

# BMJ Open Frequency of postoperative cognitive dysfunction after non-cardiac surgery and its impact on functional outcomes: protocol for a systematic review

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## ABSTRACT

**Introduction** Older surgical candidates are at increased risk of a phenomenon known as postoperative cognitive dysfunction (POCD). Several studies have looked at the incidence of POCD at different time points following surgery, using different study methods. Fewer have assessed whether changes in cognition after surgery are attributable to surgery and how they impact patient function and quality of life. The aim of this systematic review is to summarise and appraise studies addressing any of the following research questions (RQs): (RQ1) what is the frequency of POCD after non-cardiac surgery?; (RQ2) is non-cardiac surgery associated with an increased risk of cognitive decline?; (RQ3) is POCD after non-cardiac surgery associated with patient-important outcomes?

**Methods and analysis** This protocol adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols guidelines. Three electronic databases (MEDLINE, PsycINFO and EMBASE) will be systematically searched from their inception date. Identified studies will be screened by two reviewers for eligibility using Covidence, and data will be extracted into a standardised electronic form. We will evaluate methodological quality of included studies using the Quality In Prognosis Studies and its adaptation to the overall prognosis question, and the CLARITY risk of bias for cohort and case-control studies. For RQ1, we will estimate an average POCD frequency at different time points by performing a meta-analysis of included studies when appropriate. For RQ2 and RQ3, we will extract and meta-analyse the effect measures for the association of surgery with cognitive decline when compared with the non-surgical comparator, and association of cognitive changes with functional changes, quality of life and other patient-important outcomes based on available evidence. We will narratively summarise and discuss the different methods implemented in the existing studies to answer the three RQs, and when meta-analysis is deemed infeasible, we will qualitatively report the results of the included studies.

**Ethics and dissemination** This project involves the collection and analysis of data from previously published studies and therefore does not require ethics approval. We plan to present the findings of this research project at peer-reviewed conferences and publish the results in peer-reviewed journals.

**PROSPERO registration number** CRD42022370674.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This systematic review protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols guidelines.
- ⇒ We developed a comprehensive search strategy across three databases.
- ⇒ We will appraise the methodological quality of included studies using tools appropriate to each study design and research question.
- ⇒ Searches are limited to English electronic databases, which may cause a language bias.
- ⇒ We expect heterogeneity of the included studies in methods and quality, which might limit the conclusions that we can draw from this study.

## INTRODUCTION

By 2030, one in every six people globally will be 60 years of age or older.<sup>1</sup> It is projected that half of these older adults will require surgery at some point in time.<sup>2</sup>

Postoperative cognitive dysfunction (POCD), first described by Bedford in 1955, is a new cognitive impairment identified in the postoperative period.<sup>3</sup> This phenomenon has been described at different times after surgery, and after both cardiac and non-cardiac surgery. POCD is typically diagnosed by comparing the results of cognitive or neuropsychological assessments performed after surgery with the patient's preoperative baseline.<sup>4</sup> POCD has been independently associated with increased mortality at 1 and 8 years after non-cardiac surgery.<sup>5,6</sup>

A 2007 systematic review of patients undergoing non-cardiac surgery found that between 2% and 56% of patients developed POCD between 22 days and 6 months after non-cardiac surgery.<sup>7</sup> The heterogeneity of the studies included in this review explains the wide frequency range. This heterogeneity encompasses differences in the definition of POCD, types and properties of instruments



used to measure cognitive function, study designs and length of follow-up postoperatively.<sup>7</sup>

More recently, the NeuroVISION cohort study prospectively enrolled 1114 patients  $\geq 65$  years of age who were undergoing non-cardiac surgery at 12 centres in nine countries.<sup>8</sup> Cognitive decline was defined as a decrease of  $\geq 2$  points on the Montreal Cognitive Assessment (MoCA) from the preoperative baseline to 1 year after surgery. Based on this definition, 30% of patients developed POCD at 1-year.<sup>9</sup> The proportion is quite high when compared with MoCA score changes reported in community-based populations, for which studies have described an average decline of approximately 2 MoCA points every 10 years after 60 years of age.<sup>9 10</sup> Although this is an impressive difference, it represents an indirect comparison. There remains uncertainty regarding whether the same patients would have still experienced the same cognitive decline regardless of the surgery. The definition of POCD is typically descriptive and requires the objective proof of a cognitive decline after surgery; it does not require a non-surgical comparator. In the 2007 systematic review, 8 of the identified 22 cohort studies did not include a non-surgical control group.<sup>7</sup> To answer the question on whether surgery is itself a risk factor for cognitive decline requires a direct non-surgical comparator, whether that is a comparable non-surgical population, or the same individual's cognitive trajectory without or before undergoing surgery.

In 2018, experts suggested aligning postoperative cognitive impairments with the nomenclature of the Diagnostic and Statistical Manual for Mental Disorders, fifth edition for cognitive disorders in the general population.<sup>11</sup> According to this expert panel, cognitive decline diagnosed up to 30 days after surgery should be characterised as delayed neurocognitive recovery; between 30 days and 12 months after surgery, the recommended term is 'postoperative neurocognitive disorder'. Similarly to the non-operative setting, for the diagnosis of postoperative neurocognitive disorder to be made, there should be evidence of both cognitive impairment and cognitive concern by the individual, informant or clinician; there should also be documentation of functional ability.<sup>11</sup> In contrast, the existing literature has been inconsistent not only in the tests used to determine POCD but also in whether and how the cognitive change has been characterised in terms of subjective complaints and impact on function.

We plan to conduct a systematic review of the existing literature to identify and appraise existing studies answering the following research questions (RQs) and subquestions:

1. What is the frequency of POCD in non-cardiac surgical populations?
  - a. How does the reported frequency differ based on varying POCD definitions and timing of assessment?
2. Does non-cardiac surgery increase the risk of cognitive decline?

- a. What designs have been used in the existing literature to answer this question?
3. Is POCD associated with patient-important outcomes (eg, cognitive concerns, functional impairment, quality of life)?
  - a. How and how often has this been evaluated and reported in the existing literature?

This systematic review will focus on non-cardiac surgery to remove an additional reason for heterogeneity, since the epidemiology of cognitive disorders after cardiac surgery is expected to differ from that of cognitive disorders after non-cardiac surgery. For the same reason, we will not include studies on patients undergoing neurosurgery involving the brain (ie, cranial neurosurgery).

The current manuscript presents the protocol of our systematic review, including rationale and methods.

## METHODS

### Design

This study will be a systematic review of published studies that report the frequency of cognitive changes after non-cardiac surgery. We prepared the protocol in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols guidelines<sup>12</sup> and registered it on PROSPERO (CRD42022370674). If important changes to the study methods are implemented, the PROSPERO record will be updated before the publication of the final results, to reflect these amendments. Records and data pertaining to this review are filed in a McMaster University cloud repository with access shared among the authors.

### Search strategy

We will conduct a systematic search in the MEDLINE, PsycINFO and EMBASE databases. The search combines medical subject heading terms and keywords covering the cognition domain and the non-cardiac surgery domain. The databases will be searched from their inception date. We will not use language restrictions. The online supplemental appendix 1 includes the search strategies for the three databases.

### Eligibility criteria

Table 1 describes the RQs of interest, using the Population, Intervention/Exposure, Comparator, Outcomes, Time format when applicable. Studies answering one or more of the RQs of interest will be eligible. For the purpose of this systematic review, we will include all studies regardless of methods to assess POCD, as long as a change compared with a baseline status can be established.

We will include prospective or retrospective cohort (longitudinal) studies and randomised controlled trials. Case-control studies will be considered for RQ2 and RQ3. Systematic reviews will be cross-referenced to identify studies that could meet our inclusion criteria.

We will exclude:

**Table 1** Research questions using the PICOT/PECOT format as applicable

Research questions (RQs)	Population	Exposure	Comparator (non-exposure)	Outcomes	Time
RQ1	Adults ≥18 years of age undergoing any type of non-cardiac surgery (excluding cranial surgery)	PICOT format not applicable for the first RQ (overall prognosis question, that is, no comparator, no exposure)	Not applicable	Changes in cognitive performance after surgery compared with a preoperative baseline, as assessed through cognitive and/or neuropsychological assessments	Any length of follow-up beyond 1 month*
RQ2	Adults ≥18 years of age	Undergoing any type of non-cardiac surgery (excluding cranial surgery), including: general surgery, urological and gynaecological surgery, orthopaedic surgery (including spine surgery), thoracic surgery and vascular surgery	Not undergoing surgery	Changes in cognitive performance over time compared with a baseline, as assessed through longitudinal cognitive and/or neuropsychological assessments. For the patients exposed, will be postoperative changes compared with a preoperative baseline	Any length of follow-up beyond 1 month*
RQ3	Adults ≥18 years of age undergoing any type of non-cardiac surgery (excluding cranial surgery)	Experiencing changes in cognitive performance after surgery compared with a preoperative baseline, as assessed through cognitive and/or neuropsychological assessments	Not experiencing changes in cognitive performance after surgery compared with a preoperative baseline, as assessed through cognitive and/or neuropsychological assessments	Function/ability/disability (independence in basic and/or instrumental activities of daily living, employment) <ul style="list-style-type: none"> <li>▲ physical performance</li> <li>▲ frailty</li> <li>▲ falls</li> <li>▲ quality of life</li> <li>▲ subjective complaints/concerns regarding cognition and/or function</li> <li>▲ caregiver burden</li> </ul>	Any length of follow-up beyond 1 month*

\*We will not make any a priori eligibility restrictions to the timing of assessment of cognitive changes. However, in the summary and analyses of the retrieved studies, we will make a distinction across studies based on their adherence to the recommended timeline for the definition of postoperative neurocognitive disorder, that is, between 1 month and 1 year after surgery. PICOT/PECOT, Population, Intervention/Exposure, Comparator, Outcomes, Time.



- ▶ Basic science/laboratory studies, case reports and case series studies, and narrative reviews.
- ▶ Studies including only patients undergoing cranial neurosurgery (but we will include studies describing a population undergoing a mix of non-cardiac surgery including cranial surgery, if those undergoing cranial surgery represent less than 30% of the study population).
- ▶ Studies evaluating delirium and not POCD.
- ▶ Studies evaluating postoperative cognitive changes but with a single follow-up earlier than 1 month after surgery.

### Study selection

Each study identified through the initial search will undergo title and abstract screening by two independent reviewers using the above eligibility criteria. Disagreements will be resolved by a third reviewer. After this, full texts of the potential studies will be retrieved and screened by two independent reviewers. Disagreements will be resolved by a third reviewer from the study team.

### Data extraction

Relevant data will be extracted from the included studies using a standardised electronic form. Relevant data across the three RQs will include: study characteristics (country(ies), year of enrolment, year of publication, number of participating centres), study design, participant characteristics (age, comorbidities), sample size, type of surgery, type of anaesthesia; POCD definition, POCD instrument(s) and timing of assessment; presence and type of non-surgical comparator; measurements of function and other patient-important outcomes; counts and aggregate measures of frequency and risk/association. Each study will have data extracted by two investigators to verify accuracy, with a third reviewer to resolve any discrepancies. All steps for study selection and data extraction will be performed using the Covidence platform.<sup>13</sup>

### Risk of bias assessment

The risk of bias of the included studies will be assessed based on each RQ. Studies that answer more than one RQ will be assessed for their risk of bias in answering each question separately, according to the approach described below.

For RQ1 and RQ2, we will assess the included studies for their risk of bias using the Quality In Prognosis Studies (QUIPS) tool.<sup>14</sup> QUIPS includes the following methodological domains: study population selection, study attrition, prognostic factor measurement, outcome measurement, control of confounding variables and statistical presentation of the results. We will adapt the domains based on the RQ being answered. For example, the QUIPS domains of prognostic factor measurement and study confounding are not relevant to RQ1 (ie, overall research prognosis question).<sup>15</sup> For RQ2 (where surgery is the prognostic factor), these domains will instead remain relevant. For each study and research

question, each of the relevant domains will have their risk of bias rated as 'low', 'moderate' or 'high'.

For RQ3, we will use the CLARITY tool for cohort and case-control studies.<sup>16 17</sup> The assessment of each study will be independently performed by two reviewers. Discrepancies between the authors will be resolved by consensus, and the involvement of a third reviewer (as necessary).

### Data synthesis and analysis

The data extracted from the selected studies and the results of the risk of bias assessment for each RQ will be synthesised and presented.

**RQ1.** We will summarise the methods used by the included studies to define and assess POCD, narratively and with descriptive statistics.<sup>18</sup> If possible, we will estimate an average frequency of POCD by performing a pooled analysis of included studies that used a dichotomous definition of POCD and that provided a frequency or proportion measure for POCD and the overall population size. The pooled analysis will weigh individual studies based on study sample size, with increasing weight for larger samples. As the presence of cognitive decline will be treated as a dichotomous variable, the result will be presented as a proportion with a 95% CI. We will use random-effects and fixed-effects meta-analysis. We will provide the pooled estimate, with its 95% CI, and the estimate of between-study variance using  $I^2$ .

**RQ2.** Studies addressing RQ2 might be very heterogeneous in their design. Across different designs, we plan to extract and meta-analyse the effect measures for the association of surgery with cognitive decline when compared with the non-surgical comparator, wherever possible. We will extract (or calculate) and meta-analyse risk ratios (RRs) or ORs with 95% CIs, or pooled weighted mean difference (WMD) or standardised mean difference (SMD) with corresponding 95% CIs, as appropriate, depending on how the association with cognitive changes was analysed and reported in the original studies. If combining results using a meta-analysis is judged not feasible or inappropriate, we will provide a narrative description of the results, highlighting the different methodologies adopted in the literature to answer this question.

**RQ3.** We will report absolute numbers and frequency to describe how often the included studies looked at the association of POCD with functional outcomes or other patient-important outcomes. With regard to the evidence of this association, we will meta-analyse studies that are sufficiently homogeneous in their design (eg, examined the same type of patient-important outcomes and used comparable instruments). We will extract (or calculate) and meta-analyse RRs or ORs with 95% CIs, or pooled WMD or SMD with corresponding 95% CIs, as appropriate, depending on how the association of POCD with functional outcomes or other patient-important outcomes was analysed and reported in the original studies. If combining results using meta-analysis is judged



not feasible or inappropriate, we will provide a qualitative or narrative description of the results.

### Subgroup and sensitivity analyses

Studies included in this review will likely be using different definitions of POCD and different assessment tools. Across the three RQs, we will consider the possibility of subgroup analyses based on the individual studies and whether there is similarity in their definitions and assessment tools used. Based on data availability, we will study other possible sources of heterogeneity, including: age, type of surgery, length of follow-up, study quality and study year. This will be done by performing subgroup or meta-regression analyses.

For all meta-analyses with at least 10 studies, potential for publication bias will be visually assessed by funnel plot symmetry.

We will use STATA (V.16.1) and RevMan (V.5.3) for the statistical analyses.

### Certainty of the evidence assessment

We will assess the certainty of evidence for each RQ following the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) guidance. We will use the GRADE guidance adaptation for the assessment of evidence about prognosis. For RQ1, we will use the guidelines for rating confidence in estimates of event rates in broad categories of patients.<sup>15</sup> For RQ2 and RQ3, we will use the guidelines for rating certainty in identification of groups of patients with different absolute risks.<sup>19</sup> We will rank the quality of the evidence as high, moderate, low or very low. GRADE assessment will be completed by two reviewers, and discrepancies will be resolved by consensus or the involvement of a third reviewer (if needed).

### Progress to date

An initial search was conducted in March 2022. The title and abstract screening is ongoing. We plan to update the search while we proceed to the data extraction stage to ensure the most recent literature is included.

### Study significance

With increases in life expectancy, dementia and cognitive impairment are becoming a major threat to population health. Trajectories to cognitive impairment remain largely unknown.

The age and complexity of patients undergoing surgery are also increasing. POCD (or more recently, postoperative neurocognitive disorder) has been established as a concept for many years now, and some evidence has associated it with adverse outcome including increased mortality.<sup>4</sup> However, there is a need to understand the amount and quality of evidence around the extent to which this phenomenon occurs after non-cardiac surgery, if it is attributable to surgery, and how POCD affects function and quality of life for these patients. With an ageing population, many of whom require surgery, it is now increasingly important to clarify the cognitive risks of non-cardiac surgery.

By summarising and appraising this evidence, our systematic review has the potential to inform practice around surgery, shared decision-making and future research.

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**Contributors** MM and YR conceived the study and its methods. PS, YR and MP designed the search strategy. All authors have contributed to the study screening. SK, SS, OC, YR, YJ and MM drafted the initial manuscript. MM is the guarantor of this review project. All authors reviewed the final manuscript.

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