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Keywords:	delirium, systematic review and meta-analysis, incidence, Cardiac surgery < SURGERY

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

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The authors have no commercial or financial conflicts to disclose.

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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 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 over the age of 60 years after cardiac surgery.

Methods and analyses: We will undertake a comprehensive literature search among PubMed, EMBASE, and The Cochrane Library from their inception through September 2016. Prospective cohort and cross-sectional studies which described the incidence of delirium, will be eligible for inclusion. The primary outcome will be 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 ethical 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.

Trial registration number: CRD42016047773

Keywords: Delirium; incidence; cardiac surgery; elderly; systematic review; meta-analysis; protocol

Strengths of this study: 1) This is the first systematic review and meta-analysis aimed to investigate the incidence for delirium after cardiac surgery; 2) The study will provide an up to date and accurate incidence of postoperative delirium in the elderly after cardiac surgery which is necessary for future research in this area; 3) We will ascertain incidence based on certain patient characteristics, such as baseline cognitive impairment, to determine the incidence for specific populations.

Limitations of this study: Non-English articles won't be included in our study due to language difficulties, which may cause publication bias.

INTRODUCTION

Postoperative delirium is one of the most common complications for elderly patients who undergo surgery, characterized by acute onset, fluctuating course, inattention, and at times an abnormal level of consciousness. Recent studies have provided evidence that postoperative

1
2
3 delirium in elderly patients is associated with poor outcomes.
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6 Postoperative delirium is associated with an increased risk of long term
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9 cognitive dysfunction and functional decline compared to patients
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11 without postoperative delirium.¹ Moreover, patients who had experienced
12
13 delirium were also at increased risk of death.²
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16 Although systematic review and meta-analysis of incidence exist for
17
18 acute stroke, emergency department visits, intensive care units and
19
20 orthopaedic surgery, no such systematic review and meta-analysis exists
21
22 for delirium after cardiac surgery.³⁻⁵ Such a systematic review and
23
24 meta-analysis is needed for several reasons. Future intervention studies
25
26 aimed at preventing delirium will need an accurate estimate of incidence.
27
28 Currently, reports of incidence vary too widely (8% to 65%)⁶⁻⁹ to use for
29
30 comparison. Furthermore, if researchers perform placebo controlled
31
32 intervention trials, the incidence in the placebo group could be compared
33
34 to that of the meta-analysis to ensure the placebo group had the
35
36 expected incidence. The incidence could also be used to help researchers
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38 perform power calculations for number of subjects needed in trials.¹⁰
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47 Lastly, the incidence of postoperative delirium vary depending on
48
49 characteristics of patients and types of surgery.⁶⁻⁹ For example, delirium is
50
51 more common among older patients with baseline cognitive impairment
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53 compared with patients with normal cognitive function.^{11,12} Type of
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55 cardiac surgery is another factor that affects the incidence of delirium.^{13,14}
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4 A systematic review and meta-analysis that analyzes and identifies higher
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6 incidence of certain subgroups (such as baseline cognitive impairment)
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8 could help future researchers focus interventions on these higher than
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10 average risk populations.
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14 Thus, we intend to conduct a systematic review and meta-analysis to
15
16 ascertain the incidence of delirium among older people undergoing
17
18 cardiac surgery. We will also ascertain incidence based on certain patient
19
20 characteristics (if data is available) that might have higher than average
21
22 expected incidence. These characteristics include but are not limited to:
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24 age 80 years and older, baseline cognitive impairment, diabetes mellitus,
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26 depression and cerebrovascular disease, all of which have been found in a
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28 previous meta-analysis on risk factors associated with occurrence of
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30 delirium.¹⁵
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37 **METHODS**

38 **Criteria for included studies**

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40 We will conduct a comprehensive search on databases of MEDLINE,
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42 EMBASE, and The Cochrane Library from their inceptions through
43
44 September 2016. References of eligible studies and relevant review
45
46 articles or meta-analyses will be manually searched for additional studies.
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48 The MeSH word and free word were used as follow: “delirium,” “acute
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50 confusion,” “acute organic psycho syndrome,” “toxic confusion,”
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52 “delir\$”, “surg\$”, “operati\$”, “perioperati\$”, “postoperati\$”, “prevalence”,
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4 “incidence”, “occurrence”.

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6 We will include: (1) prospective studies that include pre-operative
7
8 assessment of cognition; (2) cross sectional studies and other cohort study
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10 designs as long as pre-operative assessment of cognition was done; (3)
11
12 publications in English; (4) studies in which a validated measurement tool
13
14 was used to screen for delirium as well as those that utilized diagnostic
15
16 criteria for delirium as described in the Diagnostic and Statistical Manual
17
18 of Mental Disorders (DSM-V/DSM-IV-TR) or International
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20 Classification of Diseases ICD-10; studies that provide the data necessary
21
22 to calculate incidence. We will exclude: (1) retrospective studies and
23
24 interventional studies; (2) Studies that only report prevalence of delirium
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26 because it is not clear in these studies if patients had delirium
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28 pre-operatively. Incident delirium is preferred to investigate the actual
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30 situation of delirium after cardiac surgery.
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39 Studies will be limited to human subjects aged 60 or over. The
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41 population of interest will be older hospitalized patients that undergo
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43 cardiac surgery, such as elective coronary artery surgery or heart valve
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45 replacement/repair either with or without coronary bypass grafting.
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49 **Outcome**

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

A standardized 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, and 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 with 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 by using the Risk of Bias Tool for Prevalence Studies developed by Hoy et al and the Cochrane guidelines.^{16,17} 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 have a sample size equal to or

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4 higher than the minimum sample size will be classified as “with good
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6 precision”. Small-study effect on the effect size will be explored by the
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8 funnel plots, and asymmetry will be tested using Egger’s test.
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10 11 **Statistical analysis**

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14 Estimates for the incidence of postoperative delirium will be pooled
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16 into a meta-analysis and displayed with 95 % confidence intervals (CIs).
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18 We will derive SEs where studies have provided the corresponding
19
20 numerator and denominator for delirium incidence estimates. Statistical
21
22 heterogeneity across studies will be assessed by the Cochrane Q test and
23
24 quantified by calculating the I^2 . A value of I^2 greater than 50% indicates
25
26 substantial heterogeneity. Where heterogeneity is statistically significant,
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28 we will conduct a sub-group analysis to investigate the possible sources
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30 of heterogeneity according the following variables: age, types of surgery,
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32 methods used for delirium diagnosis or assessment, pre-existing cognitive
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34 impairment diabetes mellitus, depression and cerebrovascular disease¹⁵.
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36 Furthermore, a sensitivity analysis will be performed to find out how our
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38 results would change if only high-quality studies were considered. Data
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40 will be analyzed by using Stata13.1 for Windows.
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49 **Reporting of this review**

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51 This systematic review will be reported following the guideline of
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53 Preferred Reporting Items for Systematic reviews and Meta-Analyses
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55 (PRISMA), and of meta-analyses of observational studies (MOOSE).
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DISCUSSION

This systematic review and meta-analysis will define the incidence data of delirium in the elderly after cardiac surgery. Determining the current burden of postoperative delirium in the elderly undergoing cardiac surgery will be important for clinicians providing care to this potentially vulnerable population and will help guide researchers as they develop intervention trials to prevent this important syndrome in the older population.

Acknowledgments

None.

Contributors

Yulin Liao and Jirong Yue conceived and designed the protocol, and Yulin Liao drafted the protocol manuscript. Joseph Flaherty and Jirong Yue critically revised the manuscript for methodological and intellectual content. Yanyan Wang participated in the development of the search strategy. Chuanyao Deng and Ling Chen planned the data extraction. All authors approved the final version.

Competing interests

None.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	CRD42016047773
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page1
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page9
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page3-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page5-6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page5-6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page5-6

Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review		Page6-7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)		
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators		
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications		
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale		Page6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis		Page7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised		Page8
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)		
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)		
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned		
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)		Page8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)		Page8

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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The authors have no commercial or financial conflicts to disclose.

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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 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 over the age of 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 through 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).

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Ethics and dissemination: This proposed systematic review and meta-analysis is based on published data, and thus there is no requirement for ethical 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.

Trial registration number: CRD42016047773

Keywords: Delirium; incidence; cardiac surgery; elderly; systematic review; meta-analysis; protocol

Strengths of this study: (1) This is the first systematic review and meta-analysis aimed to investigate the incidence for delirium after cardiac surgery. (2) The study will provide an up to date and accurate incidence of postoperative delirium in the elderly after cardiac surgery, which is necessary for future research in this area. (3) We will ascertain incidence based on certain patient characteristics, such as baseline cognitive impairment, to determine the incidence for specific populations. If certain subgroups have higher incidence rates, this could help future researchers focus interventions on these higher than average risk populations. Furthermore, understanding baseline (preoperative) patient characteristics that increase postoperative delirium is critical for balanced randomization in intervention trials to prevent postoperative delirium.

Limitations of this study: Non-English articles will not be included in our study due to language difficulties, which may cause publication bias.

INTRODUCTION

Postoperative delirium is one of the most common complications for elderly patients who undergo surgery, characterized by acute onset, fluctuating course, inattention, and at 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 to patients without postoperative delirium.¹ Moreover, patients who had experienced delirium were also at increased risk of death.²

Although systematic review and meta-analysis of incidence exist for acute stroke, emergency department visits, intensive care units and orthopedics surgery, no such systematic review and meta-analysis exists for delirium after cardiac surgery.³⁻⁵ 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% to 65%)⁶⁻¹¹ to use for comparison. Furthermore, if researchers perform placebo controlled intervention trials, the incidence in the placebo group could be compared to 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.¹² Lastly, the

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6 patients and types of surgery.⁶⁻⁹ For example, delirium is more common
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12 another factor that affects the incidence of delirium.^{15,16} A systematic
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16 certain subgroups (such as baseline cognitive impairment) could help
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18 future researchers focus interventions on these higher than average risk
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20 populations. Additionally, characteristics of higher than average risk
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22 populations would be important to recognize for researchers who recruit
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24 participants into study protocols so that the researchers will measure all
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26 potential baseline variables that increase risk of postoperative delirium in
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28 both the interventions and control groups.

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36 characteristics (if data is available) that might have higher than average
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38 expected incidence. These characteristics include but are not limited to:
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40 age 65 and older, (including two subgroups of older patients: ages 65-79
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42 and age 80 years and older), baseline cognitive impairment, diabetes
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44 mellitus, depression and cerebrovascular disease, type of cardiac surgery
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46 (such as 'closed' surgery like valve replacement and 'open' surgery like
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bypass surgery), all of which have been found in previous meta-analyses about risk factors associated with occurrence of delirium.^{17,18}

METHODS

Criteria for included studies

We will conduct a comprehensive search on databases of MEDLINE, EMBASE, and The Cochrane Library, PsycINFO and CINAHL from their inceptions through 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 word were used 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 Appendix 1.

We will include: (1) Prospective studies that include pre-operative assessment of cognition. (2) Cross sectional studies and other cohort study designs as long as pre-operative 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 utilized 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. (5) Studies that provide the data necessary to calculate incidence. We will exclude: (1)

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14 The DSM criteria are widely accepted as the gold standard in the
15
16 diagnosis of delirium, and the ICD criteria are also applied widely by
17
18 clinician in the clinical work. Instruments such as the
19
20 Confusion-Assessment Method (CAM)¹⁹, Delirium-Rating Scale (DRS)²⁰,
21
22 Delirium Symptom Interview (DRI)²¹ and so forth have been proven
23
24 validated against DSM or ICD criteria. Studies using any method above
25
26 for delirium diagnosis are acceptable in our review. Studies using
27
28 non-validated instruments, such as Mini-mental-Status Exam (MMSE)
29
30 ²²and Short Mental-Status Test (SMST)²³ will be excluded, for the reason
31
32 that they are developed to measure cognitive impairment rather than
33
34 delirium.²⁴
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41
42 Studies will be limited to human subjects aged 60 or over. The
43
44 population of interest will be older hospitalized patients that undergo
45
46 cardiac surgery, such as elective coronary artery surgery or heart valve
47
48 replacement/repair either with or without coronary bypass grafting.
49
50

51 Outcome

52
53 The primary outcome is the incidence of postoperative delirium.
54
55 Postoperative delirium is defined as an episode of delirium occurring
56
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4 after surgery.

5 6 **Study selection and Data extraction**

7
8
9 Two authors will independently screen the titles and abstracts of all
10 citations identified by the searches for potentially eligible studies.
11 Full-text of potentially eligible studies will be obtained and assessed
12 according to the aforementioned inclusion criteria. We will present the
13 process of search and study selection by using a flow process chart.
14
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20
21 A standardized data extraction form will be developed for data
22 extraction. Two authors will independently perform data extraction. We
23 will collect the following information from every included trial: (1)
24 Publication (title, first author, year of publication). (2) Study design. (3)
25 Patient demographics (sample size, mean age, gender ratio, and type of
26 surgery, baseline cognitive status). (4) Details of outcome measures. 5)
27 Details necessary to assess the risk of bias. Any disagreements will be
28 resolved by consulting a third author or the original authors will be
29 contacted with for further information if necessary.
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44 **Risk of bias (quality) assessment**

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46 We will incorporate quality assessment into our analyses by
47 evaluating sources of bias that may affect the overall estimations. We will
48 assess the quality of included studies by using the Risk of Bias Tool for
49 Prevalence Studies developed by Hoy and the Cochrane guidelines.^{25,26}
50 Risk of bias and quality scores will be presented in a table.
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4 In addition, a minimum sample size will be calculated to differentiate
5
6 estimates with good precision. Studies have a sample size equal to or
7
8 higher than the minimum sample size will be classified as “with good
9
10 precision.” Small-study effect on the effect size will be explored by the
11
12 funnel plots, and symmetry will be tested using Egger’s test.
13
14

15 16 **Statistical analysis** 17

18
19 Estimates for the incidence of postoperative delirium will be pooled
20
21 into a meta-analysis and displayed with 95 % confidence intervals (CIs).
22
23 We will derive SEs where studies have provided the corresponding
24
25 numerator and denominator for delirium incidence estimates. The
26
27 study-specific estimates will be pooled to obtain an overall summary
28
29 estimate of the incidence across studies by using a random effects, after
30
31 stabilizing the variance of individual studies with the Freeman-Tukey
32
33 double arc-sine transformation.²⁷ Statistical heterogeneity across studies
34
35 will be assessed by the Cochran Q test and quantified by calculating the
36
37 I^2 . A value of I^2 greater than 50% indicates substantial heterogeneity.
38
39 Where heterogeneity is statistically significant, we will conduct a
40
41 sub-group analysis to investigate the possible sources of heterogeneity
42
43 according the following variables: age, types of surgery, methods used for
44
45 delirium diagnosis or assessment, pre-existing cognitive impairment
46
47 diabetes mellitus, depression and cerebrovascular disease.¹⁷ As different
48
49 diagnostic methods for delirium have various sensitivity and specificity²⁸
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3 and this may influence the incidence of delirium to some extent²⁹, we will
4 also perform subgroup analysis based on diagnostic methods, if possible.
5
6 Furthermore, a sensitivity analysis will be performed to find out how our
7 results would change if only high quality studies were considered.
8
9 Symmetry of funnel plot will be used to assess the publication bias across
10 studies or selective reporting bias. Data will be analyzed by using
11 Stata13.1 for Windows.
12
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20 **Reporting of this review**

21 This systematic review will be reported following the guideline of
22 Preferred Reporting Items for Systematic reviews and Meta-Analyses
23 (PRISMA)³⁰, and of meta-analyses of observational studies (MOOSE).²⁶
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32 **DISCUSSION**

33 This systematic review and meta-analysis will define the incidence
34 data of delirium in the elderly after cardiac surgery. Determining the
35 current burden of postoperative delirium in the elderly undergoing
36 cardiac surgery will be important for clinicians providing care to this
37 potentially vulnerable population and will help guide researchers as they
38 develop intervention trials to prevent this important syndrome in the older
39 population.
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51 A major possible limitation of this study may be the heterogeneity of
52 studies, since the study populations' baseline of each trial and the
53 methods used to assess delirium are so heterogeneous. To explore the
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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.

ETHICS AND DISSEMINATION

Given that this is a protocol for a systematic review and based on published data, there is no requirement for ethical approval. The findings of this study will be presented at conferences and submitted to relevant health authorities. The final report of the systematic review will be published in peer-reviewed journals. We also plan to update the review in future to monitor any progressive changes on the subject.

Acknowledgments

None.

Contributors

Yulin Liao and Jirong Yue conceived and designed the protocol, and Yulin Liao drafted the protocol manuscript. Joseph Flaherty and Jirong Yue critically revised the manuscript for methodological and intellectual content. Yanyan Wang participated in the development of the search strategy. Chuanyao Deng and Ling Chen planned the data extraction. All

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4 authors approved the final version.

5 6 **Competing interests**

7
8 None.

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11
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13
14 the public, commercial, or not-for-profit sectors.
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18 19 **REFERENCES**

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 3 CRD42016047773
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 11-12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 11-12
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 5-6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 6-7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page 6 Appendix 1

Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review		Page 8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)		
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators		
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications		
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale		Page 7-8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis		Page 8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised		Page 9-10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)		
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)		
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned		
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)		Page 9-10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)		Page 9-10

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Appendix 1

Delirium Search Strategy

Medline (OVID)

- 1、 exp delirium/
- 2、 deliri\$.mp.
- 3、 acute confusion.mp.
- 4、 acute confusional state.mp.
- 5、 confusion.mp.
- 6、 postoperative psychosis.mp.
- 7、 acute organic psychosyndrome.mp.
- 8、 toxic confusion.mp.
- 9、 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
- 10、 surg\$.mp.
- 11、 operati\$.mp.
- 12、 perioperati\$.mp.
- 13、 postoperati\$.mp.
- 14、 10 or 11 or 12 or 13
- 15、 cardiac.mp.
- 16、 heart.mp.
- 17、 pump.mp.
- 18、 valve.mp.
- 19、 aneurysm.mp.
- 20、 bypass.mp.
- 21、 15 or 16 or 17 or 18 or 19 or 20
- 22、 14 and 21
- 23、 exp prevalence/
- 24、 exp Incidence/
- 25、 prevalence.mp.
- 26、 incidence.mp.
- 27、 epidemiology.mp.
- 28、 23 or 24 or 25 or 26 or 27
- 29、 9 and 22 and 28

PsycINFO.

- 1、 delirium.SH
- 2、 delirium.TI
- 3、 delirium.AB
- 4、 confusion*.TI
- 5、 confusion*.AB
- 6、 1 or 2 or 3 or 4 or 5
- 7、 surgery.SH
- 8、 surgery.TI
- 9、 surgery.AB
- 10、 surgical.TI
- 11、 surgical.AB
- 12、 operati*.TI
- 13、 operati*.AB
- 14、 postoperati*.TI
- 15、 postoperati*.AB
- 16、 perioperati*.TI
- 17、 perioperati*.AB
- 18、 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
- 19、 cardiac.AB
- 20、 cardiac.TI
- 21、 heart.AB
- 22、 heart.TI
- 23、 pump.AB
- 24、 pump.TI
- 25、 valve.AB
- 26、 valve.TI
- 27、 aneurysm.AB
- 28、 aneurysm.TI
- 29、 bypass.AB
- 30、 bypass.TI
- 31、 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
- 32、 18 and 31
- 33、 prevalence.SH
- 34、 incidence.SH
- 35、 prevalen*.AB
- 36、 inciden*.AB
- 37、 prevalen*.TI
- 38、 inciden*.TI
- 39、 epidemiology.SH
- 40、 epidemi*.TI
- 41、 epidemi*.AB
- 42、 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41

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3 43、 6 and 32 and 42
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6 **EMBASE (OVID)**

- 7 1、 exp delirium/
8 2、 exp acute confusion/
9 3、 exp confusion/
10 4、 delirium.mp.
11 5、 acute confusion.mp.
12 6、 confusion.mp.
13 7、 acute confusional state.mp.
14 8、 postoperative psychosis.mp.
15 10、 acute organic psycho syndrome.mp.
16 11、 toxic confusion.mp.
17 12、 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
18 13、 surg\$.mp.
19 14、 operati\$.mp.
20 15、 perioperati\$.mp.
21 16、 postoperati\$.mp.
22 17、 13 or 14 or 15 or 16
23 18、 exp prevalence/
24 19、 exp Incidence/
25 20、 prevalence.mp.
26 21、 incidence.mp.
27 22、 epidemiology.mp.
28 23、 18 or 19 or 20 or 21 or 22
29 24、 12 and 17 and 23
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BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-014726.R2
Article Type:	Protocol
Date Submitted by the Author:	07-Feb-2017
Complete List of Authors:	Liao, Yulin; West China Hospital, Sichuan University, Department of Geriatrics Flaherty, Joseph H.; Saint Louis University, Division of Geriatrics, Department of Internal Medicine Yue, Jirong; West China Hospital, Sichuan University, Department of Geriatrics ; The national center for Geriatric clinical research in West China Hospital Wang, Yanyan; West China Hospital, Sichuan University, Department of Geriatrics Deng, Chuanyao; West China Hospital, Sichuan University, Department of Geriatrics Chen, Ling; West China Hospital, Sichuan University, Department of Geriatrics
Primary Subject Heading:	Geriatric medicine
Secondary Subject Heading:	Mental health, Evidence based practice, Geriatric medicine
Keywords:	delirium, systematic review and meta-analysis, incidence, Cardiac surgery < SURGERY, protocol, elderly

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Manuscripts

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

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Word count: 2800

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 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 over the age of 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 inceptions through 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).

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4 **Ethics and dissemination:** This proposed systematic review and
5
6 meta-analysis is based on published data, and thus there is no requirement
7
8 for ethical approval. The study will provide an up to date and accurate
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10 incidence of postoperative delirium among the older population after
11
12 cardiac surgery, which is necessary for future research in this area. The
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14 findings of this study will be presented at conferences and disseminated
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16 through publication in a peer-reviewed journal.
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21 **Trial registration number:** CRD42016047773
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24 **Keywords:** Delirium; incidence; cardiac surgery; elderly; systematic
25
26 review; meta-analysis; protocol
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29 **Strengths and Limitations of this study:** (1) This study will provide an
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31 up to date and accurate incidence of postoperative delirium in the elderly
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33 after cardiac surgery. (2) A subgroup analysis of certain patient
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35 characteristics make it possible to determine the incidence for specific
36
37 population and screen the populations with higher than average risk of
38
39 delirium. (3) The findings of this study will help guide researchers as they
40
41 develop intervention trials to prevent delirium in the older population. (4)
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43 Non-English articles will not be included in our study due to language
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45 difficulties and this may cause publication bias to some extent.
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INTRODUCTION

Postoperative delirium is one of the most common complications for elderly patients who undergo surgery, characterized by acute onset, fluctuating course, inattention, and at 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 to patients without postoperative delirium.¹ Moreover, patients who had experienced delirium were also at increased risk of death.²

Although systematic review and meta-analysis of incidence exist for acute stroke, emergency department visits, intensive care units and orthopedics surgery, no such systematic review and meta-analysis exists for delirium after cardiac surgery.³⁻⁵ 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% to 65%)⁶⁻¹¹ to use for comparison. Furthermore, if researchers perform placebo controlled intervention trials, the incidence in the placebo group could be compared to 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.¹² Lastly, the

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4 incidence of postoperative delirium varies depending on characteristics of
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6 patients and types of surgery.⁶⁻⁹ For example, delirium is more common
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8 among older patients with baseline cognitive impairment compared with
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10 patients with normal cognitive function.^{13,14} Type of cardiac surgery is
11
12 another factor that affects the incidence of delirium.^{15,16} A systematic
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14 review and meta-analysis that analyzes and identifies higher incidence of
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16 certain subgroups (such as baseline cognitive impairment) could help
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18 future researchers focus interventions on these higher than average risk
19
20 populations. Additionally, characteristics of higher than average risk
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22 populations would be important to recognize for researchers who recruit
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24 participants into study protocols so that the researchers will measure all
25
26 potential baseline variables that increase risk of postoperative delirium in
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28 both the interventions and control groups.

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37 Thus, we intend to conduct a systematic review and meta-analysis to
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39 ascertain the incidence of delirium among older people undergoing
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41 cardiac surgery. We will also ascertain incidence based on certain patient
42
43 characteristics (if data is available) that might have higher than average
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45 expected incidence. It has been confirmed that there are numerous risk
46
47 factors or patient characteristics associated with delirium, but some of
48
49 them are mentioned much more often and we will conduct
50
51 subgroup-analysis based on these characteristics. These characteristics
52
53 include but are not limited to: age 65 and older, (including two subgroups
54
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of older patients: ages 65-79 and age 80 years and older), baseline cognitive impairment, diabetes mellitus, depression and cerebrovascular disease, type of cardiac surgery (such as ‘closed’ surgery like valve replacement and ‘open’ surgery like bypass surgery), all of which have been found in previous meta-analyses about risk factors associated with occurrence of delirium.^{17,18}

METHODS

Criteria for included studies

We will conduct a comprehensive search on databases of MEDLINE, EMBASE, and The Cochrane Library, PsycINFO and CINAHL from their inceptions through 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 word were used 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 Appendix 1.

We will include: (1) Prospective studies that include pre-operative assessment of cognition. (2) Cross sectional studies and other cohort study designs as long as pre-operative 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 utilized

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3
4 diagnostic criteria for delirium as described in the Diagnostic and
5
6 Statistical Manual of Mental Disorders (DSM-V/DSM-IV-TR) or
7
8 International Classification of Diseases ICD-10. (5) Studies that provide
9
10 the data necessary to calculate incidence. We will exclude: (1)
11
12 Retrospective studies and interventional studies. (2) Studies that only
13
14 report prevalence of delirium because it is not clear in these studies if
15
16 patients had delirium pre-operatively. Incident delirium is preferred to
17
18 investigate the actual situation of delirium after cardiac surgery.
19
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24 The DSM criteria are widely accepted as the gold standard in the
25
26 diagnosis of delirium, and the ICD criteria are also applied widely by
27
28 clinician in the clinical work. Instruments such as the
29
30 Confusion-Assessment Method (CAM)¹⁹, Delirium-Rating Scale (DRS)²⁰,
31
32 Delirium Symptom Interview (DRI)²¹, Intensive Care Delirium Screening
33
34 Checklist (ICDSC)²² and so forth have been proven validated against
35
36 DSM or ICD criteria. Studies using any method above for delirium
37
38 diagnosis are acceptable in our review. Studies using non-validated
39
40 instruments, such as Mini-mental-Status Exam (MMSE)²³ and Short
41
42 Mental-Status Test (SMST)²⁴ will be excluded, for the reason that they
43
44 are developed to measure cognitive impairment rather than delirium.²⁵
45
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51 Studies will be limited to human subjects aged 60 or over. The
52
53 population of interest will be older hospitalized patients that undergo
54
55 cardiac surgery, such as elective coronary artery surgery or heart valve
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3
4 replacement/repair either with or without coronary bypass grafting.

5 6 **Outcome**

7
8 The primary outcome is the incidence of postoperative delirium.
9
10 Postoperative delirium is defined as an episode of delirium occurring
11
12 after surgery.
13
14

15 16 **Study selection and Data extraction**

17
18 Two authors will independently screen the titles and abstracts of all
19
20 citations identified by the searches for potentially eligible studies.
21
22 Full-text of potentially eligible studies will be obtained and assessed
23
24 according to the aforementioned inclusion criteria. We will present the
25
26 process of search and study selection by using a flow process chart.
27
28

29
30 A standardized data extraction form will be developed for data
31
32 extraction. Two authors will independently perform data extraction. We
33
34 will collect the following information from every included trial: (1)
35
36 Publication (title, first author, year of publication). (2) Study design. (3)
37
38 Patient demographics (sample size, mean age, gender ratio, and type of
39
40 surgery, baseline cognitive status). (4) Details of outcome measures. 5)
41
42 Details necessary to assess the risk of bias. Any disagreements will be
43
44 resolved by consulting a third author or the original authors will be
45
46 contacted with for further information if necessary.
47
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53 54 **Risk of bias (quality) assessment**

55
56 We will incorporate quality assessment into our analyses by
57
58
59
60

1
2
3
4 evaluating sources of bias that may affect the overall estimations. We will
5
6 assess the quality of included studies by using the Risk of Bias Tool for
7
8 Prevalence Studies developed by Hoy and the Cochrane guidelines.^{26,27}
9
10 Risk of bias and quality scores will be presented in a table.
11
12

13
14 In addition, a minimum sample size will be calculated to differentiate
15
16 estimates with good precision. Studies have a sample size equal to or
17
18 higher than the minimum sample size will be classified as “with good
19
20 precision.” Small-study effect on the effect size will be explored by the
21
22 funnel plots, and a symmetry will be tested using Egger’s test.
23
24

25 26 **Statistical analysis** 27

28
29 Estimates for the incidence of postoperative delirium will be pooled
30
31 into a meta-analysis and displayed with 95 % confidence intervals (CIs).
32
33 We will derive SEs where studies have provided the corresponding
34
35 numerator and denominator for delirium incidence estimates. The
36
37 study-specific estimates will be pooled to obtain an overall summary
38
39 estimate of the incidence across studies by using a random effects, after
40
41 stabilizing the variance of individual studies with the Freeman-Tukey
42
43 double arc-sine transformation.²⁸ Statistical heterogeneity across studies
44
45 will be assessed by the Cochrane Q test and quantified by calculating the
46
47 I^2 . A value of I^2 greater than 50% indicates substantial heterogeneity.
48
49 Where heterogeneity is statistically significant, we will conduct a
50
51 sub-group analysis to investigate the possible sources of heterogeneity
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4 according the following variables: age, types of surgery, methods used for
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6 delirium diagnosis or assessment, pre-existing cognitive impairment
7
8 diabetes mellitus, depression and cerebrovascular disease.¹⁷ As different
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10 diagnostic methods for delirium have various sensitivity and specificity²⁹
11
12 and this may influence the incidence of delirium to some extent³⁰, we will
13
14 also perform subgroup analysis based on diagnostic methods, if possible.
15
16 Furthermore, a sensitivity analysis will be performed to find out how our
17
18 results would change if only high quality studies were considered.
19
20 Symmetry of funnel plot will be used to assess the publication bias across
21
22 studies or selective reporting bias. Data will be analyzed by using Stata
23
24 13.1 for Windows.

31 **Reporting of this review**

32
33 This systematic review will be reported following the guideline of
34
35 Preferred Reporting Items for Systematic reviews and Meta-Analyses
36
37 (PRISMA)³¹, and of meta-analyses of observational studies (MOOSE).²⁷
38
39

42 **DISCUSSION**

43
44 This systematic review and meta-analysis will define the incidence
45
46 data of delirium in the elderly after cardiac surgery. Determining the
47
48 current burden of postoperative delirium in the elderly undergoing
49
50 cardiac surgery based on certain baseline patient characteristics will be
51
52 important for clinicians providing care to this potentially vulnerable
53
54 population and will help guide researchers as they develop intervention
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4 trials to prevent this important syndrome in the older population.
5
6 Furthermore, understanding baseline (preoperative) patient characteristics
7
8 that increase postoperative delirium is critical for balanced randomization
9
10 in intervention trials to prevent postoperative delirium.
11
12

13
14 A major possible limitation of this study may be the heterogeneity of
15
16 studies, since the study populations' baseline of each trial and the
17
18 methods used to assess delirium are so heterogeneous. To explore the
19
20 possible source of heterogeneity, we will conduct subgroup analysis
21
22 based on patients' baseline characteristics, type of cardiac surgery and
23
24 diagnostic methods. Due to the language barrier, only English articles
25
26 will be included in our study. This may be another limitation of this study,
27
28 for which we may lose relevant data from non-English spoken areas and
29
30 may cause publication bias to some extent.
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37 **ETHICS AND DISSEMINATION**

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39 Given that this is a protocol for a systematic review and based on
40
41 published data, there is no requirement for ethical approval. The findings
42
43 of this study will be presented at conferences and submitted to relevant
44
45 health authorities. The final report of the systematic review will be
46
47 published in peer-reviewed journals. We also plan to update the review in
48
49 future to monitor any progressive changes on the subject.
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55 **Acknowledgments**

None.

Contributors

Yulin Liao and Jirong Yue conceived and designed the protocol, and Yulin Liao drafted the protocol manuscript. Joseph Flaherty and Jirong Yue critically revised the manuscript for methodological and intellectual content. Yanyan Wang participated in the development of the search strategy. Chuanyao Deng and Ling Chen planned the data extraction. All authors approved the final version.

Competing interests

None.

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For peer review only

Appendix 1

Delirium Search Strategy

Medline (OVID)

- 1、 exp delirium/
- 2、 deliri\$.mp.
- 3、 acute confusion.mp.
- 4、 acute confusional state.mp.
- 5、 confusion.mp.
- 6、 postoperative psychosis.mp.
- 7、 acute organic psychosyndrome.mp.
- 8、 toxic confusion.mp.
- 9、 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
- 10、 surg\$.mp.
- 11、 operati\$.mp.
- 12、 perioperati\$.mp.
- 13、 postoperati\$.mp.
- 14、 10 or 11 or 12 or 13
- 15、 cardiac.mp.
- 16、 heart.mp.
- 17、 pump.mp.
- 18、 valve.mp.
- 19、 aneurysm.mp.
- 20、 bypass.mp.
- 21、 15 or 16 or 17 or 18 or 19 or 20
- 22、 14 and 21
- 23、 exp prevalence/
- 24、 exp Incidence/
- 25、 prevalence.mp.
- 26、 incidence.mp.
- 27、 epidemiology.mp.
- 28、 23 or 24 or 25 or 26 or 27
- 29、 9 and 22 and 28

PsycINFO

- 1、 delirium.SH
- 2、 delirium.TI
- 3、 delirium.AB
- 4、 confusion*.TI
- 5、 confusion*.AB
- 6、 1 or 2 or 3 or 4 or 5
- 7、 surgery.SH
- 8、 surgery.TI
- 9、 surgery.AB
- 10、 surgical.TI
- 11、 surgical.AB
- 12、 operati*.TI
- 13、 operati*.AB
- 14、 postoperati*.TI
- 15、 postoperati*.AB
- 16、 perioperati*.TI
- 17、 perioperati*.AB
- 18、 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
- 19、 cardiac.AB
- 20、 cardiac.TI
- 21、 heart.AB
- 22、 heart.TI
- 23、 pump.AB
- 24、 pump.TI
- 25、 valve.AB
- 26、 valve.TI
- 27、 aneurysm.AB
- 28、 aneurysm.TI
- 29、 bypass.AB
- 30、 bypass.TI
- 31、 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
- 32、 18 and 31
- 33、 prevalence.SH
- 34、 incidence.SH
- 35、 prevalen*.AB
- 36、 inciden*.AB
- 37、 prevalen*.TI
- 38、 inciden*.TI
- 39、 epidemiology.SH
- 40、 epidemi*.TI
- 41、 epidemi*.AB
- 42、 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41
- 43、 6 and 32 and 42

EMBASE (OVID)

1
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6 exp delirium/
7 exp acute confusion/
8 exp confusion/
9 delirium.mp.
10 acute confusion.mp.
11 confusion.mp.
12 acute confusional state.mp.
13 postoperative psychosis.mp.
14 10、 acute organic psycho syndrome.mp.
15 11、 toxic confusion.mp.
16 12、 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
17 13、 surg\$.mp.
18 14、 operati\$.mp.
19 15、 perioperati\$.mp.
20 16、 postoperati\$.mp.
21 17、 13 or 14 or 15 or 16
22 18、 exp prevalence/
23 19、 exp Incidence/
24 20、 prevalence.mp.
25 21、 incidence.mp.
26 22、 epidemiology.mp.
27 23、 18 or 19 or 20 or 21 or 22
28 24、 12 and 17 and 23
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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 3 CRD42016047773
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 11-12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 12
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 3-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 6-7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page 6 Appendix 1

Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review		Page 8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)		
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms done independently, in duplicate), any processes for obtaining and confirming data from investigators		
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications		
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale		Page 7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis		Page 8-9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised		Page 9-10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)		
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)		
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned		
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)		Page 9-10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)		Page 9-10

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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