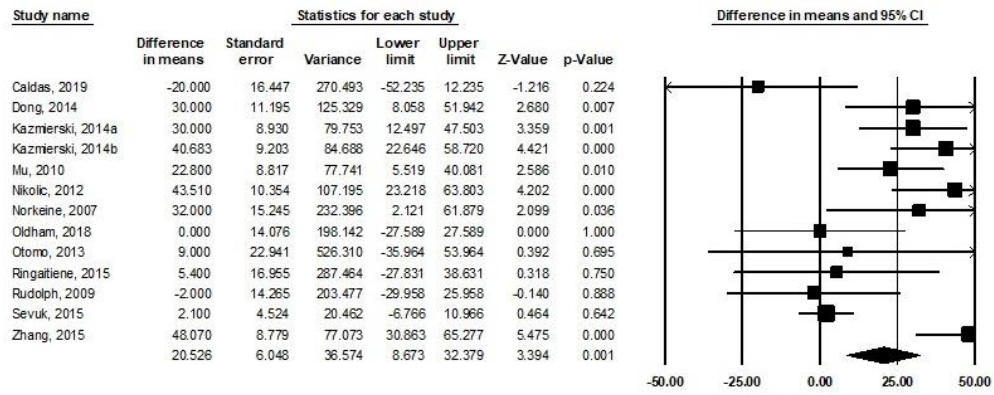


CPB time (mins)

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Caldas, 2019	-7.000	7.876	62.035	-22.437	8.437	-0.889	0.374
Cumurcu, 2008	15.260	8.490	72.077	-1.380	31.900	1.797	0.072
Eriksson, 2002	8.900	9.834	96.701	-10.374	28.174	0.905	0.365
Gottesman, 2010	5.100	1.922	3.695	1.333	8.867	2.653	0.008
Kazmierski, 2014a	12.660	3.839	14.740	5.135	20.184	3.297	0.001
Kazmierski, 2014b	15.349	4.966	24.663	5.615	25.082	3.091	0.002
Khan, 2014	2.100	3.316	10.995	-4.399	8.599	0.633	0.527
Leenders, 2018	0.764	5.346	28.576	-9.713	11.241	0.143	0.886
Li, 2015	46.200	45.417	2062.711	-42.816	135.216	1.017	0.309
Loponen, 2008	10.000	7.903	62.462	-5.490	25.490	1.265	0.206
Mardani, 2012	2.000	3.442	11.847	-4.746	8.746	0.581	0.561
Mariscalco, 2012	25.700	4.450	19.799	16.979	34.421	5.776	0.000
Nikolic, 2012	9.073	3.045	9.272	3.105	15.041	2.980	0.003
Norkeine, 2007	11.800	6.069	36.837	-0.096	23.696	1.944	0.052
Oldham, 2018	-3.000	9.730	94.681	-22.071	16.071	-0.308	0.758
Otomo, 2013	21.000	16.018	256.565	-10.394	52.394	1.311	0.190
Ringaitiene, 2015	-0.100	10.799	116.611	-21.265	21.065	-0.009	0.993
Rudolph, 2009	2.000	6.794	46.158	-11.316	15.316	0.294	0.768
Santana Santos, 2004	3.970	5.280	27.873	-6.378	14.318	0.752	0.452
Sevuk, 2015	0.282	4.949	24.492	-9.418	9.982	0.057	0.955
Siepe, 2011	20.000	11.678	136.385	-2.889	42.889	1.713	0.087
	7.406	1.724	2.972	4.027	10.784	4.296	0.000

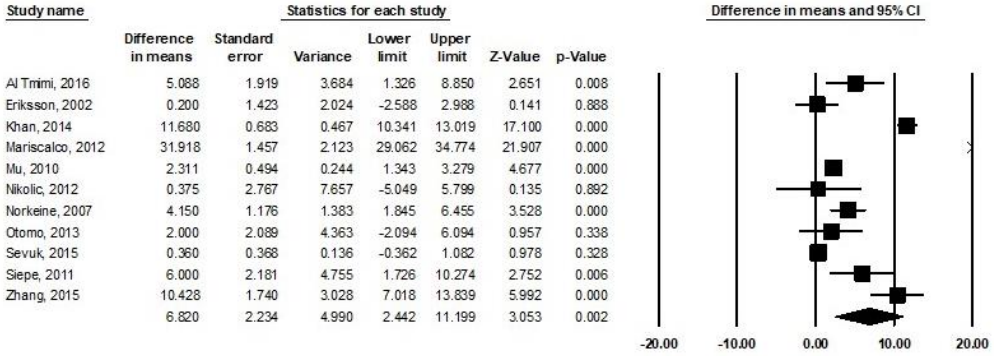


Duration of surgery (mins)



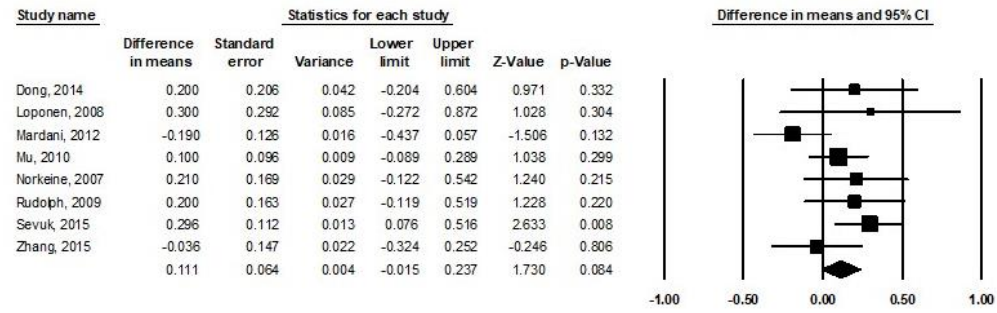
Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Caldas, 2019	-20.000	16.447	270.493	-52.235	12.235	-1.216	0.224
Dong, 2014	30.000	11.195	125.329	8.058	51.942	2.680	0.007
Kazmierski, 2014a	30.000	8.930	79.753	12.497	47.503	3.359	0.001
Kazmierski, 2014b	40.683	9.203	84.688	22.646	58.720	4.421	0.000
Mu, 2010	22.800	8.817	77.741	5.519	40.081	2.586	0.010
Nikolic, 2012	43.510	10.354	107.195	23.218	63.803	4.202	0.000
Norkeine, 2007	32.000	15.245	232.396	2.121	61.879	2.099	0.036
Oldham, 2018	0.000	14.076	198.142	-27.589	27.589	0.000	1.000
Otomo, 2013	9.000	22.941	526.310	-35.964	53.964	0.392	0.695
Ringaitiene, 2015	5.400	16.955	287.464	-27.831	38.631	0.318	0.750
Rudolph, 2009	-2.000	14.265	203.477	-29.958	25.958	-0.140	0.888
Sevuk, 2015	2.100	4.524	20.462	-6.766	10.966	0.464	0.642
Zhang, 2015	48.070	8.779	77.073	30.863	65.277	5.475	0.000
	20.526	6.048	36.574	8.673	32.379	3.394	0.001

Intubation time (hours)



Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Al Tmimi, 2016	5.088	1.919	3.684	1.326	8.850	2.651	0.008
Eriksson, 2002	0.200	1.423	2.024	-2.588	2.988	0.141	0.888
Khan, 2014	11.680	0.683	0.467	10.341	13.019	17.100	0.000
Mariscalco, 2012	31.918	1.457	2.123	29.062	34.774	21.907	0.000
Mu, 2010	2.311	0.494	0.244	1.343	3.279	4.677	0.000
Nikolic, 2012	0.375	2.767	7.657	-5.049	5.799	0.135	0.892
Norkeine, 2007	4.150	1.176	1.383	1.845	6.455	3.528	0.000
Otomo, 2013	2.000	2.089	4.363	-2.094	6.094	0.957	0.338
Sevuk, 2015	0.360	0.368	0.136	-0.362	1.082	0.978	0.328
Siepe, 2011	6.000	2.181	4.755	1.726	10.274	2.752	0.006
Zhang, 2015	10.428	1.740	3.028	7.018	13.839	5.992	0.000
	6.820	2.234	4.990	2.442	11.199	3.053	0.002

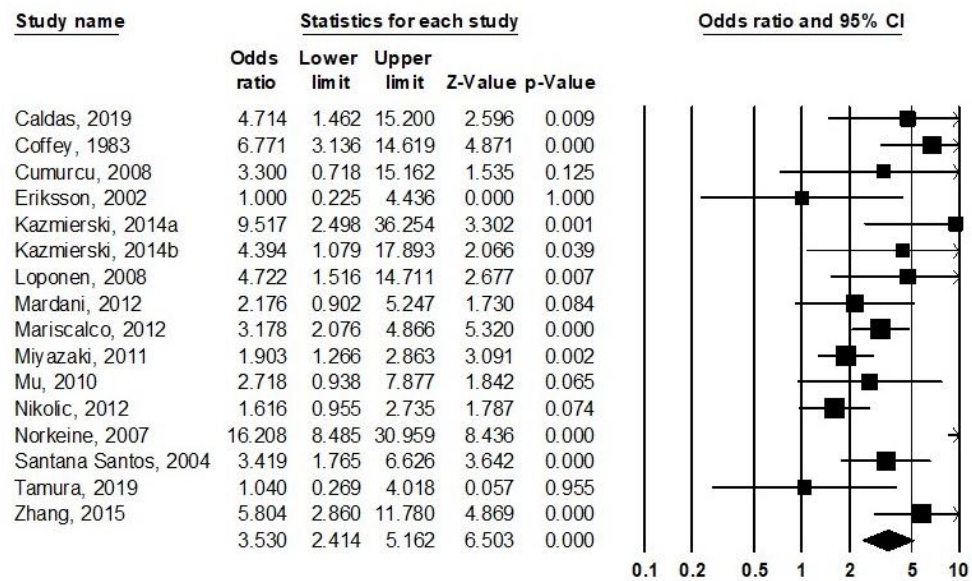
Number of grafts



Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Dong, 2014	0.200	0.206	0.042	-0.204	0.604	0.971	0.332
Loponen, 2008	0.300	0.292	0.085	-0.272	0.872	1.028	0.304
Mardani, 2012	-0.190	0.126	0.016	-0.437	0.057	-1.506	0.132
Mu, 2010	0.100	0.096	0.009	-0.089	0.289	1.038	0.299
Norkeine, 2007	0.210	0.169	0.029	-0.122	0.542	1.240	0.215
Rudolph, 2009	0.200	0.163	0.027	-0.119	0.519	1.228	0.220
Sevuk, 2015	0.296	0.112	0.013	0.076	0.516	2.633	0.008
Zhang, 2015	-0.036	0.147	0.022	-0.324	0.252	-0.246	0.806
	0.111	0.064	0.004	-0.015	0.237	1.730	0.084

Post-Operative (Categorical)

Arrhythmia, incl. AF



Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Caldas, 2019	4.714	1.462	15.200	2.596	0.009
Coffey, 1983	6.771	3.136	14.619	4.871	0.000
Cumurcu, 2008	3.300	0.718	15.162	1.535	0.125
Eriksson, 2002	1.000	0.225	4.436	0.000	1.000
Kazmierski, 2014a	9.517	2.498	36.254	3.302	0.001
Kazmierski, 2014b	4.394	1.079	17.893	2.066	0.039
Loponen, 2008	4.722	1.516	14.711	2.677	0.007
Mardani, 2012	2.176	0.902	5.247	1.730	0.084
Mariscalco, 2012	3.178	2.076	4.866	5.320	0.000
Miyazaki, 2011	1.903	1.266	2.863	3.091	0.002
Mu, 2010	2.718	0.938	7.877	1.842	0.065
Nikolic, 2012	1.616	0.955	2.735	1.787	0.074
Norkeine, 2007	16.208	8.485	30.959	8.436	0.000
Santana Santos, 2004	3.419	1.765	6.626	3.642	0.000
Tamura, 2019	1.040	0.269	4.018	0.057	0.955
Zhang, 2015	5.804	2.860	11.780	4.869	0.000
	3.530	2.414	5.162	6.503	0.000

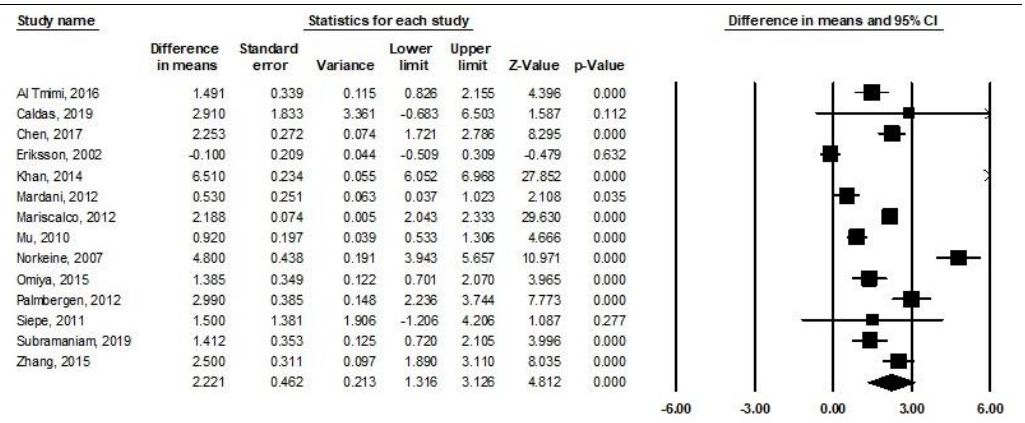
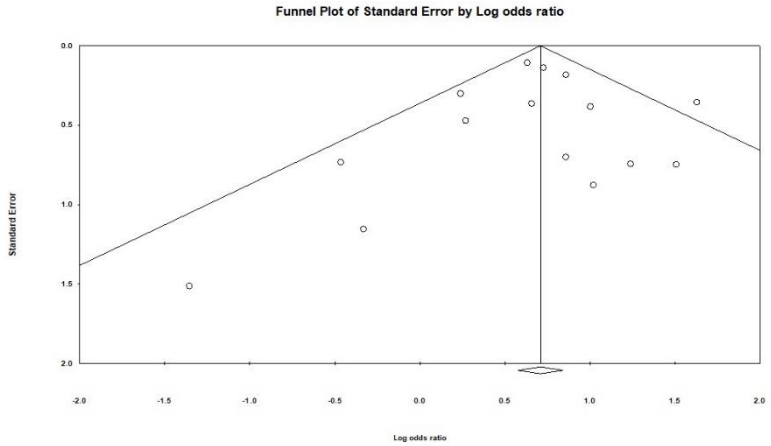
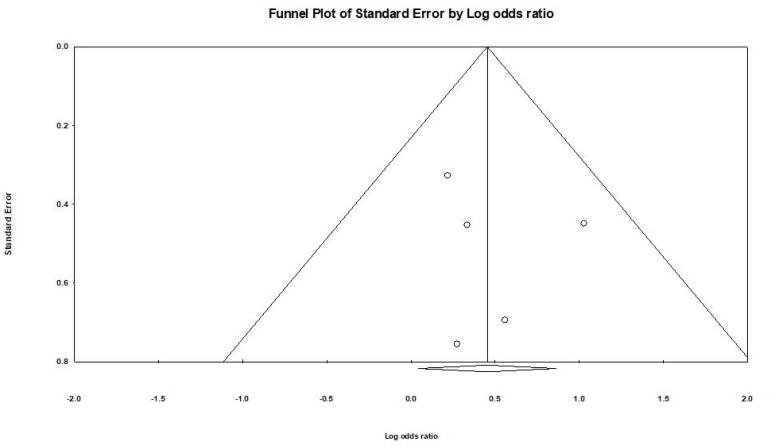
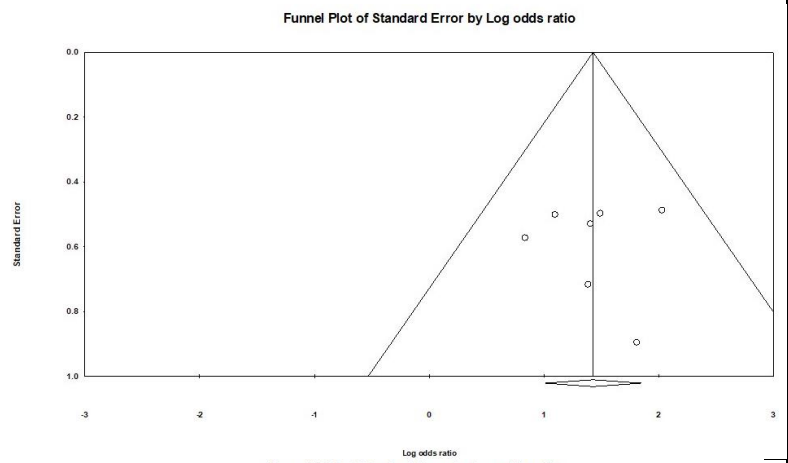
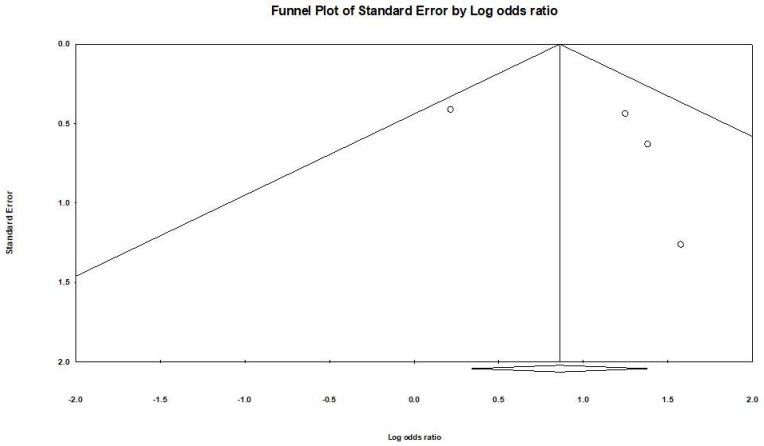
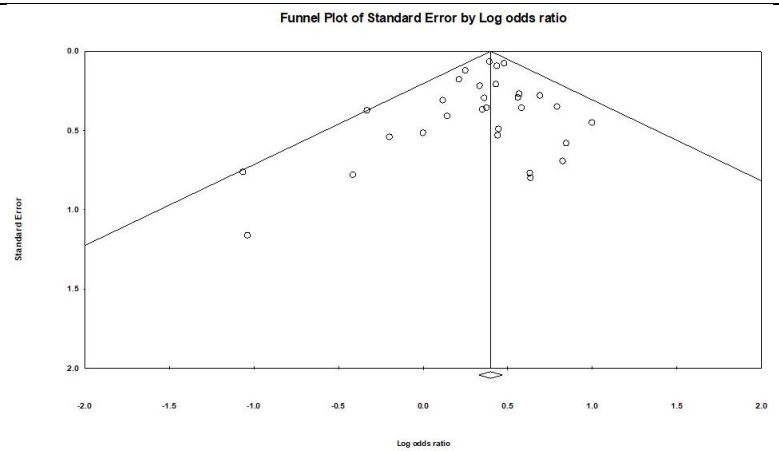
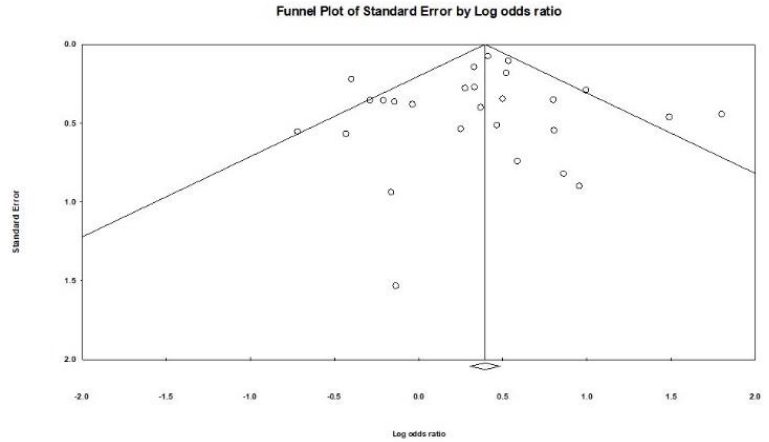
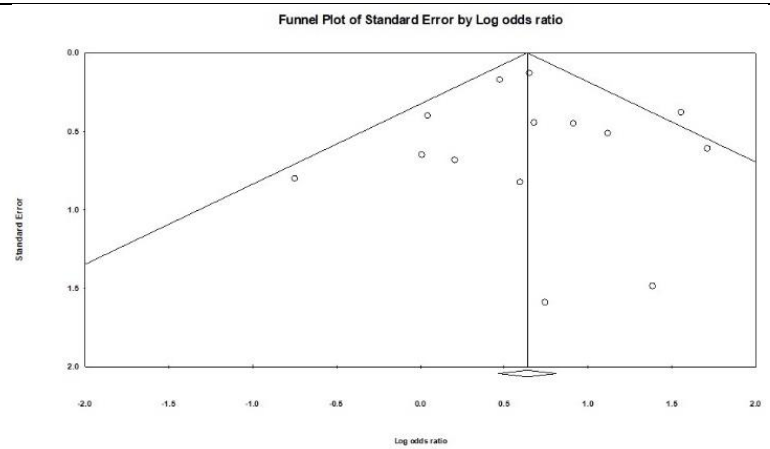
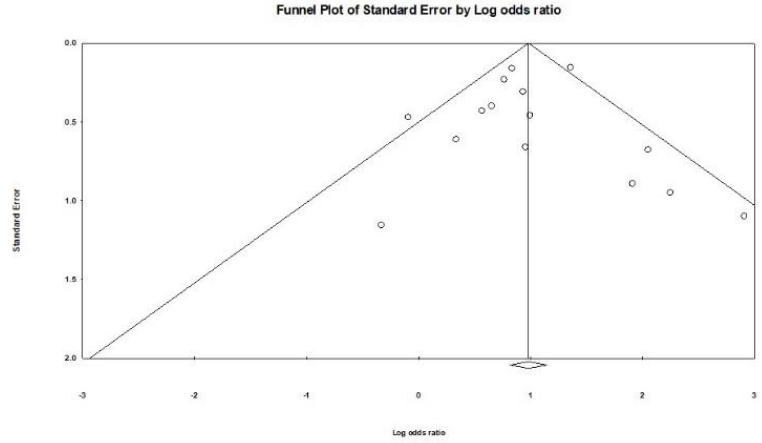
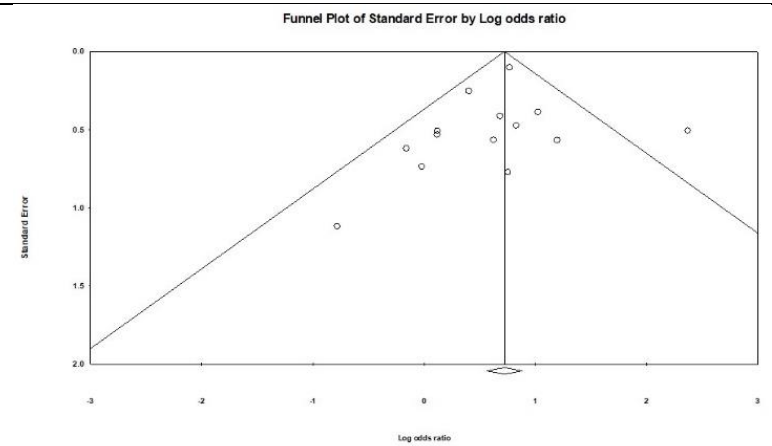
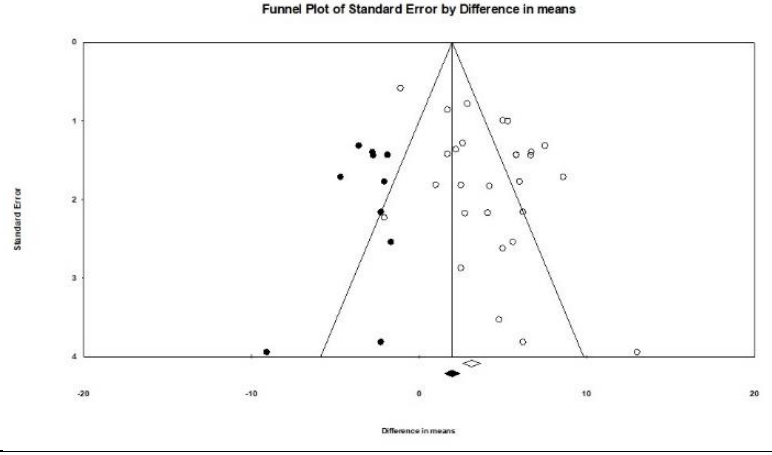
Post-Operative (Continuous)	
LOS in ICU (days)	

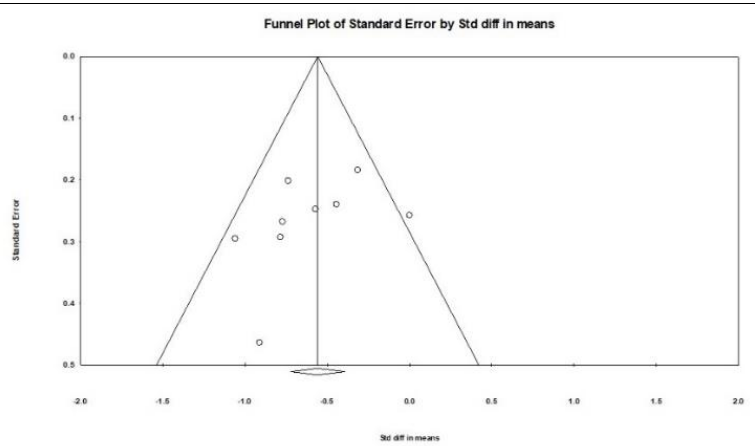
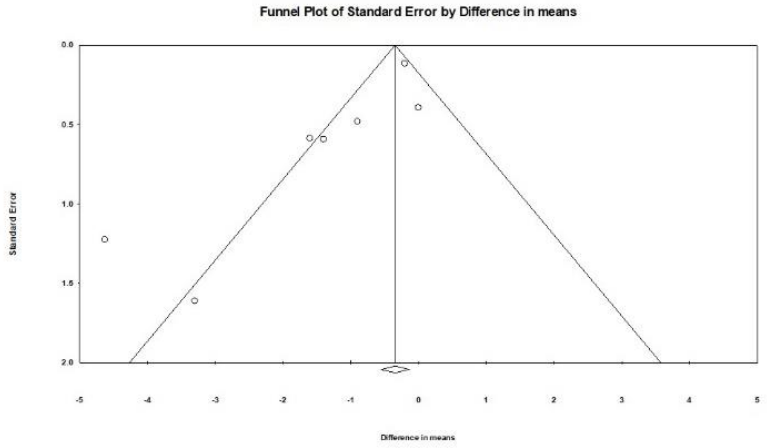
Figure S2. Funnel plots for statistically significant analyses in regard to delirium post-CABG, and results of publication bias/small-study effect investigation when more than 10 studies were available.	**Egger's Test**		**Trim and Fill**		
	Intercept	**p value (1-tailed)**	**No. imputed studies**	**OR/MD† /SMD‡**	**95%CI**
Preoperative (Categorical)					
Arrhythmia, incl. AF 	-0.08	.432	-	-	-
BMI ≥30 only 	-	-	-	-	-

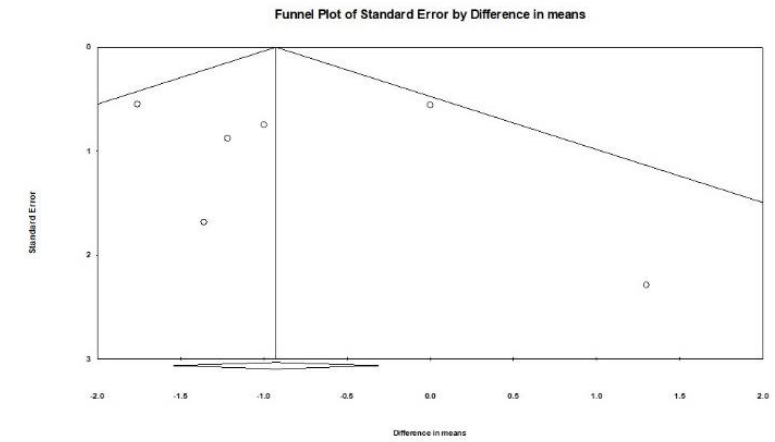
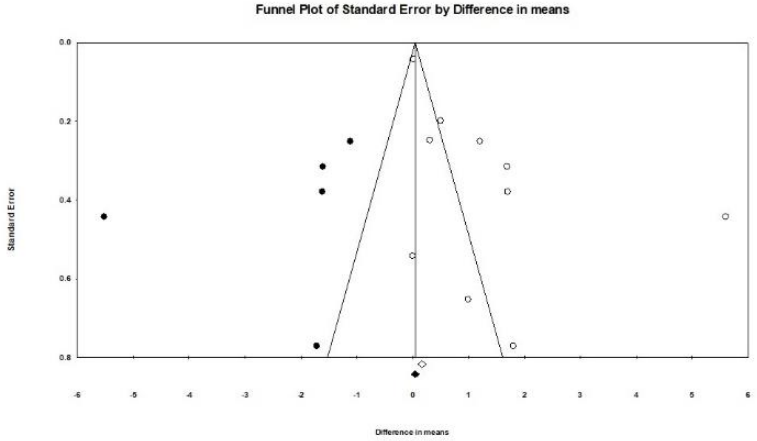
Cognitive Impairment		-	-	-	-	-
Depression		-	-	-	-	-

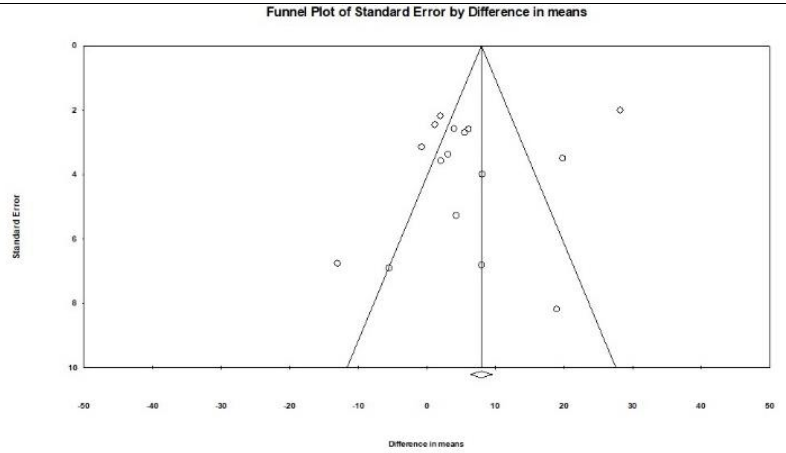
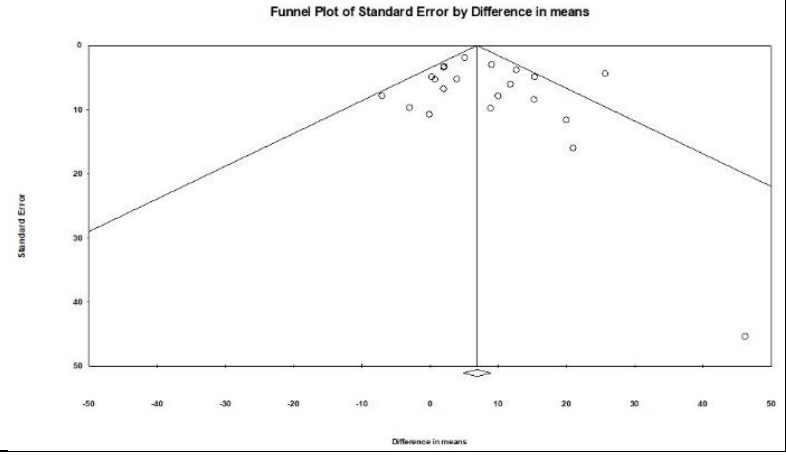
Diabetes		-0.27	.143	-	- -
Hypertension		-0.18	.347	-	- -

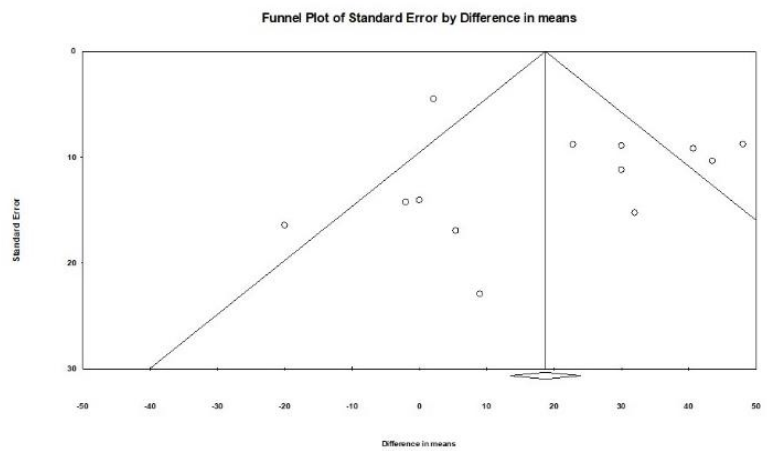
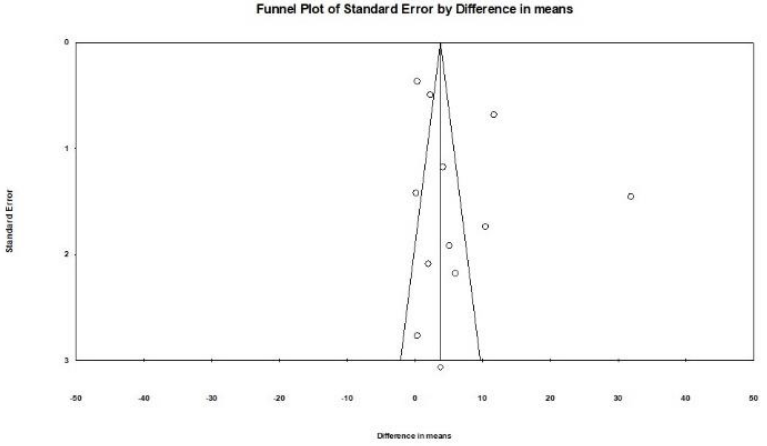
Kidney Injury		0.13	.406	-	-	-
Previous stroke, TIA, CVA		-0.03	.483	-	-	-

PVD		-0.35	.266	-	-	-
Preoperative (Continuous)						
Age		2.44	.003	11	2.24†	1.04-3.45

Cognition: All tests		-	-	-	-	-
Cognition: MMSE only		-	-	-	-	

Education (years)		-	-	-	-
EuroSCORE		4.36	.010	5	0.15† -0.60-0.90
Intra-Operative (Continuous)					

ACC time (mins)		-2.45	.143	-	-	-
CPB time (mins)		0.45	.241	-	-	-

Duration of surgery (mins)		0.77	.296	-	-	-
Intubation time (hours)		5.20	.106	-	-	-
Post-Operative (Categorical)						

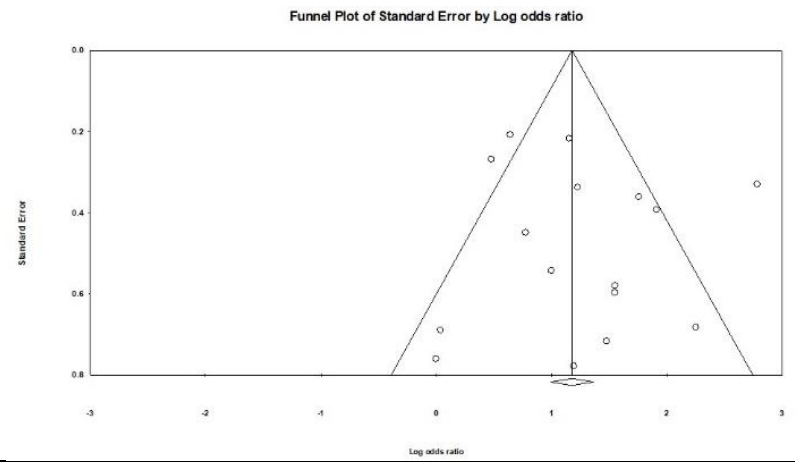
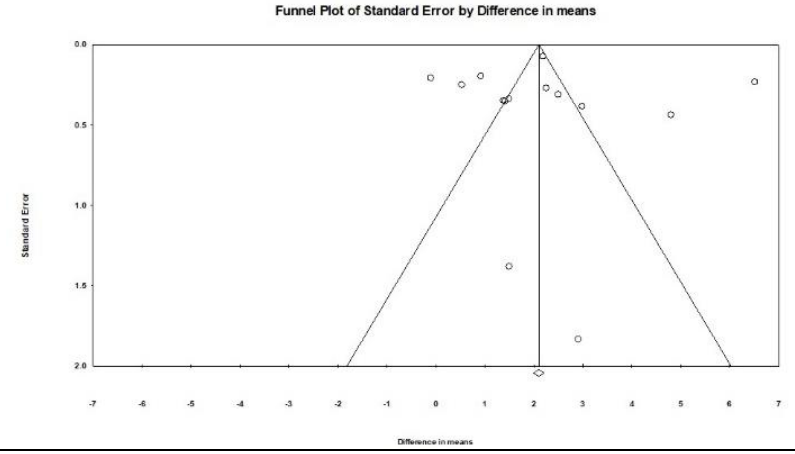
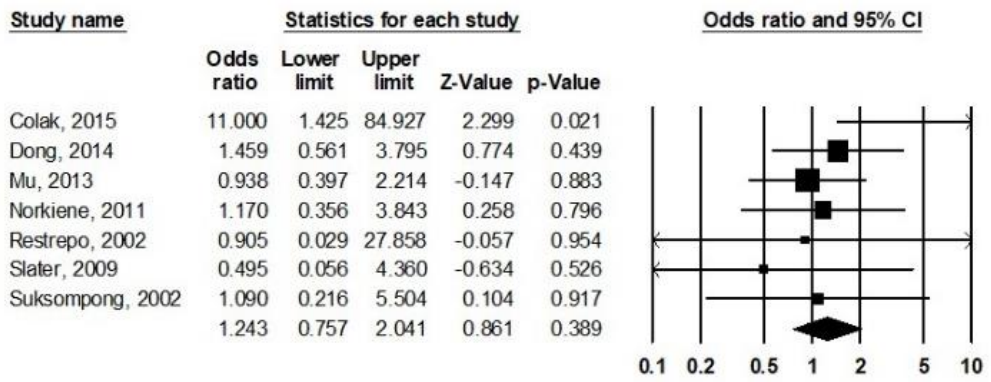
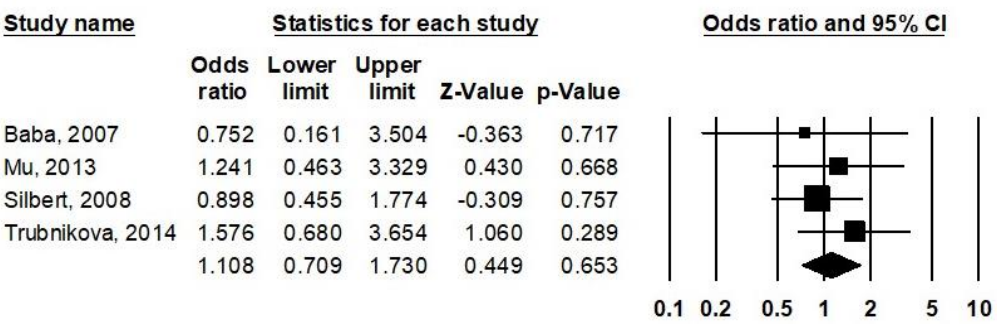
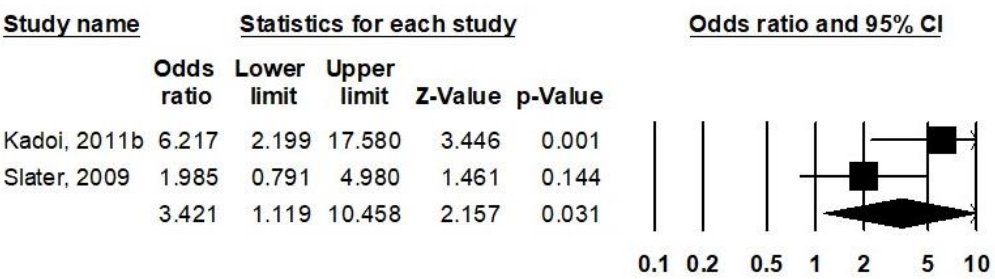
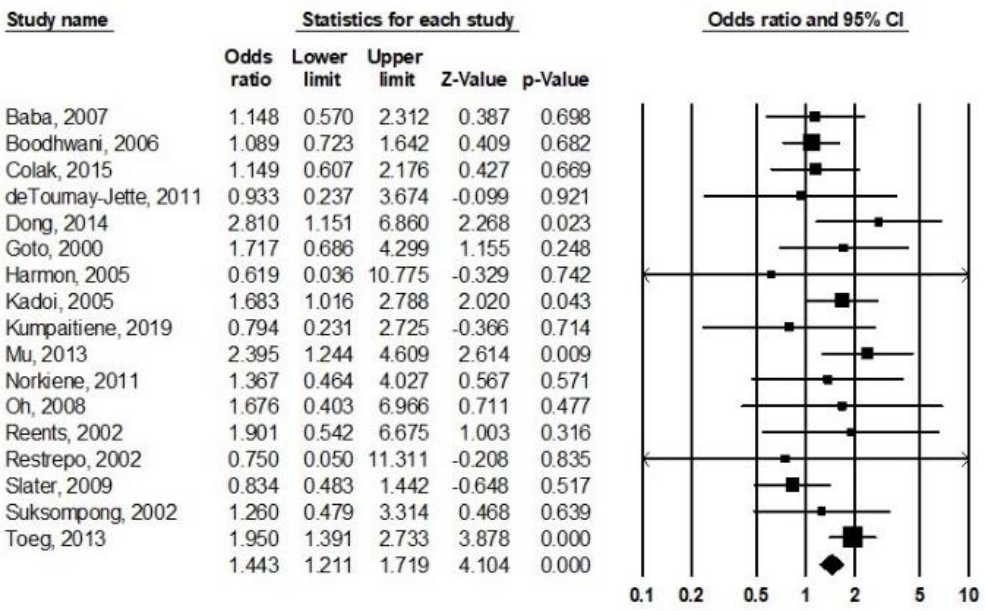
Arrhythmia, incl. AF		0.76	.260	-	-
Post-Operative (Continuous)					
LOS in ICU (days)		0.32	.459	-	- -

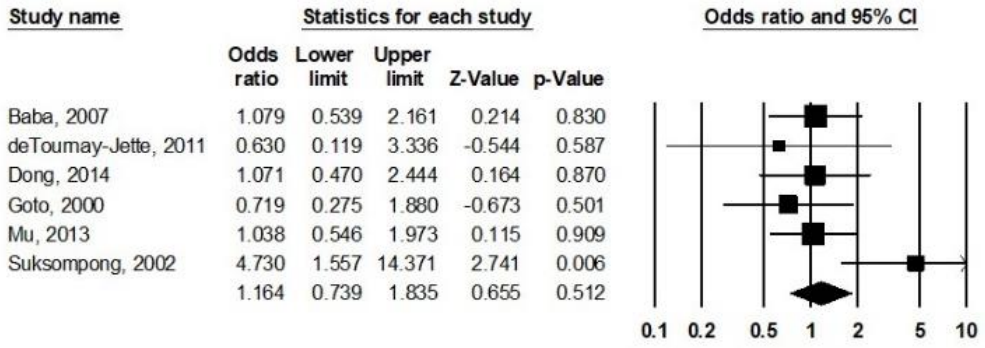
Figure S3. Forest plots for acute cognitive decline post-CABG analyses.

Variable	Forest Plot
Pre-Operative (Categorical)	
Arrhythmia, incl. AF	
Cognitive Impairment	
Depression	

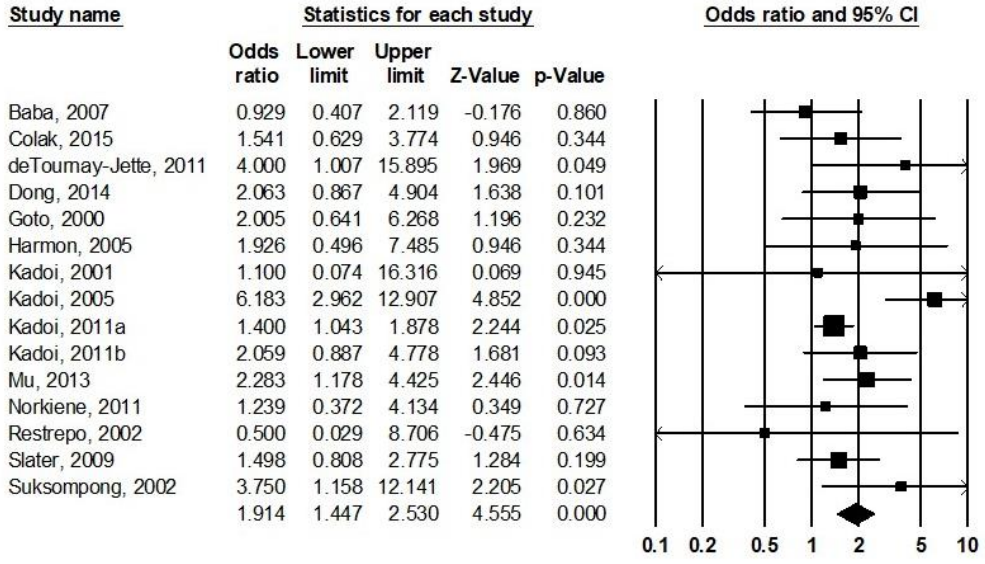
Diabetes



Dyslipidemia/Hyperlipidemia

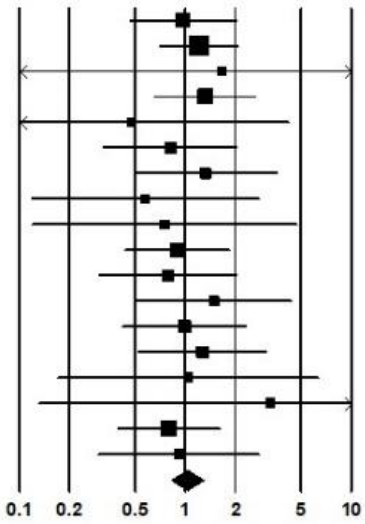


Hypertension



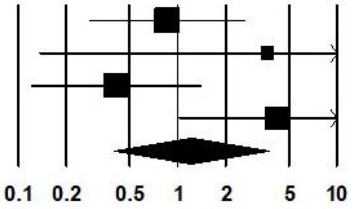
Sex (male)

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Baba, 2007	0.972	0.459	2.060	-0.074	0.941
Boodhwani, 2006	1.206	0.692	2.102	0.660	0.509
Christiansen, 2016	1.667	0.048	58.281	0.282	0.778
Colak, 2015	1.322	0.651	2.685	0.772	0.440
deTournay-Jette, 2011	0.475	0.053	4.255	-0.665	0.506
Dong, 2014	0.811	0.317	2.074	-0.437	0.662
Goto, 2000	1.324	0.486	3.607	0.548	0.584
Hall, 1999	0.574	0.117	2.810	-0.685	0.494
Harmon, 2005	0.750	0.118	4.760	-0.305	0.760
Kadoi, 2005	0.896	0.429	1.871	-0.292	0.770
Kadoi, 2011b	0.786	0.299	2.061	-0.490	0.624
Kumpaitiene, 2019	1.488	0.504	4.393	0.719	0.472
Mu, 2013	0.988	0.415	2.355	-0.027	0.979
Norkiene, 2011	1.270	0.517	3.121	0.522	0.602
Reents, 2002	1.037	0.169	6.375	0.039	0.969
Restrepo, 2002	3.267	0.130	82.036	0.720	0.472
Slater, 2009	0.795	0.387	1.634	-0.625	0.532
Suksompong, 2002	0.913	0.297	2.809	-0.159	0.874
	1.026	0.818	1.286	0.223	0.824



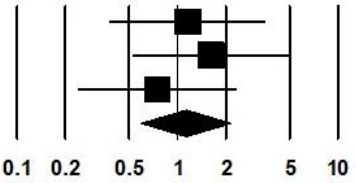
Kidney injury

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Baba, 2007	0.860	0.278	2.662	-0.262	0.793
Colak, 2015	3.668	0.135	99.509	0.772	0.440
Slater, 2009	0.411	0.119	1.416	-1.409	0.159
Suksompong, 2002	4.200	1.018	17.327	1.985	0.047
	1.213	0.396	3.716	0.338	0.735



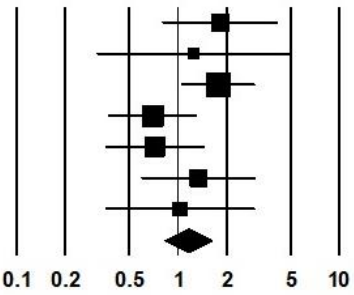
Previous MI <90 days

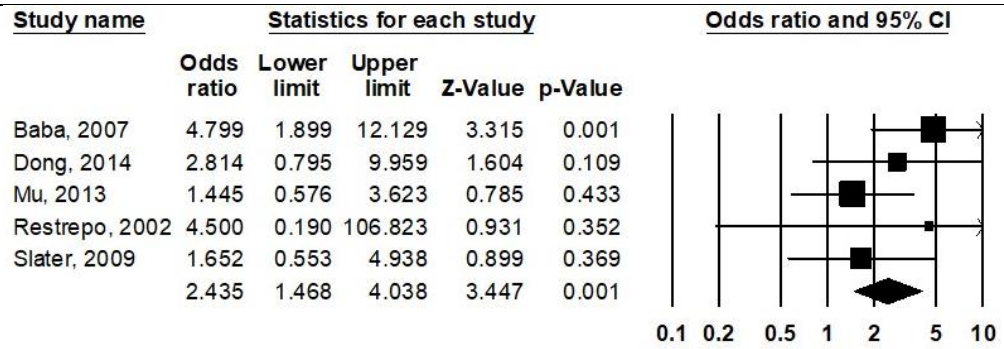
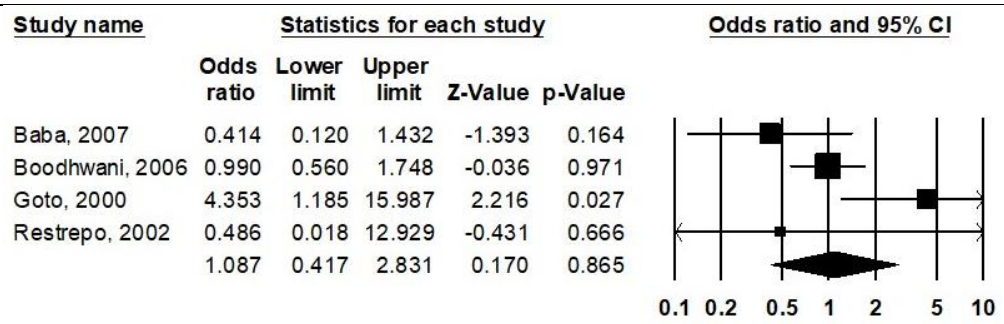
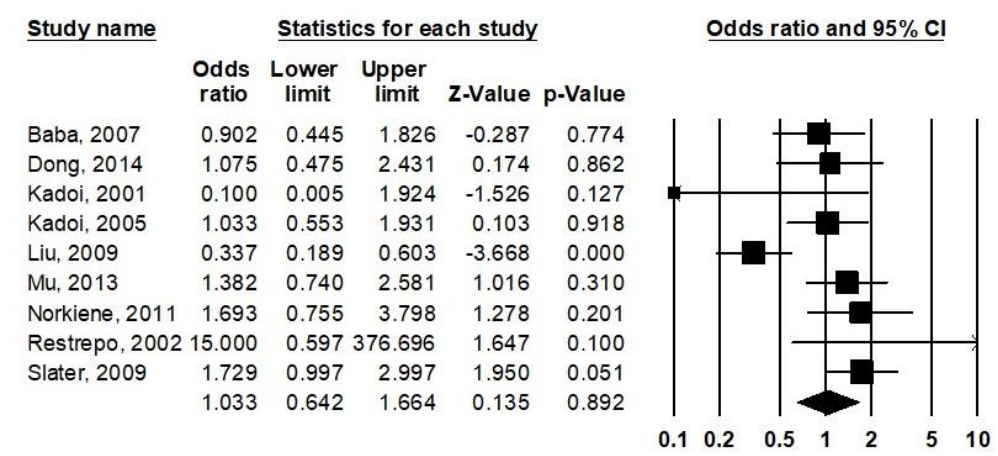
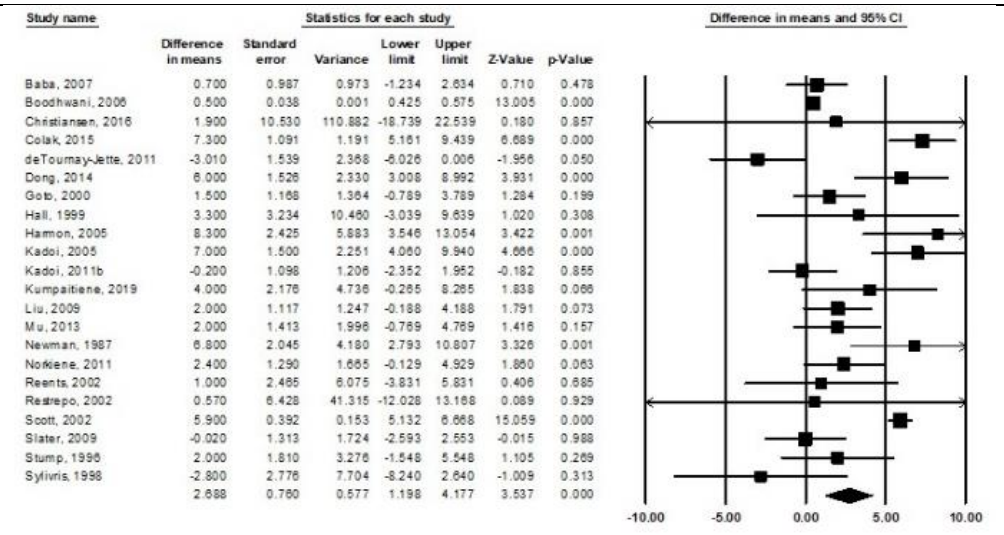
Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Colak, 2015	1.155	0.376	3.552	0.252	0.801
Norkiene, 2011	1.621	0.528	4.975	0.844	0.399
Suksompong, 2002	0.750	0.240	2.342	-0.495	0.620
	1.124	0.586	2.156	0.353	0.724



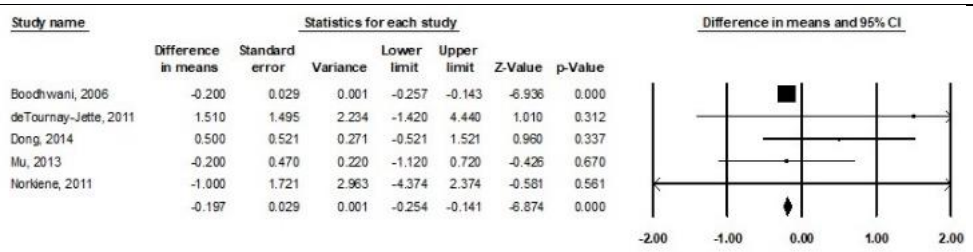
Previous MI history/ever

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Dong, 2014	1.831	0.800	4.191	1.431	0.152
Harmon, 2005	1.246	0.312	4.977	0.311	0.755
Liu, 2009	1.776	1.046	3.015	2.127	0.033
Mu, 2013	0.698	0.369	1.322	-1.103	0.270
Norkiene, 2011	0.719	0.354	1.458	-0.915	0.360
Slater, 2009	1.345	0.590	3.063	0.705	0.481
Suksompong, 2002	1.030	0.352	3.011	0.054	0.957
	1.160	0.825	1.630	0.852	0.394

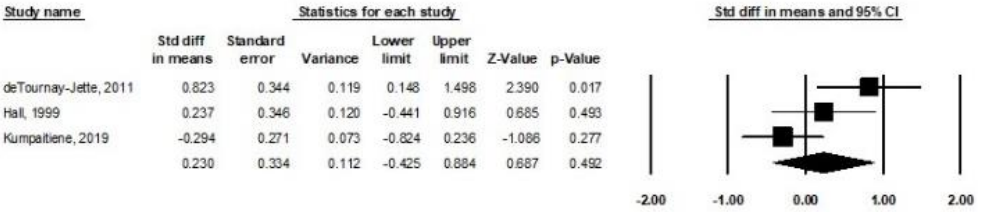


Previous stroke, TIA, CVA	
PVD	
Smoking current/history	
Pre-Operative (Continuous)	
Age (years)	

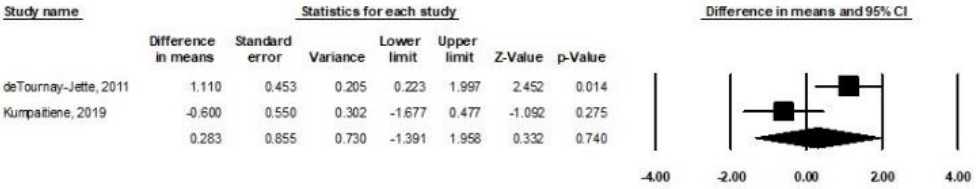
BMI



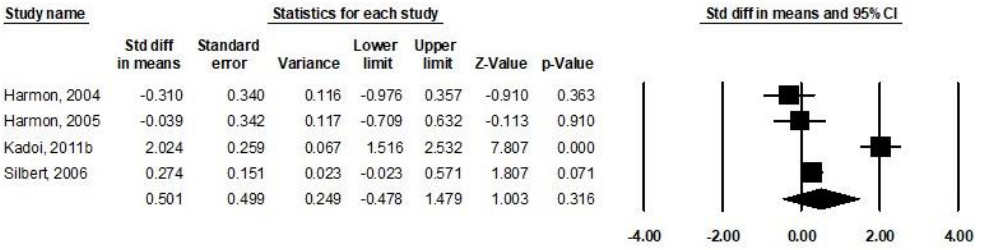
Cognition: All tests



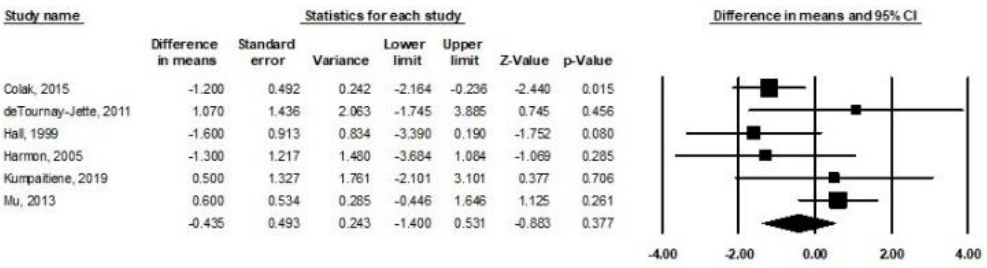
Cognition: MMSE only



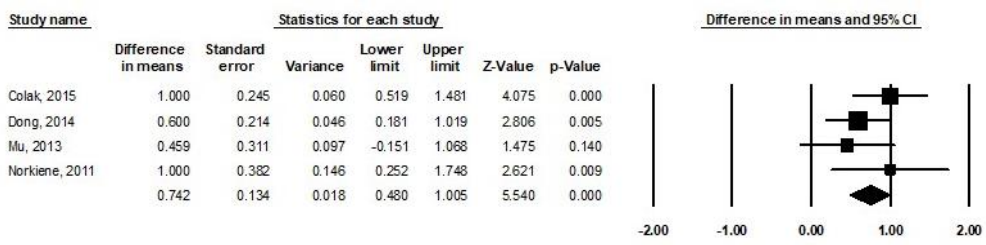
Depression: All tests



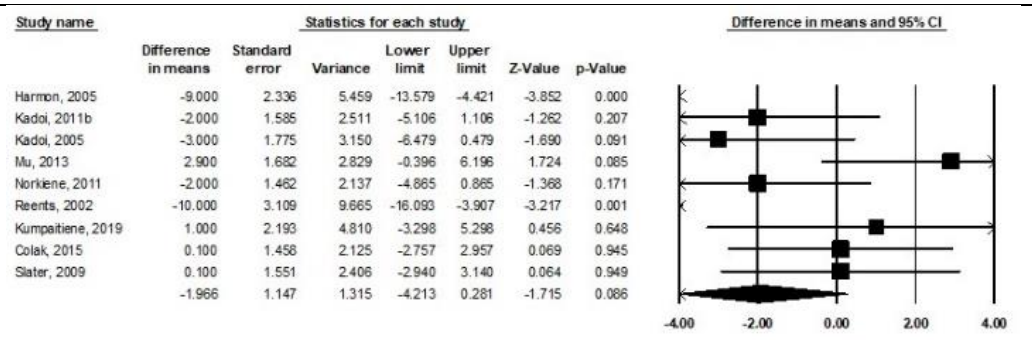
Education (years)



EuroSCORE



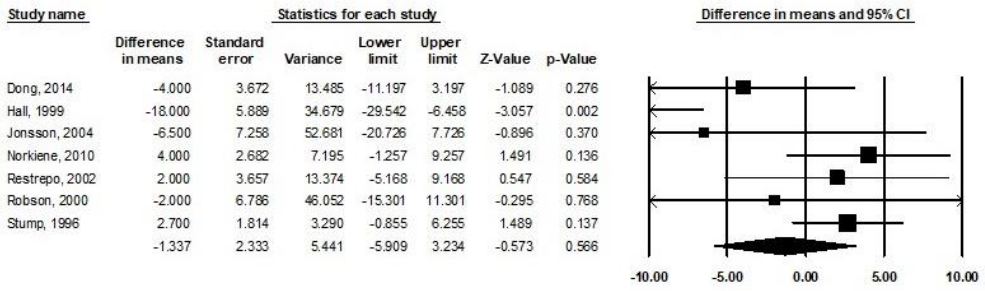
LVEF %



Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Harmon, 2005	-9.000	2.336	5.459	-13.579	-4.421	-3.852	0.000
Kadoi, 2011b	-2.000	1.585	2.511	-5.106	1.106	-1.262	0.207
Kadoi, 2005	-3.000	1.775	3.150	-6.479	0.479	-1.690	0.091
Mu, 2013	2.900	1.682	2.829	-0.396	6.196	1.724	0.085
Norkiene, 2011	-2.000	1.462	2.137	-4.865	0.865	-1.368	0.171
Reents, 2002	-10.000	3.109	9.665	-16.093	-3.907	-3.217	0.001
Kumpaitiene, 2019	1.000	2.193	4.810	-3.298	5.298	0.456	0.648
Colak, 2015	0.100	1.458	2.125	-2.757	2.957	0.069	0.945
Slater, 2009	0.100	1.551	2.406	-2.940	3.140	0.064	0.949
	-1.966	1.147	1.315	-4.213	0.281	-1.715	0.086

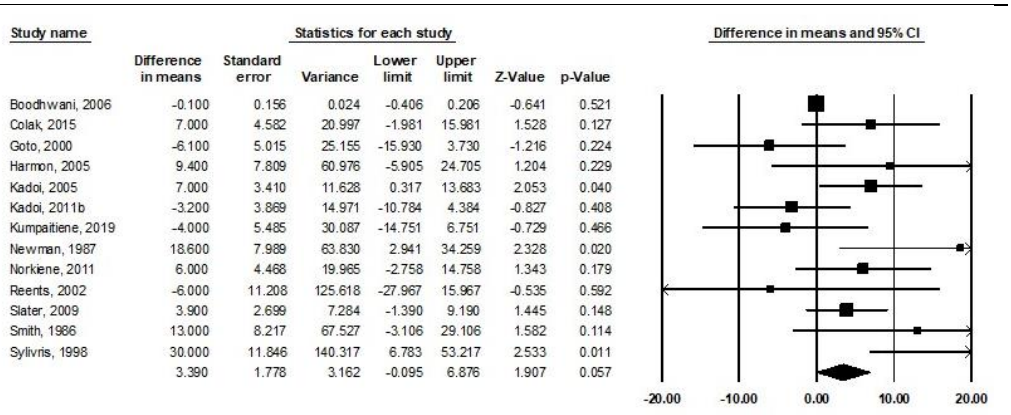
Intra-Operative (Continuous)

ACC time (mins)



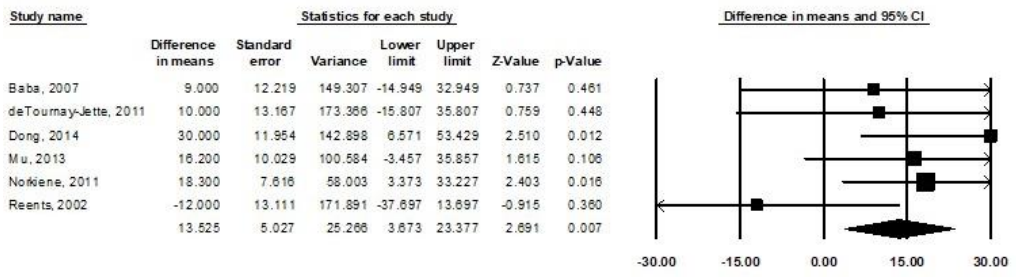
Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Dong, 2014	-4.000	3.672	13.485	-11.197	3.197	-1.089	0.276
Hall, 1999	-18.000	5.889	34.679	-29.542	-6.458	-3.057	0.002
Jonsson, 2004	-6.500	7.258	52.681	-20.726	7.726	-0.896	0.370
Norkiene, 2010	4.000	2.682	7.195	-1.257	9.257	1.491	0.136
Restrepo, 2002	2.000	3.657	13.374	-5.168	9.168	0.547	0.584
Robson, 2000	-2.000	6.786	46.052	-15.301	11.301	-0.295	0.768
Stump, 1996	2.700	1.814	3.290	-0.855	6.255	1.489	0.137
	-1.337	2.333	5.441	-5.909	3.234	-0.573	0.566

CPB time (mins)



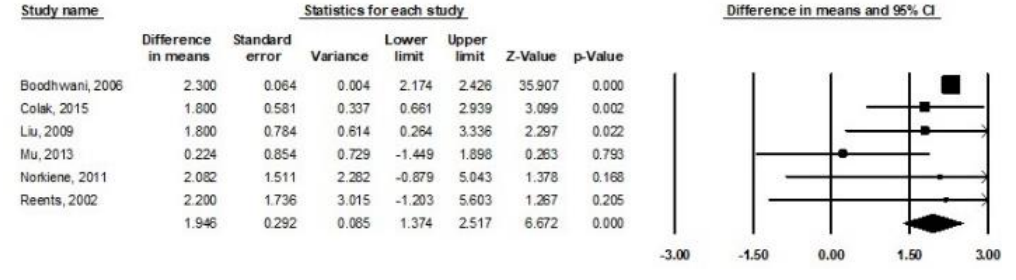
Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Boodhwani, 2006	-0.100	0.156	0.024	-0.406	0.206	-0.641	0.521
Colak, 2015	7.000	4.582	20.997	-1.981	15.981	1.528	0.127
Goto, 2000	-6.100	5.015	25.155	-15.930	3.730	-1.216	0.224
Harmon, 2005	9.400	7.809	60.976	-5.905	24.705	1.204	0.229
Kadoi, 2005	7.000	3.410	11.628	0.317	13.683	2.053	0.040
Kadoi, 2011b	-3.200	3.869	14.971	-10.784	4.384	-0.827	0.408
Kumpaitiene, 2019	-4.000	5.485	30.087	-14.751	6.751	-0.729	0.466
Newman, 1987	18.600	7.989	63.830	2.941	34.259	2.328	0.020
Norkiene, 2011	6.000	4.468	19.965	-2.758	14.758	1.343	0.179
Reents, 2002	-6.000	11.208	125.618	-27.967	15.967	-0.535	0.592
Slater, 2009	3.900	2.699	7.284	-1.390	9.190	1.445	0.148
Smith, 1986	13.000	8.217	67.527	-3.106	29.106	1.582	0.114
Sylivris, 1998	30.000	11.846	140.317	6.783	53.217	2.533	0.011
	3.390	1.778	3.162	-0.095	6.876	1.907	0.057

Duration of surgery (mins)



Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Baba, 2007	9.000	12.219	149.307	-14.949	32.949	0.737	0.461
deTournay-Jette, 2011	10.000	13.167	173.366	-15.807	35.807	0.759	0.448
Dong, 2014	30.000	11.954	142.898	6.571	53.429	2.510	0.012
Mu, 2013	16.200	10.029	100.584	-3.457	35.857	1.615	0.106
Norkiene, 2011	18.300	7.616	58.003	3.373	33.227	2.403	0.016
Reents, 2002	-12.000	13.111	171.891	-37.697	13.697	-0.915	0.360
	13.525	5.027	25.266	3.673	23.377	2.691	0.007

Intubation time (hours)



Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Boodhwani, 2006	2.300	0.064	0.004	2.174	2.426	35.907	0.000
Colak, 2015	1.800	0.581	0.337	0.661	2.939	3.099	0.002
Liu, 2009	1.800	0.784	0.614	0.264	3.336	2.297	0.022
Mu, 2013	0.224	0.854	0.729	-1.449	1.898	0.263	0.793
Norkiene, 2011	2.082	1.511	2.282	-0.879	5.043	1.378	0.168
Reents, 2002	2.200	1.736	3.015	-1.203	5.603	1.267	0.205
	1.946	0.292	0.085	1.374	2.517	6.672	0.000

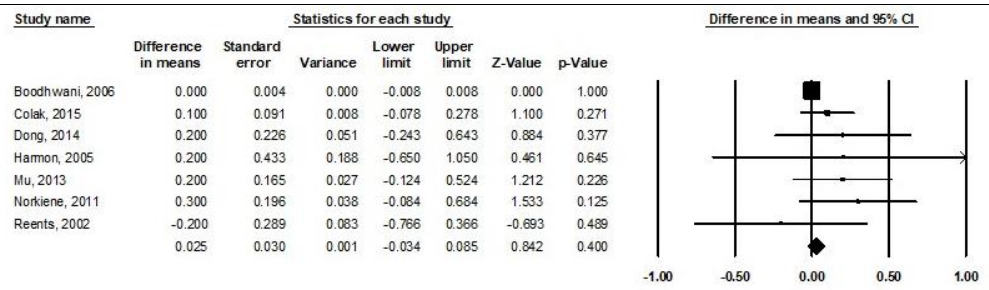
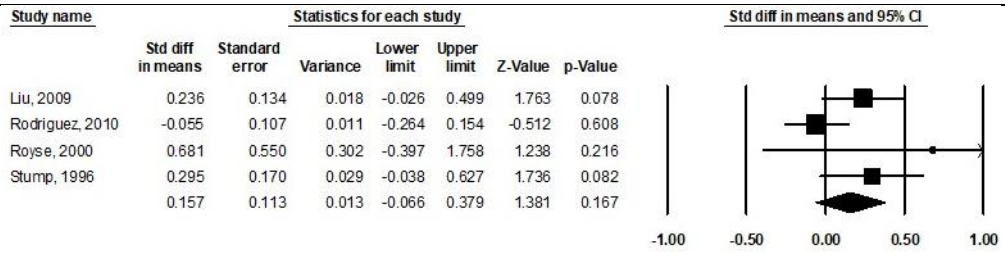
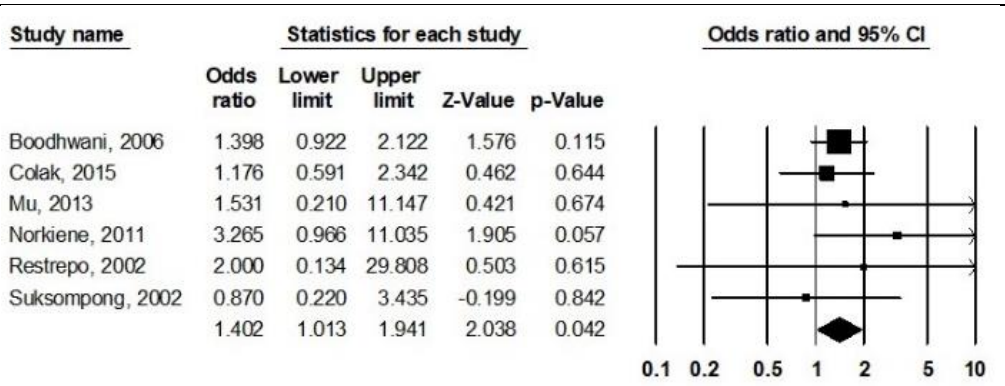
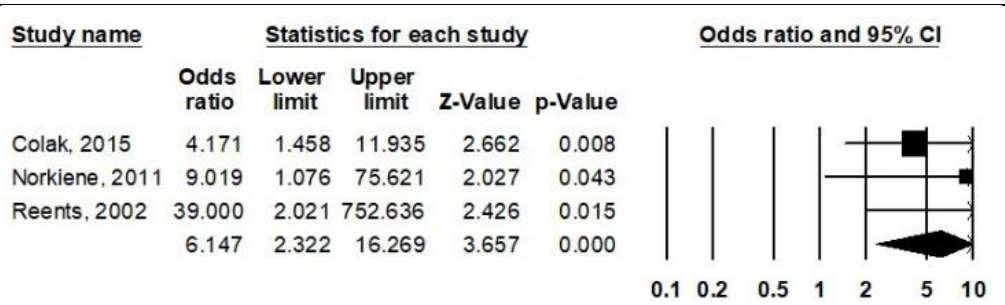
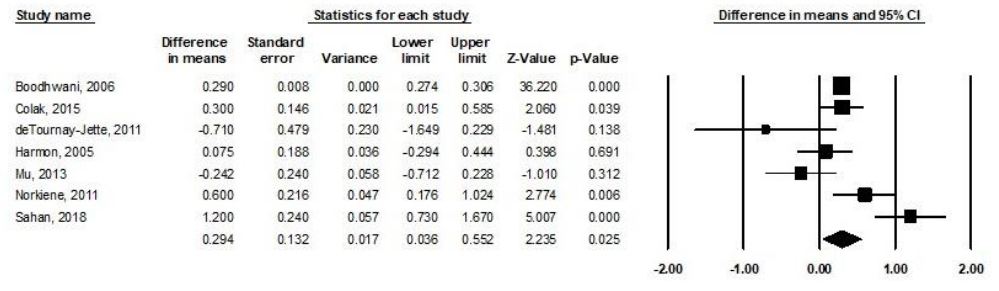
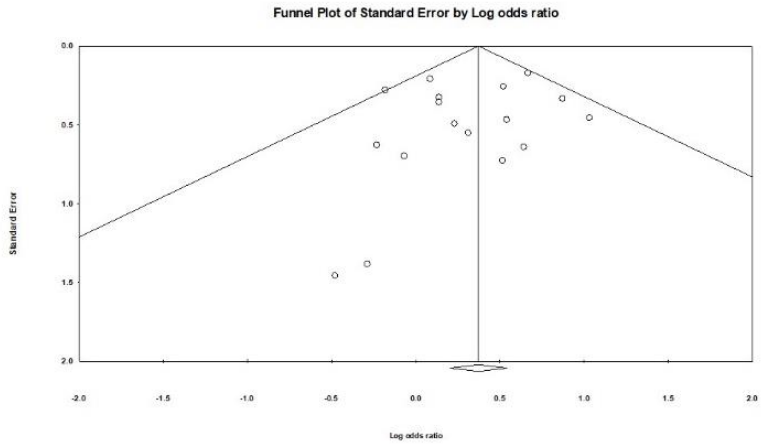
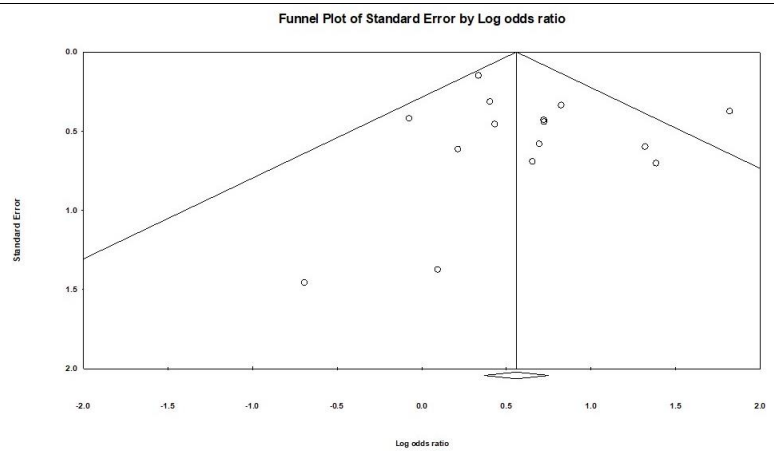
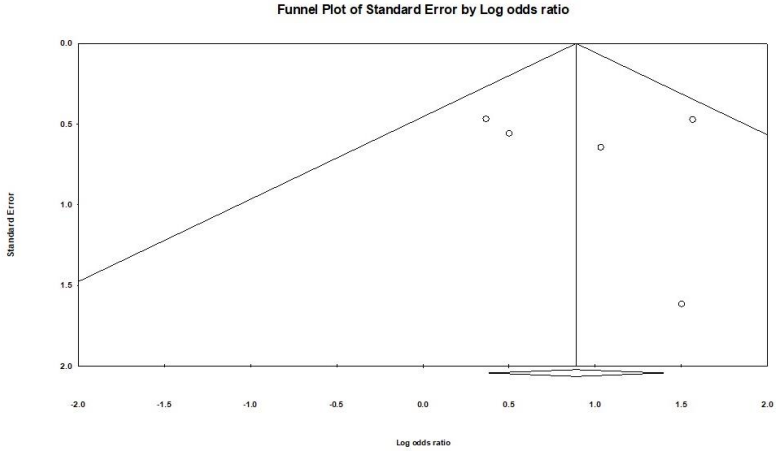
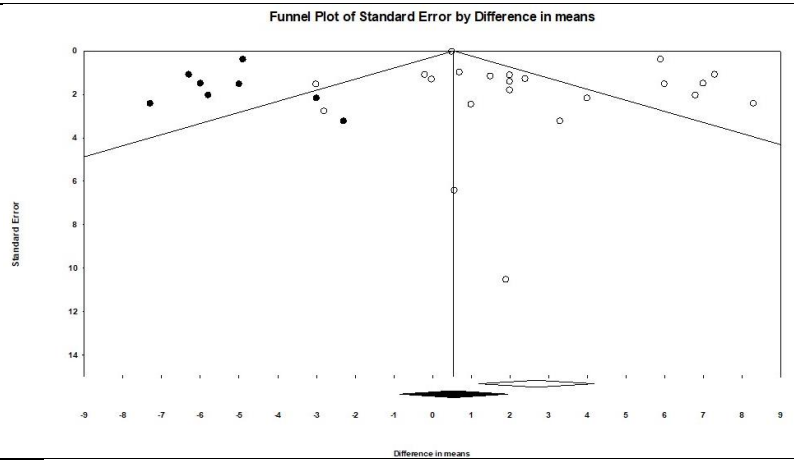
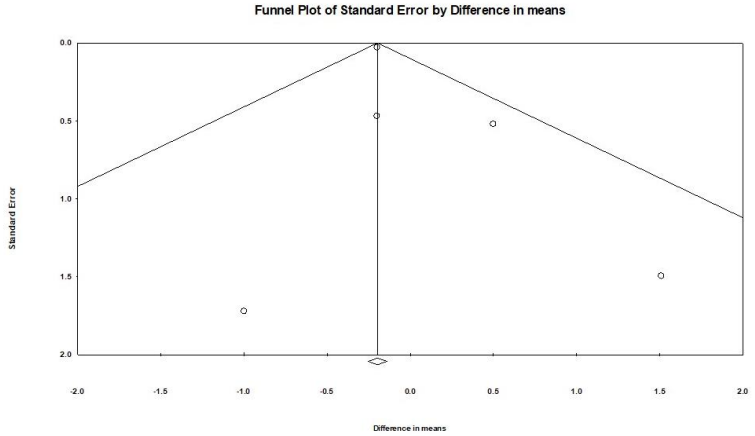
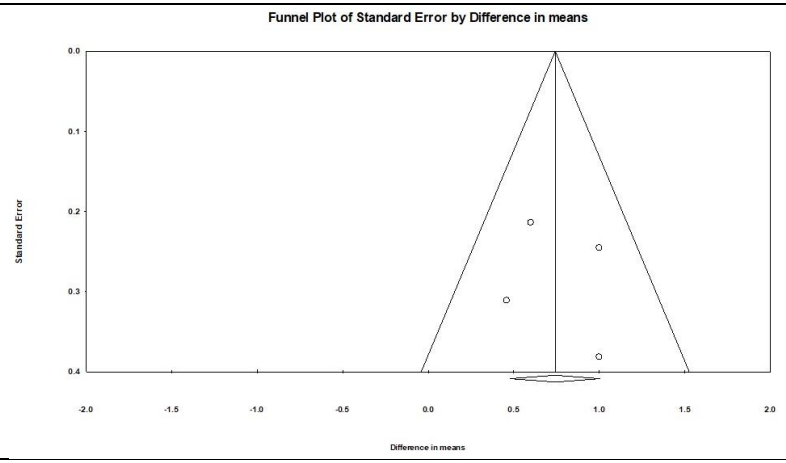
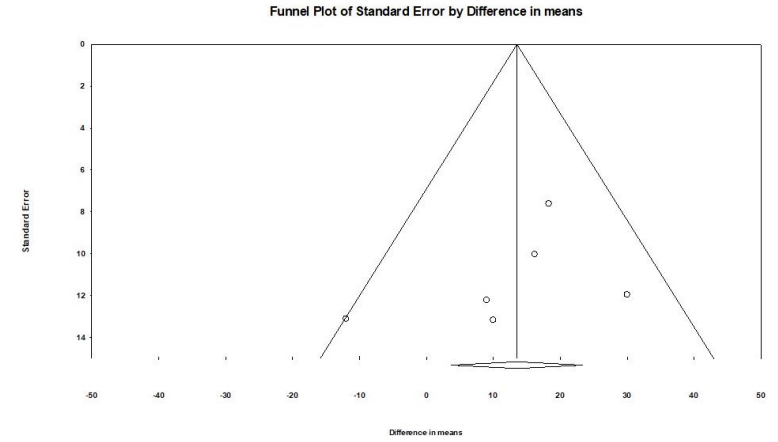
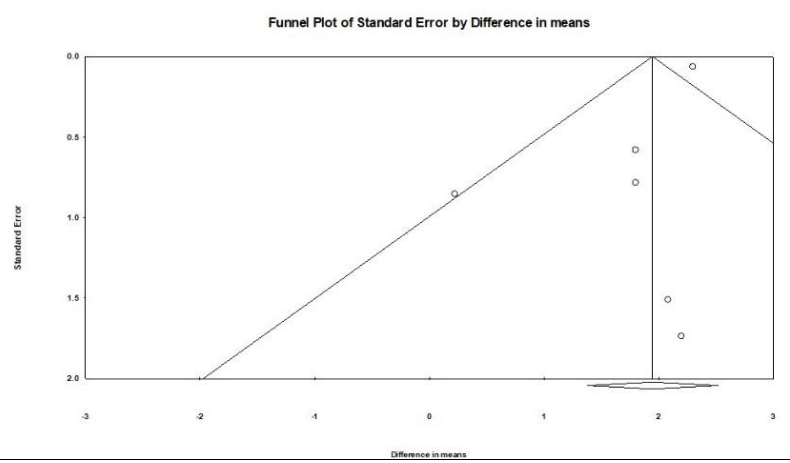
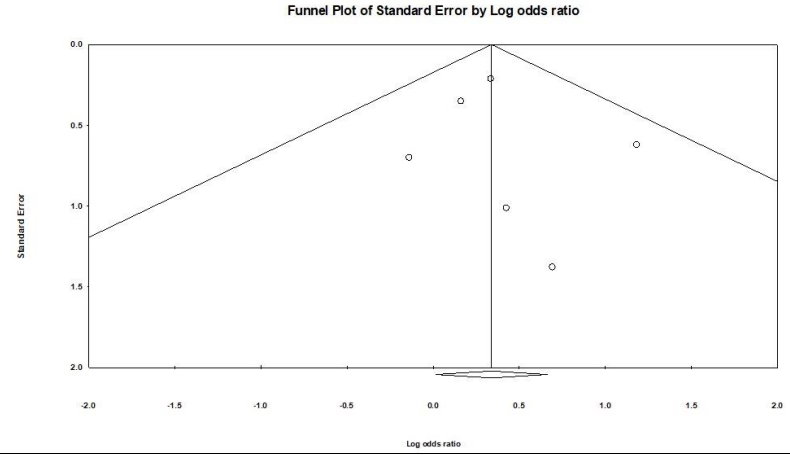
Number of grafts	
Total Microemboli	
Post-Operative (Categorical)	
Arrhythmia, incl. AF	
Delirium	
Post-Operative (Continuous)	
LOS in ICU (days)	

Figure S4. Funnel plots for statistically significant analyses in regard to acute cognitive decline post-CABG, and results of publication bias/small-study effect investigation when more than 10 studies were available.		**Egger's Test**		**Trim and Fill**		
		Intercept	**p value (1-tailed)**	**No. imputed studies**	**OR/MD† /SMD‡**	**95%CI**
Preoperative (Categorical)						
Depression	Only 2 studies, could not produce funnel plot			-	-	-
Diabetes		-0.39	.232	-	-	-

Hypertension		0.55	.197	-	-	-
Previous stroke, TIA, CVA		-	-	-	-	-
Preoperative (Continuous)						

Age		1.80	.015	8	0.55†	-0.86-1.95
BMI		-	-	-	-	-

EuroSCORE		-	-	-	-	-			
Intra-Operative (Continuous)									
Duration of surgery (mins)		-	-	-	-	-			

Intubation time (hours)		-	-	-	-	-
Post-Operative (Categorical)							
Arrhythmia, incl. AF		-	-	-	-	-

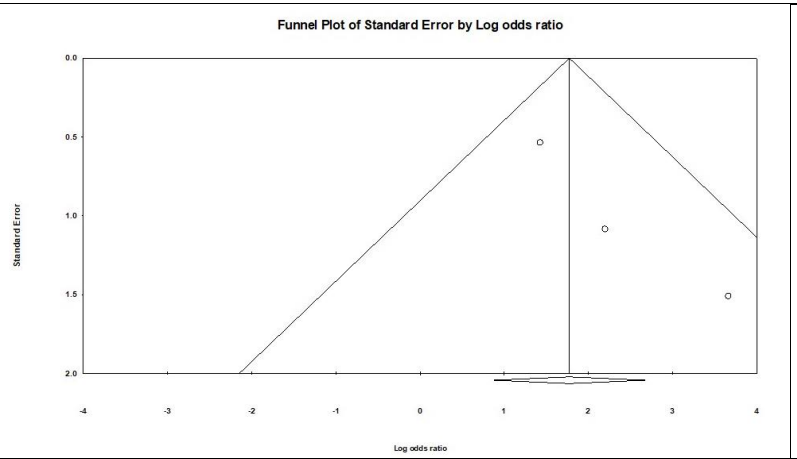
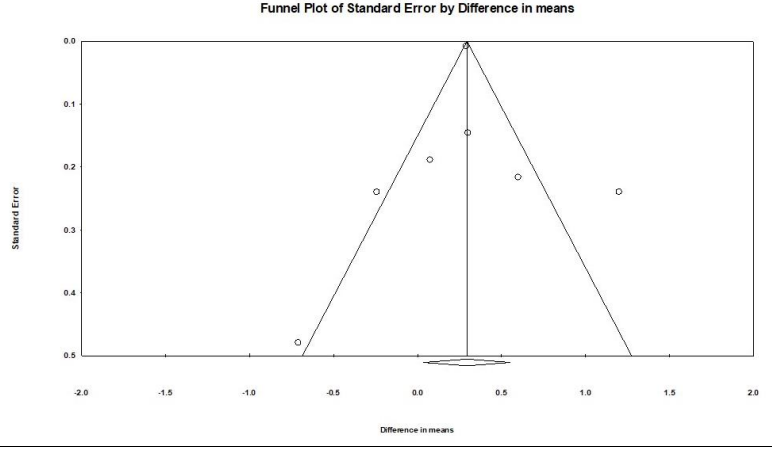
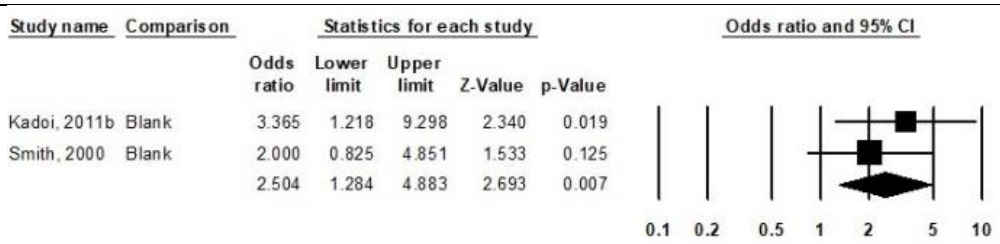
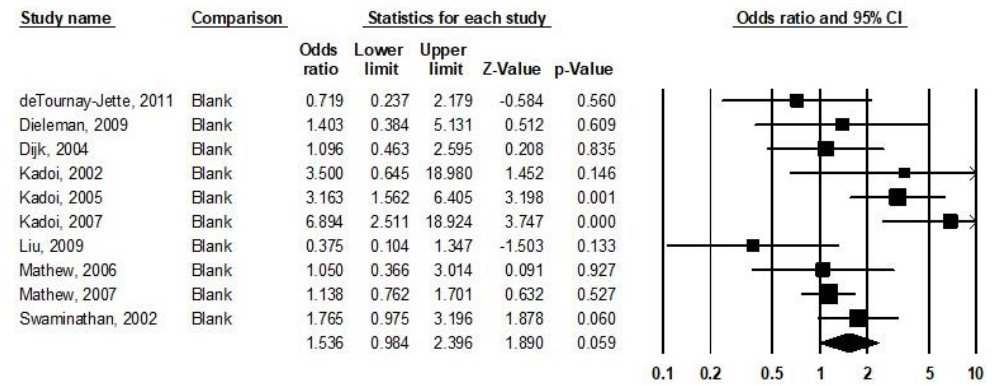
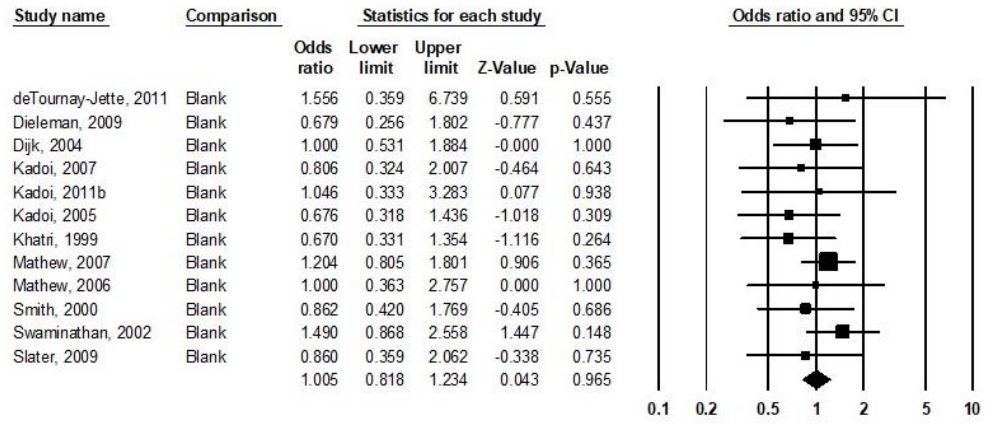
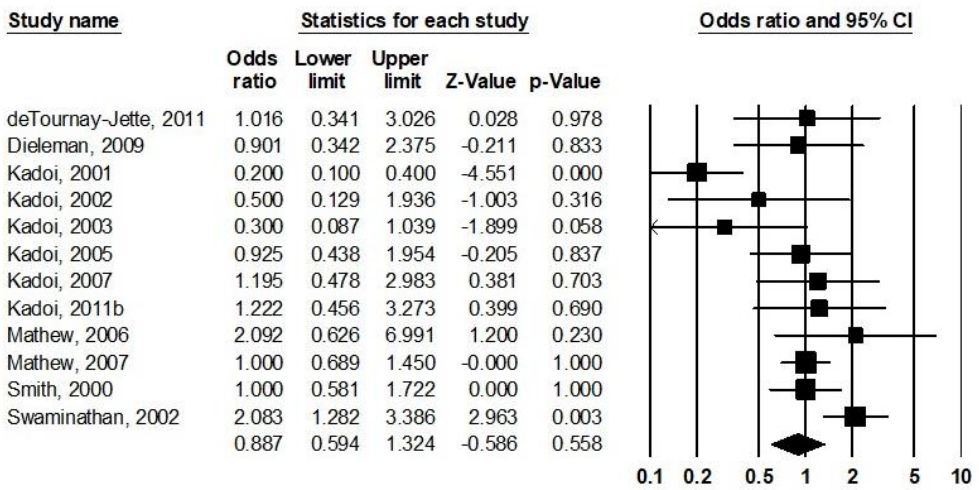
Delirium		-	-	-	-	-		
Post-Operative (Continuous)									
LOS in ICU (days)		-	-	-	-	-		

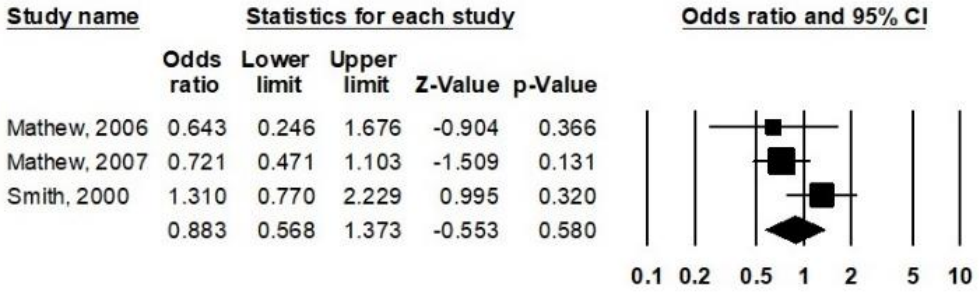
Figure S5. Forest plots for mid-term cognitive decline post-CABG analyses.

Variable	Forest Plot
Pre-Operative (Categorical)	
Depression	
Diabetes	
Sex (male)	

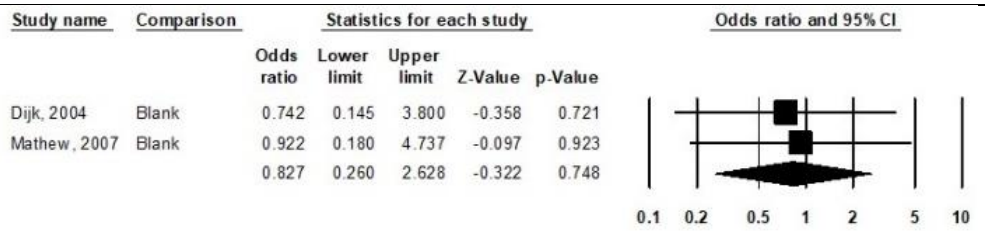
Hypertension



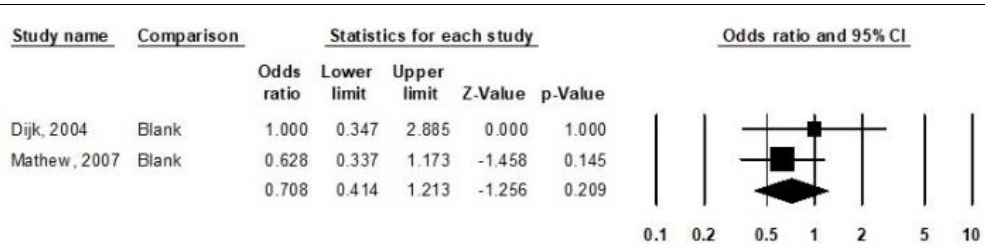
Previous MI history/ever



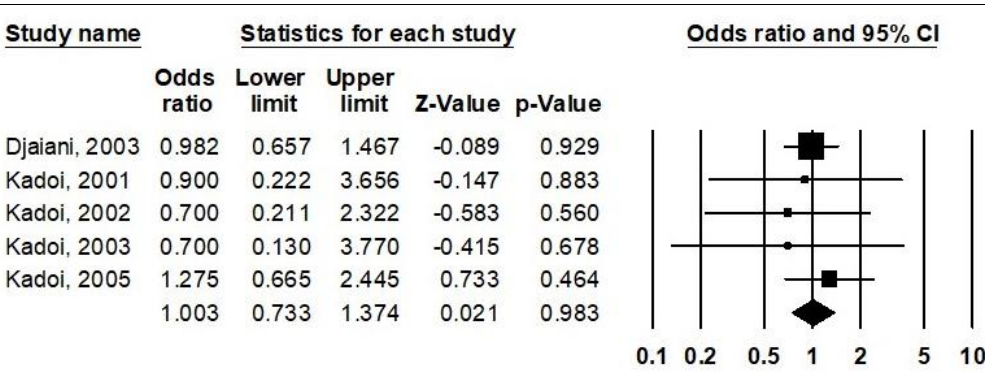
Previous stroke, TIA, CVA

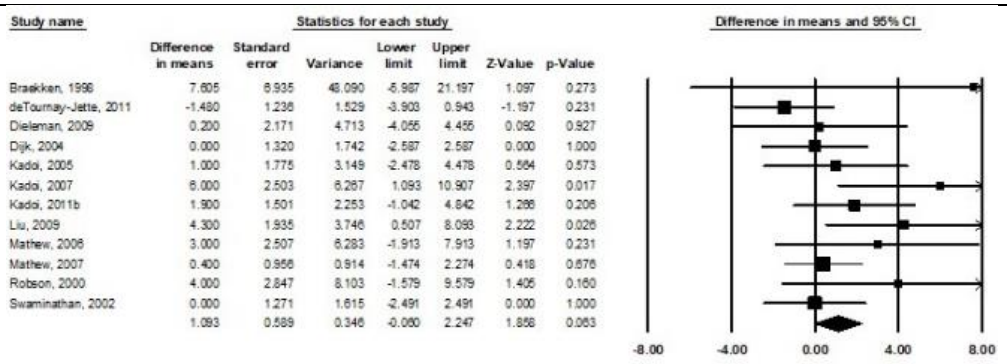
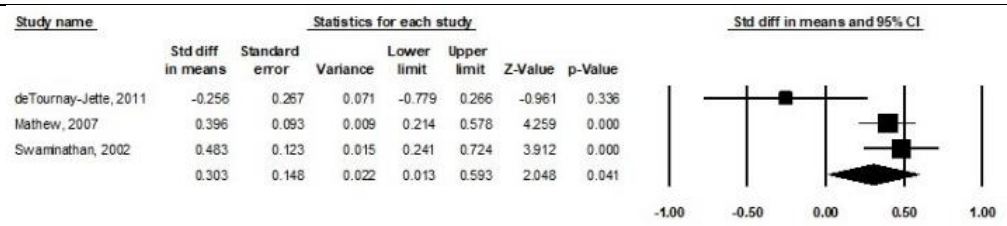
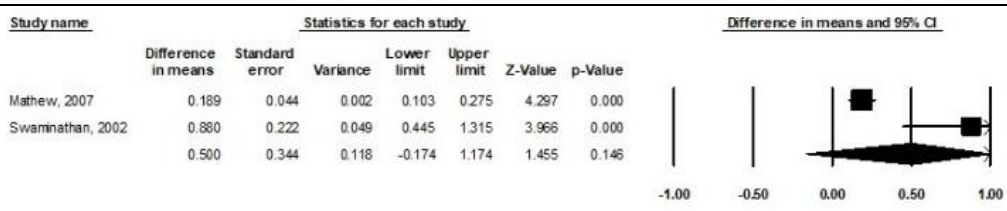
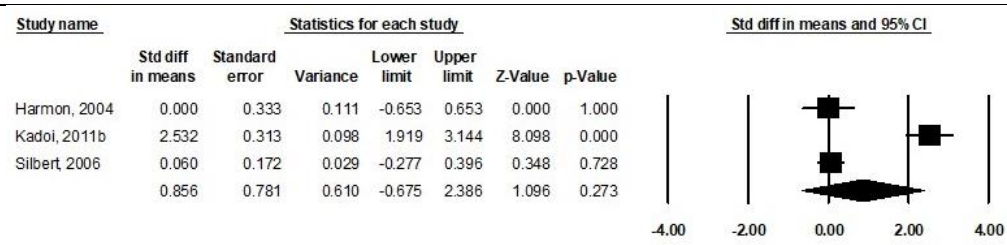
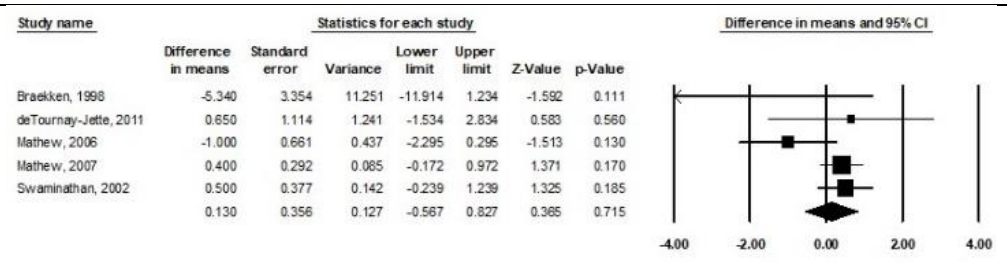
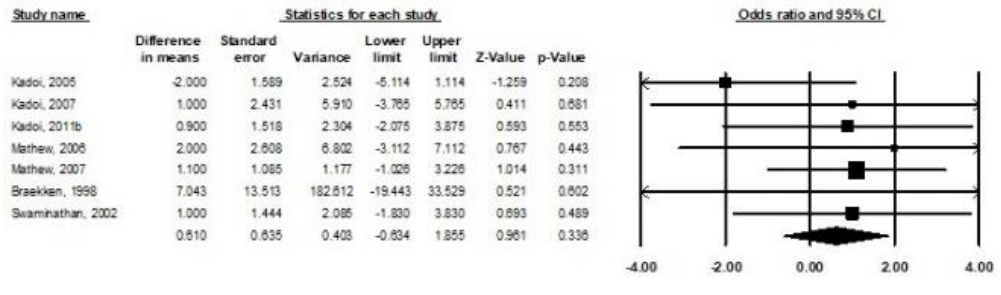


PVD



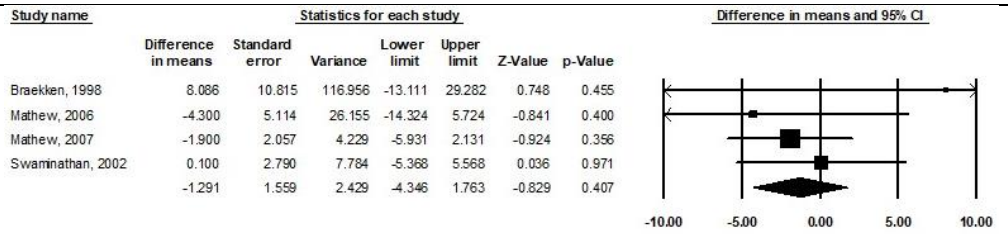
Smoking (current)



Pre-Operative (Continuous)	
Age (years)	
Cognition: All tests	
Cognition: CI only	
Depression: All tests	
Education (years)	
LVEF %	

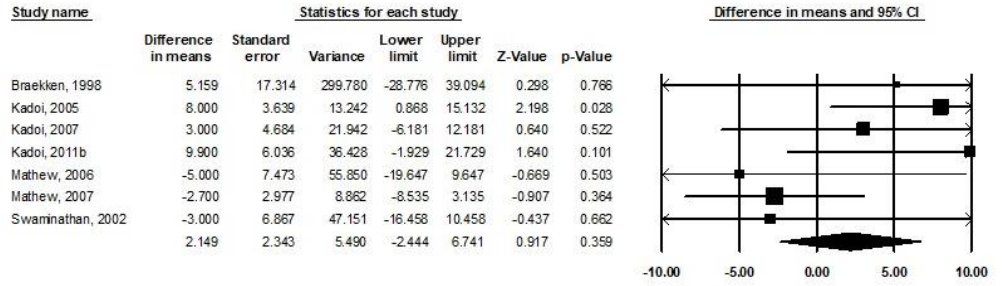
Intra-Operative (Continuous)

ACC time (mins)



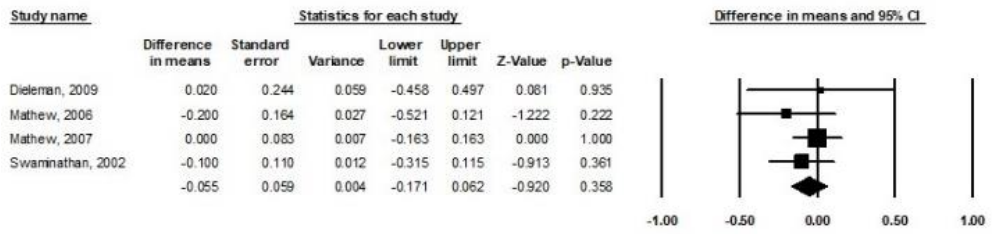
Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Braekken, 1998	8.086	10.815	116.956	-13.111	29.282	0.748	0.455
Mathew, 2006	-4.300	5.114	26.155	-14.324	5.724	-0.841	0.400
Mathew, 2007	-1.900	2.057	4.229	-5.931	2.131	-0.924	0.356
Swaminathan, 2002	0.100	2.790	7.784	-5.368	5.568	0.036	0.971
	-1.291	1.559	2.429	-4.346	1.763	-0.829	0.407

CPB time (mins)



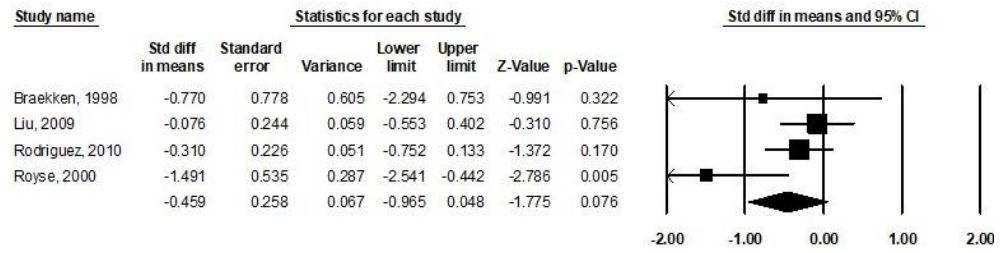
Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Braekken, 1998	5.159	17.314	299.780	-28.776	39.094	0.298	0.766
Kadoi, 2005	8.000	3.639	13.242	0.868	15.132	2.198	0.028
Kadoi, 2007	3.000	4.684	21.942	-6.181	12.181	0.640	0.522
Kadoi, 2011b	9.900	6.036	36.428	-1.929	21.729	1.640	0.101
Mathew, 2006	-5.000	7.473	55.850	-19.647	9.647	-0.669	0.503
Mathew, 2007	-2.700	2.977	8.862	-8.535	3.135	-0.907	0.364
Swaminathan, 2002	-3.000	6.867	47.151	-16.458	10.458	-0.437	0.662
	2.149	2.343	5.490	-2.444	6.741	0.917	0.359

Number of grafts



Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Dieleman, 2009	0.020	0.244	0.059	-0.458	0.497	0.081	0.935
Mathew, 2006	-0.200	0.164	0.027	-0.521	0.121	-1.222	0.222
Mathew, 2007	0.000	0.083	0.007	-0.163	0.163	0.000	1.000
Swaminathan, 2002	-0.100	0.110	0.012	-0.315	0.115	-0.913	0.361
	-0.055	0.059	0.004	-0.171	0.062	-0.920	0.358

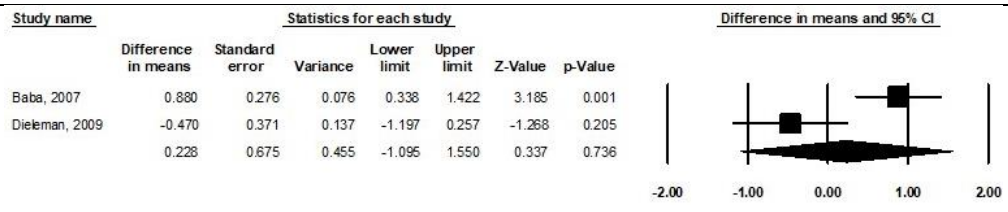
Total Microemboli



Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Braekken, 1998	-0.770	0.778	0.605	-2.294	0.753	-0.991	0.322
Liu, 2009	-0.076	0.244	0.059	-0.553	0.402	-0.310	0.756
Rodriguez, 2010	-0.310	0.226	0.051	-0.752	0.133	-1.372	0.170
Royse, 2000	-1.491	0.535	0.287	-2.541	-0.442	-2.786	0.005
	-0.459	0.258	0.067	-0.965	0.048	-1.775	0.076

Post-Operative (Continuous)

LOS in ICU (days)



Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Baba, 2007	0.880	0.276	0.076	0.338	1.422	3.185	0.001
Dieleman, 2009	-0.470	0.371	0.137	-1.197	0.257	-1.268	0.205
	0.228	0.675	0.455	-1.095	1.550	0.337	0.736

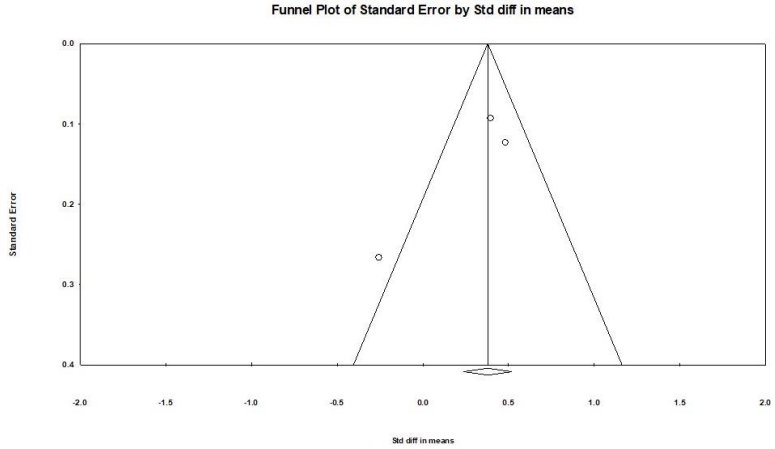
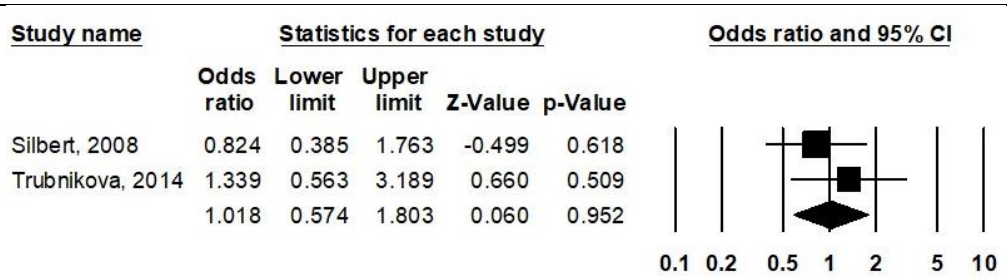
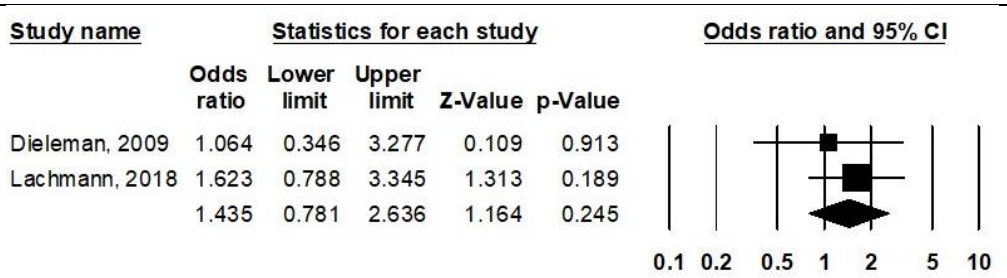
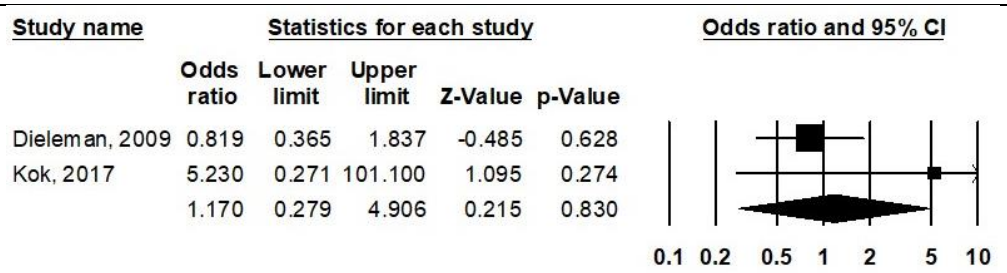
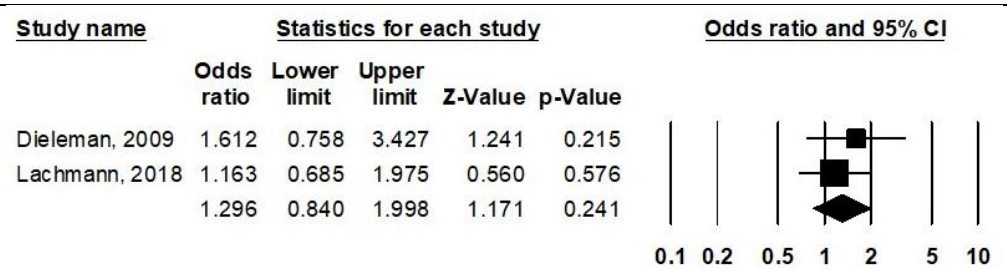
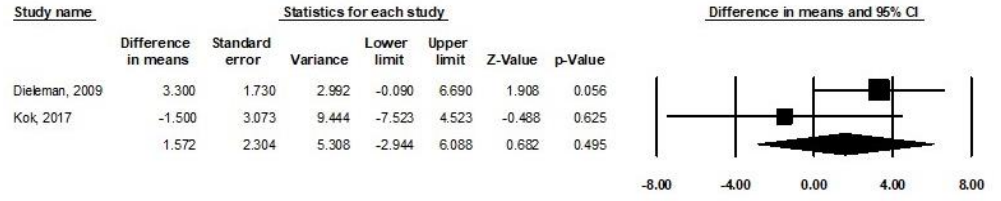
Figure S6. Funnel plots for statistically significant analyses in regard to mid-term cognitive decline post-CABG, and results of publication bias/small-study effect investigation when more than 10 studies were available.		**Egger's Test**		**Trim and Fill**		
		Intercept	**p value (1-tailed)**	**No. imputed studies**	**OR/MD† /SMD‡**	**95%CI**
Preoperative (Categorical)						
Depression	Only 2 studies, could not produce funnel plot	-	-	-	-	-
Preoperative (Continuous)						
Cognition: All tests		-	-	-	-	-

Figure S7. Forest plots for long-term cognitive decline post-CABG analyses.

Variable	Forest Plot
Pre-Operative (Categorical)	
Cognitive Impairment	
Diabetes	
Sex (male)	
Hypertension	
Pre-Operative (Continuous)	
Age (years)	
Intra-Operative (Continuous)	

Number of grafts