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# Association of diabetes, hypertension, and obesity with risk of post-operative cognitive dysfunction (POCD): observational analysis of 3 clinical trials

**Running title: Metabolic dysfunction and risk of post-operative cognitive dysfunction**

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**Abstract**

*Background/Aims.* Older people undergoing surgery are at risk of developing post-operative cognitive dysfunction (POCD), but little is known of risk factors predisposing patients to POCD. Our objective was to estimate the risk of POCD associated with exposure to pre-operative diabetes, hypertension and obesity. *Methods.* Original data from 3 randomized controlled trials (OCTOPUS, DECS, SuDoCo) were obtained for secondary analysis on diabetes, hypertension, baseline blood pressure, obesity (BMI ≥ 30 kg/m²) and BMI as risk factors for POCD in multiple logistic regression models. Risk estimates were pooled across the 3 studies. *Results.* Analyses totalled 1034 patients. POCD occurred in 5.2% of patients in DECS, in 9.4% in SuDoCo, and in 32.1% of patients in OCTOPUS. After adjustment for age, sex, surgery type, randomisation, obesity and hypertension, diabetes was associated with a 1.84-fold increased risk of POCD (OR 1.84; 95% CI 1.14, 2.97; p=0.01). Obesity, BMI, hypertension and baseline blood pressure were each not associated with POCD in fully adjusted models (all p>0.05). *Conclusion.* Diabetes, but not obesity or hypertension, is associated with increased POCD risk. Consideration of diabetes status may be helpful for risk assessment of surgical patients.

**Introduction**

Patients undergoing surgery are at risk of developing a post-operative neurocognitive disorder, or, post-operative cognitive dysfunction (POCD) – a condition that is defined by a decline in performance on neuropsychological tests from pre-surgery to post-surgery assessment. Large individual differences in POCD spanning cognitive recovery during the first few months to persistent cognitive impairment have been reported [1-5]. Although it has been the subject of extensive research during the past two decades, many questions remain unanswered, and a lack of uniform diagnostic criteria [6] and differences in length of follow-up period hamper comparability between studies. Little is currently known about potential risk factors, which help to identify at-risk patients and shed light on underlying pathophysiology. In recent systematic reviews and meta-analyses [7-10], we have shown that patients with metabolic derangement may be at an increased risk of POCD. Indicators of metabolic derangement include classical vascular risk factors such as elevated blood glucose, elevated blood pressure and obesity, which all tend to correlate [11]. In line with its well-established role as a predictor of age-related cognitive impairment [12-16], we found in our meta-analysis that diabetes was associated with a 26% increased risk of POCD [8]. Findings were less clear for obesity[17] and hypertension was overall not associated with POCD [10]. However, studies included in those meta-analyses were largely exploratory and frequently failed to apply statistical adjustment for potential confounders which is considered a major limitation. Detailed assessment of exposure to these candidate risk factors and subsequent risk of POCD on the basis of primary data is thus needed, particularly in view of their modifiable nature that leaves scope for risk alteration at individual patient level.

Here, we therefore aimed to estimate the risk of POCD associated with pre-operative exposure to diabetes, hypertension and obesity, with focus on potential mutual confounding among the risk factors in determining POCD risk. Data were provided by 3 large randomized controlled trials (RCTs) targeting factors and procedures potentially influencing POCD risk. In a secondary analysis of their primary data, we evaluated risk of POCD associated with each exposure of interest and additionally provide pooled risk estimates combined across the 3 studies.

## Materials and Methods

### *Study design*

In a quasi-observational, secondary analysis of 3 studies, the Surgery Depth of Anaesthesia Cognitive Outcome (SuDoCo) [18], Dexamethasone for Cardiac Surgery (DECS) [19, 20], and OCTOPUS [21] studies, associations of exposure to diabetes, hypertension and obesity with POCD risk were determined. None of the 3 studies had previously been used to investigate this research question. Access to their original data resulted from a cross-institutional collaboration.

### *Setting*

All 3 studies were RCTs with primary or secondary outcome POCD. Each trial evaluated intervention effects (SuDoCo: monitoring depth of anaesthesia during general surgery; DECS: dexamethasone administration versus placebo during cardiac surgery; OCTOPUS: on-pump versus off-pump methods for cardiac surgery) on POCD risk, and included repeat neuropsychological testing with several post-surgery follow-up assessments of which we analysed the respective longest follow-up period (OCTOPUS: 12 months; DECS: 12 months; SuDoCo: 3 months).

### *Participants*

A total of 1849 patients enrolled into the 3 studies between 1998 and 2011. Recruitment procedures, inclusion and exclusion criteria have been described in detail previously [18, 20, 21]. In brief, any patients with pre-existing neurological deficits were excluded in all 3 studies; in SuDoCo, MMSE<24 was also an exclusion criterion, and in DECS, patients with diagnosed mental illness were additionally excluded. Follow-up assessments were completed by 1034 patients (Figure 1). Patient drop-out between baseline and follow-up was mainly due to lack of interest and withdrawal of consent. Cognitive deficit after surgery was evaluated as either primary or secondary outcome in each of the 3 studies. Surgical procedures included cardiac (OCTOPUS; DECS) and non-cardiac surgery types (SuDoCo), and interventions compared different surgical techniques (on-pump versus off-pump CABG in OCTOPUS), preoperative administration of intravenous dexamethasone in cardiac surgery (DECS) or intraoperative neuromonitoring (SuDoCo).

*Physical examination*

Diabetes and a history of hypertension were routinely ascertained during pre-surgery interview and from medical records. Though we were unable to distinguish between type 1 and type 2 diabetes based on the data, we assume that a majority of patients with diabetes will have suffered from type 2 diabetes based on sample age. Baseline blood pressure, height and weight were measured at pre-surgery assessment, and height and weight were used to derive body mass index (BMI). In accordance with convention [22], we defined obesity as BMI ≥30 $kg/m^2$ . A conservative cut-point of BMI<20 $kg/m^2$ identified underweight patients.

*Cognitive examination and definition of POCD*

Trained staff administered several age-sensitive neuropsychological tests tapping various cognitive domains (OCTOPUS: N=11 tests; DECS: N=5 tests; SuDoCo: N=6 tests; Supplemental Table 1) to the respective patient samples and additionally to non-surgical control samples for normative data. For the purpose of this analysis, we used POCD as dichotomous outcome as it was defined in the respective original studies. This varied between studies. For DECS and SuDoCo, POCD was defined through comparison of the cognitive change of patients with the average cognitive change of the respective control group; for OCTOPUS, POCD was determined from raw change in cognitive test scores (Supplemental Table 1).

*Statistical methods*

Exposures of interest were the presence versus absence of diabetes, hypertension, and obesity respectively. In addition, we also analyzed BMI, and systolic and diastolic baseline blood pressure. Outcome was POCD at the longest follow-up assessment in each cohort. A two-step approach was used to analyze exposure-outcome relationships [23, 24]. Initially, risk of POCD according to exposure to diabetes, hypertension, obesity, BMI, systolic blood pressure and diastolic blood pressure was assessed separately for each of the 3 studies. We used logistic regression analyses with hierarchical model building: Model 0 includes unadjusted associations, model 1 includes age and sex as covariates, model 2 additionally includes type of surgery and RCT treatment group, and model 3 additionally includes all of the respective remaining predictor variables (of diabetes, obesity, hypertension) to analyse potential mutual confounding. Baseline blood pressure and BMI were not included as covariates in model 3 to avoid collinearity as these variables contributed to the definition of “hypertension” and “obesity” respectively. For OCTOPUS and DECS, we also adjusted for education in models 2

and 3 but present data without that adjustment to allow cross-study comparison, as in SuDoCo, information on education was not available. Odds ratios are provided for 1-point increments in BMI and 10-point increments in baseline blood pressure values to aid interpretability of risk estimates.

In a second step, risk estimates were pooled across all 3 studies (total patient N=1034) for each exposure variable and for each of the statistical modelling steps using fixed-effects inverse variance analyses. This approach to combining data was selected on the basis that one true underlying effect was assumed to underlie all 3 studies [25] and weighs studies according to the standard error of their estimates (i.e., studies with lower standard error are given greater weight). The respective final models (Model 3) were repeated post-hoc using random-effects models to show the mean distribution of effects [25]. The results of these analyses are shown as Supplemental Data (Supplemental Table 2). Statistical heterogeneity between studies was assessed using the $I^2$ index[26].

Analyses were repeated post-hoc with exclusion of underweight patients to ensure that findings were not driven by underweight which is a well-established risk factor for age-related cognitive impairment[27] and may also be associated with POCD. Analyses were performed with IBM© SPSS© Statistics (version 23) and Review Manager (version 5.3). The statistical analysis plan was approved by an internal committee before any of the analyses were performed.

*Ethical approval*

Participants gave written informed consent and assessments complied with the Declaration of Helsinki. Though no new data were collected, ethical approval for the present analysis (EA1/242/08) was provided by the Ethical Committee Ethikausschuss 1 at Charité Mitte, Berlin, Germany (Chairperson Prof R. Uebelhack) on 31 January 2017.

**Results**

*Study characteristics*

Characteristics of the patient samples completing follow-up of the 3 studies are shown in Table 1. Mean BMI was 26.6 kg/m$^2$ (SD=3.2) in OCTOPUS, 26.9 kg/m$^2$ (SD=4.5) in DECS and 27.3 kg/m$^2$ (SD=4.9) in SuDoCo and thus in the 'overweight' category (25 to 30 kg/m$^2$) in all 3 studies.. Underweight (BMI<20 kg/m$^2$) was rare. Mean BMI in the underweight groups was 19.2 kg/m$^2$ (SD=1.3) in OCTOPUS (N=5 underweight patients), 18.9 kg/m$^2$ (SD=0.9) in DECS (N=10 underweight patients) and 19.0 kg/m$^2$ (SD=0.9) in SuDoCo (N=17 underweight patients). In OCTOPUS, mean BMI was 31.6 kg/m$^2$ (SD=1.1) in obese patients (BMI≥30 kg/m$^2$). In DECS and SuDoCo, obese groups had mean BMIs of 33.8 kg/m$^2$ (SD=3.1) and 34.1 kg/m$^2$ (SD=4.1), respectively. Systolic and diastolic blood pressure correlated positively with one another in the 2 studies that measured blood pressure (r=0.49 to 0.57; both p<0.001) whereas neither was associated with BMI in those studies (all p>0.10).

*Associations of diabetes, hypertension, and obesity with risk of POCD*

POCD occurred in 12 patients (5.2%) at 12-month follow-up in DECS. Of these, 4 had diabetes (33.3%), 4 were obese (33.3%) and 8 had hypertension (66.7%). In SuDoCo, POCD occurred in 52 patients (9.4%) at 3 months. Sixteen (30.8%) of those 52 patients had diabetes, 12 (23.1%) were obese and 38 (73.1%) had hypertension. Eighty-one patients (32.1%) in OCTOPUS had POCD at 12 months, of whom 15 (18.5%) had diabetes, 13 (16.0%) were obese and 40 (49.4%) had hypertension. In the pooled analysis, after adjustment for age, sex, type of surgery and randomisation, diabetes was associated with a 1.97-fold (95%-CI 1.24-2.97) higher risk of POCD, while hypertension was associated with a 1.50-fold (95%-CI 1.01-2.24) higher risk (Table 2; Figure 2). In contrast, obesity was not significantly associated with risk of POCD (odds ratio, 1.22; 95%-CI 0.76-1.96). Risk estimates were similar when random-effects models were used (Supplemental Table 2), when underweight patients were excluded from analysis (data not shown) and also remained unchanged after additional adjustment for education in the 2 studies with education data (OCTOPUS; DECS; data not shown). After additional adjustment for hypertension and obesity, diabetes remained statistically significantly associated with a higher risk of POCD, with a pooled odds ratio of 1.84 (95%-CI 1.14-2.97; Model 3 in Table 2 calculated from OCTOPUS, odds ratio 1.90, 95%-CI 0.86, 4.21; DECS, odds ratio 2.94, 95%-CI 0.69, 12.52; SuDoCo, odds ratio 1.62, 95%-CI 0.84, 3.15) and no evidence of statistical heterogeneity between studies ($Chi^2$=0.55; p=0.76; $I^2$=0%). In contrast, hypertension was not significantly associated with risk of POCD after additional adjustment for diabetes and obesity (odds ratio, 1.37; 95%-CI 0.91-2.07).

Similar to the results reported above, obesity was not significantly associated with POCD in these fully adjusted models.

*Associations of BMI, systolic and diastolic baseline blood pressure with POCD*

BMI was not significantly associated with risk of POCD (Supplemental Table 3; Figure 3) in the analysis pooled across the 3 studies. Again, these results were not substantially different when random-effects models were used (Supplemental Table 2) or when underweight patients were excluded from the analysis (data not shown). Neither systolic nor diastolic baseline blood pressure was significantly associated with POCD risk, although this analysis was restricted to two studies (Supplemental Table 3).

**Discussion**

Across 3 studies, we found evidence that diabetes was associated with a 1.84-fold higher risk of POCD. Importantly, the association was independent of age, sex, type of surgery and intervention, as well as obesity and hypertension. Hypertension and obesity were not independently associated with risk of POCD. These findings extend our previous meta-analyses which, largely based on unadjusted results of exploratory studies, had found significant associations for diabetes but not for obesity or hypertension with POCD risk [7, 8, 10].

The pathophysiology of developing POCD is poorly understood. Neuroinflammation with subsequent microglial overactivation and disruption of the blood brain barrier is assumed to play a role in the development of short-term postoperative cognitive impairment [28]. Other theories on causes of POCD include impaired cerebral perfusion during surgery [29], lasting neurotoxic effects of anaesthetics as well as detrimental effects of perioperative opioid use on brain function [30, 31]. Environmental factors such as hospital environments and sleep disturbances, too, may play a role [31]. However, these theories cannot easily explain the higher POCD risk in patients with diabetes. Patients with diabetes generally show greater cerebral and hippocampal atrophy [32-34] as well as cerebral microvascular [35, 36] and macrovascular damage [37] and are also at increased risk of cognitive impairment [15, 38, 39] compared with non-diabetics. Similar observations have been made for hyperglycaemia short of diabetes diagnosis [40, 41] and poorer glycemic control in patients with diabetes [42], which indicates fundamental influences of impaired glucose metabolism on the brain. It appears that the negative impact of hyperglycemia on brain function may be accelerated due to surgery as it was observed for patients with diabetes during relatively short follow-up periods of 3 to 12 months in the present analysis. Further, our findings suggest somewhat higher odds of POCD in the 2 studies with cardiac patients (DECS; OCTOPUS) compared with the study of non-cardiac patients (SuDoCo) which reiterates a statistically non-significant trend in the same direction in our meta-analysis [8]. This warrants further evaluation. It may be the case that negative impacts of diabetes on the vasculature increase POCD risk following vascular interventions. Though we cannot determine causality on the basis of the present epidemiological findings, our results may reflect neurotoxic effects of persistently high blood glucose that ultimately impairs neurons with subsequent loss of function [43]. Surgery-associated high grade systemic inflammation [44] may have affected previously damaged neurons in patients with diabetes resulting in POCD. Further studies are

thus needed to add to our understanding of the pathophysiology of surgical brain damage in the context of hyperglycaemia and diabetes. An influence of type of anti-diabetic treatment and glycemic control including prior history of hypoglycaemia which itself seems to increase cognitive risk [45, 46] should additionally be considered in further observational studies that collect more detailed data, for instance on HbA1c levels, duration of diabetes and treatment type, of their patients with diabetes, and trial studies may also be possible. An influence of improved glycemic control during the weeks before surgery on POCD risk could be assessed in a sample of people with type 2 diabetes for example.

Hypertension is a major influencing factor for cardiovascular events such as stroke and myocardial infarction due to vascular damage [47]. However, we did not see any significant influence of a prior history of hypertension on risk of POCD that was independent of its link to diabetes. The null finding suggests that vascular damage as a consequence of hypertension may only play a minor role in POCD development and replicates results of our meta-analysis of hypertension as a candidate risk factor for POCD [10]. Though we did not assess severity of hypertension which may be important in cognitive risk prediction [48], our finding warrants further enquiry particularly in view of established associations of this risk factor with cognitive impairment per se [15, 49, 50]. A beneficial effect of anti-hypertensive treatment on cognitive risk as an explanation of the null finding appears unlikely given the balance of evidence from RCTs speaks against such effects [51, 52].

Obesity is a pro-inflammatory state characterized by raised circulating inflammatory markers [53, 54], which itself appears to promote cognitive dysfunction after surgery [55]. We therefore hypothesized that obesity may be a risk factor for POCD. The results of the present analysis and of our previous meta-analysis [7] do not appear to support this hypothesis. Indeed, when looking to age-related cognitive impairment, increasing evidence suggests that while midlife obesity appears to increase risk of later impairment, obesity in later life does not. For instance, a recent analysis of the Whitehall II study of >10 000 individuals in the UK found obesity at age 50 but not at age 60 or 70 predicted dementia risk [56]. Some studies even corroborate an ‘obesity paradox’ with beneficial effects of obesity on cognitive function in later life [57] which may reflect effects of prodromal stages of dementia on body weight [56, 58]. We have no information on body weight status at midlife or weight trajectories of participants but suspect that similar processes may underlie the lack of an association of obesity and POCD risk in the present analysis. We also cannot rule out potential harmful effects of obesity that we may have missed for lack of statistical power.

Strengths of our study include the use of primary data from 3 studies on POCD that allowed adjustment for a range of potential confounders. By entering all 3 exposures of interest into the same statistical models, our approach further allowed determination of the relative contribution of diabetes, obesity and hypertension to POCD risk. Sensitivity analyses were able to show that the absence of an association of obesity or BMI with POCD risk was not driven by inclusion of underweight patients in the main analyses.

A number of limitations must be considered. We followed a two-step approach to data analysis and pooling of estimates rather than individual-patient meta-analysis. Readers should also be aware that we assessed 3 exposures for associations with POCD, which may have increased type I statistical error. However, findings on diabetes and POCD risk remained unchanged with Bonferroni correction of the critical p-value indicative of statistical significance. Importantly, different psychological batteries for determining POCD were used in each of the 3 studies. This could have influenced POCD incidence which was particularly low for DECS and thus may have limited our statistical modelling that included a number of covariates. Prevalence of diabetes and hypertension varied between the 3 studies, and likely reflected a difference in health status between samples. Generalizability of our findings is therefore unclear. As cognitive deficits often appear to resolve over time [3, 4, 59], the pooling of effects across studies with 3- to 12-month follow-up periods was suboptimal and will have led to incidence of POCD ranging from 5.2% to 32.1%. Cohort effects were introduced by recruitment periods spanning 1998 to 2011 and our findings may not necessarily apply to patients undergoing surgery today. Further, the studies had not set out to investigate the present exposures of interest and risk of POCD. Thus, assessment of diabetes, hypertension and obesity may not have been consistently rigorous, and we were not able to discriminate between type 1 and type 2 diabetes. An influence of other well-established risk factors for POCD, such as previous cerebrovascular event known to be associated with diabetes [60] as well as POCD[1], to our findings is also plausible. We deem an influence of pre-existing cognitive impairment which, too, is associated both with diabetes [14] and POCD [8] unlikely as SuDoCo, which was weighted most heavily in the combined analyses, excluded patients with baseline cognitive impairment. Between-study differences in assessment of other factors such as blood loss during surgery meant that adjustment was not possible for all potential confounders. Residual confounding is therefore possible. Various definitions of POCD were used. In DECS and SuDoCo, POCD was defined relative to

cognitive change of non-surgical control groups, and neither had information available on prevalence of diabetes, hypertension and obesity in the control subjects. Thus, we cannot determine whether the present findings reflect associations of diabetes with POCD versus associations with cognitive decline *per se*. This also applies to the OCTOPUS study which defined POCD from raw cognitive change. Here, patients with diabetes (even if not exposed to surgery) may have simply declined at steeper rates during follow-up compared with non-diabetics. OCTOPUS also reported incidence of POCD of around one third of patients at 12 month follow-up, which is high relative to previous studies[61]. Post-surgery stroke was considered as "POCD" in OCTOPUS and DECS, which complicates the interpretation of findings on POCD as a form of impairment as opposed to overt cerebrovascular disease. Further, any non-linear associations of BMI with POCD risk were presumably not well-captured by a single cut-off at BMI≥30 kg/m$^2$ for definition of obesity. However, when we excluded underweight patients and those with post-operative stroke from analyses, findings remained unchanged.

In conclusion, our results suggest that people with diabetes are at increased risk of POCD and independently of co-morbid obesity or hypertension. Consideration of diabetes status may thus be helpful for assessment of POCD risk to help clinicians and patients alike to make informed decisions when electing surgery. Enhanced post-surgery care for patients with diabetes that includes screening for POCD may also be indicated.

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**Duality of interest**

All authors declare no conflicts of interest related to this article.

**Contribution statement**

D.D. conceived and designed OCTOPUS. T.O. conceived and designed DECS. F.M.R. conceived and designed SuDoCo. G.L. and I.F. conceived the present study and performed the statistical analyses. G.L., I.F. and F.B. drafted the manuscript. G.L., I.F., F.B., C.S. and T.P. were involved in the interpretation of findings and preparation of the final manuscript. All authors commented on the final draft.

## References


1. Rundshagen I: **Postoperative cognitive dysfunction**. *Deutsches Ärzteblatt International* 2014, **111**(8):119-125.
2. Newman MF, Kirchner JL, Phillips-Bute BS, Gaver V, Grocott H, Jones RH, Mark DB, Reves JG, Blumenthal JA: **Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery**. *New England Journal of Medicine* 2001, **344**:395-402.
3. Abildstrom H, Rasmussen LS, Rentowl P, Hanning CD, Rasmussen H, Kristensen PA, Moller JT: **Cognitive dysfunction 1–2 years after non-cardiac surgery in the elderly**. *Acta Anaesthesiologica Scandinavia* 2000, **44**:1246-1251.
4. Silbert B, Evered L, Scott DA, McMahon S, Choong P, Ames D, Maruff P, Jamrozik K: **Preexisting cognitive impairment is associated with postoperative cognitive dysfunction after hip joint replacement surgery**. *Anesthesiology* 2015, **122**:1224-1234.
5. Tan CB, Ng J, Jeganathan R, Kawai F, Pan CX, Pollock S, Turner J, Cohen S, Chorost M: **Cognitive changes after surgery in the elderly: does minimally invasive surgery influence the incidence of postoperative cognitive changes compared to open colon surgery?** *Dement Geriatr Cogn Disord* 2015, **39**(3-4):125-131.
6. Evered LA, Silbert B, Scott DA: **The impact of peri-operative period on cognition in older individuals**. *Journal of Pharmacy Practice and Research* 2015, **45**:93-99.
7. Feinkohl I, Winterer G, Pischon T: **Obesity and post-operative cognitive dysfunction: a systematic review and meta-analysis**. *Diabetes/Metabolism Research and Reviews* 2016, **32**:643-651.
8. Feinkohl I, Winterer G, Pischon T: **Diabetes is associated with risk of postoperative cognitive dysfunction: A meta-analysis**. *Diabetes Metab Res Rev* 2017, **33**(5):e2884.
9. Feinkohl I, Winterer G, Pischon T: **Associations of dyslipidaemia and lipid-lowering treatment with risk of post-operative cognitive dysfunction (POCD): A systematic review and meta-analysis**. *Journal of Epidemiology and Community Health* 2018, **epub ahead of print**.
10. Feinkohl I, Winterer G, Pischon T: **Hypertension and Risk of Post-Operative Cognitive Dysfunction (POCD): A Systematic Review and Meta-Analysis**. *Clinical practice and epidemiology in mental health : CP & EMH* 2017, **13**:27-42.
11. Lechi A: **The obesity paradox: is it really a paradox? Hypertension**. *Eating and weight disorders : EWD* 2016, **22**:43-48.
12. Chatterjee S, Peters SA, Woodward M, Mejia Arango S, Batty GD, Beckett N, Beiser A, Borenstein AR, Crane PK, Haan M *et al*: **Type 2 Diabetes as a Risk Factor for Dementia in Women Compared With Men: A Pooled Analysis of 2.3 Million People Comprising More Than 100,000 Cases of Dementia**. *Diabetes Care* 2016, **39**(2):300-307.
13. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P: **Risk of dementia in diabetes mellitus: a systematic review**. *Lancet Neurology* 2006:64-74.
14. Cukierman T, Gerstein HC, Williamson KD: **Cognitive decline and dementia in diabetes-systematic overview of prospective observational studies**. *Diabetologia* 2005, **48**:2460-2469.
15. Ma F, Wu T, Zhao J, Ji L, Song A, Zhang M, Huang G: **Prevalence of Mild Cognitive Impairment and Its Subtypes among Chinese Older Adults: Role of Vascular Risk Factors**. *Dement Geriatr Cogn Disord* 2016, **41**(5-6):261-272.
16. Dearborn JL, Knopman D, Sharrett AR, Schneider AL, Jack CR, Jr., Coker LH, Alonso A, Selvin E, Mosley TH, Wagenknecht LE *et al*: **The metabolic syndrome and cognitive decline in the Atherosclerosis Risk in Communities study (ARIC)**. *Dement Geriatr Cogn Disord* 2014, **38**(5-6):337-346.
17. Feinkohl I, Winterer G, Pischon T: **Obesity and post-operative cognitive dysfunction: a systematic review and meta-analysis**. *Diabetes/Metabolism Research and Reviews* 2016, **32**:643–651.
18. Radtke FM, Franck M, Lendner J, Krüger S, Wernecke KD, Spies CD: **Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction**. *British Journal of Anaesthesia* 2013, **110 Suppl 1**:98-

105.
19. Dieleman JM, Nierich AP, Rosseel PM, et al.: **Intraoperative high-dose dexamethasone for cardiac surgery: A randomized controlled trial**. *JAMA* 2012, **308**(17):1761-1767.
20. Ottens TH, Dieleman JM, Sauer AM, Peelen LM, Nierich AP, de Groot WJ, Nathoe HM, Buijsrogge MP, Kalkman CJ, van Dijk D: **Effects of dexamethasone on cognitive decline after cardiac surgery: a randomized clinical trial**. *Anesthesiology* 2014, **121**(3):492-500.
21. Van Dijk D, Jansen EW, Hijman R, Nierich AP, Diephuis JC, Moons KG, Lahpor JR, Borst C, Keizer AM, Nathoe HM *et al*: **Cognitive outcome after off-pump and on-pump coronary artery bypass graft surgery: a randomized trial**. *JAMA* 2002, **287**(11):1405-1412.
22. NCD Risk Factor Collaboration: **Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants**. *Lancet* 2016, **387**:1377-1396.
23. Koekkoek PS, Rutten GE, Ruis C, Reijmer YD, van den Berg E, Gorter KJ, Stehouwer CDA, Dekker JM, Nijpels G, Kappelle LJ *et al*: **Mild depressive symptoms do not influence cognitive functioning in patients with type 2 diabetes**. *Psychoneuroendocrinology* 2013, **38**(3):376-386.
24. Kivimaki M, Kuosma E, Ferrie JE, Luukkonen R, Nyberg ST, Alfredsson L, Batty GD, Brunner EJ, Fransson E, Goldberg M *et al*: **Overweight, obesity, and risk of cardiometabolic multimorbidity: pooled analysis of individual-level data for 120 813 adults from 16 cohort studies from the USA and Europe**. *The Lancet Public health* 2017, **2**(6):e277-e285.
25. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR: **A basic introduction to fixed-effect and random-effects model for meta-analysis**. *Research Synthesis Methods* 2010, **1**:97-111.
26. Higgins JPT, Thompson SG: **Quantifying heterogeneity in a meta-analysis**. *Statistics in Medicine* 2002, **21**:1539-1558.
27. Sobow T, Fendler W, Magierski R: **Body mass index and mild cognitive impairment-to-dementia progression in 24 months: a prospective study**. *European journal of clinical nutrition* 2014, **68**(11):1216-1219.
28. Muller A, Lachmann G, Wolf A, Morgeli R, Weiss B, Spies C: **Peri- and postoperative cognitive and consecutive functional problems of elderly patients**. *Curr Opin Crit Care* 2016, **22**(4):406-411.
29. Siepe M, Pfeiffer T, Gieringer A, Zemann S, Benk C, Schlensak C, Beyersdorf F: **Increased systemic perfusion pressure during cardiopulmonary bypass is associated with less early postoperative cognitive dysfunction and delirium**. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery* 2011, **40**(1):200-207.
30. Xie Z, Dong Y, Maeda U, Moir R, Inouye SK, Culley DJ, Crosby G, Tanzi RE: **Isoflurane-induced apoptosis: a potential pathogenic link between delirium and dementia**. *The journals of gerontology Series A, Biological sciences and medical sciences* 2006, **61**(12):1300-1306.
31. Krenk L, Rasmussen LS, Kehlet H: **New insights into the pathophysiology of postoperative cognitive dysfunction**. *Acta Anaesthesiologica Scandinavia* 2010, **54**:951-956.
32. Kumar R, Anstey KJ, Cherbuin N, Wen W, Sachdev PS: **Association of type 2 diabetes with depression, brain atrophy, and reduced fine motor speed in a 60- to 64-year-old community sample**. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry* 2008, **16**(12):989-998.
33. Van Elderen SG, de Roos A, de Craen AJ, Westendorp RG, Blauw GJ, Jukema JW, Bollen EL, Middelkoop HA, van Buchem MA, van der Grond J: **Progression of brain atrophy and cognitive decline in diabetes mellitus: a 3-year follow-up**. *Neurology* 2010, **75**:997-1002.
34. Hayashi K, Kurioka S, Yamaguchi T, Morita M, Kanazawa I, Takase H, Wada A, Kitagaki H, Nagai A, Bokura H *et al*: **Association of cognitive dysfunction with hippocampal atrophy in elderly Japanese people with type 2 diabetes**. *Diabetes Research and Clinical Practice* 2011, **94**:180-185.
35. Fulesdi B, Limburg M, Bereczki D, Kaplar M, Molnar C, Kappelmayer J, Neuwirth G, Csiba L: **Cerebrovascular reactivity and reserve capacity in type II diabetes mellitus**. *J Diabetes*

*Complications* 1999, **13**(4):191-199.
36. Fulesdi B, Limburg M, Bereczki D, Michels RP, Neuwirth G, Legemate D, Valikovics A, Csiba L: **Impairment of cerebrovascular reactivity in long-term type 1 diabetes**. *Diabetes* 1997, **46**(11):1840-1845.
37. van Harten B, De Leeuw FE, Weinstein HC, Scheltens P, Biessels GJ: **Brain imaging in patients with diabetes. A systematic review**. *Diabetes Care* 2006, **29**:2539-2548.
38. Chatterjee S, Peters SAE, Woodward M, Arango SM, Batty GD, Beckett N, Beiser A, Borenstein AR, Crane PK, Haan M *et al*: **Type 2 diabetes as a risk factor for dementia in women compared with men: a pooled analysis of 2.3 million people compromising more than 100,000 cases of dementia**. *Diabetes Care* 2016, **39**:300-307.
39. Strachan MWJ, Reynolds RM, Marioni RE, Price JF: **Cognitive function, dementia and type 2 diabetes mellitus in the elderly**. *Nature Reviews Endocrinology* 2011, **7**:108-114.
40. Lamport DJ, Lawton CL, Mansfield MW, Dye L: **Impairments in glucose tolerance can have a negative impact on cognitive function: a systematic research review**. *Neuroscience and biobehavioral reviews* 2009, **33**:394-413.
41. Lu Y, Lu J, Wang S, Li C, Liu L, Zheng R, Tian H, Wang X, Yang L, Zhang Y *et al*: **Cognitive function with glucose tolerance status and obesity in Chinese middle-aged and aged adults**. *Aging & mental health* 2012, **16**(7):911-914.
42. Feinkohl I, Keller M, Robertson CM, Morling JR, McLachlan S, Frier BM, Deary IJ, Strachan MW, Price JF: **Cardiovascular risk factors and cognitive decline in older people with type 2 diabetes**. *Diabetologia* 2015, **58**(7):1637-1645.
43. Tomlinson DR, Gardiner NJ: **Glucose neurotoxicity**. *Nature reviews Neuroscience* 2008, **9**(1):36-45.
44. Scott DA, Evered LA, Silbert BS: **Cardiac surgery, the brain, and inflammation**. *The journal of extra-corporeal technology* 2014, **46**(1):15-22.
45. Biessels GJ: **Hypoglycemia and cognitive decline in older people with type 2 diabetes: a bidirectional relationship**. *Diabetic Hypoglycemia* 2014, **6**:11-14.
46. Feinkohl I, Aung PP, Keller M, Robertson CM, Morling JR, McLachlan S, Deary IJ, Frier BM, Strachan MW, Price JF: **Severe hypoglycemia and cognitive decline in older poeple with type 2 diabetes: the Edinburgh Type 2 Diabetes Study**. *Diabetes Care* 2014, **37**:507-515.
47. Lakatta EG, Levy D: **Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part I: aging arteries: a "set up" for vascular disease**. *Circulation* 2003, **107**(1):139-146.
48. Muela HCS, Costa-Hong VA, Yassuda MS, Machado MF, Nogueira RC, Moraes NC, Memoria CM, Macedo TA, Bor-Seng-Shu E, Massaro AR *et al*: **Impact of hypertension severity on arterial stiffness, cerebral vasoreactivity, and cognitive performance**. *Dementia & neuropsychologia* 2017, **11**(4):389-397.
49. Van den Berg E, Kloppenborg RP, Kessels RPC, Kappelle LJ, Biessels GJ: **Type 2 diabetes mellitus, hypertension, dyslipidemia and obesity: a systematic comparison of their impact on cognition**. *Biochimicia et Biophysica Acta* 2009, **1792**:470-481.
50. Sharp SI, Aarsland D, Day S, Sonnesyn H, Alzheimer's Society Vascular Dementia Systematic Review Group, Ballard C: **Hypertension is a potential risk factor for vascular dementia: systematic review**. *International Journal of Geriatric Psychiatry* 2011, **26**:661-669.
51. McGuinness B, Craig D, Bullock R, Passmore P: **Statins for the prevention of dementia**. *The Cochrane database of systematic reviews* 2016(1):Cd003160.
52. Williamson JD, Launer LJ, Bryan RN, Coker LH, Lazar RM, Gerstein HC, Murray AM, Sullivan MD, Horowitz KR, Ding J *et al*: **Cognitive function and brain structure in persons with type 2 diabetes mellitus after intensive lowering of blood pressure and lipid levels: a randomized clinical trial**. *JAMA internal medicine* 2014, **174**(3):324-333.
53. Park HS, Park JY, Yu R: **Relationship of obesity and visceral adiposity with serum concentrations of CRP, TNF-alpha and IL-6**. *Diabetes Res Clin Pract* 2005, **69**(1):29-35.
54. Misiak B, Leszek J, Kiejna A: **Metabolic syndrome, mild cognitive impairment and Alzheimer's disease--the emerging role of systemic low-grade inflammation and adiposity**.

*Brain research bulletin* 2012, **89**(3-4):144-149.
55. Peng L, Xu L, Ouyang W: **Role of peripheral inflammatory markers in postoperative cognitive dysfunction (POCD): a meta-analysis**. *PLoS One* 2013, **8**(11):e79624.
56. Singh-Manoux A, Dugravot A, Shipley M, Brunner EJ, Elbaz A, Sabia S, Kivimaki M: **Obesity trajectories and risk of dementia: 28 years of follow-up in the Whitehall II Study**. *Alzheimer's & dementia : the journal of the Alzheimer's Association* 2018, **14**(2):178-186.
57. Monda V, La Marra M, Perrella R, Caviglia G, Iavarone A, Chieffi S, Messina G, Carotenuto M, Monda M, Messina A: **Obesity and brain illness: from cognitive and psychological evidences to obesity paradox**. *Diabetes, metabolic syndrome and obesity : targets and therapy* 2017, **10**:473-479.
58. Stewart R, Masaki K, Xue QL, Peila R, Petrovitch H, White LR, Launer LJ: **A 32-year prospective study of change in body weight and incident dementia: the Honolulu-Asia Aging Study**. *Arch Neurol* 2005, **62**(1):55-60.
59. Inouye SK, Marcantonio ER, Kosar CM, Tommet D, Schmitt EM, Travison TG, Saczynski JS, Ngo LH, Alsop DC, Jones RN: **The short-term and long-term relationship between delirium and cognitive trajectory in older surgical patients**. *Alzheimer's & dementia : the journal of the Alzheimer's Association* 2016, **12**(7):766-775.
60. Mankovsky BN, Ziegler D: **Stroke in patients with diabetes mellitus**. *Diabetes/ Metabolism Research and Reviews* 2004, **20**:268-287.
61. Androsova G, Krause R, Winterer G, Schneider R: **Biomarkers of postoperative delirium and cognitive dysfunction**. *Frontiers in Aging Neuroscience* 2015, **7**(112).
62. Jacobson NS, Truax P. **Clinical significance: a statistical approach to defining meaningful change in psychotherapy research.** J Consult Clin Psychol 1991; 59: 12-9
63. Lewis MS, Maruff P, Silbert BS, Evered LA, Scott DA. **The influence of different error estimates in the detection of postoperative cognitive dysfunction using reliable change indices with correction for practice effects.** Archives of Clinical Neuropsychology 2007; 22: 249-57

## Figure Legends

Figure 1: Enrollment flow chart and data used for present analysis (grey)
Figure 2: Pooled effects of diabetes, hypertension and obesity on risk of POCD (model 3)
Figure 3: Pooled effects of BMI, systolic and diastolic baseline blood pressure on risk of POCD (model 3). Odds ratios correspond to 1 $kg/m^2$ increment in BMI and 10 mmHg increment in blood pressure.

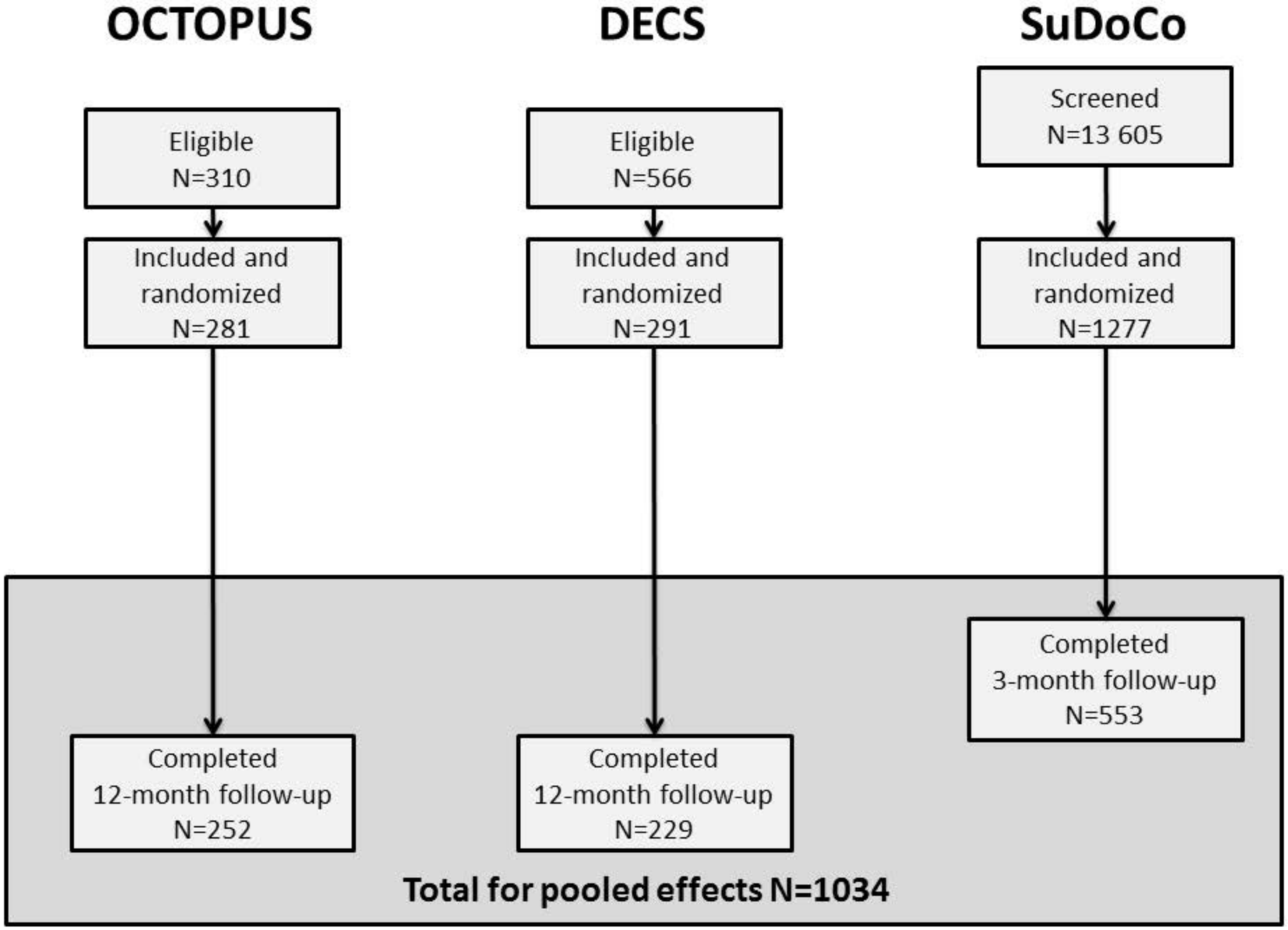
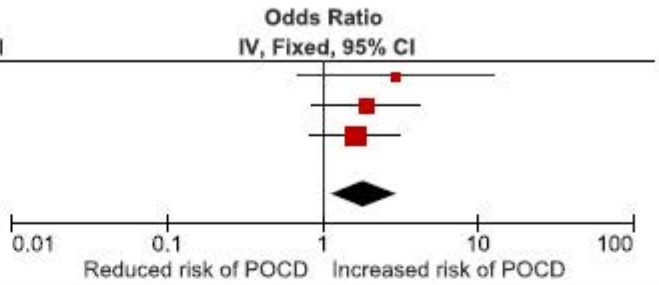

OCTOPUS
DECS
SuDoCo
Eligible
N=310
Eligible
N=566
Screened
N=13 605
Included and
randomized
N=281
Included and
randomized
N=291
Included and
randomized
N=1277
Completed
12-month follow-up
N=252
Completed
12-month follow-up
N=229
Completed
3-month follow-up
N=553
Total for pooled effects N=1034

Figure 1

## Diabetes

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Fixed, 95% CI |
|---|---|---|---|---|
| DECS | 1,0784 | 0,7394 | 11,0% | 2,94 [0,69, 12,52] |
| OCTOPUS | 0,643 | 0,4047 | 36,7% | 1,90 [0,86, 4,20] |
| SuDoCo | 0,4834 | 0,3389 | 52,3% | 1,62 [0,83, 3,15] |
| **Total (95% CI)** | | | **100,0%** | **1,84 [1,14, 2,97]** |

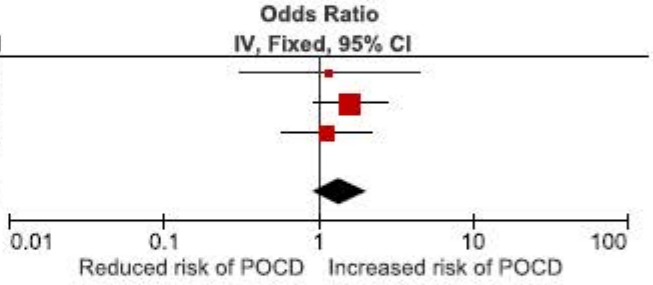
Heterogeneity: Chi² = 0,55, df = 2 (P = 0,76); I² = 0%
Test for overall effect: Z = 2,48 (P = 0,01)




## Hypertension

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Fixed, 95% CI |
|---|---|---|---|---|
| DECS | 0,1571 | 0,686 | 9,4% | 1,17 [0,31, 4,49] |
| OCTOPUS | 0,4757 | 0,2847 | 54,4% | 1,61 [0,92, 2,81] |
| SuDoCo | 0,1207 | 0,3485 | 36,3% | 1,13 [0,57, 2,23] |
| **Total (95% CI)** | | | **100,0%** | **1,37 [0,91, 2,07]** |

Heterogeneity: Chi² = 0,68, df = 2 (P = 0,71); I² = 0%
Test for overall effect: Z = 1,51 (P = 0,13)




## Obesity

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Fixed, 95% CI |
|---|---|---|---|---|
| DECS | 0,8152 | 0,7388 | 11,4% | 2,26 [0,53, 9,61] |
| OCTOPUS | -0,0888 | 0,3862 | 41,8% | 0,92 [0,43, 1,95] |
| SuDoCo | -0,0401 | 0,3647 | 46,8% | 0,96 [0,47, 1,96] |
| **Total (95% CI)** | | | **100,0%** | **1,04 [0,64, 1,69]** |

Heterogeneity: Chi² = 1,26, df = 2 (P = 0,53); I² = 0%
Test for overall effect: Z = 0,15 (P = 0,88)

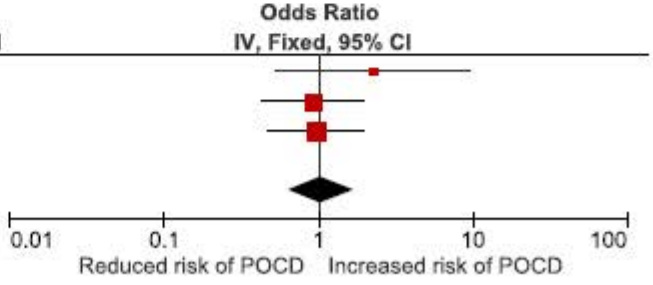
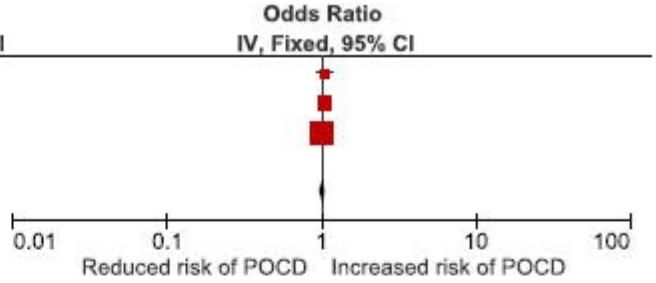



Figure 2

## BMI

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Fixed, 95% CI |
|---|---|---|---|---|
| DECS | 0,0411 | 0,0664 | 13,6% | 1,04 [0,91, 1,19] |
| OCTOPUS | 0,0445 | 0,0451 | 29,5% | 1,05 [0,96, 1,14] |
| SuDoCo | -0,0018 | 0,0325 | 56,9% | 1,00 [0,94, 1,06] |
| **Total (95% CI)** | | | **100,0%** | **1,02 [0,97, 1,07]** |

Heterogeneity: Chi² = 0,84, df = 2 (P = 0,66); I² = 0%
Test for overall effect: Z = 0,72 (P = 0,47)




## Systolic blood pressure

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Fixed, 95% CI |
|---|---|---|---|---|
| OCTOPUS | 0,1038 | 0,0714 | 56,4% | 1,11 [0,96, 1,28] |
| SuDoCo | -0,049 | 0,0812 | 43,6% | 0,95 [0,81, 1,12] |
| **Total (95% CI)** | | | **100,0%** | **1,04 [0,93, 1,15]** |

Heterogeneity: Chi² = 2,00, df = 1 (P = 0,16); I² = 50%
Test for overall effect: Z = 0,69 (P = 0,49)


## Diastolic blood pressure

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Fixed, 95% CI |
|---|---|---|---|---|
| SuDoCo | -0,1613 | 0,1284 | 53,9% | 0,85 [0,66, 1,09] |
| OCTOPUS | 0,0868 | 0,1387 | 46,1% | 1,09 [0,83, 1,43] |
| **Total (95% CI)** | | | **100,0%** | **0,95 [0,79, 1,15]** |

Heterogeneity: Chi² = 1,72, df = 1 (P = 0,19); I² = 42%
Test for overall effect: Z = 0,50 (P = 0,62)

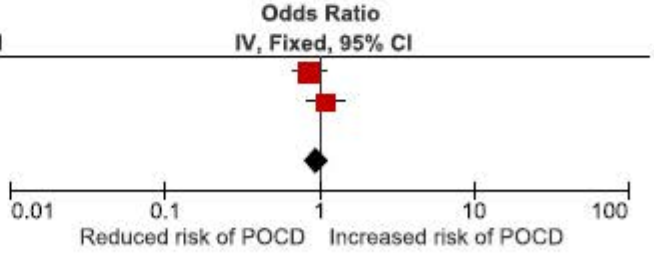



Figure 3

Table 1: Sample characteristics of the 3 studies

| | **OCTOPUS** | **DECS** | **SuDoCo** |
|---|---|---|---|
| **Country** | The Netherlands | The Netherlands | Germany |
| **Enrollment period** | March 1998 to August 2000 | August 2010 to October 2011 | March 2009 to May 2010 |
| **N enrolled** | 281 | 291 | 1277 |
| **Follow-up periods for POCD assessment** | Discharge<br>3 months<br>12 months | 1 month<br>12 months | 1 week<br>3 months |
| **Completed last follow-up (n, % of enrolled)** | 252 (89.7%) | 229 (78.7%) | 553 (43.3%) |
| **Type of surgery** | All CABG | CABG n=68 (29.7%)<br>Valve n=89 (38.9%)<br>Combination valve/CABG n=36 (15.7%)<br>Other n=20 (8.7%)<br>Missing n=16 (7.0%) | General surgery n=241 (43.6%)<br>Orthopedics n = 187 (33.8%)<br>Gynecology n=62 (11.2%)<br>Urology n=44 (8.0%)<br>Other n=19 (3.4%) |
| **Type of intervention** | On-pump versus off-pump CABG | Placebo versus Dexamethasone | BIS guided versus BIS blinded anaesthesia |
| **Type of anaesthesia*** | -- | Propofol-based n=77 (33.6%)<br>Volatile-based n=152 (66.4%) | Propofol-based n=177 (32%)<br>Volatile-based n=376 (68%) |
| **Duration of surgery (min)*** | -- | 215 ± 68 | 159 ± 97 |
| **Age, years, mean ± SD** | 61.0 ± 9.1 | 64.7 ± 11.6 | 69.5 ± 6.3 |
| **Male, n (%)** | 180 (71.4%) | 172 (75.1%) | 303 (54.8%) |
| **Female, n(%)** | 72 (28.6%) | 57 (24.9%) | 250 (45.2%) |
| **Education*, mean ± SD years, or n (%)** | 9.5 ± 2.6 years | Primary education n=101 (44.1%)<br>Secondary education n=62 (27.1%)<br>Further/higher education n=66 (28.8%) | -- |
| **Baseline systolic blood pressure*, mmHg, mean ± SD** | 139 ± 20 | -- | 136 ± 19 |
| **Baseline diastolic blood pressure*, mmHg, mean ± SD** | 80 ± 10 | -- | 74 ± 12 |
| **Diabetes, n (%)** | 36 (14.3%) | 37 (16.2%) | 119 (21.5%) |
| **Hypertension, n (%)** | 118 (46.8%) | 123 (53.7%) | 374 (67.6%) |
| **Body mass index (kg/m$^2$) mean ± SD** | 26.6 ± 3.2 | 26.9 ± 4.5 | 27.3 ± 4.9 |
| **Underweight (BMI<20 kg/m$^2$), n (%)** | 5 (2.0%) | 10 (4.4%) | 17 (3.1%) |
| **Obesity (BMI≥30 kg/m$^2$), n (%)** | 39 (15.5%) | 44 (19.2%) | 131 (23.7%) |

All data measured before surgery and shown for respective follow-up sample. For each study, loss to follow-up mainly due to non-response or change in intention of patients. Data missing on diabetes for N=1 and on obesity for N=2 patients in DECS. *data not available for all cohorts. BIS, bispectral index.

**Table 2:** Association of diabetes, hypertension, and obesity with risk of POCD in each study, and pooled estimates

| | OCTOPUS | | | DECS | | | SuDoCo | | | Pooled estimates | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **OR (95% CI)** | **p** | **Weight** | **OR (95% CI)** | **p** | **Weight** | **OR (95% CI)** | **p** | **Weight** | **OR (95% CI)** | **p** |
| ***Diabetes and risk of POCD*** | | | | | | | | | | | |
| Model 0: no adjustment | 2.20 (1.03, 4.71) | 0.04 | 35.2% | 2.77 (0.79, 9.74) | 0.11 | 12.9% | 1.72 (0.92, 3.22) | 0.09 | 51.8% | *1.99 (1.27, 3.13)* | *0.003* |
| Model 1: age, sex | 2.11 (0.98, 4.55) | 0.06 | 35.2% | 2.54 (0.71, 9.01) | 0.15 | 13.0% | 1.68 (0.89, 3.18) | 0.11 | 51.8% | *1.92 (1.22, 3.03)* | *0.005* |
| Model 2: +type of surgery, randomisation | 2.08 (0.96, 4.50) | 0.06 | 36.0% | 3.77 (0.94, 15.16) | 0.06 | 11.1% | 1.66 (0.88, 3.13) | 0.12 | 53.0% | *1.97 (1.24, 3.13)* | *0.004* |
| Model 3: +hypertension, obesity | 1.90 (0.86, 4.21) | 0.11 | 36.7% | 2.94 (0.69, 12.52) | 0.15 | 11.0% | 1.62 (0.84, 3.15) | 0.15 | 52.3% | *1.84 (1.14, 2.97)* | *0.0132* |
| ***Hypertension and risk of POCD*** | | | | | | | | | | | |
| Model 0: no adjustment | 1.76 (1.03, 3.00) | 0.04 | 53.0% | 1.77 (0.52, 6.07) | 0.36 | 10.0% | 1.33 (0.70, 2.53) | 0.38 | 37.0% | *1.59 (1.08, 2.34)* | *0.020* |
| Model 1: age, sex | 1.72 (0.99, 2.96) | 0.05 | 52.7% | 1.54 (0.44, 5.35) | 0.50 | 10.1% | 1.22 (0.64, 2.33) | 0.55 | 37.2% | *1.49 (1.00, 2.22)* | *0.047* |
| Model 2: +type of surgery, randomisation | 1.71 (0.99, 2.95) | 0.06 | 53.1% | 1.52 (0.42, 5.51) | 0.53 | 9.5% | 1.25 (0.65, 2.40) | 0.51 | 37.3% | *1.50 (1.01, 2.24)* | *0.045* |
| Model 3: +diabetes, obesity | 1.61 (0.92, 2.81) | 0.10 | 54.4% | 1.17 (0.31, 4.49) | 0.82 | 9.4% | 1.13 (0.57, 2.23) | 0.73 | 36.3% | *1.37 (0.91, 2.07)* | *0.13* |
| ***Obesity and risk of POCD*** | | | | | | | | | | | |
| Model 0: no adjustment | 1.07 (0.52, 2.20) | 0.86 | 40.3% | 2.19(0.63, 7.62) | 0.22 | 13.6% | 0.98(0.50, 1.94) | 0.96 | 46.1% | *1.13(0.71, 1.79)* | *0.60* |
| Model 1: age, sex | 1.07 (0.51, 2.22) | 0.86 | 40.5% | 2.17 (0.60, 7.76) | 0.24 | 13.4% | 1.07 (0.54, 2.13) | 0.84 | 46.1% | *1.18 (0.74, 1.87)* | *0.50* |
| Model 2: +type of surgery, randomisation | 1.06 (0.51, 2.21) | 0.88 | 41.6% | 2.93 (0.74, 11.60) | 0.13 | 11.8% | 1.11 (0.55, 2.21) | 0.77 | 46.7% | *1.22 (0.76, 1.96)* | *0.41* |
| Model 3: +diabetes, hypertension | 0.92 (0.43, 1.95) | 0.82 | 41.8% | 2.26 (0.53, 9.61) | 0.27 | 11.4% | 0.96 (0.47, 1.96) | 0.91 | 46.8% | *1.04(0.64, 1.69)* | *0.88* |

POCD determined at 12 months in OCTOPUS/DECS and at 3 months in SuDoCo. POCD occurred in 12 patients (5.2%) at 12-month follow-up in DECS, in 52 patients (9.4%) at 3 months in SuDoCo, and in 81 patients (32.1%) at 12 months in OCTOPUS. For each study, Model 3 is based on a single model.