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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

Gunnar Lachmann^{1,2*}, Insa Feinkohl^{3*}, Friedrich Borchers¹, Thomas H Ottens⁴, Hendrik M Nathoe⁵, Anne-Mette Sauer⁴, Jan M Dieleman⁴, Finn M Radtke⁶, Diederik van Dijk⁷, Claudia D Spies^{1*}, Tobias Pischon^{3,8,9*}

*contributed equally to this work

¹Department of Anesthesiology and Operative Intensive Care Medicine (CCM, CVK), Charité – Universitätsmedizin Berlin, Berlin, Germany

²Berlin Institute of Health (BIH), Anna-Louisa-Karsch-Str. 2, D-10178 Berlin, Germany

³Molecular Epidemiology Research Group, Max-Delbrueck-Center for Molecular Medicine in the Helmholtz Association (MDC), Berlin, Germany

⁴Department of Anesthesiology, University Medical Center Utrecht, Utrecht, The Netherlands

⁵Department of Cardiology, University Medical Center Utrecht, Utrecht, The Netherlands

⁶Anaestesiaafdelingen, Næstved Sygehus, Næstved, Denmark

⁷Department of Intensive Care Medicine, University Medical Center Utrecht, Utrecht, The Netherlands

⁸Charité – Universitätsmedizin Berlin, Berlin, Germany

⁹MDC/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 in the Helmholtz Association (MDC)

Robert-Roessle-Str. 10

D-13092 Berlin, Germany

Tel: 0049 30 9406-4595

Email: insa.feinkohl@mdc-berlin.de

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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 $BMI \geq 30$ 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/m² (SD=3.2) in OCTOPUS, 26.9 kg/m² (SD=4.5) in DECS and 27.3 kg/m² (SD=4.9) in SuDoCo and thus in the ‘overweight’ category (25 to 30 kg/m²) in all 3 studies.. Underweight (BMI<20 kg/m²) was rare. Mean BMI in the underweight groups was 19.2 kg/m² (SD=1.3) in OCTOPUS (N=5 underweight patients), 18.9 kg/m² (SD=0.9) in DECS (N=10 underweight patients) and 19.0 kg/m² (SD=0.9) in SuDoCo (N=17 underweight patients). In OCTOPUS, mean BMI was 31.6 kg/m² (SD=1.1) in obese patients (BMI≥30 kg/m²). In DECS and SuDoCo, obese groups had mean BMIs of 33.8 kg/m² (SD=3.1) and 34.1 kg/m² (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 (Chi²=0.55; p=0.76; I²=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 $BMI \geq 30 \text{ kg/m}^2$ 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.

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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/m² increment in BMI and 10 mmHg increment in blood pressure.

OCTOPUS

DECS

SuDoCo

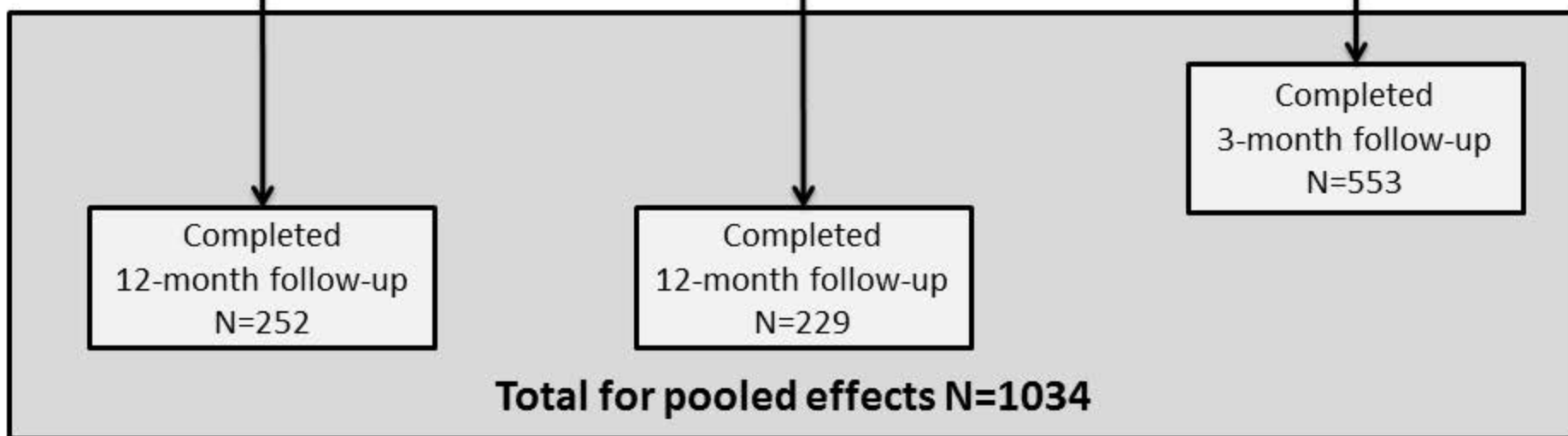
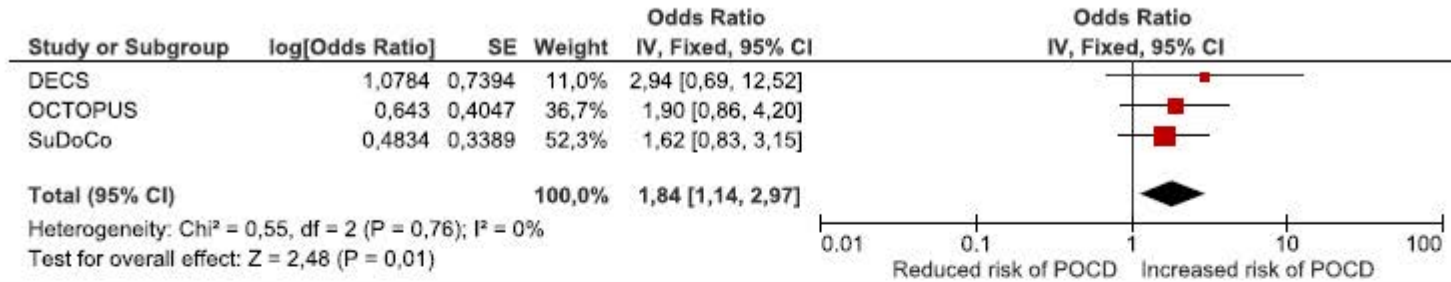
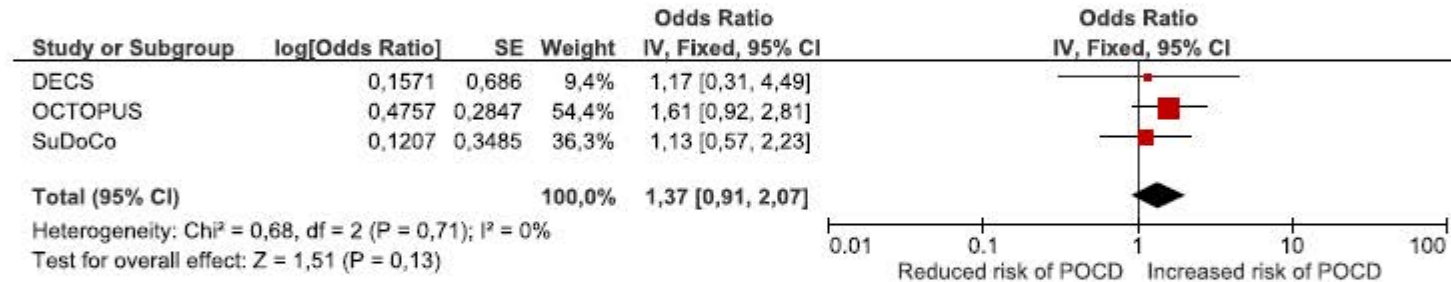


Figure 1

Diabetes



Hypertension



Obesity

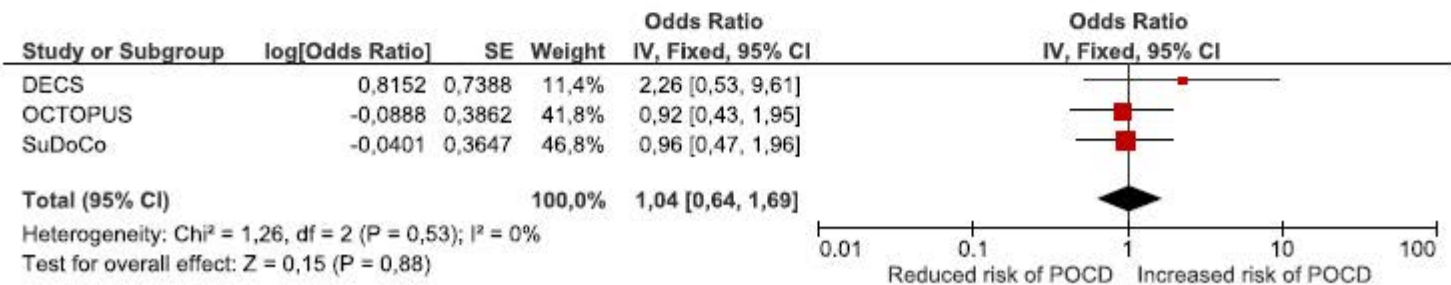
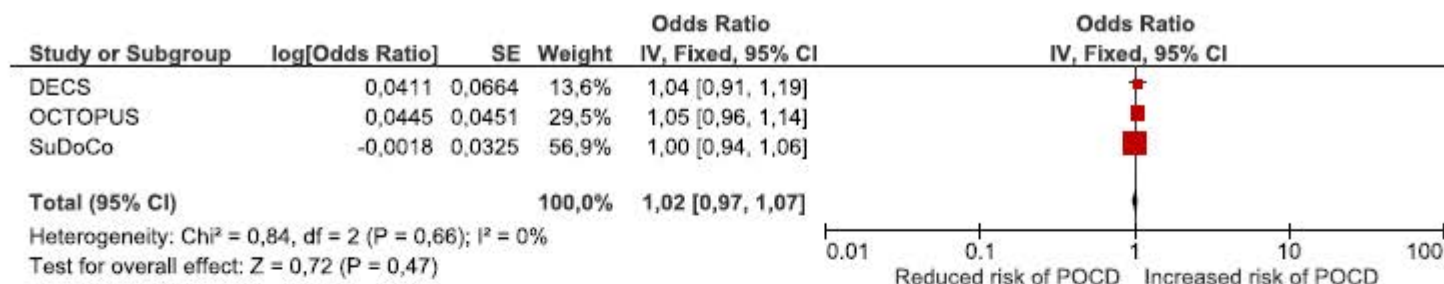
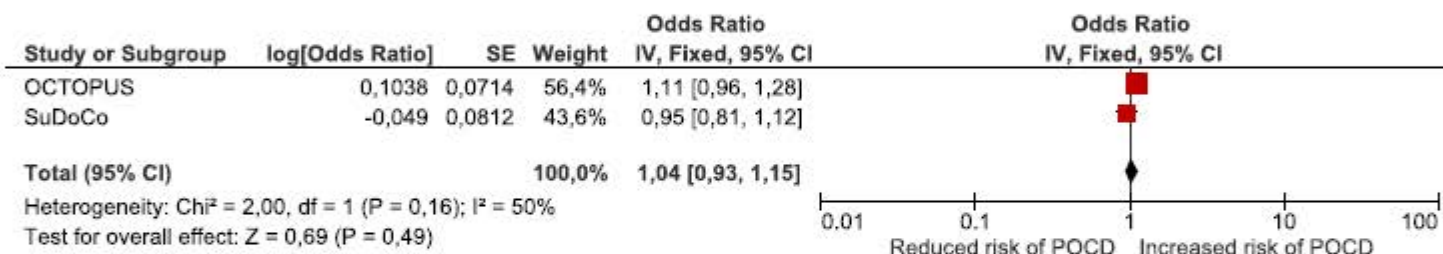


Figure 2

BMI



Systolic blood pressure



Diastolic blood pressure

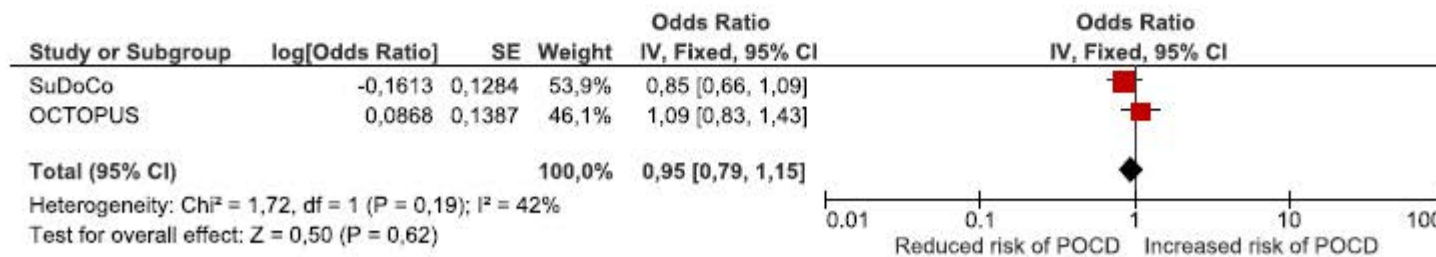


Figure 3

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 3 months 12 months	1 month 12 months	1 week 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%) Valve n=89 (38.9%) Combination valve/CABG n=36 (15.7%) Other n=20 (8.7%) Missing n=16 (7.0%)	General surgery n=241 (43.6%) Orthopedics n = 187 (33.8%) Gynecology n=62 (11.2%) Urology n=44 (8.0%) 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%) Volatile-based n=152 (66.4%)	Propofol-based n=177 (32%) 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%) Secondary education n=62 (27.1%) 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/m²) mean ± SD	26.6 ± 3.2	26.9 ± 4.5	27.3 ± 4.9
Underweight (BMI<20 kg/m²), n (%)	5 (2.0%)	10 (4.4%)	17 (3.1%)
Obesity (BMI≥30 kg/m²), 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.