

# BMJ Open The incidence of delirium after cardiac surgery in the elderly: protocol for a systematic review and meta-analysis

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## ABSTRACT

**Introduction:** Delirium is one of the most common complications after cardiac surgery in the elderly. Future studies aimed at preventing postoperative delirium will need an accurate estimate of incidence. However, there are no available systematic reviews on the incidence, and reports of incidence of postoperative delirium after a cardiac operation vary widely with significant heterogeneity. Therefore, we aim to perform a systematic review and meta-analysis to determine the most accurate incidence possible of postoperative delirium in individuals aged >65 years after cardiac surgery.

**Methods and analyses:** We will undertake a comprehensive literature search among PubMed, EMBASE, the Cochrane Library, PsycINFO and CINAHL, from their inception to January 2017. Prospective cohort and cross sectional studies that described the incidence of delirium will be eligible for inclusion. The primary outcome will be the incidence of delirium. Risk of bias and methodological quality for the included studies will be assessed using a risk of bias tool for prevalence studies and the Cochrane guidelines. Heterogeneity of the estimates across studies will be assessed. Incidence data will be pooled by selective or emergency surgery. This systematic review will be reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).

**Ethics and dissemination:** This proposed systematic review and meta-analysis is based on published data, and thus there is no requirement for ethics approval. The study will provide an up to date and accurate incidence of postoperative delirium among the older population after cardiac surgery, which is necessary for future research in this area. The findings of this study will be presented at conferences and disseminated through publication in a peer reviewed journal.

**Trial registration number:** CRD42016047773.

## INTRODUCTION

Postoperative delirium is one of the most common complications for elderly patients who undergo surgery, characterised by acute onset, fluctuating course, inattention and, at

## Strengths and limitations of this study

- This study will provide an up to date and accurate incidence of postoperative delirium in the elderly after cardiac surgery.
- A subgroup analysis of certain patient characteristics make it possible to determine the incidence for specific populations and screen the populations with higher than average risk of delirium.
- The findings of this study will help guide researchers as they develop intervention trials to prevent delirium in the older population.
- Non-English articles will not be included in our study due to language difficulties and this may cause publication bias to some extent.

times, an abnormal level of consciousness. Recent studies have provided evidence that postoperative delirium in elderly patients is associated with poor outcomes. Postoperative delirium is associated with an increased risk of long term cognitive dysfunction and functional decline compared with patients without postoperative delirium.<sup>1</sup> Moreover, patients who had experienced delirium were also at increased risk of death.<sup>2</sup>

Although systematic review and meta-analysis of incidence exist for acute stroke, emergency department visits, intensive care units and orthopaedic surgery, no such systematic review and meta-analysis exists for delirium after cardiac surgery.<sup>3–5</sup> Such a systematic review and meta-analysis is needed for several reasons. Future intervention studies aimed at preventing delirium will need an accurate estimate of incidence. Currently, reports of incidence vary too widely (8–65%)<sup>6–11</sup> to use for comparison. Furthermore, if researchers perform placebo controlled intervention trials, the incidence in the placebo group could be compared with that of the meta-analysis to ensure the placebo group had the expected incidence. The incidence could also be used to help

researchers perform power calculations for number of subjects needed in trials.<sup>12</sup> Finally, the incidence of postoperative delirium varies depending on the characteristics of patients and type of surgery.<sup>6–9</sup> For example, delirium is more common among older patients with baseline cognitive impairment compared with patients with normal cognitive function.<sup>13 14</sup> Type of cardiac surgery is another factor that affects the incidence of delirium.<sup>15 16</sup> A systematic review and meta-analysis that analyses and identifies higher incidence of certain subgroups (such as baseline cognitive impairment) could help future researchers focus interventions on these higher than average risk populations. Additionally, characteristics of higher than average risk populations would be important to recognise for researchers who recruit participants into study protocols so that the researchers will measure all potential baseline variables that increase the risk of postoperative delirium in both the interventional and control groups.

Thus we intend to conduct a systematic review and meta-analysis to ascertain the incidence of delirium among older people undergoing cardiac surgery. We will also ascertain incidence based on certain patient characteristics (if data are available) that might have a higher than average expected incidence. It has been confirmed that there are numerous risk factors or patient characteristics associated with delirium, but some are mentioned much more often and we will conduct a subgroup analysis based on these characteristics. These characteristics include, but are not limited to, age  $\geq 65$  years (including two subgroups of older patients: 65–79 years and  $\geq 80$  years), baseline cognitive impairment, diabetes mellitus, depression and cerebrovascular disease, and type of cardiac surgery ('closed' surgery, such as valve replacement and 'open' surgery, such as bypass surgery), all of which have been found in previous meta-analyses on risk factors to be associated with the occurrence of delirium.<sup>17 18</sup>

## METHODS

### Criteria for included studies

We will conduct a comprehensive search on the databases MEDLINE, EMBASE, the Cochrane Library, PsycINFO and CINAHL from their inception to January 2017. References of eligible studies and relevant review articles or meta-analyses will be manually searched for additional studies. The MeSH word and free words used are as follow: 'delirium,' 'acute confusion,' 'acute organic psycho syndrome,' 'toxic confusion,' 'delir\$', 'surg\$', 'operati\$', 'perioperati\$', 'postoperati\$', 'prevalence', 'incidence', 'occurrence' (see the Ovid search strategy in online supplementary appendix 1).

We will include: (1) prospective studies that include preoperative assessment of cognition; (2) cross sectional studies and other cohort study designs as long as preoperative assessment of cognition was done; (3) publications in English; (4) studies in which a validated

measurement tool was used to screen for delirium as well as those that utilised diagnostic criteria for delirium as described in the Diagnostic and Statistical Manual of Mental Disorders (DSM-V/DSM-IV-TR) or International Classification of Diseases ICD-10; and (5) studies that provide the data necessary to calculate incidence. We will exclude: (1) retrospective studies and interventional studies and (2) studies that only report prevalence of delirium because it is not clear in these studies if patients had delirium preoperatively. Incident delirium is preferred to investigate the actual condition of delirium after cardiac surgery.

The DSM criteria are widely accepted as the gold standard in the diagnosis of delirium, and the ICD criteria are also applied widely by clinicians. Instruments such as the Confusion Assessment Method (CAM),<sup>19</sup> Delirium Rating Scale (DRS),<sup>20</sup> Delirium Symptom Interview (DRI),<sup>21</sup> Intensive Care Delirium Screening Checklist (ICDSC),<sup>22</sup> etc, have been validated against DSM or ICD criteria. Studies using any of these methods for diagnosis of delirium are acceptable. Studies using non-validated instruments, such as the Mini-Mental Status Examination (MMSE)<sup>23</sup> and the Short Mental Status Test (SMST),<sup>24</sup> will be excluded as they were developed to measure cognitive impairment rather than delirium.<sup>25</sup>

Studies will be limited to human subjects aged  $\geq 60$  years. The population of interest will be older hospitalised patients that undergo cardiac surgery, such as elective coronary artery surgery or heart valve replacement/repair, either with or without coronary bypass grafting.

## Outcome

The primary outcome is the incidence of postoperative delirium. Postoperative delirium is defined as an episode of delirium occurring after surgery.

## Study selection and data extraction

Two authors will independently screen the titles and abstracts of all citations identified by the searches for potentially eligible studies. Full text of potentially eligible studies will be obtained and assessed according to the aforementioned inclusion criteria. We will present the process of search and study selection using a flow process chart.

A standardised data extraction form will be developed for data extraction. Two authors will independently perform data extraction. We will collect the following information from every included trial: (1) publication (title, first author, year of publication); (2) study design; (3) patient demographics (sample size, mean age, gender ratio, type of surgery, baseline cognitive status); (4) details of outcome measures; (5) details necessary to assess the risk of bias. Any disagreements will be resolved by consulting a third author or the original authors will be contacted for further information if necessary.

## Risk of bias (quality) assessment

We will incorporate quality assessment into our analyses by evaluating sources of bias that may affect the overall estimations. We will assess the quality of included studies using the risk of bias tool for prevalence studies developed by Hoy, and the Cochrane guidelines.<sup>26 27</sup> Risk of bias and quality scores will be presented in a table.

In addition, a minimum sample size will be calculated to differentiate estimates with good precision. Studies with a sample size equal to or higher than the minimum sample size will be classified as 'with good precision.' Small study effect on the effect size will be explored by funnel plots, and symmetry will be tested using Egger's test.

## Statistical analysis

Estimates for the incidence of postoperative delirium will be pooled into a meta-analysis and displayed with 95% CIs. We will derive SEs where studies have provided the corresponding numerator and denominator for delirium incidence estimates. The study specific estimates will be pooled to obtain an overall summary estimate of the incidence across studies using a random effects, after stabilising the variance of individual studies with the Freeman–Tukey double arc-sine transformation.<sup>28</sup> Statistical heterogeneity across studies will be assessed by the Cochrane Q test and quantified by calculating  $I^2$ . A value of  $I^2 > 50\%$  indicates substantial heterogeneity. Where heterogeneity is statistically significant, we will conduct a subgroup analysis to investigate the possible sources of heterogeneity according to the following variables: age, type of surgery, methods used for delirium diagnosis or assessment, pre-existing cognitive impairment, diabetes mellitus, depression and cerebrovascular disease.<sup>17</sup> As different diagnostic methods for delirium have various sensitivity and specificity<sup>29</sup> and this may influence the incidence of delirium to some extent,<sup>30</sup> we will also perform subgroup analyses based on diagnostic methods, if possible. Furthermore, a sensitivity analysis will be performed to find out how our results would change if only high quality studies were considered. Symmetry of the funnel plot will be used to assess publication bias across studies or selective reporting bias. Data will be analysed using Stata V.13.1 for Windows.

## Reporting of this review

This systematic review will be reported following the guideline of Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA),<sup>31</sup> and of meta-analyses of observational studies (MOOSE).<sup>27</sup>

## DISCUSSION

This systematic review and meta-analysis will define the incidence data for delirium in the elderly after cardiac surgery. Determining the current burden of postoperative delirium in the elderly undergoing cardiac

surgery based on certain baseline patient characteristics will be important for clinicians providing care to this potentially vulnerable population and will help guide researchers as they develop interventional trials to prevent this important syndrome in the older population. Furthermore, understanding baseline (preoperative) patient characteristics that increase postoperative delirium is critical for balanced randomisation in interventional trials to prevent postoperative delirium.

A major possible limitation of this study may be the heterogeneity of the studies, as the study populations' baseline of each trial and the methods used to assess delirium are so heterogeneous. To explore the possible source of heterogeneity, we will conduct subgroup analysis based on patients' baseline characteristics, type of cardiac surgery and diagnostic methods. Due to the language barrier, only English articles will be included in our study. This may be another limitation of this study, for which we may lose relevant data from non-English spoken areas and may cause publication bias to some extent.

**Contributors** YL and JY conceived and designed the protocol, and YL drafted the protocol manuscript. JHF and JY critically revised the manuscript for methodological and intellectual content. YW participated in the development of the search strategy. CD and LC planned the data extraction. All authors approved the final version.

**Competing interests** None declared.

**Ethics approval** Given that this is a protocol for a systematic review and based on published data, there is no requirement for ethics approval.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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## REFERENCES

1. Saczynski JS, Marcantonio ER, Quach L, *et al*. Cognitive trajectories after postoperative delirium. *N Engl J Med* 2012;367:30–9.
2. Witlox J, Eurelings LS, de Jonghe P, *et al*. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA* 2010;304:443–51.
3. Shi Q, Presutti R, Selchen D, *et al*. Delirium in acute stroke: a systematic review and meta-analysis. *Stroke* 2012;43:645–9.
4. Barron EA, Holmes J. Delirium within the emergency care setting, occurrence and detection: a systematic review. *Emerg Med J* 2013;30:263–8.
5. Bruce AJ, Ritchie CW, Blizard R, *et al*. The incidence of delirium associated with orthopedic surgery: a meta-analytic review. *Int Psychogeriatr* 2007;19:197–214.
6. Whitlock EL, Vannucci A, Avidan MS. Postoperative delirium. *Minerva Anestesiol* 2011;77:448–56.
7. Robinson TN, Eiseman B. Postoperative delirium in the elderly: diagnosis and management. *Clin Interv Aging* 2008;3:351–5.
8. Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people. *Lancet* 2014;383:911–22.
9. Rudolph JL, Marcantonio ER. Review articles: postoperative delirium: acute change with long-term implications. *Anesth Analg* 2011;112:1202–11.
10. Koster S, Hensens AG, Schuurmans MJ, *et al*. Prediction of delirium after cardiac surgery and the use of a risk checklist. *Eur J Cardiovasc Nurs* 2013;12:284–92.

11. Norkienė I, Ringaitienė D, Kuzminskaitė V, *et al.* Incidence and risk factors of early delirium after cardiac surgery. *Biomed Res Int* 2013;2013:323491.
12. Mu JL, Lee A, Joynt GM. Pharmacologic agents for the prevention and treatment of delirium in patients undergoing cardiac surgery: systematic review and metaanalysis. *Crit Care Med* 2015;43:194–204.
13. Fong TG, Davis D, Growdon ME, *et al.* The interface between delirium and dementia in elderly adults. *Lancet Neurol* 2015;14:823–32.
14. Jankowski CJ, Trener MR, Cook DJ, *et al.* Cognitive and functional predictors and sequelae of postoperative delirium in elderly patients undergoing elective joint arthroplasty. *Anesth Analg* 2011;112:1186–93.
15. Schenning KJ, Deiner SG. Postoperative delirium in the geriatric patient. *Anesthesiol Clin* 2015;33:505–16.
16. Vasilevskis EE, Han JH, Hughes CG, *et al.* Epidemiology and risk factors for delirium across hospital settings. *Best Pract Res Clin Anaesthesiol* 2012;26:277–87.
17. Gosselt AN, Slooter AJ, Boere PR, *et al.* Risk factors for delirium after on-pump cardiac surgery: a systematic review. *Crit Care* 2015;19:346.
18. Hollinger A, Siegemund M, Goettel N, *et al.* Postoperative delirium in cardiac surgery: an unavoidable menace? *J Cardiothor Vasc An* 2015;29:1677–87.
19. Inouye SK, van Dyck CH, Alessi CA, *et al.* Clarifying confusion: the confusion assessment method: a new method for detection of delirium. *Ann Intern Med* 1990;113:941–8.
20. Trzepacz PT, Baker RW, Greenhouse J. A symptom rating scale for delirium. *Psychiat Res* 1998;23:89–97.
21. Albert MS, Levkoff SE, Reilly C, *et al.* The delirium symptom interview: An interview for the detection of delirium symptoms in hospitalized patients. *Geriatr Psychol Neu* 1992;5:14–21.
22. Bergeron N, Dubois MJ, Dumont M, *et al.* Intensive care delirium screening checklist: evaluation of a new screening tool. *Intens Care Med* 2001;27:859–64.
23. Folstein MF, Folstein SE, McHugh PR. 'Mini mental state'. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–98.
24. Kokmen E, Naessens JM, Offord KP. A short test of mental status: Description and preliminary results. *Mayo Clin Proc* 1987;62:281–8.
25. Smith MJ, Breitbart WS, Platt MM. A critique of instruments and methods to detect, diagnose, and rate delirium. *J Pain Symptom Manag* 1995;10:35–77.
26. Hoy D, Brooks P, Woolf A, *et al.* Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. *J Clin Epidemiol* 2012;65:934–9.
27. Stroup DF, Berlin JA, Morton SC, *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA* 2000;283:2008–12.
28. Barendregt JJ, Doi SA, Lee YY, *et al.* Meta-analysis of prevalence. *J Epidemiol Community Health* 2013;67: 974–8.
29. Wong CL, Holroyd-Leduc J, Simel DL, *et al.* Does this patient have delirium? Value of bedside instruments. *JAMA* 2010;304:779–86.
30. Laurila JV, Pitkala KH, Strandberg TE, *et al.* The impact of different diagnostic criteria on prevalence rates for delirium. *Dement Geriatr Cogn* 2003;16:156–62.
31. Moher D, Shamseer L, Clarke M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.