Diabetes is associated with risk of postoperative cognitive dysfunction: a meta-analysis

Feinkohl, I., Winterer, G., Pischon, T.

This is the final version of the accepted manuscript, which was published in final edited form in:

Diabetes/Metabolism Research and Reviews
2017 JUL ; 33(5): e2884
2017 JAN 07 (first published online)
doi: 10.1002/dmrr.2884

Publisher: Wiley-Blackwell

Diabetes, glycemia and risk of post-operative cognitive dysfunction: A meta-analysis

Short title: Diabetes and cognition after surgery

I. Feinkohl[1], G. Winterer[2], T. Pischon[1,2,3]

[1]Molecular Epidemiology Research Group, Max-Delbrueck Center for Molecular Medicine in the Helmholtz Association (MDC), Berlin, Germany

[2]Charité – Universitaetsmedizin Berlin, Germany

[3]MDC/BIH Biobank, Max-Delbrueck Center for Molecular Medicine in the Helmholtz Association (MDC), and Berlin Institute of Health (BIH), Berlin, Germany

Corresponding author:
Insa Feinkohl
Max-Delbrueck Center for Molecular Medicine (MDC)
Robert-Roessle-Str. 10
D-13092 Berlin
Germany
Tel: 0049 30 9406-4595
Email: insa.feinkohl@mdc-berlin.de

Title word count: 10
Number of references: 56

Number of tables: 1
Number of figures: 4

Abstract word count: 250
Manuscript word count: 3417

Online Supplemental Data: Supplemental Figures S1 to S5; Supplemental Table S1

Keywords: cognitive epidemiology, blood glucose, diabetes, HbA1c, hypoglycemia, post-operative cognitive dysfunction

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/dmrr.2884

Abstract

Background

Post-operative cognitive dysfunction (POCD) occurs frequently after surgery, particularly among older people. Diabetes, chronic hyperglycemia and a history of hypoglycemia are related to cognitive impairment, but little is known about their roles in POCD. Here, we estimated their associations with risk of POCD on the basis of published epidemiological research.

Methods

The PubMed and Cochrane databases were searched for longitudinal studies of adults undergoing surgery with reporting of associations of diabetes status, glycemic levels and/or a history of hypoglycemia with risk of POCD as relative risks or odds ratios. PRISMA and MOOSE guidelines were followed.

Results

The search identified 246 publications of which 14 met inclusion criteria, reporting on a total of 2518 patients (mean age 64 years). Follow-up periods spanned 1 day to 5 years. Overall, patients with diabetes had a 1.26-fold higher risk of POCD compared with diabetes-free patients (95% CI 1.12, 1.42). A single study assessed glycemic control in patients with diabetes, and identified a higher HbA1c associated with higher POCD risk (RR per % higher HbA1c, 2.0; 95% CI 1.4, 2.6). We did not find studies on glycemic levels in the non-diabetic range or on hypoglycemia as potential predictors of POCD.

Conclusion

Patients with diabetes appear to have a higher risk of POCD compared with diabetes-free persons. Among patients with diabetes, POCD risk may further increase with poorer glycemic control as indexed by higher HbA1c, but these findings and the roles of HbA1c levels among non-diabetics and of hypoglycemia in POCD risk warrant further research.

Introduction

Post-operative cognitive dysfunction (POCD) occurs relatively frequently after surgery in the general population, particularly among older people [1]. It is loosely defined as a decline on cognitive test performance between pre-surgery and post-surgery assessments. Due to poor characterization of the syndrome and resulting lack of diagnostic criteria [2], substantial variation exists in reported incidence rates, but in older age groups incidence overall appears in the order of 10-38% [3-6] within the first 2 to 3 months and 3-24% at 6 to 12 months after major surgery [5, 7, 8]. Although it is considered as a transient condition [1], POCD has been shown to increase the risk of subsequent dementia as well as premature death [1, 4, 9]; yet research into its epidemiology – which may elucidate its etiology as well as preventive strategies – is lagging behind. Only a few risk factors for POCD have been identified to date, including advanced age and pre-existing cognitive impairment [1].

Chronic hyperglycemia in older age is well-recognized as a predictor of age-related cognitive impairment [10]. Thus, patients with diabetes are at 50%-140% increased risk of dementia [11], and even in the dementia-free range experience a 20 to 50% increased rate of cognitive decline [12]. Similar observations have been reported across the spectrum of glycemia: higher glycated hemoglobin A1c (HbA1c) levels – a marker for chronic hyperglycemia – have been linked to cognitive impairment both in people with [13] and without diabetes [14]. Due to anti-hyperglycemic treatment, patients with diabetes may also be exposed to temporary states of hypoglycemia – blood glucose levels below those of a healthy glucose metabolism – which, too, have been shown to predict impairment [15-17], with evidence suggestive of a dose-response relationship [16, 18]. It is, however, unclear whether chronic hyperglycemia or a history of hypoglycemic episodes prior to surgery may also increase the risk of POCD. Clarifying the potential role of diabetes, glycemic levels and a history of hypoglycemia is important to be able to provide reliable risk assessment prior to surgery, in order to tailor clinical care after surgery and to inform hypotheses on the mechanisms leading up to POCD.

The objective of the present study was therefore to systematically review the existing epidemiological evidence and to conduct a meta-analysis on the associations of diabetes, glycemic levels, and a prior history of hypoglycemia with risk of POCD.

Methods

Systematic search strategy

The PubMed database and Cochrane Database of Systematic Reviews were searched by IF from their respective inception onwards; the final search was performed on 22nd September 2015. The following term was used: ("hyperglyc*" OR "hypoglyc*" OR "blood sugar" OR "blood glucose" OR "glycemic control" OR "glycaemic control" OR "diabetes") AND (("post-operative" OR "postoperative" OR "POCD") OR (("surgery" OR "operation") AND ("cognit*" OR "intelligence" OR "MMSE" OR "Mini Mental" OR "dementia" OR "Alzheim*" OR "mild cognitive impairment" OR "MCI"))). Abstracts of all 'hits' were screened to determine whether they potentially matched inclusion criteria, and were accessed

for full text evaluation as appropriate. Reference lists of relevant articles and review articles were hand-searched and an independent online search was performed. Findings were reported in line with Meta-analysis Of Observational Studies in Epidemiology (MOOSE) and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [19, 20].

Study selection

Articles were included if the following criteria were met: i) original article in English language reporting on adult humans (≥18 years) undergoing surgery, ii) longitudinal study design, iii) report of change in cognitive function that is measured before and after surgery using standardized performance-based neuropsychological assessment tools, iv) ascertainment of glycemic level through blood glucose levels and/or glycated hemoglobin (HbA1c), ascertainment of diabetes status (any type of diabetes), and/or ascertainment of prior history of hypoglycemia (any severity) from hospital records and/or self-report, and v) reporting of associations of these exposures with cognitive change pre- to post-surgery as odds ratios or relative risks (both taken as RR for the purpose of this review) or in a form that could be converted to RR. Use of the term 'POCD' was not required for inclusion. Articles on exposure to acute perioperative glucose levels or on diagnosed post-operative delirium were excluded.

Data extraction

For each study identified in the search, data (if available) were extracted on first author, location, total N and N included in the analysis, proportion of males, mean age, surgical procedure and type of anesthesia, definition of POCD, exposure to diabetes, hyperglycemia and/or a prior history of hypoglycemia, associations of exposure with POCD (RR), and covariates. Data from models that included full multivariable adjustment were extracted unless no adjustment was applied. The respective longest follow-up period was selected. For two articles with insufficient reporting on longer follow-up periods, data for the respective shorter follow-up with available data were used [21, 22]. For one article that included two levels of POCD severity [23], the group with the more severe form of POCD was compared with the cognitively unimpaired group. If use of identical samples was suspected, the respective article with most complete reporting was selected. HbA1c represents the average blood glucose levels that a patient has been exposed to over the past two to three months and so reflects the entire glycemic spectrum [24]. On the basis that a low HbA1c is a risk factor for experiencing hypoglycemic episodes [25], but in itself does not indicate that a patient has experienced such an episode, however, we took HbA1c to signify hyperglycemia only in a linear (rather than U-shaped) fashion. This approach is common in the research literature on hyperglycemia and was also followed by the studies included in the present analysis.

Data were tabulated and (if possible) meta-analyzed separately for diabetes status, glycemic control in patients with diabetes, glycemic control in the normoglycemic range, and for a history of hypoglycemia.

Data synthesis

Statistical data were entered into Review Manager 5.3 (Cochrane Collaboration, 2014) to calculate summary estimates of RR (95% CI) in inverse variance meta-analyses. The method weighs studies according to standard errors of effect estimates to give greater weight to larger studies [26]. Fixed-effects models were utilized on the basis that all included studies were assumed to estimate one true underlying population effect size [27]. The main analyses were then repeated post-hoc using random-effects models. Though more conservative compared with fixed-effects models, random-effects models give greater weight to small studies that are far from the point estimate. Publication bias was assessed through visual inspection of funnel plots and was formally tested using the regression method by Egger [28]. The I^2 index was calculated to signify statistical heterogeneity among studies. Pre-specified subgroup analyses included multiple, fixed-effects meta-regression analyses exploring effect sizes according to follow-up period (≤1 month versus >1 month), sample size (≤100 versus >100), mean sample age (≤65 years versus >65 years), surgery type (cardiac; non-cardiac; mixed surgery type) and sex (≤75% males versus >75% males) as potential sources of heterogeneity. Meta-regression was performed in SAS Enterprise Guide (version 4.3). In a final step, sensitivity analyses determined influence of individual studies to pooled effects in the respective subgroup analyses.

Quality assessment

One investigator (IF) rated articles for reporting quality using the checklist for cohort studies by the STROBE Initiative with maximum score of 22 [29]. No exclusions based on reporting quality were applied.

Results

Study characteristics

The search yielded 237 articles in PubMed and 0 articles in the Cochrane Library (see Figure 1). All abstracts were screened, and full texts of 31 articles were accessed for evaluation. Screening of reference lists and an independent search identified 9 additional relevant articles. Of these 40 articles, 20 did not meet inclusion criteria and 6 articles were excluded due to suspected duplicate reporting on identical cohorts. A total of 14 articles were included in the review.

Of the 14 studies, 13 had prospective observational designs; one randomized controlled trial compared cognitive outcomes between on-pump and off-pump coronary artery bypass grafting (CABG) and analyzed their data with adjustment for surgery type [30]. A single investigation was on glycemic control in a sample of 124 patients with diabetes [31]; all other studies investigated POCD according to diabetes status and enrolled a total of N=2990 patients of which N=2518 were retained for follow-up [9, 21-23, 30, 32-39] (see Table 1). Publication dates spanned 2001 to 2015, and studies stemmed from countries in Europe, Asia, North America and Australia. Analyses were performed on between 21 and 585 patients, with mean sample age of 56 to 69 years (where reported; mean 64 ± 4 years across studies). Criteria used to diagnose diabetes and diabetes type were not specified in any of the studies except one [34], but on the basis of sample age, most patients with diabetes in the studies

likely had type 2 diabetes. A majority of studies included more males than females. Follow-up periods spanned 1 day to 5 years (median 68 days, interquartile range 4 days to 180 days). Prevalence of diabetes (where reported) in the 13 studies on diabetes status appeared to be dependent on sample characteristics including age, and ranged from 8% in an Australian study with the lowest mean sample age (56 years) of all included studies [37] to 53% in a Spanish investigation of older adults with mean age of 66 years [39]. All except two Asian studies [32, 38], which used cognitive screening instruments, applied detailed neuropsychological tests. Criteria used to define POCD varied between studies, and in many cases included comparison with change scores of a control group that did not undergo surgery. The proportion of patients who developed POCD during follow-up among studies ranged between 9% and 75%. Of 6 studies that applied statistical adjustment for potential confounders [21, 22, 31-33, 40], covariates were selected a priori in a single investigation [22]. The remaining 5 studies either used a stepwise approach to modelling, selected covariates on the basis of univariate associations with POCD, or included all available risk factor variables in their respective model. Of note, one study with three month follow-up adjusted for POCD at one week after surgery [40] to counteract possible confounding by delirium during the time period immediately following surgery.

No studies were found that related blood glucose levels in the non-diabetic range or a prior history of hypoglycemia with risk of POCD.

Findings of included studies, meta-analysis and subgroup analyses: Diabetes status

Individual and pooled effect sizes of the 13 studies that assessed diabetes status and risk of POCD are shown in Figure 2. When the results were pooled across studies in a fixed-effects meta-analysis, diabetes was associated with a 26% increased risk of POCD (RR 1.26; 95% CI 1.12, 1.42; $p<0.001$), though statistical heterogeneity among the studies was indicated ($chi^2(12) = 31.94$; $p<0.001$; $I^2=62\%$). Visual inspection of the funnel plot and Egger's regression analysis ($p=0.346$) suggested no evidence of publication bias (see Figure 3). Findings were similar when the analysis was repeated using a random-effects model (RR 1.39; 95% CI 1.09, 1.78; $p=0.008$).

Results of subgroup analyses that explored potential sources of heterogeneity and their contribution to the overall pooled effects in further fixed-effects models are summarized in Figure 4; details of studies included in each subgroup analysis and I^2 indices of heterogeneity are shown as Online Supplemental Data. Pooled effects were larger in studies with follow-up period >1 month (RR 1.65; 95% CI 1.35, 2.01; $I^2=65\%$) compared with a statistically non-significant associations found for studies with ≤1 month follow-up (RR 1.10; 95% CI 0.95, 1.27; $I^2=42\%$; meta-regression $p=0.009$; see Supplemental Figure S1) though statistical heterogeneity was substantial in this subgroup ($I^2=65\%$). Sample size ≤100 was associated with a significantly larger pooled effect (RR 1.72; 95% CI 1.36, 2.17; $I^2=31\%$) compared with studies of >100 patients (RR 1.14; 95% CI 1.00, 1.30; $I^2=57\%$; meta-regression $p=0.012$; see Supplemental Figure S2). Pooled effects across studies with mean sample age >65 years (RR 1.74; 95% CI 1.35, 2.24; $I^2=26\%$) were larger compared with studies with mean sample age ≤65 years which again were affected by a substantial degree of

heterogeneity (RR 1.20; 95% CI 1.04, 1.39; I^2=65%; meta-regression p=0.032; see Supplemental Figure S3). However, sensitivity analyses showed that the difference in pooled effects between studies with mean age >65 versus ≤65 years appeared to be driven by a single study in the ≤65 years group [38] (see Supplemental Table S1). Neither proportion of males nor surgery type were significant moderators of the association diabetes with risk of POCD (all meta-regression p>0.05; subgroup I^2 range 0% to 72%; see Supplemental Figures S4, S5).

Findings of included studies: Glycemic control in patients with diabetes

A single study assessed risk of POCD according to glycemic control in a sample consisting entirely of older patients with diabetes [31]. The study found that pre-surgery HbA1c predicted patients' risk of POCD: Independent of diabetic retinopathy or insulin therapy, each % unit increase in HbA1c at baseline was associated with a two-fold increased risk of POCD defined as declines of ≥1SD on at least 2 of 6 cognitive tests between pre-surgery assessment and 6-month follow-up (RR 2.0; 95% CI 1.4, 2.6). The sample mean of HbA1c was within the diabetic range (mean 6.9%) with a relatively modest standard deviation (SD 1.6).

Discussion

The results of our systematic review and meta-analysis suggest that middle-aged to older adults with diabetes are overall at 26% increased risk of POCD compared with diabetes-free patients though overall moderate statistical heterogeneity between included studies as well as substantial heterogeneity in terms of study designs and sample characteristics was indicated. The association of diabetes with POCD risk appeared to be driven mainly by studies with relatively longer follow-up periods. We assume that publication bias likely accounts for the observation of a larger effect size in smaller samples. Among patients with diabetes, our findings suggest that the risk of POCD may increase with poorer glycemic control, as indexed by higher HbA1c concentrations. No study was identified on either chronic hyperglycemia in the non-diabetic range or on a prior history of hypoglycemic episodes as predictors of POCD, and so further research in this direction is urgently needed.

The evidence presented here extends the relatively well-established role of hyperglycemia in age-related cognitive impairment. Diabetes is thought to increase the risk of dementia and mild cognitive impairment (MCI), as well as an accelerated cognitive decline in the dementia-free range [11, 12]. It has further been linked to an increased risk of post-operative delirium [41] – a condition that despite differences in etiology and disease course is strongly related to POCD [42]. Previous review articles on predictors of POCD have often followed a narrative rather than systematic approach, and have not considered glycemia in any detail [1, 43, 44]. A single systematic review has investigated diabetes as a potential risk factor for POCD, but concluded that diabetes was unrelated to POCD [45]. Reasons for disparity from the present findings are difficult to evaluate, as no analysis details were provided in that article, but we assume it is due to a discrepancy in inclusion criteria. In the present analysis, we speculate that true effect sizes for the association of diabetes and POCD may have been underestimated: diabetes status was presumably often ascertained through self-report so that

(as the condition frequently remains undiagnosed [46]), patients with undiagnosed diabetes may have been included in the respective 'no diabetes' groups. With hyperglycemia as a continuum and arbitrary cut-off values for diabetes diagnosis, similar prediction of POCD risk by higher blood glucose levels in the non-diabetic range and by poorer glycemic control in diabetes would be plausible. Our finding of an increased risk in patients with diabetes who have higher HbA1c concentrations (albeit based on a single investigation [31]) indeed finds support in poorer glycemic control as a risk factor for age-related cognitive impairment in patients with diabetes [14, 47].

Associations of chronic hyperglycemia with POCD are likely to involve pathways similar to those that link it with age-related cognitive impairment in the general population (for review, see [48]). Glucose-induced formation of advanced glycation endproducts (AGE), which following a reaction with specific cell surface receptors (RAGE) result in neurodegeneration and atherogenesis [49], for instance, predicts cognitive decline in older age [50]. It may be the case that the insult of surgery increases the vulnerability of patients with diabetes to such underlying neuropathological changes, resulting in a higher impact of surgery on cognitive function in patients with diabetes compared with non-diabetic patients.

Confounding by sociodemographic and clinical risk factors is also possible, however, and in fact casts doubt on the role of causality in the association of diabetes with age-related cognitive impairment. For instance, some evidence suggests that a lower pre-morbid ability in young adulthood predisposes people both to diabetes and to cognitive impairment in older age [51]. Such links may render the diabetes-cognitive impairment association – potentially including that with POCD – partly or entirely spurious. Clinical factors, such as co-morbidity or exposure to vascular risk, also likely affected the present results given that few of the included studies applied adjustment for such factors. Readers should therefore be aware that the increased risk of POCD in patients with diabetes or poorer glycemic control may be driven partly or entirely by other factors that were not considered by the individual included studies.

Cognitive impairment is generating huge economic costs and an understanding of its etiology is needed to intervene disease risk and disease progression. Identification of risk factors predisposing patients to the type of impairment that occurs after surgery provides a step toward that goal. The present observation of diabetes as increasing the risk of cognitive impairment following surgery is certainly alarming in light of the current diabetes epidemic. From a clinical perspective, our findings may help optimize screening systems for POCD. Its systematic approach and inclusion criteria that permitted any operationalization of POCD are strengths of the present review. Our findings are limited by heterogeneity between included studies. Due to individual differences in trajectories of POCD [52], heterogeneity particularly in terms of length of follow-up complicated cross-study comparison. Studies with brief follow-ups may have captured effects of delirium on cognitive scores, though survival of an association of diabetes with POCD at three-month follow-up following adjustment for POCD at one week in one study [40] as well as the fact that overall pooled effects were driven by studies with follow-up >1 month speaks against a major influence of this factor. The meta-regression analyses presented here are to be interpreted with caution in view of the

fact that five potential sources of heterogeneity were investigated across a small number of included studies. With between-study differences in the operationalization of POCD, we are also unable to meaningfully translate the pooled risk estimate to recommendations for clinical practice.

Finally, we cannot rule out that investigations were missed due to exploratory designs of studies and/or failure to report on any predictors that were not associated with POCD, due to our search which was restricted to only two of the main databases of medical research, or due to our focus on English-language articles. However, in support of our findings, three excluded Chinese-language articles reported associations of diabetes with POCD at 7 days after surgery in their abstracts, and all three found a statistically significantly increased risk in patients with diabetes (RR 1.62 to RR 4.22 where reported) [53-55]. We are thus relatively confident that our language restriction did not skew findings toward statistical significance.

Further epidemiological studies that consider potential confounders including intra-operative glycemic control in their analyses are needed to evaluate the present preliminary findings. With evidence for an increased risk of POCD in insulin-treated patients [31, 34], attempts should also be made to tease out the role of endogenous insulin levels and/or insulin therapy in the relationship of diabetes and POCD risk, while considering potential effects of hypoglycemia. A prior history of hypoglycemic episodes in patients with diabetes has previously been associated with an increased risk of age-related cognitive impairment [15-17] and so its potential contribution to POCD risk as well as to associations of diabetes with POCD risk should be clarified. A lower cognitive capacity has been implicated as a risk factor for hypoglycemia [15, 56], and so risk of exposure to subsequent hypoglycemia in patients who experience POCD, too, could be explored.

In this systematic review and meta-analysis, we found that people with diabetes appear to be at increased risk of developing cognitive dysfunction following surgery. Among these patients, the risk of cognitive dysfunction may further increase with higher HbA1c. Though additional research is needed in this field, our findings suggest that routine testing for diabetes and assessment of HbA1c levels among patients with diabetes prior to surgery may be indicated for risk assessment of POCD.

Acknowledgement
I.F. was supported by funding from the European Union, Seventh Framework Programme [FP7/2007-2013], under grant agreement No. HEALTH-F2-2014-602461 BioCog (Biomarker Development for Postoperative Cognitive Impairment in the Elderly): www.biocog.eu. We are grateful for statistical advice from Stefan Konigorski.

Conflicts of interest
None declared

Author contributions

I.F. performed the literature search and data analysis. T.P. and I.F. interpreted the findings and wrote the manuscript. I.F., T.P. and G. W. commented on the final manuscript.

1. Rundshagen I. Postoperative cognitive dysfunction. Deutsches Ärzteblatt International. 2014;111(8):119-25.
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th edition. United States: American Psychiatric Publishing; 2013.
3. van Dijk D, Keizer AMA, Diephuis JC, Durand C, Vos LJ, Hijman R. Neurocognitive dyfunction after coronary artery bypass surgery: A systematic review. Journal of Thoracic and Cardiovascular Surgery. 2000;120(4):632-9.
4. Monk TG, Weldon C, Garvan CW, Dede DE, van der Aa MT, Heilman KM, et al. Predictors of cognitive dysfunction after major noncardiac surgery. Anesthesiology 2008;108:18-30.
5. Silbert B, Evered L, Scott DA, McMahon S, Choong P, Ames D, et al. Preexisting cognitive impairment is associated with postoperative cognitive dysfunction after hip joint replacement surgery. Anesthesiology. 2015;122:1224-34.
6. Shoair OA, Grasso MPI, Lahaye LA, Daniel R, Biddle CJ, Slattum PW. Incidence and risk factors for postoperative cognitive dysfunction in older adults undergoing major noncardiac surgery: A prospective study. Journal of Anaesthesiology Clinical Pharmacology. 2015;31:30-6.
7. Leiendecker J, Höcker J, Meybohm P, Fudickar A, Bein B. Postoperative neurocognitive function and microembolus detection in patients undergoing neck dissection: a pilot study. European Journal of Anaesthesiology. 2010;27:417-24.
8. Newman MF, Kirchner JL, Phillips-Bute BS, Gaver V, Grocott H, Jones RH, et al. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. New England Journal of Medicine. 2001;344:395-402.
9. Heyer EJ, Mergeche JL, Wang S, Gaudet JG, Connolly ES. Impact of cognitive dysfunction on survival in patients with and without statin use following carotid endarterectomy. Neurosurgery. 2015. doi: 10.1227/NEU.0000000000000904.
10. Strachan MWJ, Reynolds RM, Frier BM, Mitchell RJ, Price JF. The relationship between type 2 diabetes and dementia. British Medical Bulletin. 2008;88:131-46.
11. Lu FP, Lin K-P, Kuo H-K. Diabetes and the risk of multi-system aging phenotypes: a systematic review and meta-analysis. PLoS ONE. 2009;4:e4144.
12. Cukierman T, Gerstein HC, Williamson KD. Cognitive decline and dementia in diabetes-systematic overview of prospective observational studies. Diabetologia. 2005;48:2460-9.
13. Geijselaers SL, Sep SJS, Stehouwer CDA, Biessels GJ. Glucose regulation, cognition, and brain MRI in type 2 diabetes: a systematic review. Lancet Diabetes and Endocrinology. 2015;3:75-89.
14. Ravona-Springer R, Moshier E, Schmeidler J, Godbold J, Akrivos J, Rapp M, et al. Changes in glycaemic control are associated with changes in cognition in non-diabetic elderly. Journal of Alzheimer's Disease. 2012;30:299-309.
15. Feinkohl I, Aung PP, Keller M, Robertson CM, Morling JR, McLachlan S, et al. Severe hypoglycemia and cognitive decline in older poeple with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. Diabetes Care. 2014;37:507-15.
16. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CPJ, Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes. Journal of the American Medical Association. 2009;301:1565-72.
17. Prinz N, Stingl J, Dapp A, Denkinger MD, Fasching P, Jehle PM, et al. High rate of hypoglycemia in 6770 type 2 diabetes patients with comorbid dementia: A multicenter cohort study on 215,932 patients from the German/Austrian diabetes registry. Diabetes Research and Clinical Practice. 2015. Epub 30th Oct 2015.

18. Aung PP, Strachan MWJ, Frier BM, Butcher I, Deary IJ, Price JF. Severe hypoglycaemia and late-life cognitive ability in older people with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. Diabetic Medicine. 2012;29:328-36.
19. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology. A proposal for reporting. Journal of the American Medical Association. 2000;283:2008-12.
20. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Medicine. 2009;6(7):e10000097.
21. Evered LA, Scott DA, Silbert B, Maruff P. Postoperative cognitive dysfunction is independent of type of surgery and anesthetic. Anesthesia & Analgesia 2011;112(5):1179-85.
22. McDonagh DL, Mathew JP, White WD, Phillips-Bute B, Laskowitz DT, Podgoreanu MV, et al. Cognitive function after major noncardiac surgery, apolipoprotein E4 genotype, and biomarkers of brain injury. Anesthesiology 2010;112:852-9.
23. Di Carlo A, Perna AM, Pantoni L, Basile AM, Bonacchi M, Pracucci G, et al. Clinically relevant cognitive impairment after cardiac surgery: a 6-month follow-up study. Journal of the Neurological Sciences. 2001;188:85-93.
24. Nathan DM, Turgeon H, Regan S. Relationship between glycated haemoglobin levels and mean glucose levels over time. Diabetologia. 2007;50(11):2239-44.
25. Karges B, Kappellen T, Wagner VM, Steigleder-Schweiger C, Karges W, Holl RW, et al. Glycated hemoglobin A1c as a risk factor for severe hypoglycemia in pediatric type 1 diabetes. Pediatric Diabetes. 2015. Epub 29th Dec 2015.
26. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions The Cochrane Collaboration, editor2011.
27. Hedges LV, Vevea JL. Fixed- and random-effects models in meta-analysis. Psychological Methods. 1998;3(4):486-504.
28. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. British Medical Journal. 1997;315:629-34.
29. STROBE Initiative. STROBE checklist for cohort studies, Version 4. University of Bern; 2007.
30. Dieleman J, Sauer A-M, Klijn C, Nathoe H, Moons K, Kalkman C, et al. Presence of coronary collaterals is associated with a decreased incidence of cognitive decline after coronary artery bypass surgery. European Journal of Cardio-thorcacic Surgery. 2009;35:48-53.
31. Kadoi Y, Kawauchi C, Kuroda M, Takahashi K, Saito S, Fujita N, et al. Association between cerebrovascular carbon dioxide reactivity and postoperative short-term and long-term cognitive dysfunction in patients with diabetes mellitus. Journal of Anesthesia. 2011;25:641-7.
32. Suksompong S, Prakanrattana U, Chumpathong S, Sriyoschati S, Pornvilawan S. Neuropsychological alterations after coronary artery bypass graft surgery. Journal of the Medical Association of Thailand. 2002;85 (Suppl 3):S910-S6.
33. Heyer EJ, Wilson DA, Sahlein DH, Mocco J, Williams SC. APOE-ε4 predisposes to cognitive dysfunction following uncomplicated carotid endarterectomy. Neurology. 2005;65(11):1759-63.
34. Kadoi Y, Goto F. Factors associated with postoperative cognitive dysfunction in patients undergoing cardiac surgery. Surgery Today. 2006;36:1053-7.
35. Wilson DA, Mocco J, D'ambrosio AL, Komotar RJ, Zurica J, Kellner CP, et al. Post-carotid endarterectomy neurocognitive decline is associated with cerebral blood flow asymmetry on post-operative magnetic resonance perfusion brain scans. Neurological Research. 2008;30:302-6.
36. Liu YH, Wang DX, Li LH, Wu XM, Shan GJ, Su Y, et al. The effects of cardiopulmonary bypass on the number of cerebral microemboli and the incidence of cognitive dysfunction after coronary artery bypass graft surgery. Anesthesia & Analgesia. 2009;109:1013-22.
37. Medi C, Evered L, Silbert B, Teh A, Halloran K, Morton J, et al. Subtle post-procedural cognitive dysfunction after atrial fibrillation ablation. Journal of the American College of Cardiology. 2013;62:531-9.

38. Joudi M, Fathi M, Harati H, Joudi M, Izanloo A, Rahdari A, et al. Evaluating the incidence of cognitive disorders following off-pump coronary artery bypass surgery and its predisposing factors. Anesthesiology and Pain Medicine. 2014;4:e18545.
39. Pérez-Belmonte LM, San Román-Terán CM, Jiménez-Navarro M, Barbancho MA, García-Alberca JM, Lara JP. Assessment of long-term cognitive impairment after off-pump coronary-artery bypass grafting and related risk factors. Journal of the American Medical Directors Association. 2015;15(3):263.e9-11.
40. Liu YH, Wang DX, Li LH, Wu XM, Shan GJ, Su Y, et al. The effects of cardiopulmonary bypass on the number of cerebral microemboli and the incidence of cognitive dysfunction after coronary artery bypass graft surgery. Anesthesia & Analgesia. 2009;109:1013-22.
41. Lin Y, Chen J, Wang Z. Meta-analysis of factors which influence delirium following cardiac surgery. Journal of Cardiac Surgery. 2012;27:481-92.
42. Krenk L, Rasmussen LS. Postoperative delirium and postoperative cognitive dysfunction in the elderly - what are the differences? Minerva Anestesiologica. 2011;77(7):742-9.
43. Androsova G, Krause R, Winterer G, Schneider R. Biomarkers of postoperative delirium and cognitive dysfunction. Frontiers in Aging Neuroscience. 2015;7(112).
44. Krenk L, Rasmussen LS, Kehlet H. New insights into the pathophysiology of postoperative cognitive dysfunction. Acta Anaesthesiologica Scandinavia. 2010;54:951-6.
45. Fink HA, Hemmy LS, MacDonald R, Carlyle MH, Olson CM, Dysken MW, et al. Cognitive outcomes after cardiovascular procedures in older adults: a systematic review. Minneapolis, USA: Minnesota Evidence-based Practice Center, 2014.
46. Beagley J, Guariquata L, Weil C, Motala AA. Global estimates of undiagnosed diabetes in adults. Diabetes Research and Clinical Practice. 2014;103:150-60.
47. Cukierman-Yaffe T, Gerstein HC, Williamson JD, Lazar RM, Lovato L, Miller ME, et al. Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors. Diabetes Care. 2009;32:221-6.
48. Frisardi V, Solfrizzi V, Seripa D, Capurso C, Santamato A, Sancarlo D, et al. Metabolic-cognitive syndrome: a cross-talk between metabolic syndrome and Alzheimer's disease. Aging Research Reviews. 2010;9:399-417.
49. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature. 2001;414:813-20.
50. Yaffe K, Lindquist K, Schwartz AV, Vitartas C, Vittinghoff E, Satterfield S, et al. Advanced glycation end product level, diabetes, and accelerated cognitive aging. Neurology. 2011;77:1351-6.
51. Mõttus R, Luciano M, Starr JM, Deary IJ. Diabetes and life-long cognitive ability. Journal of Psychosomatic Research. 2013;75(3):275-8.
52. McKhann GM, Goldsborough MA, Borowicz LM, Selnes OA, Mellits ED, Enger C, et al. Cognitive outcome after coronary artery bypass: a one-year prospective study. Annals of Thoracic Surgery. 1997;63:510-5.
53. Zhang Y, Qian Y, Si Y, Bao H, Zhou J. Differential expressions of serum cytokines in cognitive dysfunction patients after colorectal surgery. Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi. 2015;31(2):231-4.
54. Cui QT, Fu QL, Han PL, Zhang J. [Risk factors of cognitive impairment after off-pump coronary artery bypass grafting]. Zhonghua xin xue guan bing za zhi. 2012;40(2):104-7. Epub 2012/04/12. PubMed PMID: 22490708.
55. Mu DL, Wang DX, Li LH, Shan GJ, Su Y, Yu QJ, et al. [Postoperative delirium is associated with cognitive dysfunction one week after coronary artery bypass grafting surgery]. Beijing Da Xue Xue Bao. 2011;43(2):242-9. Epub 2011/04/20. PubMed PMID: 21503120.
56. Biessels GJ. Hypoglycemia and cognitive decline in older people with type 2 diabetes: a bidirectional relationship. Diabetic Hypoglycemia. 2014;6:11-4.

Table 1: Summary of included studies on diabetes status or glycemic control and POCD

Author, year, location	Total N enrolled in study	N completed follow-up	% male	Type of surgery, anesthesia	Mean baseline age ± SD	Follow-up	Cognitive measurement	Definition of POCD/ proportion of patients with POCD	Diabetes exposure	Adjustment variables	Exposure association with POCD	STROBE reporting quality score
Studies on glycemic control and POCD in people with diabetes												
Kadoi et al. (2011) Japan.	129	124	80	CABG. General anesthesia.	61 ± 6 years	6 months	Rey Auditory Verbal Learning; Trail-Making Tests A and B; Digit Span Forward; Grooved Pegboard; MMSE.	POCD defined as decline of ≥1SD on ≥ 2 of 6 cognitive tests. POCD in n=30/124 (24.2%).	All patients diagnosed with diabetes. HbA1c mean 6.9% ± 1.6 (N=124).	Diabetic retinopathy, insulin therapy.	RR 2.0 (95% CI 1.4, 2.6).	13/22
Studies on diabetes status and POCD												
Di Carlo et al. (2001) Italy.	123	110	71	CPB. General anesthesia.	64 ± 9 years	6 months	Randt Memory Test; Token Test; naming test; test of abstract thinking; MMSE.	Consensus rating of patients as 'unchanged/ improved', 'mildly or moderately deteriorated' or 'severely deteriorated' by 2 neuro-psychologists. POCD defined as 'severely deteriorated' (n=10/110; 9.1%) versus 'unchanged/ improved' (n=22/110; 20.0%) for purpose of present analysis.	Diabetes diagnosis (n=23/110; 20.9%).	None.	RR 0.40 (95% CI 0.05, 2.99).	19/22
Suksompong et al. (2002) Thailand.	110	110	76	CABG. General anesthesia.	62 ± 8 years	3 to 5 days	Thai Mental State Exam.	POCD defined as decline of ≥1SD on cognitive test. POCD in n=20/110 (18.2%) of patients.	Diabetes diagnosis (n unreported).	Age, sex, total of 16 clinical factors.	RR 1.26 (95% CI 0.48, 3.32).	14/22
Heyer et al. (2005) USA.	75	75	61	Carotid endarter-ectomy. General anesthesia.	69 ± 9 years	1 month	Boston Naming Test; Halstead-Reitan Trails A and B; Controlled Oral Word Association Test; Rey Complex Figure Test. Calculation of RCI[a] for each test. RCI scores used to derive 'total deficit score' according to point system (score	POCD defined as sum total deficit score of ≥7. POCD in n=8/75 (10.7%).	Diabetes diagnosis (n=19/75; 25.3%).	Age, BMI, APOEe4.	RR 51.42 (95% CI 1.94, 1363).	17/22

							range 0-6 for each test). Total deficit score summed across tests. Control group n=46.					
Kadoi & Goto (2006) Japan.	95	88	80	CABG. General anesthesia.	62 ± 11 years	6 months	Rey Auditory Verbal Learning Test; Trail-Making Tests A and B; Digit Span Forward; Grooved Pegboard; MMSE.	Definition of POCD unclear. POCD in n=24/88 (27.3%).	Diabetes diagnosis (n= 21/88; 23.9%).	None.	RR 1.8 (95% CI 1.2, 2.4)	11/22
Wilson et al. (2008) USA.	22[c]	21[c]	76	Carotid endarter-ectomy. General anesthesia.	69 ± 8 years	1 day	Boston Naming Test; Halstead-Reitan Trails A and B; Controlled Oral Word Association Test; Rey Complex Figure Test. For each test, calculation of RCI[a]. RCI used to derive 'total deficit score' according to point system (score range 0-6 for each test). Total deficit score summed across tests. Control group n=20.	POCD defined as total deficit score ≥2SD mean change in total deficit score of control group. POCD in n=6/21 (28.6%).	Diabetes diagnosis (n=3/21; 14.3%).	None.	RR 1.48 (95% CI 0.78, 2.82).	16/22
Dieleman et al. (2009) Netherlands.	281	240	73	CABG. Anesthesia unreported.	61 ± 9 years	5 years	Ten neuro-psychological tests of motor skill, memory, attention, visuospatial ability, information processing.. For each test, calculation of RCI[a].and composite RCI.Control group n=112.	POCD defined as a composite RCI ≤ -1.96 and/or RCI ≤--1.96 in ≥2 cognitive tests, or dementia diagnosis or stroke during follow-up. POCD in n=82/240 (34.2%).	Diabetes diagnosis (n=31/240; 12.9%).	None.	RR 1.39 (95% CI 0.90, 2.14)	17/22

Liu et al. (2009) China.	227	169	90	CABG. General anesthesia.	61 ± 8 years	3 months	Mental Control Test; Visual Retention Test; Paired-associates Verbal Learning; Digit Span; Digit Symbol Test; Trail-Making Test A; Grooved Pegboard dominant and non-dominant hand. . For each test, calculation of RCI[a.] and composite RCI.	POCD defined as RCI ≥2 on cognitive tests and/or composite RCI >1.96, or death or stroke during follow-up. POCD in n=19/169 (11.2%).	Diabetes diagnosis (n unreported).	Age, CPB during surgery, POCD at 1 week follow-up.	RR 3.024 (95% CI 1.040, 8.791).	18/22
McDonagh et al. (2010) USA.	394	350	50[b]	Vascular, thoracic, major orthopedic surgery. General or regional anesthesia.	68 ± 8 years[b]	1.5 months	Randt Memory Test; Digit Span; Modified Visual Reproduction Test; Digit Symbol Test; Trail-Making Test B overall yielding 10 scores. Factor analysis to obtain scores on four cognitive domains.	POCD defined as decline of ≥1SD on at least 1 of 4 cognitive domains. POCD in n=190/350 (54.3%).	Diabetes diagnosis[b] (n=63/394; 16%).	Age, education, surgery type, anesthesia type, sex, age x APOEe4 interaction.	RR 2.34 (95% CI 1.22, 4.51).	20/22
Evered et al. (2011) Australia.	644	443	63	Coronary angio-graphy, CABG, total hip replace-ment surgery. Local, spinal or general anesthesia.	68 ± 8 years	7 days	Auditory Verbal Learning Test; Digit Symbol Test; Trail-Making Test A and B; Controlled Oral Word Association Test; verbal fluency; Grooved Pegboard dominant and non-dominant hand. For each test, calculation of RCI[a]. To obtain composite RCI, RCI summed across tests and divided by SD of RCI sum of	POCD defined as RCI <1.96 on ≥2 tests and/or composite RCI <-1.96. POCD in n=150/443 (33.9%).	Diabetes diagnosis (n=134/644; 20.8%).	Age, BMI, hyper-cholesterolemia, beta blockers, statins, PAD, MI, type of surgery.	RR 1.52 (95% CI 0.89, 2.59).	16/22

							controls. Control group n=34.					
Medi et al. (2013) Australia.	150	120	72	Radio-frequency ablation for atrial fibrillation. General anesthesia.	56 ± 11 years	3 months	Auditory Verbal Learning Test; Trail-Making Tests A and B; Digit Symbol Test; Controlled Oral Word Association Test; verbal fluency (semantic); Grooved Pegboard dominant and non-dominant hand. For each test, calculation of RCI[a].. To obtain composite RCI, RCI summed across tests and divided by SD of RCI sum of controls. Control group n=30.	POCD defined as RCI <-1.96 on ≥2 tests and/or composite RCI <-1.96. POCD in n=15/120 (12.5%).	Diabetes diagnosis (n=9/120; 7.5%).	None.	RR 0.2 (95% CI 0.03, 0.79).	15/22
Joudi et al. (2014) Iran.	171	171	Unreported.	CABG. General anesthesia.	64 ± 10 years	1 day	MMSE.	Unclear definition of POCD. POCD in 129/171 (75.4%).	Diabetes diagnosis (n=53/171; 31.0%).	None.	RR 1.07 (95% CI 0.90, 1.27).	13/22
Pérez-Belmonte et al. (2015) Spain.	36	36	69	CABG. Anesthesia unreported.	66 ± 1 years	12 months	Trail-Making Test; Stroop Test; Selective Reminding Test; verbal fluency (semantic, phonological); Judgment of Line Orientation Test. Scores for each patient converted to norm-compared reference scores (adjusted for age, education).	POCD defined as percentile ranks of scores ≤18% on ≥1 test. POCD in n=11/36 (30.6%).	Diabetes diagnosis (n=19/36; 52.8%).	None.	RR 1.7 (95% CI 1.1, 2.5).	11/22
Heyer et al. (2015)	662	585	65	Carotid endarter-ectomy.	34.4% ≥75 years old	1 day	Unclear number of neuro-psychological	POCD defined as ≥2 SD worse performance on ≥2	Diabetes diagnosis (n=125/585;	None.	RR 0.92 (95% CI 0.64, 1.31).	17/22

USA.				General anesthesia.			tests of four cognitive domains. Calculation of RCI[a]. Control group n=156.	cognitive domains and/or ≥1.5 SD worse performance on all 4 cognitive domains. POCD in n=145/585 (24.8%).	21.4%).			

All data refer to analysis sample that completed follow-up, unless otherwise indicated. BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CPB, cardiopulmonary bypass; MI, myocardial infarction; MMSE, Mini Mental State Examination; PAD, peripheral arterial disease; RCI, reliable change index; RR, relative risk; SD, standard deviation; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

[a]formula for Reliable Change Index (RCI) (often referred to as 'z-score'): RCI = (change score of patient – change score of control group)/SD of change score of control group.

[b]based on total sample enrolled into study (data on analysis sample completing follow-up unreported).

[c]N uncertain based on article.

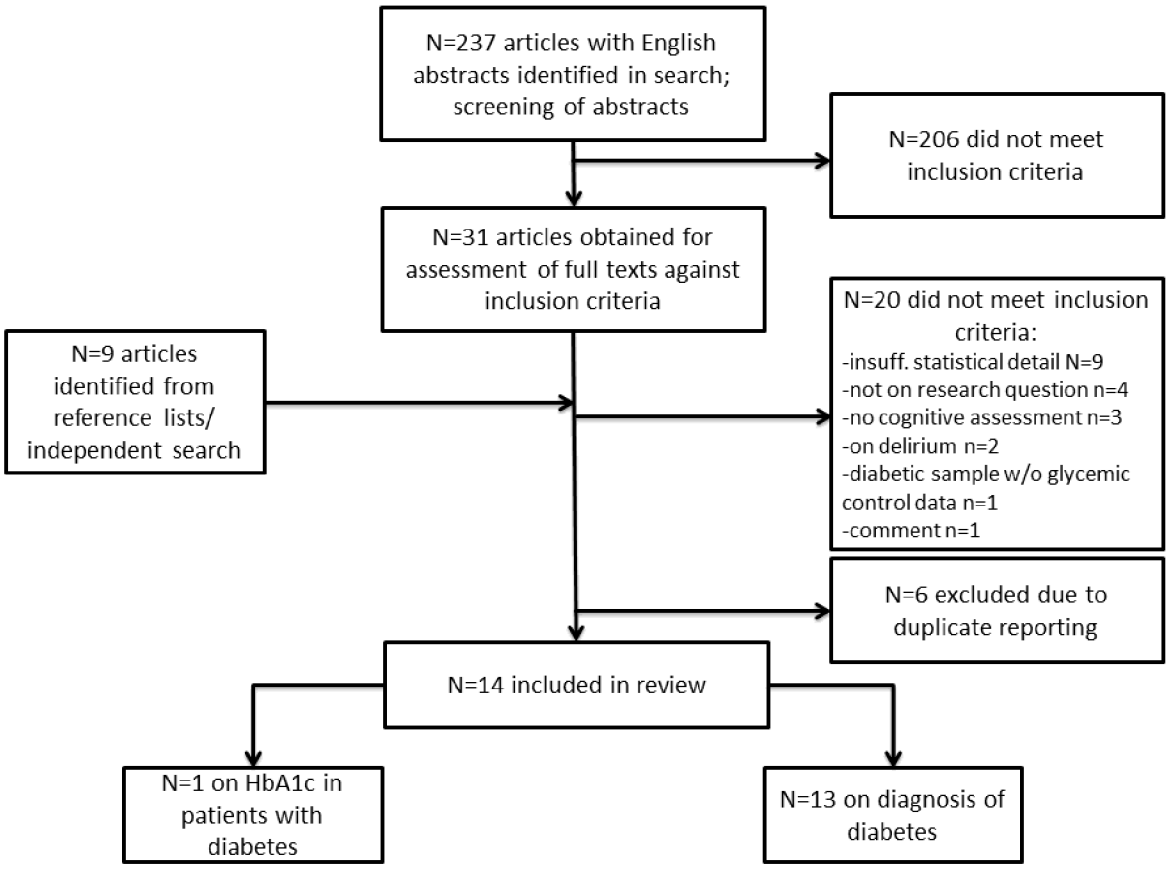

Figure 1: Results of systematic search

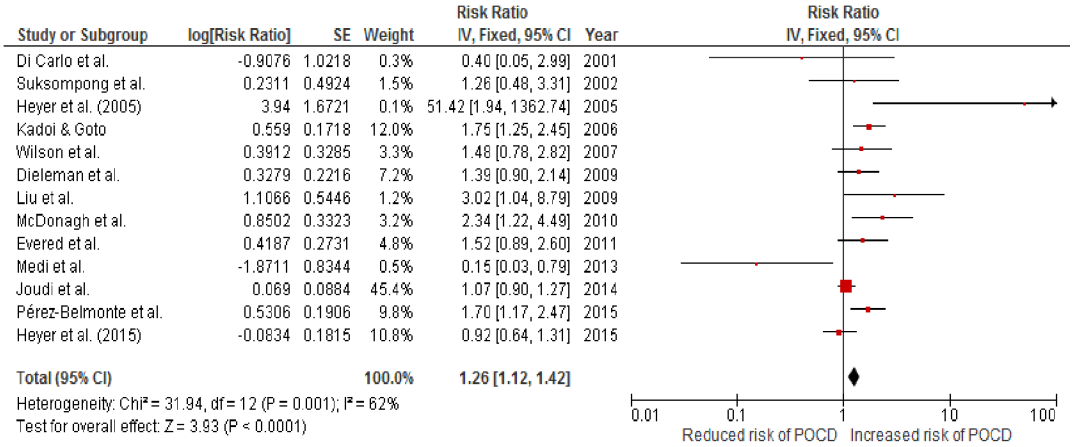

Figure 2: Forrest plot for fixed-effects meta-analysis of diabetes and risk of POCD. Disparity in decimal places of confidence intervals compared with original reporting (0.01 to 0.02) [21, 22, 31, 38] presumably due to rounding.

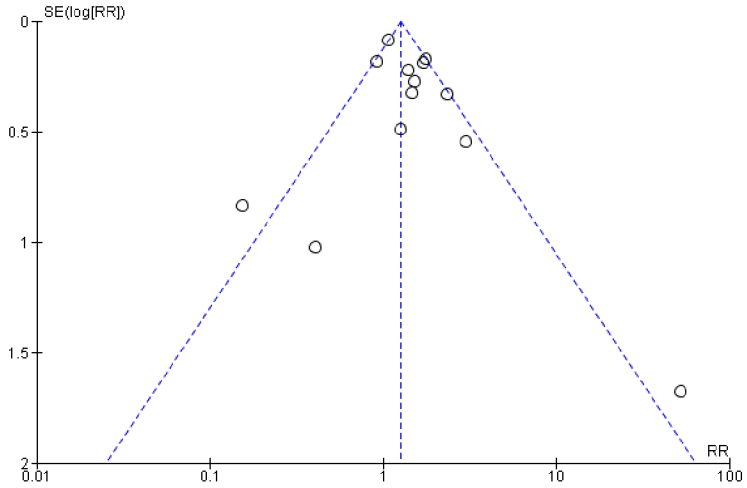

Figure 3: Funnel plot for meta-analysis of diabetes and risk of POCD

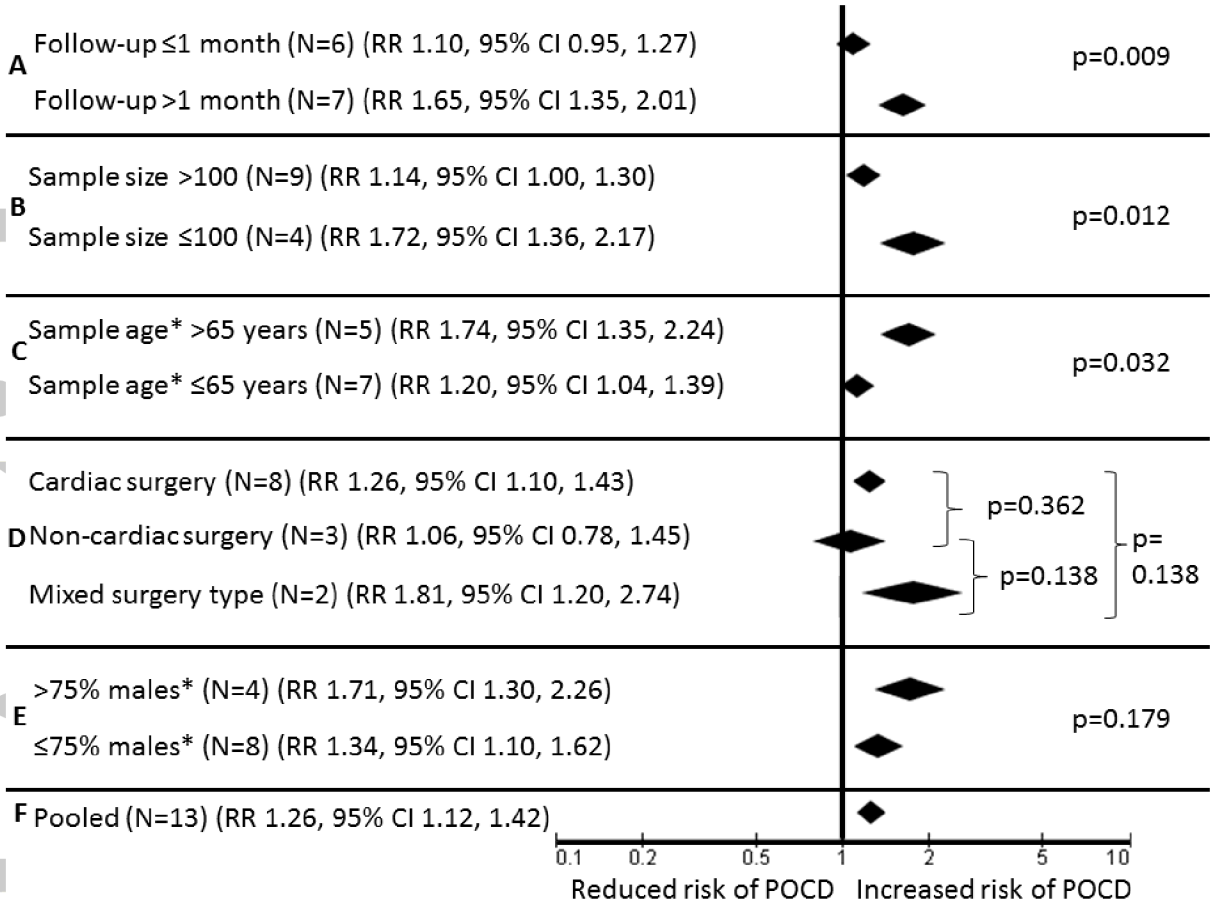

Figure 4: Diabetes and risk of POCD in subgroup analyses according to follow-up period (A), sample size (B), mean sample age (C), surgery type (D) and sex (E), and across all studies (F). P-values are shown for meta-regression analyses to determine contribution of study characteristics to overall pooled estimates. All results are from fixed-effects models. *data missing for N=1 study.