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**Associations of dyslipidaemia and lipid-lowering treatment with risk of post-operative cognitive dysfunction (POCD): A systematic review and meta-analysis**

**Running head: Lipids and cognitive risk after surgery**

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**What is already known on this subject?**

Older people undergoing surgery often experience post-operative cognitive dysfunction (POCD), but little is known about pre-surgical risk factors that predispose patients to the condition. Dyslipidaemia and lipid-lowering treatment have been implicated as risk modifiers for age-related cognitive impairment so are plausible potential determinants of POCD risk.

**What this study adds?**

To our knowledge, this is the first study to integrate the evidence on dyslipidaemia, lipid-lowering treatment and POCD risk. Our results suggest that although hypercholesterolaemia per se does not appear to be associated with POCD risk, statin users are at reduced risk of POCD.

**Abstract**

**Background:** Lipid imbalance is linked to age-related cognitive impairment, but its role in post-operative cognitive dysfunction (POCD) is unknown. Here, we present a systematic review and meta-analysis on dyslipidaemia, lipid-lowering treatment and POCD risk.

**Methods:** PubMed, Ovid SP and Cochrane databases were searched for longitudinal studies that reported on associations of any measure of dyslipidaemia and/or lipid-lowering treatment with POCD as relative risks (RR) or odds ratios. Fixed-effects inverse variance models were used to combine effects.

**Results:** Of 205 articles identified in the search, 17 studies on 2725 patients (grand mean age 67 years; mean age range 61 to 71 years) with follow-up periods of 1 day to 4 years (median 7 days; interquartile range 1 to 68 days) were included. Studies focused almost exclusively on hypercholesterolaemia as a measure of dyslipidaemia and on statins as lipid-lowering treatment. Across 12 studies on hypercholesterolaemia, we found no association with POCD risk (RR=0.93; 95% CI=0.80, 1.08;  $P=0.34$ ). Statin use before surgery was associated with a reduced POCD risk across 8 studies (RR=0.81; 95% CI= 0.67, 0.98;  $P=0.03$ ), but data on treatment duration were lacked.

**Conclusion:** Statin users appear to be at reduced risk of POCD although hypercholesterolaemia per se may not be associated with POCD risk. Trial studies are needed to evaluate the usefulness of statins in POCD prevention.

## INTRODUCTION

Surgery in older age is often accompanied by complications such as post-operative cognitive dysfunction (POCD) <sup>1</sup>. POCD is not currently recognized as a condition in the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) and thus lacks diagnostic criteria. Nonetheless, when defined as a perioperative decline in function measured by a reduction in cognitive test performance, POCD is known to affect a considerable proportion of older adults. POCD has been reported in between 10 to 38% of older patients during the first few months after surgery <sup>2</sup> and though symptoms may resolve over time <sup>1</sup>, it appears to persist over the course of years in some patients <sup>3</sup> and irrespectively of surgery type <sup>4-6</sup>.

Little is known about risk factors for POCD, but – given it is a type of cognitive impairment – we can turn to age-related cognitive impairment to identify potential predictors. Increasing attention is being paid to lipid imbalance in this context. Markers of dyslipidaemia, such as high total cholesterol, high low-density lipoprotein (LDL) cholesterol, high triglycerides, and low high-density lipoprotein (HDL) have frequently been associated with presence <sup>7-9</sup> and, when measured in midlife, risk of future cognitive impairment <sup>10,11</sup>. Pharmaceutical treatment for dyslipidaemia is effective, widely available and relatively cheap, and statins, the most commonly prescribed form of lipid-lowering treatment, have repeatedly been linked to a reduced risk of cognitive impairment in epidemiological studies (e.g., for a review, see <sup>12</sup>).

Potential associations of dyslipidaemia and lipid-lowering treatment with POCD risk are currently unknown, but warrant clarification given the high global prevalence of dyslipidaemia <sup>13</sup>, high proportion of the population of developed nations on lipid-lowering treatment <sup>14</sup> and the large number of surgical procedures performed each year <sup>15</sup>. We therefore aimed to determine whether parameters of dyslipidaemia and lipid-lowering treatment before surgery predict POCD risk, hypothesizing an increased and decreased risk associated with dyslipidaemia and lipid-lowering treatment, respectively. The totality of relevant published research was combined for overall estimates.

## **METHODS**

### **Systematic search strategy**

A search was performed on 13<sup>th</sup> June 2017 of the PubMed, Ovid SP and Cochrane Database of Systematic Reviews, combining terms on parameters of dyslipidaemia (total cholesterol, LDL, HDL, triglycerides, and related terms) and those on lipid-lowering treatment with terms on cognitive dysfunction after surgery: (((cholesterol[tiab] OR low-density lipoprotein[tiab] OR high-density lipoprotein[tiab] OR LDL[tiab] OR \*HDL[tiab] OR triglycer\*[tiab] OR TC[tiab] OR dyslipid\*[tiab] OR hypercholest\*[tiab] OR lipid-lowering[tiab] OR statins[tiab] OR \*statin[tiab] OR ezetimibe[tiab] OR ezetrol[tiab]))) AND ((post-operative cognit\*[tiab] OR postoperative cognit\*[tiab] OR POCD[tiab]) OR (("surgery"[tiab] OR "operation"[tiab]) AND ("cognit"[tiab] OR "intelligence"[tiab] OR "MMSE"[tiab] OR "Mini Mental"[tiab] OR "dementia"[tiab] OR "Alzheimer\*" [tiab] OR "mild cognitive impairment"[tiab] OR "MCI"[tiab])))). Following exclusion of duplicates, abstracts of all 'hits' were screened for potential matching to inclusion criteria (see Figure 1). Reference lists of relevant review articles and of included studies were hand searched for further relevant articles, and an online search was performed. Our approach complies with guidelines issued by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)<sup>16,17</sup>. The search was registered on the PROSPERO database (CRD42017069013).

### **Study selection**

Studies were included if all of the following criteria were met: i) longitudinal study design, ii) sample of human adults (≥18 years old) undergoing surgery, iii) full text in English language, iv) exposure to any parameter indicative of dyslipidaemia, or exposure to lipid-lowering treatment, ascertained before surgery, v) reporting of exposure associations with risk of POCD as relative risks (RR) or odds ratios (both taken as RR for the purpose of the present analysis or in a form that allowed calculation of RR). Studies with observational design and intervention studies were considered separately. Studies on lipid-lowering treatment at hospital discharge were excluded. Prescription of lipid-lowering drugs at discharge is affected by economic and health-related factors, and does not necessarily correlate with long-term pre-operative treatment<sup>18</sup>.

### **Data extraction**

Data were extracted and tabulated for country of origin, type of anesthesia and surgery, patient number, proportion of males, follow-up period, definition of POCD, associations of exposure to measures of dyslipidaemia or lipid-lowering treatment with POCD (RR), and covariates. For each study, the respective longest follow-up period and fully adjusted models (if any adjustment was applied) were considered. Duplicate reporting was identified by comparison of authors, institutions and sample characteristics between articles. Where duplicate reporting was suspected, the article with the most complete reporting was selected for inclusion. Corresponding authors were contacted for unreported statistical detail. This way, unpublished data was obtained for one study<sup>19</sup>.

If unspecified, the term “cholesterol” was taken to mean “total cholesterol”, and “statins” were seen to refer to *pre-operative* statin use. Three articles had insufficient reporting of data on exposure associations with POCD for their respective longest follow-up periods, so data on shorter follow-ups were used<sup>20-22</sup>. In 2 studies, POCD was graded according to severity, and the category reflecting the most severe dysfunction was selected for analysis<sup>22,23</sup>.

### **Data synthesis**

Data were entered into Review Manager 5.3 (Cochrane Collaboration, 2014). For each exposure, inverse variance meta-analyses pooled risk estimates across included studies to obtain summary estimates (95% confidence intervals, CI). Fixed-effects models were selected based on the assumption that effect sizes reported for each study estimate one true underlying population effect size<sup>24</sup>. Analyses were repeated post-hoc with random-effects models which are more conservative compared with fixed-effects models. Funnel plots assessed publication bias and pre-specified meta-regression analyses compared risk estimates between groups of studies according to follow-up period ( $\leq 1$  versus  $> 1$  month), sample size ( $\leq 100$  versus  $> 100$ ), mean sample age ( $\leq 65$  versus  $> 65$  years), surgery type (cardiac; non-cardiac; and mixed surgery type) and sex ( $\leq 75\%$  males versus  $> 75\%$  males). Cut-points for all of those subgroups analyses were specified a priori; one additional subgroup analysis comparing risk estimates according to definition of “hypercholesterolaemia” was performed post-hoc. Meta-regression was calculated in SAS Enterprise Guide (version 4.3).

## Quality assessment

Reporting quality was assessed by one investigator (IF) using the 22-item checklist for cohort studies issued by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Initiative

<sup>25</sup>. A score of reporting quality was derived based on the number of items an article scored positively on (maximum score 22). Of note, the STROBE checklist is limited to reporting quality and does not reflect the quality of a study.

## RESULTS

### Study characteristics

A total of 171 unique articles identified in the search and 34 articles were identified independently (see Figure 1). Of all articles, 17 met inclusion criteria. All included studies had observational designs.

Publication years spanned 2001 to 2017 and studies stemmed from USA, Asia, Europe and Australia. One US lab was overrepresented but appeared to report on different patient samples in each of their articles <sup>26-30</sup> (see Supplemental Table 1). Studies included a total of N=2725 patients who were followed up for between 1 day and 4 years after surgery (median 7 days; interquartile range 1 to 68 days). Where reported, mean sample age ranged from 61 to 71 years (mean 67 years). All except one study <sup>19</sup> had recruited more males than females. Surgical procedures included cardiac surgery (N=8) and non-cardiac surgery (N=8); one study included both <sup>21</sup>.

POCD was defined inconsistently. Two studies identified POCD using brief screening instruments <sup>31,32</sup> and 1 study defined it through consensus rating by two neuropsychologists <sup>23</sup> (see Supplemental Table 1). All of the remaining investigations used detailed batteries of cognitive testing. Of these, 5 used raw change in cognitive scores to define POCD <sup>18,20,33-35</sup> and 9 compared patients' cognitive change to control subjects who performed the same battery of cognitive tests but did not undergo surgery <sup>19,21,22,26-30,36</sup>.

Of all included studies, only 2 had set out to address the present research question <sup>18,27</sup>. All of the remaining investigations reported on parameters of dyslipidaemia or lipid-lowering treatment and POCD risk in descriptive form. Statistical adjustment for potential confounders was rare.

## Parameters of dyslipidaemia

A single study assessed total cholesterol, LDL, HDL and triglycerides as continuous measures of dyslipidemia<sup>26</sup>; another reported on hypertriglyceridemia but did not specify cut-offs<sup>23</sup>. Twelve articles reported on hypercholesterolaemia. Of these, 1 used a combination of self-report and medical history for definition<sup>19</sup>, 4 used laboratory measurements (total cholesterol  $\geq 240$  mg/dl<sup>23</sup>; total cholesterol  $\geq 240$  mg/dl and/or triglycerides  $\geq 150$  mg/dl<sup>33</sup>; total cholesterol  $\geq 200$  mg/dl and/or medication<sup>29,30</sup>), and 7 used the terms “hypercholesterolaemia” or “hyperlipidemia” without definition<sup>20,21,31,32,34-36</sup>. Eight articles reported on statin use<sup>18,22,26-30</sup>. Of those 8 articles, only 2 specified that statins were taken pre-operatively<sup>18,21</sup>. For the remaining 6 studies, we inferred this based on the fact that data were presented in tables showing baseline characteristics of patient samples<sup>22,26-30</sup>. No studies on forms of lipid-lowering treatment other than statins were found.

## Findings of included studies

### *Total cholesterol, LDL, HDL, triglycerides*

In the study on continuous parameters of dyslipidaemia, total cholesterol (RR=1.00; 95% CI 0.99, 1.01; p=0.72), LDL (RR=1.00; 95% CI=0.99, 1.01; p=0.79), HDL (RR=1.03; 95% CI=1.00, 1.07; p=0.59) and triglycerides (RR=1.00; 95% CI=0.99, 1.01; p=0.78) were each unrelated to POCD risk at 1 day after surgery<sup>26</sup>.

### *Hypertriglyceridemia*

“Hypertriglyceridemia” was unrelated to POCD risk at 6-month follow-up (RR=2.21, 95% CI=0.34, 4.30; p=0.77) in the only study to assess this risk factor<sup>23</sup>.

### *Hypercholesterolaemia: Meta-analysis*

Twelve studies were entered into meta-analysis on hypercholesterolemia. When results were pooled across all of those studies, we found no association of hypercholesterolemia exposure with risk of POCD (RR=0.93; 95% CI=0.80, 1.08; p=0.34) (see Figure 2). There was no evidence of statistical heterogeneity ( $\chi^2(11)=10.65$ ; p=0.47;  $I^2=0\%$ ) or publication bias (see Supplemental Figure 1). A random-effects model yielded identical results (RR=0.93; 95% CI=0.80, 1.08; p=0.34).



### *Hypercholesterolaemia: Subgroup analysis and meta-regression*

Hypercholesterolaemia did not predict POCD risk in any of the subgroup analyses according to follow-up period, sample size, age, surgery type, proportion of males, or definition of “hypercholesterolaemia” (all  $p > 0.10$ ; Supplemental Table 2). Effect sizes also did not differ statistically significantly between subgroups (all meta-regression  $p > 0.10$ ).

### *Statin use: Meta-analysis*

Across 8 included studies with data on pre-operative statin use and POCD risk, exposure to statins was associated with a reduced risk of POCD (RR=0.81; 95% CI=0.67, 0.98;  $p=0.03$ ) with evidence of moderate statistical heterogeneity between studies ( $\chi^2(7) = 11.96$ ;  $p=0.10$ ;  $I^2=41\%$ ; see Figure 3). Only 2 of the 8 studies considered sociodemographic, genetic and clinical covariates in their analyses<sup>21,26</sup>. Those 2 studies did not weigh heavily in the meta-analysis due to large standard errors of their estimates (see Figure 3), so that the pooled risk estimate can be considered largely unadjusted. Results were similar but were no longer statistically significant when a random-effects model was used (RR=0.76; 95% CI=0.57, 1.01;  $p=0.059$ ) and there was no evidence of publication bias (see Supplemental Figure 2).

### *Statin use: Subgroup analysis and meta-regression*

Results from subgroup analyses are shown in Figure 4 and Supplemental Table 3. The association of pre-operative statin use with POCD risk did not differ statistically significantly between groups of studies according to follow-up period ( $\leq 1$  month, RR=0.71, 95% CI=0.55, 0.92;  $> 1$  month RR=0.93, 95% CI=0.71, 1.22; meta-regression  $p=0.257$ ), sample size ( $\leq 100$ , RR=0.49, 95% CI=0.31, 0.78;  $> 100$ , RR=0.89, 95% CI=0.73, 1.09; meta-regression  $p=0.538$ ), mean sample age ( $\leq 65$  years, RR=0.93, 95% CI=0.71, 1.22;  $> 65$  years, RR=0.77, 95% CI=0.55, 1.07; meta-regression  $P=0.442$ ) or sex ( $\leq 75\%$  males, RR=0.84, 95% CI=0.69, 1.02;  $> 75\%$  male, RR=0.60, 95% CI=0.32, 1.13; meta-regression  $p=0.364$ ). However, when results were pooled according to surgery type, the association of statin use with POCD risk only reached statistical significance in studies of non-cardiac surgery (RR 0.60, 95% CI 0.44, 0.80). That risk estimate was lower than that of a study with mixed surgery type which had applied statistical adjustment for sociodemographic and clinical covariates including hypercholesterolaemia and failed to find statistically significant associations of statin use with POCD risk (RR=1.37, 95% CI=0.78, 2.39; meta-regression  $p=0.049$ ). A trend was observed for a lower risk estimate in the

subgroup of studies on non-cardiac surgery compared with a study of patients undergoing cardiac surgery (RR=0.93, 95% CI=0.71, 1.22; meta-regression p=0.079).

#### *Statin use: Narrative evidence on statin type, dosage, and use at hospital discharge*

Of the 8 included studies on statin use, one assessed statin type and dosage. The study reported that statin non-users were at similar POCD risk compared with a group receiving atorvastatin (RR=1.26, 95% CI=0.71, 2.26; p=0.421) whereas non-users were at increased risk compared with a group on simvastatin (RR=6.65; 95% CI=1.63, 27.22; p=0.008). Relative to the latter group, patients receiving atorvastatin, too, were at increased risk (RR=5.27; 95% CI=1.25, 22.26; p=0.024). Interestingly, the study also suggested that there may be a dose-response relationship of statins with POCD risk. Patients treated with maximum dosage of any statin were at reduced risk compared with patients receiving sub-maximum dosage (RR=0.17, 95% CI=0.04, 0.71; p=0.001) although results of that study were limited by large confidence intervals<sup>27</sup>. One study additionally assessed statins at discharge (rather than pre-operatively) and found that of 100 patients discharged on statins (of whom 21 received statins for the first time), 42.0% had POCD at 6 week follow-up compared with 34.5% not receiving statins (RR=1.23, 95% CI=0.93, 1.60; p=0.173). Yet, when cognitive change was modeled as a continuous outcome, statins at discharge were statistically significantly associated with a *reduced* rate of cognitive improvement (p=0.011)<sup>18</sup>.

#### **Excluded studies**

A number of studies failed to meet inclusion criteria but are considered here as additional evidence. Those on parameters of dyslipidaemia all reported no association with POCD risk. In one study of 124 patients with diabetes, “hypercholesterolaemia” was entered but not retained in models of 7-day and 6-month POCD risks but the article did not report effect sizes<sup>37</sup>. Another study that followed 54 coronary artery bypass graft (CABG) patients for 3 to 5 years described that there was no association of “hyperlipidemia” before surgery with POCD risk. Statistical results were not provided<sup>38</sup>. In a sample of 55 older adults undergoing non-cardiac surgery, “hypercholesterolaemia” before surgery was not associated with cognitive decline to 1 month follow-up (p=0.61)<sup>39</sup>. One study of 40 patients undergoing intracranial surgery reported no association of Mini-Mental State Examination (MMSE) scores with “dyslipidaemia” (p=0.97) but did not specify whether the analysis was of pre-surgery, post-surgery or change in MMSE scores<sup>40</sup>. Finally, in one of the earliest studies of POCD, higher

cholesterol levels correlated with higher motor speed at 1 month after cardiac surgery ( $p=0.015$ ), but the article did not report on effect sizes, and we have concerns over whether “motor speed” was interpreted in the correct direction. Cholesterol did not correlate with any of the other 7 cognitive tests in that study<sup>41</sup>.

One observational study on lipid-lowering treatment failed to meet our inclusion criteria due to assessing statin use at hospital discharge only. In that study of 229 cardiac surgery patients, 126 (55.0%) had developed POCD by 1-year follow-up and statin use at discharge was unrelated to POCD risk (RR=1.10, 95% CI=0.87, 1.38;  $p=0.441$ )<sup>42</sup>. Two trials were excluded from our analysis due to non-English language<sup>43</sup> or initiation of statin treatment *after* surgery<sup>44</sup>. One Russian study compared the effects of pre-operative rosuvastatin treatment for 10 to 14 days before surgery and until hospital discharge versus not receiving that treatment. The sample consisted of 109 middle-aged to older males undergoing CABG, and at 7 to 10-day follow-up the group receiving rosuvastatin outperformed the control group on tests of memory, attention and processing speed<sup>43</sup>. The finding is contrasted with a recent UK randomized controlled trial. Here, either simvastatin or placebo was administered to 142 patients and no effect of intervention on risk of POCD 6 months after surgery was found<sup>44</sup>. However, that study was of critically ill patients, i.e. not necessarily representative of the general older population undergoing surgery, had high loss to cognitive follow-up (66.2%) and, unlike the Russian trial<sup>43</sup> initiated statin treatment immediately *after* surgery<sup>44</sup>. Effects of longer-term pre-operative statin use on POCD risk were not addressed.

## DISCUSSION

In this systematic review, we had set out to combine the evidence on parameters of dyslipidaemia and lipid-lowering treatment as potential modifiers of POCD risk. Across 17 included studies, the exposure under assessment was limited almost exclusively to hypercholesterolaemia and statin use, and studies reported predominantly unadjusted, descriptive data. Hypercholesterolaemia – though defined inconsistently across studies – was overall not associated with POCD risk, whereas use of pre-operative statins was linked to a 19% reduction in POCD risk. The association of statins with a reduced risk appeared to be limited to studies of non-cardiac surgery type although the study number in the subgroup analysis according to surgery type was insufficient to allow definitive conclusions. There was further preliminary epidemiological evidence (albeit

based on a single article) suggestive of an inverse dose-response relationship of statins and POCD risk as well as superiority of simvastatin over atorvastatin in POCD prevention<sup>27</sup>.

Cholesterol is known to have atherogenic<sup>45</sup>, pro-inflammatory<sup>10</sup> and beta amyloid promoting properties<sup>12</sup>. Dyslipidaemia also appears to cause POCD in animal studies<sup>46</sup>. Further, dyslipidaemia is a relatively well-established risk factor for age-related cognitive impairment<sup>7</sup>. On that basis, we had expected to find a link to POCD, and can only speculate as to underlying reasons. Firstly, the epidemiological evidence on age-related cognitive impairment suggests a role of midlife dyslipidaemia<sup>47,48</sup> more so than of cholesterol measured in later life<sup>49-52</sup> (for reviews, see<sup>10,11</sup>). For instance, in the Women's Health and Aging Study II, total and HDL cholesterol measured at age 75 did not predict cognitive decline during 9-year follow-up<sup>53</sup>. The disparity of midlife versus late-life cholesterol levels may in part be due to an effect of cognitive impairment on reducing cholesterol levels<sup>54</sup>. In the studies included in our analysis, hypercholesterolaemia was ascertained immediately before surgery, i.e. in later life. Secondly, "hypercholesterolaemia" was frequently undefined in the included studies, and in those studies may well have been based on a combination of laboratory measurements with statin use. In that case, detrimental effects of cholesterol itself on POCD risk were perhaps eliminated by statin users in the "hypercholesterolemia" groups. Finally, it is possible that dyslipidemia is in fact unrelated to POCD risk. Analyses of genetic biomarkers appear to support this explanation. The e4 allele of apolipoprotein E (ApoE) gene involved in cholesterol metabolism is a well-established risk factor for cognitive impairment<sup>55</sup>, but reports on associations with POCD have been mixed<sup>19,28,56</sup>.

A number of epidemiological studies have implicated statin use as reducing the risk of future age-related cognitive impairment<sup>12</sup>. For instance, women participating in the Heart and Estrogen/Progestin Replacement Study who received statins had higher cognitive function compared with non-users<sup>8</sup>. Reduced risk of POCD in statin users is also in line with beneficial effects on other post-operative outcomes such as risk of stroke and cardiovascular events<sup>57,58</sup>. Importantly, we had no information on duration of statin treatment for any of the included studies; patients' statin use over the course of decades prior to surgery is thus unknown. Given that the trial that had initiated statins after surgery found no effect on POCD risk<sup>44</sup> whereas the Russian study that had used statins for 10 to 14 days before surgery reported beneficial effects<sup>43</sup> implies a central role of treatment duration in risk modification which warrants clarification in future randomized controlled trials.

With statins as a form of lipid-lowering treatment, it would appear plausible that any associations of statins with reduced POCD risk are due to reduced cholesterol levels in statin users, but two arguments speak against this. Firstly, we did not find an association of hypercholesterolaemia itself with POCD risk. Secondly, the study that had compared statin types found that patients receiving simvastatin were at lower risk of POCD compared with those on atorvastatin<sup>27</sup> despite the latter as the more intensive form of lipid-lowering drug<sup>59</sup>.

Alternative underlying causal mechanisms linking statins to a reduced risk of POCD may include anti-thrombotic and anti-inflammatory effects, as well as effects on endothelial function<sup>60</sup>. Statins further reduce beta amyloid levels – a hallmark of Alzheimer’s disease – and have been linked to a lower severity of Alzheimer’s disease pathology in observational studies<sup>12</sup>. Contrasting with the epidemiological evidence presented here and with the Russian trial showing a beneficial effect of statins on POCD risk<sup>43</sup>, trials on age-related cognitive impairment have been unpromising, however. Some RCTs have suggested that statins may temporarily lead to cognitive decrements<sup>61</sup> – a concern that even led to the US Food and Drug Administration to include cognitive side-effects in its safety profile of statins<sup>62</sup>; whereas others including a Cochrane review of RCTS reported no effect of statins on cognitive decline<sup>63,64</sup>. Similarly, for PCSK9 inhibitors as another form of lipid-lowering drug, a meta-analysis reported adverse cognitive effects. However, that analysis was affected by low study number and inconsistent definition of cognitive outcome that included confusional states<sup>65</sup>. A more recent RCT reported no effects of PCSK9 inhibition on 19-month cognitive decline<sup>66</sup> so that overall the evidence from RCTs on the roles of statins and PCSK9 inhibitors in age-related cognitive decline is not entirely clear at present.

In light of potential adverse effects of lipid-lowering treatment on cognitive function, the present epidemiological evidence of a reduced risk of POCD in statin users may well be due to counterbalancing of statin-induced cognitive decrements by reduced cholesterol levels. The finding could also reflect reverse causality. Statin use may depend on a range of factors such as cognitive reserve indexed by socioeconomic status, education and pre-morbid intelligence. People with a lower cognitive reserve may have lower healthcare uptake<sup>67</sup> and also appear to be at reduced risk of POCD<sup>68</sup>. Relatedly, people with beginning cognitive impairment in older age may have difficulty with treatment adherence<sup>69</sup> and are also at increased POCD risk<sup>1</sup>. Confounding by other factors such as health status at the time of undergoing surgery, too, is

possible. The association of statins with reduced POCD risk could therefore be spurious. We are unable to determine this from the present data.

The unclear role of causality in statin use and POCD risk limits the clinical implications of our findings. Trials mirroring the recent Russian investigation<sup>43</sup> with additional inclusion of a placebo group are needed and should test for dose-response and statin-type-specific effects. Comparison of benefits according to duration of treatment before surgery is also necessary to determine whether patients benefit from short-term treatment initiated at the time when surgery is planned.

Strengths of our study include the systematic search of three databases with wide inclusion criteria that captured studies which did not label their outcome "POCD". Our analysis is limited by heterogeneous sample characteristics and length of follow-up between included studies. Heterogeneity in cut-offs of laboratory data and parameters used for definition of "hypercholesterolaemia" highlights the need for streamlining of research studies. Finally, no data on duration of treatment were reported in any of the included studies on statins so that we are unable to comment on risk modification associated with long-term versus short-term use.

In the first systematic review of parameters of dyslipidaemia and lipid-lowering treatment before surgery as potential modifiers of POCD risk, we found evidence of a reduced risk of POCD in statin users. We are unable to determine the role of treatment duration on the basis of the present data. Questionable causality in the association of statin use with age-related cognitive decline further suggests confounding of the association, so that further trial studies manipulating duration of treatment, as well as statin type and dosage are urgently needed.

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### **Competing Interest**

GW is coordinator of the BioCog consortium and CEO of Pharmaimage Biomarker Solutions GmbH

(<http://www.pi-pharmaimage.com>). The company is one of the partners of the BioCog consortium. TP is workpackage leader (WP3) of BioCog. TP and IF declare that they have no conflict of interest.

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### **Author contributions**

IF performed the literature search and data analysis. TP and IF interpreted the findings and wrote the manuscript. All authors commented on the final manuscript.

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N=138 articles in PubMed      N=126 articles in Ovid SP      N=1 article in Cochrane

N=171 unique articles

N=152 not relevant

N=19 articles obtained for assessment of full texts against inclusion criteria

N=34 articles identified from reference lists/ in independent search

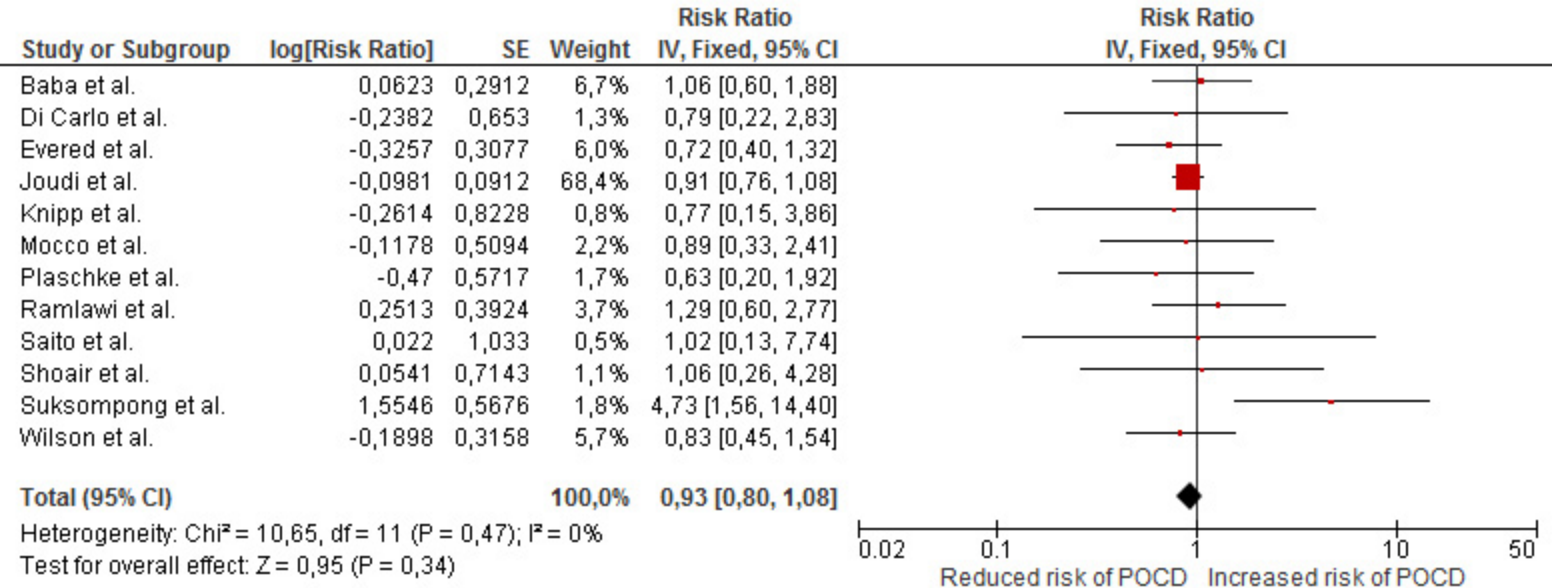
N=18 not on research question or did not meet inclusion criteria (including N=4 relevant but non-English)

N=3 relevant reviews

N=7 duplicate reporting

N=8 lack of statistical detail/ unsuccessful author contact

N=17 were included in review



Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio
				IV, Fixed, 95% CI
Evered et al.	0,3148	0,2848	11,3%	1,37 [0,78, 2,39]
Gaudet et al.	-0,9426	0,3516	7,4%	0,39 [0,20, 0,78]
Heyer et al. (2013a)	-0,4494	0,8292	1,3%	0,64 [0,13, 3,24]
Heyer et al. (2013b)	-0,6059	0,2691	12,6%	0,55 [0,32, 0,92]
Heyer et al. (2014)	-0,1578	0,356	7,2%	0,85 [0,43, 1,72]
Mathew et al.	-0,0716	0,1379	48,0%	0,93 [0,71, 1,22]
Mocco et al.	-0,0916	0,5094	3,5%	0,91 [0,34, 2,48]
Wilson et al.	-0,5169	0,3246	8,7%	0,60 [0,32, 1,13]
<b>Total (95% CI)</b>			<b>100,0%</b>	<b>0,81 [0,67, 0,98]</b>

Heterogeneity:  $\text{Chi}^2 = 11,96$ ,  $\text{df} = 7$  ( $P = 0,10$ );  $I^2 = 41\%$

Test for overall effect:  $Z = 2,20$  ( $P = 0,03$ )

