ORIGINAL ARTICLE

Cognitive Reserve and the Risk of Postoperative Cognitive Dysfunction

A Systematic Review and Meta-Analysis

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SUMMARY

Background: Post-operative cognitive dysfunction (POCD) occurs in 10 to 54% of older patients during the first few weeks after surgery, but little is known about risk factors predisposing to POCD.

Methods: Systematic literature review and meta-analysis of cognitive reserve indicators and POCD risk.

Results: Fifteen studies on 5104 patients were included. Follow-up periods spanned 1 day to 6 months. Educational level was the most commonly assessed cognitive reserve indicator, and a longer time spent in education was associated with a reduced risk of POCD (relative risk [RR] per year increment 0.90; 95% confidence interval: [0.87; 0.94]), i.e. each year increase in education was associated with a 10% reduced risk. Similar findings were made for some analyses on education as a categorical predictor (high school versus further/higher education, RR 1.71, [1.30; 2.25]; lower than high school versus further/higher education, RR 1.69, [1.17; 2.44]) though risk was equivalent for patients with high school education and those with lower than high school education (RR 1.02; [0.78; 1.32]).

Conclusion: Patients with a relatively higher level of education are at reduced risk of POCD. Risk stratification of surgical patients according to educational level may prove useful.

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Post-operative cognitive dysfunction (POCD) occurs relatively frequently, in 10 to 54% of patients during the first few weeks after surgery (1). It is usually transient (2), but unlike for post-operative delirium (POD), clear diagnostic criteria are lacking for POCD (3, 4).

Despite its high prevalence, POCD is under-researched and well-established risk factors for POCD are few and far between (for a review, see [2]) so that at present the cognitive risk of a surgical patient is unpredictable. Recent research has shown that diabetes (5) and pre-existing cognitive impairment (6) may predispose patients to POCD. Compared with these types of clinical risk factors, however, research into the contribution of cognitive reserve to POCD has essentially been neglected.

Cognitive reserve is a theoretical construct that aims to explain links between factors such as a lower level of education, lower socioeconomic status (SES), or lower pre-morbid cognitive ability and an increased risk of cognitive impairment in older age (7–11). The account assumes that people differ in their ability to functionally ‘buffer’ neuropathological insult due to aging and disease according to their cognitive reserve capacity (12–14). Simply put, brain networks of high-reserve individuals are thought to be better able to cope with disruptions due to working more efficiently and more flexibly compared with low-reserve individuals. Neuropathological burden may further be compensated for through recruitment of novel brain networks (13).

POCD is known to negatively impact on subjective cognitive function and quality of life in affected patients (15, 16). Studies suggest that it also increases the risk of dementia and mortality (17–19). POCD is thus a cause for concern from a public health perspective that exceeds problems associated with cognitive deficits alone. With a lower cognitive reserve capacity as a predictor of age-related cognitive impairment, it appears reasonable to expect an association with POCD. A lower level of education is indeed frequently discussed as a contributing factor to POCD, though empirical evidence is rarely mentioned (2, 20–23). If such evidence was to be confirmed, measures of cognitive reserve could supplement cognitive risk prediction on the basis of clinical risk factors. Because low cognitive reserve

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could reasonably constitute the starting point of a causal chain leading up to POCD, the identification of cognitive reserve parameters as risk factors for POCD would further add to our understanding of the processes underlying the condition.

Here, we aim to integrate the current epidemiological evidence on cognitive reserve and the risk of POCD in view of providing guidance for clinical practice.

Methods

Systematic search strategy

An electronic search (*eTable 1*, *eBox 1*) was performed by one investigator (IF) in accordance with the MOOSE and PRISMA guidelines (24, 25).

Study selection

Studies were eligible for inclusion if they

- followed a prospective study design,
- included human adults undergoing surgery (age ≥ 18 years),
- had full texts published in English
- reported original data on associations of cognitive reserve indicators (*eTable 1*) with POCD in the form of odds ratios or relative risks (RR; both termed RR in the present analysis) or as descriptive data that allowed calculation of RR. Any operationalization of POCD qualified for inclusion provided it was based on performance-based neuropsychological assessment.

Data extraction

Fully adjusted RR statistics were extracted unless no adjustment was made. If more than one article reported on the same sample, the article with the most complete reporting was selected. Data were extracted on the longest follow-up period. For 2 studies with multivariate-adjusted data at 7 day follow-up but not at 3 months, the 7 day follow-up was selected (26, 27). For one study comparing three levels of cognitive change, ‘severe deterioration’ was used to represent POCD (28). Enquiries were made to corresponding authors for unreported information.

Data synthesis and analysis

Studies were analyzed separately for each cognitive reserve indicator. We used the standard I^2 index to identify statistical heterogeneity (29) and inverse variance fixed-effect models to calculate summary estimates of RR (95% CI) in meta-analyses across studies. Forest plots were generated to present pooled estimates. The main meta-analyses were repeated using random-effects models (*eBox 2*). Potential sources of heterogeneity were explored in subgroup and meta-regression analyses. Review Manager 5.3 and SAS Enterprise Guide 4.3 were used.

Results

The search retrieved 109 unique articles (*eFigure 1*); an independent search identified a further 28 articles. Overall, 64 full text articles were assessed. Of these,

40 did not meet our inclusion criteria and 9 articles (30–38) were excluded due to suspected duplicate reporting (19, 26, 27, 39). In total, 15 articles were included.

The included studies originated in Europe, USA, Australia, and Asia (*eTable 2*). Surgical procedures included cardiac surgery ($n = 7$) and non-cardiac surgery ($n = 8$) under general ($n = 9$) or a combination of general and regional anesthesia ($n = 4$) (where reported) (*Table*). A total of 5104 patients were analyzed. Sample characteristics varied substantially between studies. The proportion of males ranged from 26% to 79% and the mean sample age from 51 to 75 years (mean 63 ± 8 years). Patients were followed up for between 1 and 180 days after surgery (median: 25 days; interquartile range: 7 to 45 days). All studies except one (40) applied detailed batteries of neuropsychological tests, though the criteria used to define POCD were heterogeneous. POCD occurred in 8% to 67% of patients.

Findings of included studies and meta-analysis

a) Years of education—Eight articles reported data on years of education. The mean years of education in these studies ranged from 8 years in 2 studies from Italy and China (28, 40) to 14 years in 2 US studies (17, e1) (mean 12 ± 3 years). When effects were pooled, each year increase in education was associated with a 0.90 risk of POCD (RR 0.90 per year increment; 95% CI: [0.87; 0.94]; $p < 0.001$) (*Figure*), i.e. a 10% reduced risk of POCD. Statistical heterogeneity between studies was moderate ($\chi^2 [7] = 12.49$; $I^2 = 44\%$; $p = 0.09$) with no evidence of publication bias (*eFigure 3*). The finding was universal across study designs and sample characteristics (*eTable 3*, *eFigure 2*).

b) to d) Level of education as a categorical predictor—Five studies assessed education as a categorical variable. Of these, 3 studies ascertained whether patients had completed a lower level than high school, had completed high school and/or had completed further/higher education (26, 27, e2). For the purpose of the present analyses, “middle school education” in one Chinese study (e3) was equated with “high school education.” For one US study (19), “ >16 years of education” was equated with “further/higher education.”

b) High school education versus further/higher education—When effects were pooled across 4 studies (19, 27, e2, e3), high school level of education was associated with a 71% increased risk of POCD compared with a higher level of education (RR 1.71 [1.30, 2.25]; $p < 0.001$) (*Figure*; *eFigure 4*). No statistical heterogeneity was indicated ($\chi^2 [3] = 0.67$; $I^2 = 0\%$; $p = 0.88$).

c) High school versus lower than high school education—No statistically significant associations emerged on high school versus not having attained high school education when effects were pooled across

4 studies (26, 27, e2, e3) (RR 1.02 [0.78; 1.32]; $p = 0.89$) (Figure; eFigure 5). Statistical heterogeneity was substantial ($\chi^2 [3] = 15.19$; $I^2 = 80\%$; $p = 0.002$).

d) Lower than high school education versus further/higher education—Four studies compared the POCD risk of patients with lower than high school education with that of those with further/higher education (26, 27, e2, e3). Two of these studies (26, 27) adjusted their analyses for a range of covariates. Across all four studies, having attained lower than high school education was associated with a 69% increased risk of POCD (RR 1.69 [1.17; 2.44]; $p = 0.005$) (Figure; eFigure 6). Statistical heterogeneity was low ($\chi^2 [3] = 3.08$; $I^2 = 3\%$; $p = 0.38$).

Other indicators of cognitive reserve

One study (e2) showed a trend for an increased risk of POCD in illiterate patients; however, this was not statistically significant (RR 1.47 [0.46; 4.69]; $p = 0.52$). Another study (e4), that derived a composite measure of reserve capacity from occupation, vocabulary, education, ethnicity, geographical region of the country, and sex found a statistically non-significantly reduced risk of POCD in low-reserve patients (RR 0.71 [0.45; 1.12]; $p = 0.14$). In one study (e5), no association was found between National Adult Reading Test (NART) scores and POCD risk (RR per NART score increment: 1.01 [0.96; 1.07]; $p = 0.68$).

Discussion

Here, we set out to integrate reports on indicators of cognitive reserve and risk of POCD. Only few studies were identified. Education was the most commonly ascertained reserve indicator and overall having attained a higher level of education was associated with a reduced risk of POCD. Due to considerable heterogeneity between studies, we are unable to comment on a potential dose–response relationship.

Several studies controlled for baseline level of cognitive function (39, e1, e6, e7) which in the assessment of education as a predictor represents overadjustment. True effects may therefore be larger than reported here though the role of confounding factors is entirely unclear. Our finding by no means implies causation. Null findings for reserve indicators other than education (e2, e4, e5) may be due to limited statistical power and the low study number. As reserve indicators tend to correlate (e8–e11), lower pre-morbid ability and illiteracy, too, may be identified as contributing to POCD in the future. One study found a trend for a protective effect of lower cognitive reserve (e4). As cognitive reserve in that study was defined by a range of reserve indicators as well as demographics, this may suggest an influence by some factor other than education.

Our findings are supported by several studies that report associations of low education level with an increased risk of POCD in their abstracts but were excluded due to non-English language (e12–e15). A lower reserve capacity may also increase the risk of

post-operative delirium (POD) (e16, e17) and is well-established as a risk factor for age-related cognitive impairment. For instance, lower compared to higher levels of education have been associated with a 59 to 88% increased risk of dementia (7, 8).

Candidate pathophysiological mechanisms underlying POCD include surgery-induced inflammation (e18) and, potentially, anesthesia-induced neurodegeneration (e19). In line with the cognitive reserve model (12–14, e20), patients with a higher cognitive reserve as indicated by a higher level of education may have a functional advantage: they may be able to better cope with such damage through adjusting existing or recruiting novel brain networks. Morphological advantages, such as a larger brain size, correlate with cognitive reserve (e21) and may also play a role (e22). Finally, associations may be mediated by clinical and lifestyle factors (e23). Low-reserve individuals tend to be exposed to higher levels of environmental hazards (e24) and detrimental lifestyle (e25) across their life span, yielding greater brain pathology in older age (e26). Low-reserve patients may then have presented for surgery with greater subclinical neuropathology, such as beta amyloid burden (e27), which was exacerbated by surgery to become expressed as cognitive deficits. This account is the most plausible explanation of the health consequences associated with POCD (17–19, e28) and could be evaluated through adjustment of analyses for lifestyle and clinical risk factors; however in the studies included here, adjustment was inconsistent.

Research into the epidemiology of POCD is in its infancy and firm knowledge of all of its risk factors is lacking. We have recently shown that the metabolic syndrome may be associated with POCD (5, e29). The present findings are in line with that type of evidence as a lower cognitive reserve predisposes to metabolic syndrome in later life (e30). Clearly, further studies in this area are needed. These should consider multimorbidity as well as lifespan developments and could—once all risk factors for POCD have been identified—feed into the development of a risk score and of preventive measures. A large proportion of older patients in hospitals is cognitively impaired (e31) so that putting a halt to POCD would be immensely beneficial to global health.

Limitations

A number of limitations must be considered. There was substantial overlap in studies included in meta-analyses b) to d), level of education as a categorical predictor, which each were based on a small number of studies. Thus, no firm conclusions should be drawn on the basis of those analyses. RR and OR estimates are also not strictly equivalent (e32) but were equated here. Further, a single investigator performed the search and non-English articles were excluded from our analysis. Included studies were heterogeneous with respect to sample characteristics and definitions of POCD, so that the generalizability of our findings is uncertain. With the inclusion of studies that applied no adjustment at

TABLE

Overview of included studies

Author, year (reference)	N	Type of surgery and anesthesia	Mean age $\pm$ standard deviation /median (interquartile range)	Follow-up	Exposure variable	Exposure association with POCD ^{a1}
Moller et al. 1998 (26)	1011	Major abdominal or orthopedic surgery No restriction on anesthetic technique	42.0% $\geq$ 70 (years)	7 days	1. High school education versus lower than high school education 2. Further/higher education versus lower than high school education	1. RR: 0.6 (95% CI: [0.4; 0.9]) 2. RR: 0.5 [0.3; 0.8] (reversed to RR: 2.0 [1.23; 3.26])
Di Carlo et al. 2001 (28)	110	Cardiac surgery requiring cardiopulmonary bypass General anesthesia	64 $\pm$ 9	6 months	Years of education (mean 8 $\pm$ 4)	RR: 0.53 [0.31; 0.90]
Johnson et al. 2002 (27)	463	Major abdominal or orthopedic surgery General anesthesia	51 (41–59) ^{*2}	7 days or discharge if the latter occurred earlier (median 6 days after surgery)	1. Lower than high school education versus further/higher education 2. High school education versus further/higher education 3. High school education versus lower than high school education	1. RR: 1.01 [0.51; 2.03] 2. RR: 1.52 [0.80; 2.89] 3. RR: 2.09 [1.29; 3.37]
Ropacki et al. 2007 (e4)	42	CABG General anesthesia	64 $\pm$ 8	2 to 6 weeks	CR calculated from occupation, vocabulary, education, ethnicity, geographical region of the country, and sex. Sample split at median to obtain high CR and low CR groups.	RR: 0.72 [0.45; 1.12]
Mathew et al. 2007 (e6)	85	CABG General anesthesia	69 $\pm$ 6 ^{*2}	6 weeks	Years of education (mean 13 $\pm$ 4) ^{*2}	RR: 0.91 [0.78; 1.07]
Mathew et al. 2007 (39)	513	CABG Anesthesia unreported	61 $\pm$ 10	6 weeks	Years of education (mean 12 $\pm$ 3) ^{*2}	RR: 0.90 [0.83; 0.98]
Hong et al. 2008 (e37)	100	Valvular heart surgery General anesthesia	53 $\pm$ 11	7 days	Years of education (mean 10 $\pm$ 5)	RR: 0.87 [0.76; 0.99]
Monk et al. 2008 (17)	926	Major non-cardiac surgery General anesthesia	51 $\pm$ 17 ^{*2}	3 months	Years of education (mean 14 $\pm$ 3) ^{*2}	RR: 0.84 [0.76; 0.93]
McDonagh et al. 2010 (e1)	350	Vascular, thoracic or major orthopedic surgery General or regional anesthesia	68 $\pm$ 8 ^{*2}	6 weeks	Years of education* (mean 14 $\pm$ 3) ^{*2}	RR: 0.98 [0.91; 1.07]

Author, year (reference)	N	Type of surgery and anesthesia	Mean age $\pm$ standard deviation /median (interquartile range) (years)	Follow-up	Exposure variable	Exposure association with POCD ^a
Mathew et al. 2013 (e7)	316	Cardiac surgery General anesthesia	69 $\pm$ 8 ²	6 weeks	Years of education (mean 13 $\pm$ 4) ²	RR: 0.93 [0.85; 1.00]
Medi et al. 2013 (e5)	120	Cardiac surgery General anesthesia	56 $\pm$ 11	3 months	NART score (mean 116 $\pm$ 10)	RR: 1.01 [0.96; 1.07]
Koilekar et al. 2014 (e2)	200	Non-cardiac surgery General or regional anesthesia	15.0% > 70	3 to 30 days	1. Illiterate versus literate 2. High school education versus lower than high school education 3. High school education versus further/higher education 4. Lower than high school education versus further/higher education	1. RR: 1.47 [0.46; 4.69] 2. RR: 1.03 [0.59; 1.78] 3. RR: 2.51 [0.90; 7.03] 4. RR: 2.44 [0.92; 6.50]
Zhu et al. 2014 (40)	205	Total hip replacement surgery Spinal or general anesthesia	75 $\pm$ 6	7 days	Years of education (mean 8 $\pm$ 3)	RR: 0.83 [0.74; 0.93]
Hever et al. 2015 (19)	585	Carotid endarterectomy General anesthesia	34.4% $\geq$ 75	1 day	$\leq$ 16 versus >16 years of education	RR: 2.00 [1.33; 2.98]
Ni et al. 2015 (e3)	78	Total knee arthroplasty Intrathecal anesthesia	70 $\pm$ 4	6 days	1. Middle school education versus lower than middle school education 2. Middle school education versus further/higher education 3. Lower than middle school education versus further/higher education	1. RR: 1.07 [0.78; 1.32] 2. RR: 1.80 [0.12; 27.25] 3. RR: 1.61 [0.11; 22.70]

Data are on analysis sample unless otherwise indicated.

CABG, coronary artery bypass grafting; CI, confidence interval; CR, cognitive reserve; NART, National Adult Reading Test; POCD, postoperative cognitive dysfunction; RR, relative risk; SD, standard deviation; ^adefinition of POCD varied between studies; see eTable 2 in Supplementary Material. ²Based on total sample enrolled in the study (data on analysis sample unreported)

FIGURE

a) Years of education

b) High school education versus further/higher education

c) High school education versus lower than high school education

d) Lower than high school education versus further/higher education

Forest plot of a) $n = 8$ studies on years of education and risk of POCD, b) $n = 4$ studies on high school education versus further/higher education and risk of POCD, c) $n = 4$ studies on high school education versus lower than high school education and risk of POCD and d) $n = 4$ studies on lower than high school education versus further/higher education and risk of POCD. Meta-analyses shown here are from fixed-effects models. SE, standard error; IV, inverse variance; POCD, postoperative cognitive dysfunction; CI, confidence interval

all, confounding of our results by any other sociodemographic and/or clinical variables is plausible. Grouping studies according to the categories “lower than high school education”; “high school education”, and “further/higher education” may have been suboptimal for those that did not explicitly refer to these categories (19, e3), and included studies were set in a total of 13 countries. Thus, our results will have been affected by cross-cultural differences between school systems and may not necessarily transfer to German hospitals. Readers are also advised that the relative risk estimates presented here do not reflect absolute risks. Nonetheless, our findings illustrate a trend to suggest that—while considering other coexisting factors—enquiry into patients’ educational background during pre-surgery interview may be a straightforward and non-invasive way to identify at-risk patients.

Conclusion

The importance of patients’ cognitive reserve capacity is becoming increasingly recognized (e33). Virtually all previous studies of POCD have assessed indicators of cognitive reserve and could re-analyze their data to determine the roles of the frontal cortex and associated cognitive function, potential lifestyle mediators, and clinical mediators. Attention should be paid to over-adjustment for variables that are closely related to both predictor and outcome and render statistical analyses non-significant despite an underlying relationship. Here, we identified only two studies that used a vocabulary-based estimate of peak pre-morbid ability as a reserve indicator. Future investigations are well-advised to take advantage of such tests, which are easily administered and well-validated (e34) and are unaffected by surgery (e35) or, unlike education, by societal constraints.

Our results show that middle-aged to older surgical patients with a higher level of education are at reduced risk of POCD compared with less educated patients. Mechanisms, contributing clinical and environmental factors, and strategies to reduce POCD risk in low-education patients warrant detailed research, but for now, we recommend that anesthetists and surgeons consider routine ascertainment of patients’ level of education in geriatric surgery.

KEY MESSAGES

- Postoperative cognitive dysfunction is a frequent occurrence, yet few risk factors have been established.
- In a systematic search of studies on reserve capacity and risk of POCD, we identified 15 relevant studies.
- Education was the most commonly assessed reserve indicator.
- In meta-analysis, a longer time spent in education was protective of POCD risk.
- Awareness of patients’ educational level may be useful in geriatric surgery.

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Conflict of interest statement

Prof Winterer is coordinator of the BioCog Consortium and chief executive of the company Pharmimage Biomarker Solutions GmbH. The company is one of the partners of the BioCog Consortium.

The remaining authors declare that they have no conflicts of interest.

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Supplementary material

For eReferences please refer to:
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Supplementary material to:

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eTABLE 1

Parameters assessed in the present review with corresponding search terms

Parameter	Search terms
Education	"Education" "School"
Socioeconomic status	"Socioeconomic status" "SES"
Pre-morbid ability	"Pre-morbid ability" "Premorbid ability" "Pre-morbid cognit**" "Premorbid cognit**" "National Adult Reading Test" "NART" "Mill Hill Vocabulary Test" "MHVS"
Postoperative cognitive dysfunction (POCD)	"Post-operative cognit**" "Postoperative cognit**" "POCD"

eBOX 1

Systematic search strategy:

PubMed, OvidSP and the Cochrane Database of Systematic Reviews were searched for potentially eligible studies from the earliest available date up to May 2nd, 2016. Sensitive search strategies were designed to identify all studies on reserve indicators and postoperative cognitive dysfunction (POCD) (*eTable 1*). Search terms combined POCD with terms related to education, socioeconomic status, and vocabulary (which remains stable across the lifespan and may therefore be used at any point in life to estimate peak, pre-morbid cognitive ability in young adulthood [e34, e36]). Here, we term these factors 'reserve indicators'. Articles entered the stage of full text assessment with formal comparison against our inclusion criteria if on the basis of titles and abstracts they appeared to match the inclusion criteria or if they provided data on both reserve indicators and POCD (e.g., adjusted analyses of POCD for education). In addition, the reference lists of review articles and of included articles were hand-searched, and an independent online search was conducted. The review was registered with PROSPERO (Registration Number: CRD42016032299).

Search terms: (SES OR socioeconomic status OR cognitive reserve OR education OR school* OR premorbid ability OR pre-morbid ability OR premorbid cognit* OR pre-morbid cognit* OR NART OR National Adult Reading Test OR MHVS OR Mill Hill Vocabulary) AND (post-operative cognit* OR postoperative cognit* OR POCD).

eBOX 2

Results of main analyses in fixed effects models and random effects models

- **Years of education**

- Fixed effects model: RR 0.90; 95 % CI 0.87, 0.94; p<0.001
- Random effects model: RR 0.90; 95% CI 0.85, 0.94; p<0.001

- **High school education versus further/higher education**

- Fixed effects model: RR 1.71; 95% CI 1.30, 2.25; p<0.001
- Random effects model: RR 1.71; 95% CI 1.30, 2.25; p<0.001

- **High school education versus lower than high school education**

- Fixed effects model: RR 1.02; 95% CI 0.78, 1.32; p = 0.89
- Random effects model: RR 1.08; 95% CI 0.57, 2.02; p = 0.82

- **Lower than high school education versus further/higher education**

- Fixed effects model: RR 1.69; 95% CI 1.17, 2.44; p = 0.005
- Random effects model: RR 1.69; 95% CI 1.16, 2.46; p = 0.006

RR, relative risk; CI, confidence interval

Flow chart for search on cognitive reserve and post-operative cognitive reserve (POCD)

Years of education and risk of POCD in subgroup analyses according to

- a) follow-up period,
- b) sample size,
- c) mean sample age,
- d) surgery type,
- e) proportion of males, and
- f) across all studies in fixed effects models.

P-values are shown for meta-regression analyses to determine the contribution of study characteristics to overall pooled estimates. Of sample size, sample age, proportion of males, and follow-up period, none moderated the relationship of education with POCD. Pooled risks per year increment in education were smaller for 2 studies on non-cardiac surgery (RR 0.84; 95% CI 0.78, 0.90) compared with 1 study on mixed type of surgery (RR 0.98; 95% CI 0.91, 1.07) (meta-regression $p = 0.036$).

POCD, postoperative cognitive dysfunction; RR, relative risk; CI, confidence interval

eTABLE 2

Detailed summary of included studies

Author (reference), year, location	N enrolled	N followed up	% male	Type of surgery and anesthesia	Mean age $\pm$ SD/median (interquartile range) (years)	Follow-up	Cognitive measurement	Definition and incidence of POCD	Exposure variable	Covariates	Original statistical reporting	Exposure association with POCD	STROBE score ³
Møller et al. (26), 1998 Denmark, France, Germany, Netherlands, Spain, Greece, UK, USA	1218	1011	51% ^{a1}	Major abdominal or orthopedic surgery No restriction on anesthetic technique	42.0% $\geq$ 70	7 days	6 neuro-psychological tests	For each patient, RCI ² summed across tests and divided by SD of RCI sum of controls to obtain composite RCI. POCD defined as RCI $\geq$ 1.96 on $\geq$ 2 individual tests or combined RCI $\geq$ 1.96 Control group n=321 POCD in n=262/1011 (25.6%)	1. High school education (n = 290/1011) versus lower than high school education (n = 576/1011) 2. Further/higher education (n = 145/1011) versus lower than high school education	Age, hypoxemia, hypotension, duration of anesthesia, second operation, respiratory complication, infectious complication, study center	OR	1. RR 0.6 (95% CI 0.4, 0.9) 2. RR 0.5 (0.3, 0.8) (reversed to RR: 2.0 [1.23, 3.26])	20/22
Di Carlo et al. (28), 2001 Italy	123	110	71%	Cardiac surgery requiring cardiopulmonary bypass General anesthesia	64 $\pm$ 9	6 months	4 neuro-psychological tests; MMSE Rating by 2 neuro-psychologists as "unchanged/improved", "mild deterioration", "severe deterioration"	"Severe deterioration" used as POCD in present analysis. POCD in n=10/110 (9.1%).	Years of education (mean 8 $\pm$ 4)	Hypertension, pulmonary function (along with education these are the only covariates retained in stepwise model selection)	OR	RR 0.53 (95% CI 0.31, 0.90)	19/22

Author (reference), year, location	N enrolled	N followed up	% male	Type of surgery and anesthesia	Mean age $\pm$ SD/median (interquartile range) (years)	Follow-up	Cognitive measurement	Definition and incidence of POCD	Exposure variable	Covariates	Original statistical reporting	Exposure association with POCD	STROBE score ²³
Johnson et al. (27), 2002 Finland, Spain, UK, Denmark, USA	508	463	26% ^{*1}	Major abdominal or orthopedic surgery General anesthesia	51 (41–59) ^{*1}	7 days or discharge if the latter occurred earlier (median 6 days after surgery)	4 neuropsychological tests	For each patient, RCI ^{1,2} summed across tests and divided by SD of RCI sum of controls to obtain composite RCI. POCD defined as RCI ≥ 1.96 on ≥ 2 individual tests or combined RCI ≥ 1.96 Control group n=183 POCD in n=89/463 (19.2%)	1. Lower than high school education (n=189/463) versus further/higher education n=169/463 2. High school education (n=105/463) versus further/higher education 3. High school education versus lower than high school education	For 1.) and 2.): Epidural analgesia, nitrous oxide, ASA class, type of surgery, duration of anesthesia, heart disease, no alcohol intake, opioid use <24 hours before surgery, study center For 3.): none	OR	1. RR 1.01 (0.51; 2.03) 2. RR 1.52 (0.80; 2.89) 3. RR 2.09 (1.29; 3.37)	18/22
Ropacki et al. (64), 2007 USA	51	42	78%	CABG General anesthesia	64 $\pm$ 8	2 to 6 weeks	9 neuropsychological tests	POCD defined as deterioration ≥ 1 SD of sample mean change on ≥ 2 cognitive tests POCD in n = 28/42 (66.7%)	CR calculated from education, vocabulary, ethnicity, geographical region of the country, sex Sample split at median to obtain high CR (n = 22/42) and low CR groups (n = 20/42)	None	Descriptive data	POCD in 17/22 high CR patients, POCD in 11/20 low CR patients. RR 0.71 (0.45; 1.12)	17/22
Mathew et al. (66), 2007 USA	108	85	79% ^{*1}	CABG General anesthesia	69 $\pm$ 6 ^{*1}	6 weeks	4 factor scores of cognitive domains derived from 5 neuropsychological tests	POCD defined as ≥ 1 SD decline on ≥ 1 of the 4 factor scores POCD in n=34/85 (40.0%)	Years of education (mean 13 $\pm$ 4) ^{*1}	Age, pre-operative cognitive function, treatment arm, age-by-treatment arm interaction	OR	RR 0.91 (0.78; 1.07)	19/22
Mathew et al. (39), 2007 USA	677	513	71%	CABG Anesthesia unreported	61 $\pm$ 10	6 weeks	4 factor scores of cognitive domains derived from 5 neuropsychological tests	POCD defined as ≥ 1 SD deterioration on ≥ 1 of the 4 factor scores POCD in n = 152/443 (34.3%)	Years of education (mean 12 $\pm$ 3) ^{*1}	Age, baseline cognitive score, presence of two genetic variants	OR	RR 0.90 (0.83; 0.98)	19/22

Author (reference), year, location	N enrolled	N followed up	% male	Type of surgery and anesthesia	Mean age $\pm$ SD/median (interquartile range) (years)	Follow-up	Cognitive measurement	Definition and incidence of POCD	Exposure variable	Covariates	Original statistical reporting	Exposure association with POCD	STROBE score ²³
Hong et al. (637), 2008 South Korea	103	100	38%	Valvular heart surgery General anesthesia	53 $\pm$ 11	7 days	MMSE, TMT-A, Grooved Pegboard	*Impairment: MMSE decline ≥ 3 points; TMT-A $\geq 20\%$ increase in time needed POCD defined as impairment on ≥ 1 of the 3 tests POCD in n = 23/100 (23.0%)	Years of education (mean 10 $\pm$ 5)	Age, sex, baseline cardiac index, baseline body temperature, left ventricular ejection fraction, duration of intubation	OR	RR 0.87 (0.76, 0.99)	17/22
Monk et al. (17), 2008 USA	1064	926	36% ^{*1}	Major non-cardiac surgery General anesthesia	51 $\pm$ 17 ^{*1}	3 months	5 neuropsychological tests	For each patient, RCI ² summed across tests and divided by SD of RCI sum of controls to obtain composite RCI POCD defined as RCI ≥ 1.96 on ≥ 2 individual tests or combined RCI ≥ 1.96 Control group n=210 POCD in n=74/926 (8.0%)	Years of education (mean 14 $\pm$ 3) ^{*1}	Age, baseline instrumental activities of daily living, ASA physical status, duration of hospital stay, POCD at discharge, MI, cerebrovascular accident, NYHA functional classification	OR	RR 0.84 (0.76, 0.93)	21/22
McDonagh et al. (61), 2010 USA	394	350	50% ^{*1}	Vascular, thoracic or major orthopedic surgery General or regional anesthesia	68 $\pm$ 8 ^{*1}	6 weeks	5 neuropsychological tests	POCD defined as ≥ 1 SD change on ≥ 1 of 5 tests POCD in n = 190/350 (54.3%)	Years of education ^{*1} (mean 14 $\pm$ 3)	Age, baseline cognitive function, sex, diabetes, type of surgery, type of anesthesia, APOE ϵ 4	OR	RR 0.98 (0.91, 1.07)	20/22

Author (reference, year, location)	N enrolled	N followed up	% male	Type of surgery and anesthesia	Mean age $\pm$ SD/median (interquartile range) (years)	Follow-up	Cognitive measurement	Definition and incidence of POCD	Exposure variable	Covariates	Original statistical reporting	Exposure association with POCD	STROBE score ²³
Mathew et al. (e7), 2013 USA	389	316	69% ²¹	Cardiac surgery General anesthesia	69 $\pm$ 8 ¹	6 weeks	4 factors of cognitive domains derived from 5 neuropsychological tests	POCD defined as ≥ 1 SD decline on ≥ 1 of 4 factors. POCD in n = 141/316 (44.6%)	Years of education (mean 13 $\pm$ 4) ¹	Age, baseline cognitive function, sex, ethnicity, treatment arm, body weight, treatment arm-by-body weight interaction	OR	RR 0.926 (0.851; 1.004)	20/22
Medi et al. (e5), 2013 Australia	120	120	72%	Cardiac surgery General anesthesia	56 $\pm$ 11	3 months	8 neuropsychological tests; MMSE	For each patient, RCI ² summed across tests and divided by SD of RCI sum of controls to obtain composite RCI POCD defined as RCI < -1.96 on ≥ 2 individual tests or composite RCI < -1.96 Control group n = 30 POCD in n = 15/120 (12.5%)	NART score (mean 116 $\pm$ 10)	None	OR	RR 1.0 (0.96; 1.07)	15/22
Kotekar et al. (e2), 2014 USA	200	200	58%	Non-cardiac surgery General or regional anesthesia	15.0% >70	3 to 30 days	3 neuropsychological tests	Unclear definition of POCD POCD in n = 46/200 (23.0%)	1. Illiterate (n=6/200) versus literate (n = 194/200) 2. High school education (n = 53/200) versus lower than high school education (n = 109/200) 3. High school education versus further/higher education (n = 38/200) 4. Lower than high school education versus further/higher education	None	Descriptive data	1. RR 1.47 (0.46; 4.69) 2. RR 1.03 (0.59; 1.78) 3. RR 2.51 (0.90; 7.03) 4. RR 2.44 (0.92; 6.50)	17/22

Author (reference), year, location	N enrolled	N followed up	% male	Type of surgery and anesthesia	Mean age $\pm$ SD/median (interquartile range) (years)	Follow-up	Cognitive measurement	Definition and incidence of POCD	Exposure variable	Covariates	Original statistical reporting	Exposure association with POCD	STROBE score ²³
Zhu et al. (40), 2014 China	274	205	51%	Total hip replacement surgery Spinal or general anesthesia	75 $\pm$ 6	7 days	MMSE	POCD defined as ≥ 1 SD decline on MMSE POCD in n = 56/205 (27.3%)	Years of education (mean 8 $\pm$ 3)	Age, body weight, hemoglobin levels, estimated blood loss, hydroxyethyl starch transfusion, red blood cell transfusion	OR	RR 0.83 (0.74; 0.93)	15/22
Heyer et al. (19), 2015 USA	662	585	65%	Carotid endarterectomy General anesthesia	34.4% $\geq$ 75	1 day	Unclear number of tests of 4 cognitive domains	POCD defined as RCI ¹⁻² ≥ 2 on ≥ 2 cognitive domains or RCI ≥ 1.5 on all 4 cognitive domains Control group n = 156 POCD in n = 145/585 (24.8%)	Education ≤ 16 (n = 341/585) versus > 16 years (n = 244/585)	None	Descriptive data	239/440 in no-POCD group had ≤ 16 years of education 201/440 in no-POCD group had > 16 years of education 102/145 in POCD group had ≤ 16 years of education 43/145 in POCD group had > 16 years of education RR 2.00 (1.33; 2.98)	17/22

Author (reference), year, location	N enrolled	N followed up	% male	Type of surgery and anesthesia	Mean age $\pm$ SD/median (interquartile range) (years)	Follow-up	Cognitive measurement	Definition and incidence of POCD	Exposure variable	Covariates	Original statistical reporting	Exposure association with POCD	STROBE score ²³
Ni et al. (e3), 2015 China	80	78	46%	Total knee arthroplasty Intrathecal anesthesia	70 $\pm$ 4	6 days	5 neuro-psychological tests; MMSE	POCD defined as ≥ 2 RCI ²² on >2 tests Control group n = 20 POCD in n = 15/585 (24.8%)	1. Middle school education (n = 19/78) versus lower than middle school education (n = 56/78) 2. Middle school education versus further/higher education (n = 3/78) 3. Lower than middle school education versus further/higher education	None	Descriptive data	11/15 POCD patients with lower than middle school education 4/15 POCD patients with middle school education 0/15 POCD patients with further/higher education 45/63 no-POCD patients with lower than middle school education 15/63 no-POCD patients with middle school education 3/63 no-POCD patients with further/higher education 1. RR 1.07 (0.78; 1.32) 2. RR 1.80 (0.12; 27.25) 3. RR 1.61 (0.11; 22.70)	19/22

Data are on analysis sample unless otherwise indicated. APOE4, apolipoprotein e4 allele; ASA class, American Association of Anesthesiology class of physical status; CABG, coronary artery bypass grafting; CR, cognitive reserve; MI, myocardial infarction; MMSE, Mini Mental Status Examination; NART, National Adult Reading Test; NYHA, New York Heart Association Functional Classification for cardiac risk; OR, odds ratio; RR, relative risk; SD, standard deviation; TMT-A, Trail-Making Test-A.

²¹ based on total sample enrolled in the study (data on analysis sample unreported)

²² RCI, Reliable Change Index (sometimes referred to as 'z-scores' in original publications). Formula to obtain RCI for each patient: (change score of patient - mean control group change score) / SD of control group change score (see [4]).

²³ Reporting quality of articles was rated by one investigator (JF) using the STROBE checklist for cohort studies, Version 4. University of Bern, 2007

eTABELLE 3

Subgroup analyses of included studies on education (years) and POCD (total N = 8)

	Characteristic	Number of studies	Study, year, reference	Pooled estimates and index of heterogeneity	Moderator analysis p-value*
Surgery type	Cardiac surgery	5	Di Carlo 2001 (28) Hong 2008 (e37) Mathew 2007a (e6) Mathew 2007b (39) Mathew 2013 (e7)	RR: 0.90 (95% CI: [0.86; 0.95]) chi ² (4) = 4.48; I ² = 11%; p = 0.34	Versus mixed surgery type: p = 0.139 Versus non-cardiac surgery: p = 0.166
	Non-cardiac surgery	2	Monk 2008 (17) Zhu 2014 (40)	RR: 0.84 [0.78; 0.90] chi ² (1) = 0.05 I ² = 0%; p = 0.82	Versus mixed surgery type: p = 0.036
	Mixed	1	McDonagh 2010 (e1)	RR: 0.98 [0.91; 1.07]	Reference category
Sample size	n ≤ 100	2	Mathew 2007a (e6) Hong 2008 (e37)	RR: 0.89 [0.80; 0.98] chi ² (1) = 0.21 I ² = 0%; p = 0.65	p = 0.735
	n > 100	6	Di Carlo 2001 (28) Mathew 2007b (39) Monk 2008 (17) McDonagh 2010 (e1) Mathew 2013 (e7) Zhu 2014 (40)	RR: 0.91 [0.87; 0.94] chi ² (5) = 12.16 I ² = 59%; p = 0.03	
Mean age	≤ 65 years	4	Di Carlo 2001 (28) Mathew 2007b (39) Hong 2008 (e37) Monk 2008 (17)	RR: 0.87 [0.83; 0.92] chi ² (3) = 4.49; I ² = 33%; p = 0.21	p = 0.172
	> 65 years	4	McDonagh 2010 (e1) Mathew 2007a (e6) Mathew 2013 (e7) Zhu 2014 (40)	RR: 0.93 [0.88; 0.97] chi ² (3) = 5.65 I ² = 47%; p = 0.13	
Sex	≤ 50% male	3	Hong 2008 (e37) McDonagh 2010 (e1) Monk 2008 (17)	RR: 0.92 [0.86; 0.97]) chi ² (2) = 5.99 I ² = 67%; p = 0.05	p = 0.889
	> 50% male	5	Di Carlo 2001 (28) Mathew 2007a (e6) Mathew 2007b (39) Mathew 2013 (e7) Zhu 2014 (40)	RR: 0.89 [0.85; 0.94] chi ² (4) = 6.11 I ² = 35%; p = 0.19	
Follow-up	≤ 1 month	2	Hong 2008 (e37) Zhu 2014 (40)	RR: 0.85 [0.78; 0.92] chi ² (1) = 0.29 I ² = 0%; p = 0.59	p = 0.159
	> 1 month	6	Di Carlo 2001 (28) Mathew 2007b (39) Mathew 2007a (e6) McDonagh 2010 (e1) Mathew 2013 (e7) Monk 2008 (17)	RR: 0.92 [0.88; 0.96] chi ² (5) = 9.64; I ² = 48%; p = 0.09	

RR, relative risk per year increment in education

*p-values of fixed effects moderator analyses

Funnel plot for meta-analysis of years of education and POCD

Funnel plot for meta-analysis of high school education versus further/higher education and POCD

eFIGURE 5

Funnel plot for meta-analysis of high school education versus lower than high school education and POCD

eFigure 6

Funnel plot for meta-analysis of lower than high school education versus further/higher education and POCD